Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study title	**An open-label, randomised, non-comparative phase 2 study evaluating S 95005 (TAS-102) plus bevacizumab and capecitabine plus bevacizumab in patients with previously untreated metastatic COlorectal cancer who are non-eligible for intensive therapy (TASCO1 study)**
Test drug code	S 95005 (trifluridine/tipiracil)
Indication	First-line treatment of metastatic colorectal cancer in patients non-eligible for intensive therapy
Development phase	Phase II
Protocol code	CL2-95005-002
EudraCT Number	2015-004544-18
Universal Trial Number	Not applicable
Sponsor	Institut de Recherches Internationales Servier (I.R.I.S.)
International Coordinator	Prof. Eric Van Cutsem, MD, PhD Gastroenterology/Digestive Oncology Leuven Cancer Institute University Hospitals Leuven 3000 Leuven- Belgium
Date of the document	25th January 2017
Version of the document	Final Version
Substantial Amendment integrated	

No	Final version date	Countries concerned
1	17th March 2016	ITA
2	17th May 2016	All
3	30th August 2016	DEU
4	25th January 2017	All

CONFIDENTIAL

FOLLOW-UP OF VERSIONS

Substantial amendment No	Final version date	Countries concerned	Nature of amendments
1	17th March 2016	ITA	See Appendix 6
2	17th May 2016	All	- Title update and addition of an acronym - Update of inclusion / non-inclusion criteria and forbidden treatment to be in line with capecitabine and bevacizumab SmPC, - Addition of a DSMB, - Addition of haematological assessment at CXD15 in the experimental arm, - Clarification and update of the study duration for the patient (under treatment and after treatment withdrawal), - Clarification about laboratory tests (time point, CEA dosage…) - Corrections/clarifications of inconsistencies and typo
3	30th August 2016	DEU	See Appendix 8
4	25th January 2017	All	- The main objective of this substantial amendment is to implement the urgent safety measure which aims to revise the instructions given in the study protocol for the dose modifications for S 95005 in case of febrile neutropenia to be in line with the European Summary of Product Characteristics of Lonsurf®, - Update of the end of recruitment period, - Clarification on the definition of the end of the study, - Clarification on t he population targeted in the study that's to say the first-line treatment of patients with unresectable metastatic colorectal cancer who are non-eligible for intensive therapy, - Update of inclusion, non-inclusion and withdrawal criteria, - Precision that all samplings for biochemistry in fasting condition is preferable but not mandatory, - Bicarbonate assessment becomes optional, - The section "8.4.1.1 Adverse events" has been updated to be in line with the upcoming "EMA guidelines on evaluation of an anticancer treatment"; - Corrections/clarifications of inconsistencies and typo.

STUDY SUMMARY SHEET

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: S 95005 (TAS-102)	**Volume:**	
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Page:**	

Title of study:
An open-label, randomised, non-comparative phase 2 study evaluating S 95005 (TAS-102) plus bevacizumab and capecitabine plus bevacizumab in patients with previously untreated metastatic COlorectal cancer who are non-eligible for intensive therapy. (TASCO1 study).
Protocol No.: CL2-95005-002

Coordinator(s)
National coordinators and investigators: listed in a separate document

Study centre(s):
Total number of centres: Approximately 60
Total number of countries: Approximately 12

Study period (event driven trial)**:**	**Study development phase:**
- Study duration for the patient: approximately 1 year of treatment + follow-up - Planned study initiation date (planned date of first visit first patient): Q2 2016 - Planned end of recruitment period (planned date of first visit last patient): Q1 2017 ~~March 2018 (approximately 24 months)~~ - Planned study completion date: (12 months after the follow-up start date of the last patient withdrawn ~~planned date of last visit last patient~~): Q2 2019	Phase II

Objectives:
Primary
Progression-free survival (PFS) based on Investigator assessment of radiologic images

Secondary
- Overall response rate (ORR)
- Duration of response (DR)
- Disease control rate (DCR)
- Overall survival (OS)
- Safety and tolerability
- Quality of life (QoL) (EORTC QLQ-C30 and QLQ-CR29) (Aaronson NK *et al*., 1993)

Exploratory
Evaluate the biomarkers potentially predictive of response and resistance to S 95005 given in combination using blood samples and archived tumour biopsy (if available).

Methodology:
This is a multinational, open-label, two-arm, randomised phase 2 study evaluating S 95005 + bevacizumab and capecitabine + bevacizumab in the first-line treatment of patients with ~~previously untreated~~ unresectable metastatic colorectal cancer (mCRC) who are non-eligible for intensive therapy.
Patients will be randomised in a (1:1) ratio with the minimisation procedure proposed by Pocock and Simon (Pocock SJ *et al*., 1975). The stratification factors will be RAS status (wild-type, mutant type), ECOG performance status (0 vs. 1 vs. 2) and country.

Number of participants:
Total: approximately 150

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: S 95005 (TAS-102)	**Volume:**	
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Page:**	

In each group: approximately 75
Number of primary events*:* 100 Progression Free Survival (PFS) events

Diagnosis
First-line treatment of patients with unresectable mCRC ~~previously untreated~~ who are non-eligible for intensive therapy.

Inclusion criteria

Informed consent
1. Written informed consent will be obtained prior to any study-specific procedure.

Demographic characteristics
2. Male or Female participant aged ≥18 years old.

Disease characteristics
3. Has ECOG performance status of 0, 1 or 2 at the time of the randomisation.
4. Has definitive histologically or cytologically confirmed adenocarcinoma of the colon or rectum.
5. RAS status must have been determined (mutant or wild) based on local biological assessment on tumour biopsy. At least the following mutation must be determined: KRAS and NRAS Exon 2: codon 12 and 13.
6. Has at least one measurable metastatic lesion (as defined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1). Note: Unresectable metastatic disease must have been diagnosed within 6 months prior to first day of study drug administration.
7. No previous systemic anticancer therapy for unresectable metastatic colorectal cancer.
8. Previous adjuvant (or neoadjuvant for patients with rectal cancer) chemotherapy is allowed only if it has been completed more than 6 months before start of study treatment.
9. Patient is not a candidate for combination chemotherapy with irinotecan or oxaliplatin according to investigator's judgment based on decision taken during a multidisciplinary meeting (if organised in the centre).
10. Patient is not a candidate for curative resection of metastatic lesions according to investigator's judgment based on decision taken during a multidisciplinary meeting (if organised in the centre).

Medical and therapeutic criteria
11. Is able to take medication orally (*i.e.*, no feeding tube).
12. Has adequate organ function as defined by the following laboratory values obtained within 5 days prior to randomisation:
    - 12.1. Haemoglobin value of ≥9.0 g/dL based on measurements obtained 2 weeks or more after last prior transfusion.
    - 12.2. Absolute neutrophil count (ANC) of ≥1.5 x 10^9/L.
    - 12.3. Platelet count ≥100 x 10^9/L.
    - 12.4. Total serum bilirubin of ≤1.5 x upper limit of normal (ULN) (except for ~~Grade 1~~ hyperbilirubinemia due solely to a medical diagnosis of Gilbert's syndrome).
    - 12.5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5 x ULN.
    - 12.6. Creatinine clearance > 50 mL/min (using Cockcroft Gault formula).
    - 12.7. Urine dipstick test for proteinuria < 1+ or 24-hour urine collection <1000 mg for patients found with ≥ 1+ on dipstick.
13. Coagulation parameters in normal limit (or in therapeutic limit for patients treated with anticoagulant drugs): activated partial thromboplastin time (aPTT) and international normalized ratio (INR).
14. Women of childbearing potential must have been tested negative in a serum pregnancy test within 5 days prior to randomisation.
    Within the frame of this study, female participants of childbearing potential and male participants with partners of childbearing potential must agree to use a highly effective method of birth control (*i.e.*, pregnancy rate of less than 1% per year) during the study and for 6 months after the discontinuation of

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: S 95005 (TAS-102)	**Volume:**	
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Page:**	

study medication.
Contraceptive methods that result in a low failure rate when used consistently and correctly include methods such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), some intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, or a female partner who is not of childbearing potential or a male partner who has had a vasectomy. Women and female partners using hormonal contraceptive must also use a barrier method i.e. condom or occlusive cap (diaphragm or cervical/vault caps).

15. Is willing and able to comply with scheduled visits and study procedures.

Non-inclusion criteria

General criteria

16. Foreseeable poor compliance to the study procedures.
17. Is a pregnant or lactating female.
18. Is inappropriate for entry into this study in the judgment of the Investigator.

Medical and therapeutic criteria

19. Has a serious illness or serious medical condition(s) including, but not limited to the following:
    - 19.1. Other ~~concurrently active~~ malignancies excluding malignancies that are in remission for more than 5 years, ~~or~~ carcinoma-in-situ deemed cured by adequate treatment or basal cell carcinoma.
    - 19.2. Known brain metastasis or leptomeningeal metastasis.
    - 19.3. Active systemic infection (*i.e.*, body temperature ≥38°C due to infection).
    - 19.4. At the time of screening, intestinal obstruction, pulmonary fibrosis, interstitial pneumonitis, renal failure, liver failure, or cerebrovascular disorder.
    - 19.5. Uncontrolled diabetes.
    - 19.6. Deep venous/arterial thromboembolic complication or bleeding diatheses or any other haemorrhage/bleeding event CTCAE grade > 3 within 4 weeks prior to randomisation.
    - 19.7. Cerebrovascular accident or myocardial infarction within the last 12 months, severe/unstable angina, uncontrolled or symptomatic arrhythmia, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV, uncontrolled hypertension.
    - 19.8. Known coagulopathy that increases risk of bleeding or a history of clinically significant haemorrhages in the past (including Grade ≥3 gastrointestinal haemorrhage) within 4 weeks prior to randomisation.
    - 19.9. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or hepatitis B or C as determined by serologic tests.
    - 19.10. Patients with autoimmune disorders or history of organ transplantation who require immunosuppressive therapy.
    - 19.11. Psychiatric disease that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results.
    - 19.12. In the investigator's opinion, significant malabsorption syndrome, significant chronic digestive or gastrointestinal inflammatory syndrome.
20. Major surgery within 4 weeks prior to randomisation (the surgical incision should be fully healed prior to study drug administration). Note: indwelling catheter and portacath implantation are allowed.
21. Extended field radiation within 4 weeks or limited field radiation within 2 weeks prior to randomisation.
22. Any investigational agent received within 4 weeks prior to randomisation.
33. Participant already enrolled in the study (informed consent signed).

Non-inclusion criteria related to administration of S 95005:

23. Has previously received S 95005 or history of allergic reactions attributed to compounds of similar composition to S 95005 or any of its excipients.

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: S 95005 (TAS-102)	**Volume:**	
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Page:**	

31. Hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Non-inclusion criteria related to administration of bevacizumab:

24. History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients.
25. History of hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
32. Any contraindication present in the SmPC of bevacizumab.

Non-inclusion criteria related to administration of capecitabine:

26. History of allergic reactions or hypersensitivity to capecitabine or any of its excipients or fluorouracil.
27. History of severe and unexpected reaction to fluoropyrimidine therapy.
28. Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
29. Treatment with sorivudine or its chemical related analogues, such as brivudine, within 4 weeks prior to randomisation
30. Any contraindication present in the SmPC of capecitabine.

Test drug/experimental arm: S 95005 + bevacizumab arm

S 95005 (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.

Control arm: Capecitabine + bevacizumab

Capecitabine (1250 mg/m²) will be administered orally BID on Days 1–14 of each cycle, with bevacizumab (7.5 mg/kg, IV) administered on Day 1 of each cycle. This treatment cycle will be repeated every 3 weeks.

Note: According to local clinical practice the starting dose of capecitabine could be reduced to 1000 mg/m² but could not be lower.

Duration of treatment:

Patients will be treated by the assigned combined regimen until they meet a discontinuation criterion as described in section 5.4.1. Patients will be considered to be on treatment as long as either component of the combination regimen continues to be administered unless the investigator judges that it is in the interest of the patient to withdraw from the study and to be treated outside of this protocol with a combine modality. If a patient discontinues study treatment for reasons other than radiologic disease progression (*e.g.*, intolerable side effects), patients will be followed for tumour response until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first). After progression, patients will be followed for survival until the end of the study (defined as the last visit of the last patient).

The selection will be stopped once 100 PFS events (progression of disease [PD] or death) are reached or 150 patients are randomised (whichever occurs first) and the on-going patients will continue the study without change until the end of the study.
Once 100 PFS events (progression of disease [PD] or death) are reached the main study analysis will be performed.

Criteria for evaluation:

Efficacy measurements:
Tumour assessments will be analysed using RECIST 1.1 (Eisenhauer EA *et al.*, 2009). Every 8 weeks until progression, death or initiation of a new anticancer treatment (whichever occurs first).
Quality of life assessments will be performed every 12 weeks.

Safety measurements:
Standard safety monitoring will be performed and adverse events (AEs) will be graded using the National

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: S 95005 (TAS-102)	**Volume:**	
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Page:**	

Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The Event Requiring Immediate Notification (ERIN) not related will be reported during 100 days after the last study drug 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.

Pharmacokinetic measurements:
Not applicable

Biomarkers measurements:

- At C1D1 blood samples for proteomic and genomic analysis will be collected and at withdrawal visit only proteomic blood samples.
- Intratumoural biomarkers analysis (proteomic and genomic) will be performed from archival tumour biopsy (if available).

Statistical methods:

Study population

- Full Analysis Set (FAS): All randomised patients who have taken at least one dose of IMP will be included in the FAS. Based on the intention-to-treat principle, patients in the FAS will be analysed in the arm they were assigned by randomisation.
- Per Protocol Set (PPS): All patients of the FAS without relevant deviation(s), which could affect the evaluation of the IMP effect on the primary efficacy endpoint.
- Tumour Response (TR) Population: All patients in the PPS with measurable disease (at least one target lesion) at baseline and with at least one tumour evaluation while on treatment (with the same method of measurement as baseline). Patients who have a cancer-related death prior to their first tumour evaluation will also be considered evaluable with PD as best overall response.
- Safety Set (SS): This set will correspond to patients who received at least one dose of IMP. Patients will be analysed according to the treatment actually received. Each patient will be classified into and analysed consistently within one (and only one) treatment group.
- Quality of Life Set (QLS): To be included in the QLS for the QLQ-C30 questionnaire, patients should have completed at least two third (*i.e*. at least 20 questions) of the questions of the baseline QLQ-C30 questionnaire, and at least two third of the questions of a QLQ-C30 questionnaire during the study period. Same conditions for the QLQ-CR29 questionnaires.

Efficacy analysis:
All efficacy analyses will be performed in the FAS, unless otherwise specified.

Primary endpoint:
For the primary efficacy endpoint, PFS, the hazard ratio (HR) and the corresponding 2-sided 80% and 95% confidence intervals (CI) for S 95005+ bevacizumab versus capecitabine + bevacizumab will be estimated using a Cox proportional hazard model adjusting for the 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 6, 12, 18, and 24 months along with the corresponding 2-sided 80% and 2-sided 95% CI for the estimates.
The primary analysis will be conducted in the FAS.

Secondary endpoints:

As a secondary analysis, the primary analysis of PFS will be repeated in the PPS.
In order to assess the consistency of the primary analysis of PFS, another sensitivity analysis taking into account the further anti-cancer therapy as an event will be carried out both in the FAS and the PPS.

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier **Volume:**	*(For National Authority Use only)*
Name of Finished Product: S 95005 (TAS-102)		
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Page:**	

Additional exploratory analyses for PFS will investigate the effect of specific factors either in a multivariate analysis setting (Cox regression model) or as the marginal effect in specific subgroups. These factors will include, but are not limited to, region, ECOG performance status, gender, age (<75, ≥75 years), prior adjuvant treatment, location of primary disease, surgical resection, number of metastatic sites (1, ≥2), presence of liver metastasis, and KRAS/BRAF/NRAS status. Additional exploratory analyses will be defined in the SAP.
Analysis of OS will be performed in the FAS.
Analysis of DR will be performed in the TR Population.
DCR and ORR based on the TR Population will be evaluated in each treatment arms with their 2-sided 95% Clopper-Pearson CIs.

Study patients (disposition, baseline characteristics and follow-up) and Safety analysis:
Simple descriptive statistics will be provided for safety endpoints and demographic/baseline characteristics and will be presented for the entire Safety Population.
EORTC QLQ-C30 and QLQ-CR29 questionnaire responses will be described separately on the QLS, using descriptive statistics in each arm.

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, GCP and the applicable regulatory requirements.

NAME **DATE** **SIGNATURE**

COORDINATOR / INVESTIGATOR :

PPD

CENTER NUMBER	

PPD

PPD

FOR SERVIER:

Table of contents

List of tables

List of figures

List of appendices

List of abbreviations

ADL	:	Activities of Daily Living
AE	:	Adverse Event
AIDS	:	Acquired ImmunoDeficiency Syndrome
ALAT	:	ALanine aminoTransferase
am	:	ante meridiem
ANC	:	Absolute Neutrophil Count
aPTT	:	Activated Partial Thromboplastin Time
ASAT	:	ASpartate aminoTransferase
ß-HCG	:	Beta-Human Chorionic Gonadotrophin
BID	:	bis in die (twice a day)
BP	:	Blood Pressure
BRAF		v-Raf murine sarcoma viral oncogene homolog B
BRM	:	Biological Response Modifiers
BSA	:	Body Surface Area
BSC	:	Best Supportive Care
BUN	:	Blood Urea Nitrogen
CD-ROM	:	Compact Disc – Read Only Memory
CEA	:	CarcinoEmbryonic Antigen
CI	:	Confidence Interval
CR	:	Complete Response
CRA	:	Clinical Research Associsate
CRC	:	ColoRectal Cancer
e-CRF	:	Electronic Case Report Form
CRF	:	Case Report Form
CRO	:	Contract Research Organisation
CT	:	Computed Tomography
CTCAE	:	Common Toxicity Criteria for Adverse Event
CV	:	Curriculum Vitae
DCR	:	Disease Control Rate
dL	:	Decilitre
DNA	:	DeoxyriboNucleic Acid
DR	:	Duration of Response
DSMB	:	Data Safety Monitoring Board
ECG	:	ElectroCardioGram
ECOG	:	Eastern Cooperative Oncology Group
e.g.	:	Exempli gratia (for example)
ERIN	:	Event Requiring Immediate Notification
ESMO	:	European Society for Medical Oncology
FAS	:	Full Analysis Set
FDG-PET	:	FluoroDeoxyGlucose Positron Emission Tomography
FTD	:	Trifluridine
g	:	gram
G-CSF	:	Granulocyte Colony-Stimulating Factor
GCP	:	Good Clinical Practice
GGT	:	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
HIV	:	Human Immunodeficiency Virus
HR	:	Heart Rate
HR	:	Hazard Ratio
I.R.I.S.	:	Institut de Recherches Internationales Servier
IB	:	Investigator's Brochure
ICH	:	International Conference on Harmonisation
ICF	:	Informed Consent Form
i.e.	:	id est (that is)
IEC	:	Independent Ethics Committee

IMP	:	Investigational Medicinal Product: a p harmaceutical 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 Ration
IRB	:	Institutional Review Board
IWRS	:	Interactive Web Response System
IUD	:	IntraUterine (contraceptive) Device
IV	:	IntraVenous (route)
IWRS	:	Interactive Web Response System
KRAS		V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
kg	:	kilogram
L	:	Litre
LDH	:	Lactate DeHydrogenase
mCRC	:	Metastatic Colorectal Cancer
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	milligram
min	:	minute
mL	:	Millilitre
mm	:	Millimetre
MRI	:	Magnetic Resonance Imaging
NA	:	Not Applicable
NCI	:	National Cancer Institute
NCI-CTCAE	:	National Cancer Institute Common Toxicity Criteria for Adverse Event
NCCN	:	National Comprehensive Cancer Network
NE	:	Not Evaluated
ng	:	nanogram
NIS	:	Non Included Set
NYHA	:	New York Heart Association
ORR	:	Overall Response Rate
OS	:	Overall Survival
pm	:	post meridiem
PD	:	Progressive Disease
PET	:	Positron Emission Tomography
PFS	:	Progression-Free Survival
PPS	:	Per Protocol Set
PR	:	Prothrombine Ratio
QoL	:	Quality of Life
QLQ	:	Quality of Life Questionnaire
QLS	:	Quality of Life Set
QTc	:	QT interval corrected for heart rate
RBC	:	Red Blood Cells
RECIST	:	Response Evaluation Criteria in Solid Tumours
RS	:	Randomised Set
RTV	:	Relative Tumour Volume
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SD	:	Standard Deviation
SD	:	Stable Disease
SE	:	Standard Error
SI	:	International System
SmPC	:	Summary of Product Characteristics
SS	:	Safety Set
test drug	:	Drug substance in a given dosage form, tested in a clinical trial. It usually corresponds to the Servier S 95005
TP	:	Thymidine Phosphorylase
TPI	:	Tipiracil Hydrochloride
TR	:	Tumour Response
TS	:	Thymidilate Synthase
TU	:	Therapeutic Units
ULN	:	Upper Limit of reference range

VEGF	:	Vascular Endothelial Growth Factor
vs	:	versus
WBC	:	White Blood Cells
WHO	:	World Health Organization
WHO-DD	:	World Health Organization, Drug Dictionary

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

This section is described in a separate document entitled “Administrative part of clinical study protocol”.
This document, attached to the protocol, describes the following:

- Non sponsor parties;
- Sponsor parties;
- CRO responsible for local management of the study.

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 8.4.4 and 12.4.

2. BACKGROUND INFORMATION

2.1. Overview of disease pathogenesis, epidemiology and current treatment

In 2012, there were 447 000 new cases of colorectal cancer (CRC) in Europe. CRC is the second most frequent cancer and represents 13.2% and 12.7% of all cancer cases in men and women, respectively. CRC was responsible for 215 000 deaths in Europe in 2012 (Ferlay J *et al.*, 2013). This represents 11.6% and 13.0% of all cancer deaths in men and women, respectively (National Comprehensive Cancer Network (NCCN), Colon Cancer-Version 3. 2015; National Comprehensive Cancer Network (NCCN), Rectal Cancer-Version 3. 2015). 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. The CRC-related 5-year survival rate approaches 60%.

The treatment of mCRC is dependent upon many factors including the disease stage at presentation and the extent of metastatic spread. For most patients with mCRC, the treatment intent is palliative rather than curative. For a small proportion of patients with resectable metastasis, surgery is the treatment option of choice. In patients with unresectable disease, chemotherapy is the mainstay of treatment.

First-line treatment options in patients with unresectable mCRC depend on whether the patient is appropriate for intensive therapy. Current European Society for Medical Oncology (ESMO) (Van Cutsem E *et al.*, 2014) guidelines define a subpopulation of patients who are without major symptoms or risk of rapid deterioration, and with low tolerance for aggressive therapies. For these patients, the primary aim of therapy is prevention of tumour progression with prolongation of survival and maintenance of quality of life.

Among patients with mCRC who are non-eligible for intensive therapy, recent ESMO and National Comprehensive Cancer Network (NCCN) (Van Cutsem E *et al.*, 2014; National Comprehensive Cancer Network (NCCN), Colon Cancer-Version 3. 2015; National Comprehensive Cancer Network (NCCN), Rectal Cancer-Version 3. 2015) guidelines recommend fluorouracil or capecitabine with or without bevacizumab as first-line treatment.

2.2. Mechanism of action of S 95005

S 95005, also known as TAS-102, is a combination of an antineoplastic thymidine-based nucleoside analogue (trifluridine [FTD]) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride [TPI]). It is marketed in Japan and USA since May 2014 and September 2015 respectively. It has a marketing authorisation in the European Union since 25 April 2016 for the treatment of patients with metastatic colorectal cancer who have been previously treated with or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents and currently being developed by Taiho and Institut de Recherches Internationales Servier.

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.

FTD incorporation into DNA is markedly higher than that of other nucleoside analogues. The degree of incorporation of FTD into DNA ranges from approximately 10-fold up to 700-fold greater in comparison with that of 2'-deoxy-5-fluorouridine (FdUrd). FTD also exhibits

thymidylate synthase (TS) inhibition. However, results of *in vivo* studies show FTD incorporation into DNA to be the primary mechanism of antitumor activity with oral administration.
This mechanism of action of S 95005 differentiates it from conventional fluoropyrimidines, which are uracil-based, and for which the primary mode of action is TS inhibition. In nonclinical studies, S 95005 demonstrated antitumor activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines.
Detailed information on the nonclinical and clinical experience with S 95005 is provided in the Investigator's Brochure (IB).

2.3. S 95005 in Refractory Metastatic Colorectal Cancer (mCRC): Summary of clinical data

2.3.1. Clinical efficacy

In a Phase 3, multinational, randomized, double-blind study (RECOURSE; TPUI-TAS-102-301) (Mayer JR *et al*., 2015) **,** the efficacy and safety of TAS-102 (35 mg/m^2 twice daily [BID] for 5 days a week followed by 2 days of rest; for 2 weeks, followed by a 14-day rest, repeated every 4 weeks) plus best supportive care (BSC) was compared to placebo plus BSC in patients with histologically or cytologically confirmed metastatic colorectal cancer, who had received prior treatment with, or were not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy. The primary efficacy endpoint was overall survival (OS), and the supportive secondary endpoint was progression-free survival (PFS).
A total of 800 patients were randomized (2:1) to receive TAS-102 (n=534) or placebo (n=266) at a total of 101 study sites in 13 countries. Patients were stratified by KRAS status (wild type, mutant); time since diagnosis of first metastasis (<18 months, ≥18 months); and region (Region 1: Asia [Japan]; Region 2: Western [United States, European Union and Australia]).
The median OS was 7.1 months for the S 95005 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 TAS-102 compared to placebo (HR=0.48, 95% CI: 0.41, 0.57, p< 0.0001); median PFS was 2.0 months for the TAS-102 group versus 1.7 months for the placebo group.
In general, results for OS consistently favoured TAS-102 across the stratification groups (KRAS status, time since diagnosis of 1st metastasis, and geographic region) and other pre-specified subgroups including age (<65 vs ≥65 years) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). Among all randomized 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 TAS-102 remained favourable and statistically significant (HR=0.75).
Among the population evaluable for tumour response (502, TAS-102; 258, placebo) there was no difference between the treatment groups with respect to overall response rate (ORR) (8 patients with partial response in the TAS-102 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%, S 95005; 15.9%, placebo) leading to a significant difference in disease control rate (DCR) between the TAS-102 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 TAS-102 compared to placebo, suggesting that quality of life was maintained while on TAS-102 treatment.
This phase 3 study was the basis for the recent registration of the product in USA in September 2015 and in EU in April 2016 for the treatment of patients with metastatic colorectal cancer who have been previously treated with or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents (ref: FDA label information of Lonsurf, 22 sept 2015 and EU product information of Lonsurf, 25 April 2016).

2.3.2. Clinical safety and tolerability

In the RECOURSE study, the most common adverse events (AEs) associated with TAS-102 treatment were myelosuppressive and gastrointestinal toxicities. Among the 533 patients who received TAS-102, 38% had neutropenia of grade 3 or higher, 4% had febrile neutropenia and 18% experienced anaemia of grade 3 or higher. These events were generally manageable with reductions in dose, delays in cycle initiation and occasional use of granulocyte colony-stimulating factor (G-CSF) (Aapro MS *et al*., 2011). 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 TAS-102 group (20.1% to 39.4%); however, these AEs were rarely Grade 3 or 4. The incidence of stomatitis among patients receiving TAS-102 was 7.9%; Grade 3/4 events of stomatitis were rare (0.4%). In addition, hand-foot syndrome was reported in only 2.3% of patients receiving TAS-102 (all Grade 1 or 2), which was the same percentage reported in the placebo arm.

2.4. Rationale for Study and selection of dose

As mentioned in section 2.1, among patients with mCRC who are non-eligible for intensive therapy, recent ESMO and NCCN (Van Cutsem E *et al*., 2014; National Comprehensive Cancer Network (NCCN), Colon Cancer-Version 3. 2015; National Comprehensive Cancer Network (NCCN), Rectal Cancer-Version 3. 2015) guidelines recommend fluorouracil or capecitabine with or without bevacizumab as first-line treatment. In a Phase 3 study of patients with unresectable mCRC considered suitable for first-line treatment with capecitabine monotherapy, the combination of capecitabine and bevacizumab resulted in a significant prolongation of PFS (primary endpoint) compared to capecitabine alone (median PFS of 8.5 months versus 5.7 months; HR=0.63 [95%CI: 0.50, 0.79], p<0.001) (Tebbutt NC *et al*., 2010). The addition of mitomycin to the combination regimen did not result in any further increase in PFS. There was no significant difference in median OS between groups. The most common Grade 3 or 4 toxicities were hand-foot syndrome (16% in capecitabine arm; 26% in capecitabine+bevacizumab arm; 28% in capecitabine+bevacizumab+mitomycin arm) and diarrhoea (11% in capecitabine arm; 17% in capecitabine+bevacizumab arm; 16% in capecitabine+bevacizumab+mitomycin arm).
Moreover, a subgroup analysis of this trial has been made to investigate whether age affected the improved outcome found in mCRC when bevacizumab is added to capecitabine chemotherapy (Price TJ *et al*., 2012). The addition of bevacizumab significantly improved PFS in geriatric patients (5.8 months in capecitabine arm versus 8.8 months in capecitabine + bevacizumab arm). Treatment was well tolerated with no signal of increased toxicity (including thromboembolism) when compared with those aged <75 years.

In a Phase 3 study of elderly patients (≥70 years) with previously untreated mCRC, the combination of bevacizumab and capecitabine was well tolerated and resulted in a significant increase in PFS (primary endpoint) compared to capecitabine alone (median PFS of 9.1 months vs 5.1 months; HR=0.53 [95% CI: 0.41, 0.69], p<0.0001) (Cunningham D *et al*., 2013). There was no significant difference in OS. In this study, the frequency of chemotherapy-related Grade ≥3 events was similar for the two treatment groups except for hand-foot syndrome, which was more frequent in the combination therapy group.

This exploratory study will be performed to evaluate S 95005 + bevacizumab (experimental arm) and capecitabine + bevacizumab (control arm) as first-line treatment for unresectable metastatic colorectal cancer in patients non-eligible for intensive therapy. Metastatic colorectal cancer is mainly a disease of elderly patients and the diagnosis of colorectal cancer is about 69 years (median), however there is also a population younger which present decline organ function and comorbidities at diagnosis. Such patients are often excluded from randomised trials or are difficult to treat.

2.4.1. S 95005 in combination with bevacizumab-Non-clinical data

The antitumor effects of TAS-102 in combination with bevacizumab were assessed using a nude mouse xenograft model of colorectal cancer (Tsukihara H *et al*., 2015) TAS-102 and bevacizumab either alone or in combination, were administered to mice bearing SW48 (KRAS wild type cell lines) or HCT116 (KRAS mutant cell lines) colorectaltumors. TAS-102 and bevacizumab alone inhibited tumor growth. Moreover, combined TAS-102 and bevacizumab treatment had superior antitumor activity compared to either drug alone, and had no significant effect on the body weight compared to TAS-102 monotherapy.
Growth inhibitory activity, based on the relative tumour volume (RTV) after 2 weeks of drug administration and time taken for the relative tumour volume to increase five-fold (RTV5), was significantly better with TAS-102 and bevacizumab combination treatment than with either TAS-102 or bevacizumab alone in SW48 and HCT116 tumour models.

2.4.2. S 95005 in combination with bevacizumab-Clinical data

Based on the demonstrated efficacy and tolerability of TAS-102 in patients with previously treated mCRC, including patients refractory to prior fluoropyrimidine treatment, a Phase 2 study to evaluate the benefit of TAS-102 plus bevacizumab as first-line treatment of unresectable mCRC is warranted. The results of a Phase 1/2 study conducted in Japan suggest that the combination of TAS-102 and bevacizumab is well tolerated in patients with mCRC (Kuboki Y *et al*., 2015).In this study, the most common Grade ≥3 events were neutropenia (68%), leukopenia (40%), febrile neutropenia (16%), and hypertension (8%). Sixty-eight per cent (68%) of patients required a treatment delay, 24% required at least one dose reduction (primarily due to neutropenia), and there were no treatment-related deaths. In addition, as noted in section 2.3.2. above, the incidence of hand-foot syndrome among patients treated with TAS-102 is lower than that commonly observed with fluoropyrimidines including capecitabine. Thus, TAS-102 in combination with bevacizumab may offer a more tolerable treatment option for patients with unresectable mCRC requiring non-intensive therapy.

2.4.3. Study design

This present study is designed as a randomised, open-label Phase 2 study evaluating S 95005 plus bevacizumab and capecitabine plus bevacizumab as first-line treatment of unresectable mCRC in patients who are non-eligible for intensive therapy.
In this phase 2 trial, 100 Progression Free Survival (PFS) events are required to show a significant difference between the two arms with a 2-sided 80% confidence interval.

In this Phase 2 trial, PFS was chosen as the primary endpoint because delaying disease progression (with or without tumour shrinkage) is a key treatment aim in this population of patients non-eligible for intensive therapy.

The primary aim of the translational part of the study is to assess potential predictive biomarkers for S 95005 in order to identify subgroup of patients having a greater degree of benefit with S 95005. This biomarker program also proposes to assess potential biomarkers of resistance to enable a better understanding of reasons for possible progression under treatment (Kalia M, 2015; Coghlin C *et al.*, 2015; Gonzales-Pons M *et al.*, 2015).

2.4.4. Selection of Dose Regimens

Experimental Arm
S 95005 (35 mg/m^2/dose) 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 (5 mg/kg) administered IV every 2 weeks (Day 1 and Day 15). This treatment cycle will be repeated every 4 weeks.
The safety and tolerability of a TAS-102 regimen of 35 mg/m²/dose BID for 5 days with 2 days rest for 2 weeks, repeated every 28 days has been demonstrated in patients with mCRC. A bevacizumab regimen of 5 mg/kg every 2 weeks is a recommended dose for use in combination with fluoropyrimidine-based regimens for treatment of metastatic mCRC. In a Japanese Phase 1/2 study, this combination regimen of TAS-102 plus bevacizumab was well tolerated in patients with unresectable mCRC (Kuboki Y *et al.*, 2015).

Control Arm
Capecitabine (1250 mg/m2) will be administered orally BID on Days 1–14 of each cycle, with IV bevacizumab (7.5 mg/kg) administered on Day 1 of each cycle. This treatment cycle will be repeated every 3 weeks.

According to local clinical practice the starting dose of capecitabine could be reduced to 1000 mg/m². This regimen capecitabine at a dose of 1000 mg/m² plus bevacizumab at 7.5 mg/kg was shown to be effective and well-tolerated as demonstrated in the Avex study (Cunningham D *et al.*, 2013) (survival and progression free survival are similar to general population) and the subgroup analysis of the AGITG MAX trial (Price TJ *et al.*, 2012).

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND PURPOSE

The objectives of this study are to evaluate the following endpoints in patients receiving S 95005 + bevacizumab (experimental arm) or capecitabine + bevacizumab (control arm) as first-line treatment for unresectable metastatic colorectal cancer in patients non-eligible for intensive therapy.

3.1. Primary objectives

- Progression-free survival (PFS) based on Investigator assessment of radiologic images

3.2. Secondary objectives

- Overall response rate (ORR)
- Duration of response (DR)
- Disease control rate (DCR)
- Overall survival (OS)
- Safety and tolerability
- Quality of Life (QoL) (EORTC QLQ-C30, QLQ-CR29) (Aaronson NK *et al*., 1993; Appendix 1).

3.3. Exploratory objectives

- Evaluate the biomarkers potentially predictive of response and resistance to S 95005 given in combination using blood samples and archived tumour biopsy (if available).

4. STUDY DESIGN

This present study is designed as a randomised, open-label phase 2 study evaluating S 95005 plus bevacizumab and capecitabine plus bevacizumab as first-line treatment of unresectable mCRC in patients who are non-eligible for intensive therapy.

In this phase 2 trial, 100 Progression Free Survival (PFS) events are required to show a significant difference between the two arms. In order to observe this number of events, approximately 150 patients will be randomised 1:1 to S 95005 plus bevacizumab (experimental arm) or capecitabine plus bevacizumab (control arm).

Patients will be randomised with the minimisation procedure proposed by Pocock and Simon (Pocock SJ *et al.*, 1975). The stratification factors will be RAS status (wild-type, mutant type), ECOG performance status (0 vs. 1 vs. 2) (Appendix 2) and country.

PFS was chosen as the primary endpoint because delaying disease progression (with or without tumour shrinkage) is a key treatment aim in this population of patients eligible for non-intensive therapy.

4.1. Endpoints

4.1.1. Primary endpoint

- Progression free survival (PFS) is defined as the time from the date of randomisation until the date of the investigator-assessed radiological disease progression or death due to any cause according to RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3).

4.1.2. Secondary endpoints

- Overall Response Rate (ORR). The assessment of ORR will be based on Investigator review of the images according to RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3).
- Duration of Response (DR) is derived for those patients with objective evidence of PR or CR.
- Disease control rate (DCR)
- Overall Survival
- Safety and tolerability assessed by:
  - Incidence of Adverse Events (AE).
  - Laboratory tests: haematology, blood biochemistry, coagulation, urinalysis.
  - Physical examination and performance status (ECOG).
  - Vital signs: blood pressure (BP), heart rate (HR), body temperature, respiration rate, body weight.
  - 12-leads ECG parameters.
- Quality Of Life assessed by a quality of life questionnaire (QLQ) (Aaronson NK *et al.*, 1993; Appendix 1).

4.1.3. Exploratory endpoints

- Biomarkers using blood samples and archived tumour biopsy (if available).

4.2. Experimental design

4.2.1. Study plan

This is a multinational, open-label, two-arm, randomised phase 2 study evaluating S 95005 + bevacizumab and capecitabine + bevacizumab in the first-line treatment of patients with ~~previously untreated~~ unresectable mCRC who are non-eligible for intensive therapy.

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

- **Screening period and Inclusion (up to 28 days prior to randomisation):** to obtain informed consent and to check the eligibility of the patient to be included and randomised in the study.
  Note: for the first patient in a centre, a period of at least 7 days is required between first connection to Interactive Web Response System (IWRS) during screening period (after ICF signature) and first day of study drug administration (Day 1 of Cycle 1) for logistical reasons (bevacizumab supply).
- **Randomisation:** Included patients will be randomly assigned to one of the two treatment groups:
  - S 95005 + bevacizumab: S 95005 (35 mg/m^2/dose) will be administered orally BID, within 1 hour after completion of morning and evening meals, 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.
  - Capecitabine + bevacizumab: Capecitabine (1250 mg/m^2) will be administered orally BID on Days 1–14 of each cycle, with IV bevacizumab (7.5 mg/kg) administered on Day 1 of each cycle. This treatment cycle will be repeated every 3 weeks.

  Note**:** According to local clinical practice the starting dose of capecitabine could be reduced to 1000 mg/m² but could not be lower.
- **Treatment period:** Randomised patients should receive the first dose of study treatment (Day 1 of Cycle 1) no later than 3 days after randomisation. Each patient should receive at least 28 days of combination of S 95005+ bevacizumab or at least 21 days of combination of capecitabine + bevacizumab except in case of safety concerns. Patients will be treated by the assigned combined regimen until they meet a discontinuation criterion as described in section 5.4.1. Patients will be considered to be on treatment as long as either component of the combination regimen continues to be administered unless the investigator judges that it is in the interest of the patient to withdraw from the study and to be treated outside of this protocol with a combine modality. The estimated PFS is 11.7 months in the S 95005 + bevacizumab group and 9 months in the capecitabine + bevacizumab group (please refer to section 10 for more details).
- **Withdrawal visit**: up to 4 weeks after the last dose of study drug administration.
- **Follow-up period:** to obtain tumour assessment (every 8 weeks until disease progression or initiation of new anticancer therapy), patient survival data (date of death), and new anticancer treatments. During this period, the patient will be allowed to participate in a new clinical study or receive a new

The study plan of both arms is shown in Figure (4.2.1) 1 and Figure (4.2.1) 2.

Figure (4.2.1) 1 - Study plan of S 95005 + bevacizumab arm

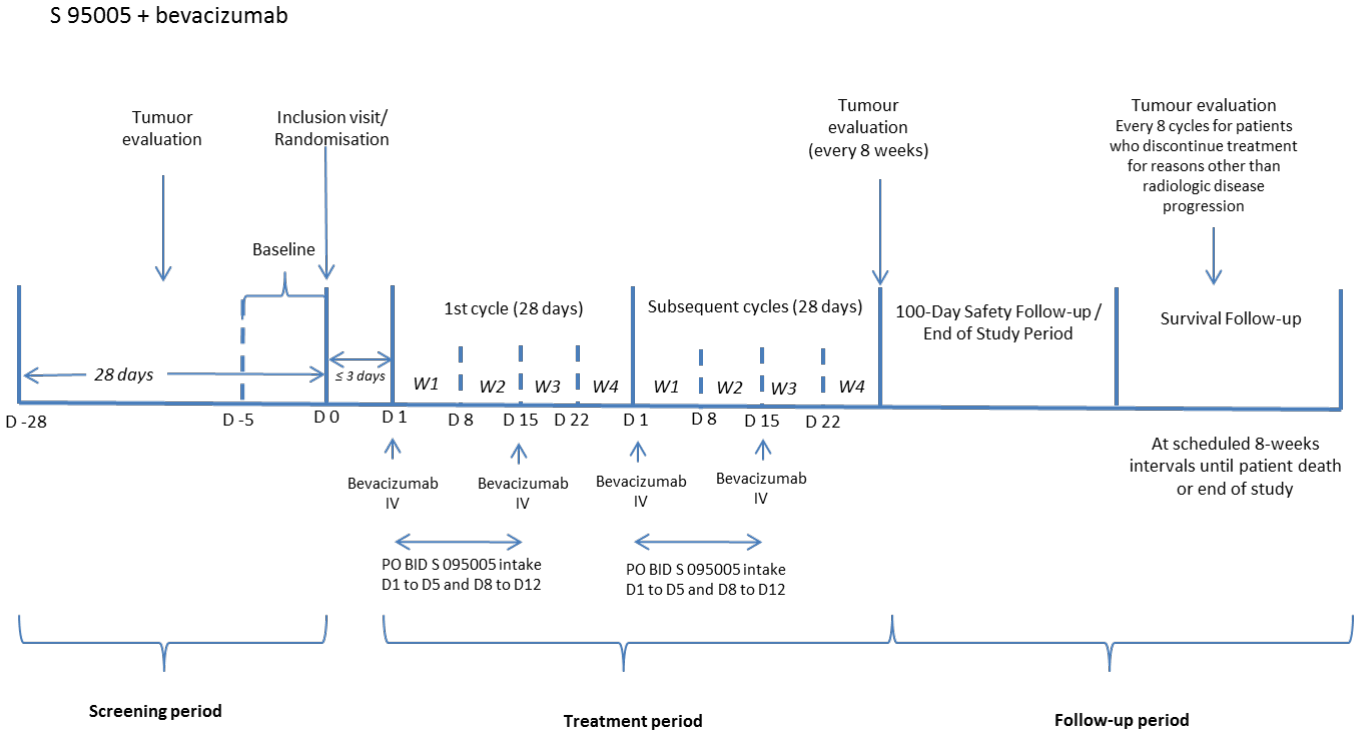
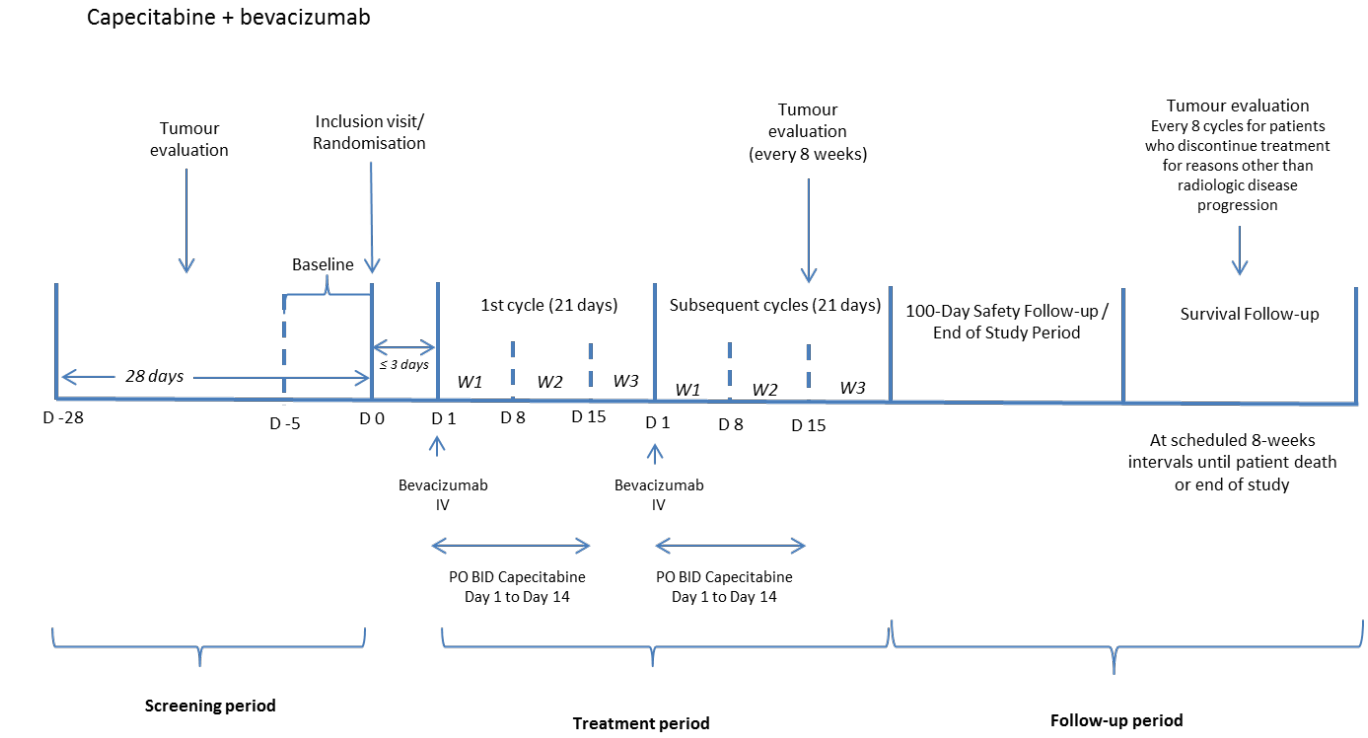


Figure (4.2.1) 2 - Study plan of capecitabine + bevacizumab arm



4.2.2. Study duration

Patients will be treated by the assigned combined regimen until they meet a discontinuation criterion as described in section 5.4.1. Patients will be considered to be on treatment as long as either component of the combination regimen continues to be administered unless the investigator judges that it is in the interest of the patient to withdraw from the study and to be treated outside of this protocol with a combine modality.

After study drugs discontinuation:

- If a p atient discontinues study treatment for reasons other than radiologic disease progression (*e.g.*, intolerable side effects), patients will be followed for tumour response until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).
- After progression, patient will be followed for survival status until the end of the study.

~~The end of the study is defined as the last visit of the last patient.~~

The selection will be stopped once 100 PFS events (progression of disease [PD] or death) are reached or 150 patients are randomised (whichever occurs first) and the on-going patients will continue the study without change until the end of the study.

End of clinical study:

- The planned **main study analysis** will be performed **after 100 PFS events are observed,** leading to the release of the **primary clinical study report.**
- The **end of clinical study** is planned 12 months after the follow-up start date of the last patient withdrawn, leading to the release of **the final statistical analysis and the final clinical study report.**

4.2.3. Replacement of patients

No patients will be replaced at any time during this study.

4.2.4. Discontinuation of study treatments

For both treatment arms (experimental and control arm), treatment with either component of the combination regimen may continue after discontinuation of the other component unless the investigator judges that it is in the interest of the patient to withdraw from the study and to be treated outside of this protocol with a combine modality. Patients will be considered on treatment as long as either component of the combination regimen continues to be administered.

A patient is considered discontinued from study treatment when the decision to permanently stop both components of the treatment regimen is made, including those decisions made during study medication interruptions and recovery periods.

Study medication should be continued whenever possible. In case study medication is stopped, it should be determined if the stop can be made temporarily; permanent study medication discontinuation should be a last resort. A ny study medication discontinuation should be fully documented. In any case, the patient should remain in the study as long as possible.

4.2.5. Investigation schedule

Table (4.2.5) 1 and Table (4.2.5) 2 describe the measurement of safety and activity, assessed during the study. More details regarding methods and time-points are provided in section 4.2.6.

The results of all investigations / tests performed before inclusion visit must be available for patient's visit and prior to the first study drug administration.
During the course of the study, the results of all investigations / tests should be available at the time of the visit.
Note: a window of +/- 3 days is allowed for study procedures and +/- 7 days for tumour assessment, as long as the proper order is maintained.

Table (4.2.5) 1 - Investigation schedule of S 95005 + bevacizumab arm

Procedure	Screening period/Inclusion		On-Treatment period						Withdrawal visit	Follow-up period
			CYCLE 1 (28 days)		SUBSEQUENT CYCLES (28 days)					
			Day of Cycle[17]		Day of Cycle[17]					
	≤ 28 days prior randomisation	≤ 5 days prior randomisation	1/Randomisation	15	1	15	Every 8 Weeks	Every 12 Weeks		
Sign ICF	X[1]									
Demography	X									
Medical History	X									
Histological Confirmation	X									
Previous surgery, radiotherapy and treatments	X									
ECG	X								X	
Inclusion/Non-inclusion criteria	X									
Pregnancy Testing		X[2]			X[3]				X[3]	
IWRS[4]										
Patient number	X									
Randomisation[5]			X							
Dispense S 95005[6]			X		X					
Administer IV Bevacizumab[6]			X	X	X	X				
Efficacy measurements										
Tumour Measurements[7]	X[7]						X[7]		X[7]	X[7]
CEA dosage		X					X[8]		X[8]	
Survival Status			→	→	→	→	→	→	→	X[9]
Safety measurements										
Baseline Signs & Symptoms		X								
Physical Examination		X	X[10]		X[11]				X	
ECOG Performance Status[12]		X	X		X				X	
Height		X								
Vital Signs & Weight		X	X[10]	X	X[11]	X			X	
Haematology		X	X[10]	X	X[11]	X			X	
Coagulation		X	X[10]		X[11]				X	
Biochemistry		X	X[10]	X	X[11]				X	
Urinalysis		X	X[10]	X	X[11]				X	
Concomitant treatments	X	→	→	→	→	→	→	→	X	X[13]
AE Assessment[14]	X	→	→	→	→	→	→	→	X	X
Biomarkers assessment										
RAS/BRAF status[15]	X									
Archived tumour biopsy (if available)			X[18]							
Blood samples			X[19]						X	
Quality of Life Assessment		X						X[16]	X[16]	

1. Sign Informed Consent Form (ICF): Written informed consent must be obtained prior to the performance of any study procedure.
2. Pregnancy Testing at screening period: performed within 5 days prior to randomisation only with serum βHCG test.
3. Pregnancy Testing from randomisation: performed from C2, within 48 h prior to Day 1, to withdrawal visit (only if not performed within the previous 4 weeks) with serum βHCG or highly sensitive urine test.
4. IWRS: Once patient has signed ICF, connection to the IWRS for patient's registration and e-CRF patient number (see the IWRS manual for details).
5. Randomisation: Central randomisation via IWRS following confirmation of baseline eligibility criteria. Study medication should begin within 3 days after randomisation.
6. Study Medication: Patients should receive the first dose of S 95005 (Day 1 of Cycle 1) within 3 days of randomisation. A connection to the IWRS should be performed to know the allocated kit number(s) to be dispensed to the patient. Bevacizumab will be provided by the Sponsor. Bevacizumab 5 mg/kg should be administered via IV infusion on Day 1 and Day 15 of each cycle following bevacizumab SmPC. NOTE: treatment with either component of the combination regimen may continue after discontinuation of the other component according to investigator judgment.
7. Tumour Measurements: Obtain imaging based evaluation of the chest, abdomen, and pelvis (as clinically indicated) and clinical examination within 28 days prior to Day 1 of Cycle 1 and every 8 weeks thereafter. Images obtained prior to patient signed ICF may be used if the date of the images is within 28 days of randomisation.
   For patients who discontinue treatment for reasons other than radiologic disease progression, obtain tumour measurements within 8 weeks after the last previous tumour assessment. Every effort should be made to perform the end of treatment tumour assessment prior to the start of new anticancer therapy. Tumour Measurement at withdrawal visit will be performed only if not performed within previous 8 weeks. During the follow-up period, perform tumour measurements every 8 weeks until documentation of radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).
   Tumour assessments should be performed according to RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3).
8. CEA dosage: This tumour marker will be followed with a dosage every 8 weeks (aligned on tumour assessments) and at withdrawal visit. Note: RECIST 1.1 request normalisation of tumour markers to have a complete response.
9. Survival Status: Obtain survival status (alive/dead) at scheduled 8-week intervals until patient death or end of the study.
10. Assessments to be performed within 24 hours (for clinical examination and vital signs/weight) or 48 hours (for laboratory assessments) before the first study drug administration on C1D1. If the screening assessments are done within 24/48 hours before C1D1, they do not need to be repeated.
11. Subsequent Cycles ≥2: Obtain within 24 hours (for clinical examination and vital signs/weight) or 48 hours (for laboratory assessments) prior to Day 1 study drug administration. Prior to starting subsequent cycles, verify that patients with toxicities have met resumption criteria prior to administering study drug.
12. ECOG Performance Status: The patient's performance status must remain 0, 1 or 2 during the baseline period and at the time of randomisation for the patient to remain eligible. Collect within 24 hours prior to Day 1 study drug administration for all cycles (Appendix 2).
13. Concomitant Medications: Collect only anticancer therapies during survival follow-up.
14. AE Assessment: AE will be recorded from the first dose of study medication until the withdrawal visit. Any AE that occur prior to the first dose of study medication should be recorded as Medical History except events 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. Up to 100 days after last study drug intake report all ERIN, regardless of the supposed role of the research and all serious adverse event related to the research irrespective of the time of onset after the end of the study. For AE reporting instructions please refer to section 8.4.2.4.
15. RAS/BRAF status: RAS mutation status should be documented prior to randomisation based on local biological assessment of tumour biopsy. At least the following mutation must be determined: KRAS and NRAS Exon 2: codon 12 and 13. BRAF mutation status will be documented if available.
16. Quality of Life: Patients should complete the EORTC – QLQ-C30 and QLQ-CR29 questionnaires every 12 weeks during study treatment; and at the end of treatment if not performed within the prior 8 weeks.
17. Assessment Windows: A window of +/-3 days is allowable for study procedures (+/-7 days allowable for images), as long as the proper order is maintained.
18. Archived biopsy: the archived biopsy can be provided within 21 days after C1D1.
19. Blood sample for genomic and proteomic analysis: To be obtained pre-dose.

Table (4.2.5) 2 - Investigation schedule of capecitabine + bevacizumab arm

Procedure	Screening period/Inclusion		On-Treatment period					Withdrawal visit	Follow-up period
			CYCLE 1 (21 days)		SUBSEQUENT CYCLES (21 days)				
			Day of Cycle[17]		Day of Cycle[17]				
	≤ 28 days prior randomisation	≤ 5 days prior randomisation	1/Randomisation	15	1	Every 8 Weeks	Every 12 Weeks		
Sign ICF	X[1]								
Demography	X								
Medical History	X								
Histological Confirmation	X								
Previous surgery, radiotherapy and treatments	X								
ECG	X							X	
Inclusion/Non-inclusion criteria	X								
Pregnancy Testing		X[2]			X[3]			X[3]	
IWRS[4]									
Patient number	X								
Randomisation[5]			X						
Dispense capecitabine[6]			X		X				
Administer IV Bevacizumab[6]			X		X				
Efficacy measurements									
Tumour Measurements[7]	X[7]					X[7]		X[7]	X[7]
CEA dosage		X				X[8]		X[8]	
Survival Status			→	→	→	→	→	→	X[9]
Safety measurements									
Baseline Signs & Symptoms		X							
Physical Examination		X	X[10]		X[11]			X	
ECOG Performance Status[12]		X	X		X			X	
Height		X							
Vital Signs & Weight		X	X[10]		X[11]			X	
Haematology		X	X[10]	X	X[11]			X	
Coagulation		X	X[10]		X[11]			X	
Biochemistry		X	X[10]	X	X[11]			X	
Urinalysis		X	X[10]	X	X[11]			X	
Concomitant treatments	X	→	→	→	→	→	→	X	X[13]
AE Assessment[14]	X	→	→	→	→	→	→	X	X
Biomarkers assessment									
RAS/BRAF status[15]	X								
Archived tumour biopsy (if available)			X[18]						
Blood samples			X[19]					X	
Quality of Life Assessment		X					X[16]	X[16]	

1. Sign Informed Consent Form (ICF): Written informed consent must be obtained prior to the performance of any study procedure.
2. Pregnancy Testing at screening period: performed within 5 days prior to randomisation only with serum βHCG test.
3. Pregnancy Testing from randomisation: performed from C2, within 48 h prior to Day 1, to withdrawal visit (only if not performed within the previous 4 weeks) with serum βHCG or highly sensitive urine test.
4. IWRS: Once patient has signed ICF, connection to the IWRS for patient's registration and e-CRF patient number (see the IWRS manual for details).
5. Randomisation: Central randomisation via IWRS following confirmation of baseline eligibility criteria. Study medication should begin within 3 days after randomisation.
6. Study Medication: Patients should receive the first dose of capecitabine (Day 1 of Cycle 1) within 3 days of randomisation. A connection to the IWRS should be performed to know the allocated kit number(s) to be dispensed to the patient. Bevacizumab will be provided by the Sponsor. Bevacizumab 7.5 mg/kg should be administered via IV infusion on Day 1 of each cycle following bevacizumab SmPC. NOTE: treatment with either component of the combination regimen may continue after discontinuation of the other component according to investigator judgment.
7. Tumour Measurements: Obtain imaging based evaluation of the chest, abdomen, and pelvis (as clinically indicated) and clinical examination within 28 days prior to Day 1 of Cycle 1 and every 8 weeks thereafter. Images obtained prior to patient signed ICF may be used if the date of the images is within 28 days of randomisation.
   For patients who discontinue treatment for reasons other than radiologic disease progression, obtain tumour measurements within 8 weeks after the last previous tumour assessment. Every effort should be made to perform the end of treatment tumour assessment prior to the start of new anticancer therapy. Tumour Measurement at withdrawal visit will be performed only if not performed within previous 8 weeks. During the follow-up period, perform tumour measurements every 8 weeks until documentation of radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).
   Tumour assessments should be performed according to RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3).
8. CEA dosage: This tumour marker will be followed with a dosage every 8 weeks (aligned on tumour assessments) and at withdrawal visit. Note: RECIST 1.1 request normalisation of tumour markers to have a complete response.
9. Survival Status: Obtain survival status (alive/dead) at scheduled 8-week intervals until patient death or end of the study
10. Assessments to be performed within 24 hours (for clinical examination and vital signs/weight) or 48 hours (for laboratory assessments) before the first study drug administration on C1D1. If the screening assessments are done within 24/48 hours before C1D1, they do not need to be repeated.
11. Subsequent Cycles ≥2: Obtain within 24 hours (for clinical examination and vital signs/weight) or 48 hours (for laboratory assessments) prior to Day 1 study drug administration. Prior to starting subsequent cycles, verify that patients with toxicities have met resumption criteria prior to administering study drug.
12. ECOG Performance Status: The patient's performance status must remain 0, 1 or 2 during the baseline period and at the time of randomisation for the patient to remain eligible. Collect within 24 hours prior to Day 1 study drug administration for all cycles (Appendix 2).
13. Concomitant Medications: Collect only anticancer therapies during survival follow-up.
14. AE Assessment: AE will be recorded from the first dose of study medication until the withdrawal visit. Any AE that occur prior to the first dose of study medication should be recorded as Medical History except events 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. Up to 100 days after last study drug intake report all ERIN, regardless of the supposed role of the research and all serious adverse event related to the research irrespective of the time of onset after the end of the study. For AE reporting instructions please refer to section 8.4.2.4.
15. RAS/BRAF status: RAS mutation status should be documented prior to randomisation based on local biological assessment of tumour biopsy. At least the following mutation must be determined: KRAS and NRAS Exon 2: codon 12 and 13. BRAF mutation status will be documented if available.
16. Quality of Life: Patients should complete the EORTC – QLQ-C30 and QLQ-CR29 questionnaires every 12 weeks during study treatment; and at the end of treatment if not performed within the prior 8 weeks.
17. Assessment Windows: A window of +/-3 days is allowable for study procedures (+/-7 days allowable for images), as long as the proper order is maintained.
18. Archived biopsy: the archived biopsy can be provided within 21 days after C1D1
19. Blood sample for genomic and proteomic analysis: To be obtained pre-dose.

4.2.6. Study Assessments

The study assessments are described by procedure in section 4.2.6.1 and by visit in section 4.2.6.2 and also indicated in the investigation schedules (Table (4.2.5) 1 and Table (4.2.5) 2). All information required by the protocol must be recorded.

The study schedule must be followed. However, under special conditions (*e.g.*, holidays, weekends, etc.) a window of +/ 3 days is allowed for study procedures and +/- 7 days for tumour assessment, **as long as the proper order is maintained**.
During the screening period (up to 28 days prior to randomisation), these windows are not applicable except for tumour assessment.

Any significant abnormality detected during safety assessments will need to be reported as an adverse event.
The safety assessments will include:

- Record of adverse events and toxicity according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE) version v4.03 Jun 14, 2010.
- Physical examination, ECOG performance status (Appendix 2).
- ECG measurement.
- Vital signs measurements.
- Biological tests: haematology, blood biochemistry, coagulation, urinalysis.

Abnormal laboratory values or test results will constitute an Adverse Event if they are :

- associated with signs and symptoms, or
- clinically significant in the investigators'opinion, or
- if they requires curative therapies.

The intensity of all AEs will be graded according to NCI-CTCAE, V4.03 on a five-point scale (Grade 1 to 5).

4.2.6.1. All Study Procedures

4.2.6.1.1. Informed consent

Obtain signed and dated Informed Consent Form (ICF) from the patient prior to the implementation of study procedures required by the protocol. An original copy of the signed and dated ICF should be given to the patient.

4.2.6.1.2. Patient Numbering

Once the patient has signed ICF, the centre will connect to the Interactive Web Response System (IWRS) for patient's registration and e-CRF patient number during the screening period (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.

4.2.6.1.3. Histological/Cytological Confirmation

Histological or cytological confirmation of adenocarcinoma of the colon or rectum should be documented in the patient's source documents within 28 days prior to randomisation. The pathology report should be available in the patient's source documents.

4.2.6.1.4. RAS/BRAF status

RAS mutation status based on local tumour biopsy assessment should be documented in the patient's source documents within 28 days prior to randomisation. At least the following mutation must be determined: KRAS and NRAS Exon 2: codon 12 and 13.
BRAF status will be documented in the eCRF if available.

4.2.6.1.5. Demography

Collect demography data within 28 days prior to randomisation.

4.2.6.1.6. Medical history

Obtain full relevant medical history within 28 days prior to randomisation.
Any AE/SAEs that occur prior to the start of study drug administration should be reported as medical history, except for any event associated with any procedure/condition required by the study protocol which must be reported in the AE form (see section 8.4.2.1).

4.2.6.1.7. Previous surgery, radiotherapy and treatments related to the studied disease

Collect previous surgery, radiotherapy and treatments related to the studied disease within 28 days prior to randomisation.

4.2.6.1.8. Baseline Signs and Symptoms

Signs and symptoms present following ICF signature and within 5 days prior to randomisation should be recorded in the patient's source documents.

4.2.6.1.9. Physical Examination

Perform a complete physical examination at the time points listed below:

- Within 5 days prior to randomisation.
- At pre-dose of C1D1 only if there is more than 24 hours since screening period.
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle.
- Withdrawal visit.

4.2.6.1.10. 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.
- Withdrawal visit.

4.2.6.1.11. Height, Vital Signs, Weight

Obtain the patient's height within 5 days prior to randomisation.
Collect the patient's vital signs (BP, HR, body temperature and respiration rate) and body weight at the time points listed below. Obtain all the vital signs in a position that is consistent for all time points for each patient.

- Within 5 days prior to randomisation.
- At pre-dose of C1D1 only if there is more than 24 hours since screening period and C1D15.
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle.
- At CxD15 (experimental arm only).
- Withdrawal visit.

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;
- place the cuff at heart level.

4.2.6.1.12. ECOG Performance Status

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

- Within 5 days prior to randomisation.
- At pre-dose of C1D1 only if there is more than 24 hours since screening period.
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle.
- Withdrawal visit.

4.2.6.1.13. Clinical Laboratory Evaluations

All laboratory tests performed during patient's visit (D1) will be assayed in identified laboratory at hospital. Inter visits laboratory tests (D15 or unscheduled tests) could be assayed by local laboratories.
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.
~~All samplings for biochemistry should be taken in fasting conditions.~~
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.

4.2.6.1.13.1. Haematology

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

- Within 5 days prior to randomisation.
- At pre-dose of C1D1 only if there is more than 48 hours since screening period.
- On Day 15 of Cycle 1 in the control arm and at Day 15 of each cycle in the experimental arm.
- For all subsequent cycles, obtain within 48 hours prior to Day 1 study treatment of each cycle.
- Withdrawal visit.

In addition, follow the criteria for repeat testing listed in section 8.2.1.2 as needed.

Measure the following haematology parameters: haemoglobin, haematocrit, Red Blood Cell (RBC) count, White Blood Cell (WBC) count and differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets.

4.2.6.1.13.2. Biochemistry

Collect sample at the following time points for biochemistry assessments:

- Within 5 days prior to randomisation.
- At pre-dose of C1D1 only if there is more than 48 hours since screening period.
- On Day 15 of Cycle 1.
- For all subsequent cycles, obtain within 48 hours prior to Day 1 study treatment of each cycle.
- Withdrawal visit.

In addition, follow the criteria for repeat testing listed in section 8.2.1.2 as needed.

Measure the following serum chemistry parameters: albumin, ionogram (Na, K, Cl, Ca, Mg, bicarbonate [optional], phosphate), Blood urea nitrogen (BUN), creatinine clearance, total proteins, glucose, ASAT, ALAT, GGT, Alkaline phosphatase, total bilirubin (in case of elevation in total bilirubin, fractionation (direct/indirect) should be performed), LDH.

4.2.6.1.13.3. Coagulation

Collect sample at the following time points for coagulation:

- Within 5 days prior to randomisation.
- At pre-dose of C1D1 only if there is more than 48 hours since screening period.
- For all subsequent cycles, obtain within 48 hours prior to Day 1 study treatment of each cycle.
- Withdrawal visit.

In addition, follow the criteria for repeat testing listed in section 8.2.1.2 as needed.

Measure the following coagulation parameters: activated partial thromboplastin time (aPTT) and International normalized ration (INR).

4.2.6.1.13.4. Urinalysis

Collect urine samples for qualitative (dipstick) analysis, to include tests for protein, glucose, urobilinogen, RBC, and WBC, at the time points listed below:

- Within 5 days prior to randomisation.
- At pre-dose of C1D1 only if there is more than 48 hours since screening period.
- On Day 15 of Cycle 1.
- For all subsequent cycles, obtain within 48 hours prior to Day 1 study treatment of each cycle.
- Withdrawal visit.

If a new abnormality is identified, quantitative urinalysis should be performed.
In addition, follow the criteria for repeat testing listed in section 8.2.1.2 as needed.
If dipstick proteinuria ≥ 2+, a 24 hours-collection urine is required and quantitative assessment of proteinuria will be performed.

4.2.6.1.13.5. Pregnancy Testing

If the patient is female and 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 5 days prior to randomisation (only serum test).
- Beginning with Cycle 2, obtain within 48 hours prior to Day 1 study drug administration of each cycle.
- Withdrawal visit (if not performed within previous 4 weeks).

Female patients who are considered not to be of childbearing potential must have a history of being post-menopausal (with a minimum of 1 year without menses without an alternative medical cause), bilateral salpingectomy, bilateral oophorectomy, or hysterectomy that is clearly documented in the patient's source documents.

4.2.6.1.14. Dosage of Carcinoembryonic Antigen (CEA)

Collect blood at the following time points for serum chemistry assessments:

- Within 5 days prior to randomisation.
- Withdrawal visit (if not performed within previous 8 weeks).
- Every 8 weeks (aligned on tumour assessments).

Note: RECIST 1.1 request normalisation of tumour markers to have a complete response.

4.2.6.1.15. Tumour Measurements

Imaging studies of the chest, abdomen and pelvis (as clinically indicated) must be obtained at each time point listed below for all patients:

- Within 28 days prior to randomisation. Tumour assessment obtained prior to patient ICF may be used if the date of the images is within 28 days of randomisation.
- Every 8 weeks during study treatment.
- Withdrawal visit if not performed within previous 8 weeks.
- For patients who discontinue treatment for reasons other than radiologic disease progression, within 8 weeks after the last previous tumour assessment. Every effort

should be made to perform the end of treatment tumour assessment prior to the start of new anticancer therapy.

- For patients who discontinued treatment for reasons other than radiologic disease progression, every 8 weeks until the patient develops radiologic progression or the start of new anticancer treatment (whichever occurs first).

On-site tumour assessments will be performed by the Investigator/local radiologist according to RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3). Results of these assessments including response for target and non-target lesions and appearance of new lesions will be the basis for the continuation or discontinuation of study medication. Response definitions are provided in section 7.

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 treatment. Symptoms of clinical progression must be documented in the patient's source documents. Every effort should be made to document objective progression even after discontinuation of treatment.

If a patient is withdrawn due to radiologic disease progression, additional tumour assessments are not required at the end of treatment.

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at screening period, throughout the study, and during the follow-up period.

All patients' files and radiological assessments must be available for source verification. Results of any unscheduled evaluations should be recorded in the patient's source documents.

4.2.6.1.16. Concomitant treatments

Concomitant treatments are collected from the screening period through the end of therapy. Use of concomitant treatment should be documented in the patient's source documents.

At the Follow-Up Visit, collect any new anticancer therapy and the date of initiation.

4.2.6.1.17. Adverse Event Assessment

See section 8.4 for definitions and detailed reporting of AEs and SAEs.

4.2.6.1.18. Quality of Life

EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) and CRC-specific module (QLQ-CR29) (Appendix 1) will be completed by the patient, independently of the study personnel at the following time points, at the beginning of each concerned visit prior to other study measures:

- Within 5 days prior to randomisation
- Every 12 weeks during study treatment (*i.e.*, every 3 cycles for the S 95005 plus bevacizumab arm and every 4 cycles for the capecitabine plus bevacizumab arm). Note: QoL questionnaires should be completed prior to the administration of study medication at these time points.
- Withdrawal visit (if not performed within the previous 8 weeks).

4.2.6.1.19. Biomarkers assessment

Blood samples will be collected at:

- C1D1 for proteomic and genomic analysis (after randomisation) pre-dose.
- Withdrawal visit for proteomic analysis.

If available archived tumour biopsy will be collected at:

- Within 21 days after C1D1 for proteomic and genomic analysis (after randomisation).

4.2.6.1.20. Inclusion/Non-inclusion criteria

Confirm eligibility of patient within 28 days prior to randomisation.

4.2.6.1.21. Randomisation/Start of treatment

Following confirmation of eligibility, patients will be randomised via IWRS and should receive the first dose of study treatment (Day 1 of Cycle 1) within 3 days after randomisation.

4.2.6.2. Assessments by Visit

See section 4.2.6.1 for details about specific assessments.

4.2.6.2.1. Baseline procedures prior to randomisation: screening period/Inclusion visit

4.2.6.2.1.1. Day -28 through Day 0

- Signature of Informed Consent Form
- Connection to IWRS for patient's registration and e-CRF patient number
- Histological confirmation of adenocarcinoma of colon or rectum
- RAS status
- BRAF status (if available)
- Demography
- Inclusion/Non-inclusion criteria
- Medical history
- Previous surgery, radiotherapy and treatments related to the studied disease
- 12-lead ECG
- Tumour measurement
- Concomitant treatments
- AE assessment: only events associated with any procedure/condition required by the study protocol: procedure (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 have to be reported in AE form (See section 8.4. for definitions and detailed reporting of AEs and SAEs)

4.2.6.2.1.2. Day -5 through Day 0

- Physical examination
- Baseline signs and symptoms
- Height
- Vital signs (BP, HR body temperature, respiration rate) and body weight
- ECOG performance status
- Blood samples for haematology, serum chemistry, coagulation

- CEA dosage
- Urine sample for urinalysis
- Pregnancy test (only serum test)
- Quality of life assessment (EORTC QLQ-C30, QLQ-CR29)
- Concomitant treatments
- AE assessment

4.2.6.2.2. Randomisation

Contact the IWRS when the patient complies with all inclusion criteria for initiation of study treatment to randomise the patient. Instructions for randomisation are described in detail in the IWRS Instructions Manual.
Randomisation will be based on last ECOG, vital signs and clinical laboratory evaluations.
Randomised patients should receive the first dose of study treatment (Day 1 of Cycle 1) no later than 3 days after randomisation.
First dose of study treatment can be given on the same day as randomisation.

4.2.6.2.3. Procedures prior to first study drug administration:

Assessments to be performed only if there is more than 24 hours since screening period:

- Physical examination and ECOG performance status
- Vital signs (BP, HR, body temperature and respiration rate) and body weight

Assessments to be performed only if there is more than 48 hours since screening period:

- Clinical laboratory evaluations (haematology, biochemistry, coagulation and urinalysis)

4.2.6.2.4. C1D1

- Blood samples for proteomic and genomic analysis (pre-dose)
- Dispense S 95005 (experimental arm) or capecitabine (control arm)
- Administer IV bevacizumab (experimental and control arm)
- Records of any change or addition of a new concomitant treatment
- AE assessment
- Archived tumour biopsy (if available) for proteomic and genomic analysis (within 21 days after C1D1)

4.2.6.2.5. Cycle 1 Day 15

- Blood samples for haematology and biochemistry (obtain within 48h before the visit).
- Urine sample for urinalysis (obtain within 48h before the visit).
- Vital signs and weight (experimental arm only) (obtain within 24h before bevacizumab administration).
- Administer IV bevacizumab (experimental arm only)
- Records of any change or addition of a new concomitant treatment
- AE assessment

4.2.6.2.6. Subsequent Cycles (Cycle X Day 1)

Prior to starting subsequent cycles, verify that patients with toxicities have met resumption criteria prior to administering study drug.

Obtain within 48 hours prior to Day 1 study drug administration:
- Blood samples for haematology, biochemistry and coagulation
- Urine sample for urinalysis
- Pregnancy test (serum or highly sensitive urine test)

Obtain within 24 hours prior to Day 1 study drug administration:
- Physical examination
- Vital signs (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status

On Day 1:
- Dispense S 95005 (experimental arm) or capecitabine (control arm)
- Administer IV bevacizumab (experimental and control arm)
- Records of any change or addition of a new concomitant treatment
- AE assessment

4.2.6.2.7. Subsequent Cycles (Cycle X Day 15) (experimental arm only)

- Blood samples for haematology (obtain within 48h be fore bevacizumab administration).
- Vital signs and weight (obtain within 24h before bevacizumab administration).
- Administer IV bevacizumab
- Records of any change or addition of a new concomitant treatment
- AE assessment

4.2.6.2.8. Every 8 Weeks from Start of Treatment

- Tumour assessment
- CEA dosage aligned on tumour assessments.

4.2.6.2.9. Every 12 Weeks from Start of Treatment

- Quality of life assessment (EORTC QLC-C30, QLQ-CR29) prior to other study measures and to administration of study medication.

4.2.6.2.10. Withdrawal visit (up to 4 weeks after the last test drug administration)

- Physical examination
- 12-lead ECG
- Vital signs (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status
- Blood samples for haematology, biochemistry and coagulation
- Urine sample for urinalysis
- Pregnancy test if not performed within the previous 4 weeks (serum or highly sensitive urine test)

- Quality of life assessment (EORTC QLQ-C30, QLQ-CR29) if not performed within the previous 8 weeks
- Tumour assessment (if not performed within previous 8 weeks).
- CEA dosage if not performed within previous 8 weeks.
- Records of any change or addition of a new concomitant treatment
- AE assessment
- Blood samples for proteomic analysis

The withdrawal visit will be conducted up to 4 weeks after the patient's last dose of study medication. If the patient will be starting new anticancer therapy within the 4 weeks window after the last dose of study medication, the withdrawal visit should be performed prior to the start of new anticancer therapy.

During treatment period, unscheduled exams could be performed on investigator's judgment.

4.2.6.2.11. Follow-up

After the end of the participation in the study, the following assessments should be obtained during the follow-up period:

- For patients who discontinued treatment for reasons other than disease progression: tumour assessment every 8 weeks until radiologic disease progression (or initiation of new anticancer therapy (whichever occurs first),
- Concomitant treatments – collect antitumor therapies only,
- Contact patient/caregiver every 8 weeks to determine survival status (alive/dead),
- AE assessment (please refer to section 8.4.2.1 for reporting instructions):
  - up to 100 calendar days after the participant's last study drug intake report all Events Requiring Immediate Notification (ERIN), regardless of the supposed role of the research.
  - irrespective of the time of onset after the end of the study in case of Serious Adverse Events (SAE) related to the research.

Patients will be followed for survival until the end of the study. The Investigators will be informed when this time point is reached.

4.3. Measures to minimise bias

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

- Balanced central randomisation with a minimisation procedure stratified by RAS status (wild-type, mutant type), ECOG performance status (0 vs. 1 vs. 2) and country.
- Treatment allocation through an IWRS.
- The EORTC Quality of Life Questionnaires – Core questionnaire (EORTC QLQ-C30) and CRC-specific module (QLQ-CR29) will be completed by the patient, independently of the study personnel, at the beginning of each concerned visit prior to other study measures.

4.4. Study products and blinding systems

This is an open-label study. No study medication blinding is required.

4.4.1. Products administered

Les Laboratoires Servier Industrie (Gidy, France) will manufacture the therapeutic units (TU) of S 95005.
S 95005 contains trifluridine (FTD) and tipiracil hydrochloride (TPI) as active ingredients with a molar ratio of 1:0.5.
Capecitabine and bevacizumab will be supplied by Les Laboratoires Servier Industrie (Gidy, France).

, Table (4.4.1) 2 and Table (4.4.1) 3 provide a description of the study products

Table (4.4.1) 1 - Description of S 95005

	S 95005	**S 95005**
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 (4.4.1) 2 - Description of capecitabine

	Capecitabine 150 mg	**Capecitabine 500mg**
Pharmaceutical form	film-coated tablet	film-coated tablet
Unit dosage	150 mg	500 mg
Appearance, colour	light peach tablets of biconvex, oblong shape with the marking '150' on the one side and 'Xeloda' on the other side	peach tablets of biconvex, oblong shape with the marking '500' on the one side and 'Xeloda' on the other side
Composition	150 mg of capecitabine anhydrous lactose	500 mg of capecitabine anhydrous lactose

Table (4.4.1) 3 - Description of bevacizumab

	Bevacizumab 4ml	**Bevacizumab 16ml**
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 (4.4.1) 4, Table (4.4.1) 5 and Table (4.4.1) 6 provide a description of the packaging of the study products

Table (4.4.1) 4 - Description of the packaging of S 95005

	S 95005 15mg	**S 95005 20mg**
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 "S95005 15" of 1 cards with desiccant	1 Aluminium foil pouch "S95005 20" of 1 cards with desiccant

Table (4.4.1) 5 - Description of the packaging of capecitabine

	Capecitabine 150 mg	**Capecitabine 500mg**
Number of units of the pharmaceutical form per primary packaging	10 tablets	10 tablets
Number of primary packaging per secondary packaging	6 blisters "Capecitabine 150"	12 blisters "Capecitabine 500"

Table (4.4.1) 6 - Description of the packaging of bevacizumab

	Bevacizumab 4ml	**Bevacizumab 16ml**
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, as well as the recommendations in appendix 13 of the European Guide to Good Manufacturing Practice.

4.4.2. IMPs management

In this study the Investigational Medicinal Products (IMP) are S 95005, capecitabine and bevacizumab.

The IMP will be sent by Les Laboratoires Servier Industrie (Gidy, France) either directly to the investigational centres or to sub-distribution centres or to local pharmacies depending on the geographic areas and the local regulatory requirements.

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to section 6.2), accountability and collection are the responsibility of the investigator and/or pharmacist of the medical institution.

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

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

All defects or deterioration of IMPs or their packaging are to be reported to the study monitor, and to the IWRS. The investigator will notify the monitor of all complaints set out by a participant (change of taste, appearance…).
In the event of anticipated return of IMPs to the sponsor (batch recall), the sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study centre. On receipt of the letter, the investigator and/or the pharmacist will identify the participants in possession of the IMP 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.

Destruction

Destruction of the IMPs is the responsibility of the sponsor or the pharmacist of the medical institution.
Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMP management.
A certificated 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 IMP will be defined by the sponsor and adapted to the centre. An IMP collection and destruction form will be completed before the shipment of IMP to destruction. Destruction of IMP 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 Therapeutic Units (TUs) will be collected by the centre at the time of preparation/administration along with other wastes to be destroyed according to local

procedure. Thus, accountability and recovery by monitor are not applicable for used TUs of bevacizumab.

Stability and storage

Any country-specific requirements regarding packaging and storage of investigational drugs should be followed.
The pharmacist is responsible for the IMP temperature monitoring on a daily basis using FONT-CIRT-FORM-311 "Therapeutic Unit temperature log sheet - centre" (recording Min-Max temperature every working day) or an equivalent document.
In case of temperature deviation, the pharmacist should immediately:

1. block the IWRS for the concerned IMPs and place them in quarantine,
2. alert the monitor or the local project manager if the monitor is absent, forward him all needed information and implement the instructions received.

Furthermore, the pharmacist must put in place an adequate corrective/preventive action once the first temperature deviation occurs in order to avoid recurrence.

IMPs should be stored in a secure area with restricted access. Specific storage conditions, if any, are mentioned on IMP labelling.

4.4.2.1. Handling conditions and cleaning procedures.

Study staff will carefully instruct patients on how to take S 95005 or capecitabine and the correct dose to take.

4.4.2.2. S 95005

S 95005 tablets should not be sucked, chewed, crushed or kept in mouth. Direct contact of the powder from tablets containing S 95005 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. Personnel and patient should avoid exposure to crushed tablets.
The patient must be instructed in the handling of study medication as follows:

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

4.4.2.3. Bevacizumab

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

4.4.2.4. Capecitabine

Capecitabine will be provided as commercially available product with clinical labelling. For handling conditions and cleaning procedures instructions, please refer to the package insert and SmPC (Appendix 7).

4.4.3. Management of blinding systems

Not applicable

4.5. Discontinuation of the study

4.5.1. Premature discontinuation of the study

After having informed the coordinators/investigators, the sponsor or the Coordinator or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or the Competent Authorities may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the coordinators. The IECs and Competent Authorities will be informed according to local regulations.

4.5.2. Discontinuation of the study in the event of objective reached (event driven trial)

The selection ~~inclusion~~ will be stopped once 100 PFS events (progression of disease [PD] or death) are reached or 150 patients are randomised (whichever occurs first) and the on-going patients will continue the study without change until the end of the study.
Once 100 PFS events (progression of disease [PD] or death) are reached the main study analysis will be performed.

After having informed the coordinators/investigators, the sponsor may terminate the study before its scheduled term. The IEC(s) and Competent Authorities will be informed according to local regulations.

4.6. Source data

Source data and source documents of the centre 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), patient diary, quality of life questionnaires (paper copies) will be considered as source document.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Inclusion criteria

5.1.1. Informed consent

1. Written informed consent will be obtained prior to any study-specific procedure.

5.1.2. Demographic characteristics

2. Male or Female participant aged ≥18 years old.

5.1.3. Disease characteristics

3. Has ECOG performance status of 0, 1 or 2 (Appendix 2) at the time of the randomisation.
4. Has definitive histologically or cytologically confirmed adenocarcinoma of the colon or rectum.
5. RAS status must have been determined (mutant or wild) based on local biological assessment on tumour biopsy. At least the following mutation must be determined: KRAS and NRAS Exon 2: codon 12 and 13.
6. Has at least one measurable metastatic lesion (as defined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1; Eisenhauer EA *et al.*, 2009; Appendix 3). Note: Unresectable metastatic disease must have been diagnosed within 6 months prior to first day of study drug administration.
7. No previous systemic anticancer therapy for unresectable metastatic colorectal cancer.
8. Previous adjuvant (or neoadjuvant for patients with rectal cancer) chemotherapy is allowed only if it has been completed more than 6 months before start of study treatment.
9. Patient is not a candidate for combination chemotherapy with irinotecan or oxaliplatin according to investigator's judgment based on decision taken during a multidisciplinary meeting (if organised in the centre).
10. Patient is not a candidate for curative resection of metastatic lesions according to investigator's judgment based on decision taken during a multidisciplinary meeting (if organised in the centre).

5.1.4. Medical and therapeutic criteria

11. Is able to take medication orally (*i.e.*, no feeding tube).
12. Has adequate organ function as defined by the following laboratory values obtained within 5 days prior to randomisation:
    - 12.1. Haemoglobin value of ≥9.0 g/dL based on measurements obtained 2 weeks or more after last prior transfusion.
    - 12.2. Absolute neutrophil count (ANC) of ≥1.5 x 10^9/L.
    - 12.3. Platelet count ≥100 x 10^9/L.
    - 12.4. Total serum bilirubin of ≤1.5 x upper limit of normal (ULN) (except for ~~Grade 1~~ hyperbilirubinemia due solely to a medical diagnosis of Gilbert's syndrome).

12.5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5 x ULN.
12.6. Creatinine clearance > 50 mL/min (using Cockcroft Gault formula)
12.7. Urine dipstick test for proteinuria < 1+ or 24-hour urine collection <1000 mg for patients found with ≥ 1+ on dipstick.

13. Coagulation parameters in normal limit (or in therapeutic limit for patients treated with anticoagulant drugs): activated partial thromboplastin time (aPTT) and international normalized ratio (INR)
14. Women of childbearing potential must have been tested negative in a serum pregnancy test within 5 days prior to randomisation.
    Within the frame of this study, female participants of childbearing potential and male participants with partners of childbearing potential must agree to use a highly effective method of birth control (*i.e.*, pregnancy rate of less than 1% per year) during the study and for 6 months after the discontinuation of study medication.
    Contraceptive methods that result in a low failure rate when used consistently and correctly include methods such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), some intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, or a female partner who is not of childbearing potential or a male partner who has had a vasectomy. Women and female partners using hormonal contraceptive must also use a barrier method (i.e. condom or occlusive cap (diaphragm or cervical/vault caps)).
15. Is willing and able to comply with scheduled visits and study procedures.

5.2. Non-inclusion criteria

5.2.1. General criteria

16. Foreseeable poor compliance to the study procedures.
17. Is a pregnant or lactating female.
18. Is inappropriate for entry into this study in the judgment of the Investigator.

5.2.2. Medical and therapeutic criteria

19. Has a serious illness or serious medical condition(s) including, but not limited to the following:
    19.1. Other ~~concurrently active~~ malignancies excluding malignancies that are in remission for more than 5 years, ~~or~~ carcinoma-in-situ deemed cured by adequate treatment or basal cell carcinoma.
    19.2. Known brain metastasis or leptomeningeal metastasis.
    19.3. Active systemic infection (i.e., body temperature ≥38°C due to infection).

19.4. At the time of screening, intestinal obstruction, pulmonary fibrosis, interstitial pneumonitis, renal failure, liver failure, or cerebrovascular disorder.
19.5. Uncontrolled diabetes.
19.6. Deep venous/arterial thromboembolic complication or bleeding diatheses or any other haemorrhage/bleeding event CTCAE grade > 3 within 4 weeks prior to randomisation.
19.7. Cerebrovascular accident or myocardial infarction within the last 12 months, severe/unstable angina, uncontrolled or symptomatic arrhythmia, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV, uncontrolled hypertension.
19.8. Known coagulopathy that increases risk of bleeding or a history of clinically significant haemorrhages in the past (including Grade ≥3 gastrointestinal haemorrhage) within 4 weeks prior to randomisation.
19.9. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or hepatitis B or C as determined by serologic tests.
19.10. Patients with autoimmune disorders or history of organ transplantation who require immunosuppressive therapy.
19.11. Psychiatric disease that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results.
19.12. In the investigator's opinion, significant malabsorption syndrome, significant chronic digestive or gastrointestinal inflammatory syndrome

20. Major surgery within 4 weeks prior to randomisation (the surgical incision should be fully healed prior to study drug administration). Note: indwelling catheter and portacath implantation are allowed.
21. Extended field radiation within 4 weeks or limited field radiation within 2 weeks prior to randomisation.
22. Any investigational agent received within 4 weeks prior to randomisation.
33. Participant already enrolled in the study (informed consent signed).

Non-inclusion criteria related to administration of S 95005:

23. Has previously received S 95005 or history of allergic reactions attributed to compounds of similar composition to S 95005 or any of its excipients.
31. Hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Non-inclusion criteria related to administration of bevacizumab:

24. History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients.
25. History of hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
32. Any contraindication present in the SmPC of bevacizumab (Appendix 7).

Non-inclusion criteria related to administration of capecitabine:

26. History of allergic reactions or hypersensitivity to capecitabine or any of its excipients or fluorouracil.
27. History of severe and unexpected reaction to fluoropyrimidine therapy.
28. Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
29. Treatment with sorivudine or its chemical related analogues, such as brivudine, within 4 weeks prior to randomisation
30. Any contraindication present in the SmPC of capecitabine (Appendix 7).

5.3. Additional information recorded at the inclusion visit

Not applicable

5.4. Participant withdrawal

5.4.1. Withdrawal criteria

Information to be collected during the last visit of these patients is given in section 4.2.6.2.10. These follow-up modalities are used to ensure the efficacy and safety evaluation of all participants who received the IMP.

Reason for premature discontinuation of the IMP(s) and premature discontinuation from the study are described below. Patients that discontinued from the study are also discontinued from IMP(s).

The reasons for premature discontinuation of IMP(s) are:

- Patient experiences an irreversible, treatment-related, Grade 4, clinically relevant, non-hematologic event.
- Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, including:
  - A maximum dose delay >28 days from the scheduled start date of the next cycle for patients receiving S 95005 + bevacizumab
  - A maximum dose delay >21 days from the scheduled start date of the next cycle for patients receiving capecitabine + bevacizumab
  - Need for more than 3 dose reductions of S 95005 (maximum of 3 dose reductions allowed as described in section 8.3) for patients receiving S 95005 + bevacizumab.
- Refer to the bevacizumab and to the capecitabine SmPC (Appendix 7) for events requiring discontinuation of treatment.
- Physician's decision including need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being evaluated in this protocol.
- RECIST 1.1-defined disease progression.
- Clinical progression.

Patients who withdrawn from treatment for another reason than progression will be followed:

- for tumour assessment until progression, death or initiation of a new anticancer therapy (whichever occurs first)
- for survival until the end of the study defined as the last visit of the last patient.

Patients who withdrawn from treatment for progression will be followed for survival until the end of the study defined as the last visit of the last patient.

The reasons for premature discontinuation of study are:

- Patient request at any time irrespective of the reason.
- Pregnancy.
- 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 (section 6.3.1).

If there is strong evidence of clinical benefit and reasons to justify continuation of dosing with study medication on protocol even though treatment discontinuation criteria have been met, this decision must be reviewed with the sponsor on a case by case basis. Pregnancy will lead to definitive treatment discontinuation in all cases.
Note: patients will be considered to be on treatment as long as either component of the combination regimen continues to be administered.

5.4.2. Procedure

Upon discontinuation of treatment the Investigator must:

- Notify your Clinical Research Associate (CRA) immediately;
- Register End of Treatment for the patient in the IWRS;
- Specify the data to be reported in the medical file and in the eCRF, with their chronology, with respect to the reason for the premature discontinuation of IMP for the withdrawal from the study, the main assessment criteria, and the medical follow-up data. If there are several reasons, the investigator must indicate the main reason.

A withdrawal visit should always be suggested to the patient in case of discontinuation of both treatments in each arm and when it should be arranged (at the same time as the date of discontinuation of IMP, at the theoretical end-of-study date…).
In the case of premature withdrawal from the study due to an adverse event (event requiring immediate notification 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 8.4.2.4). This information is recorded in that part of the electronic case report form which concerns adverse events. If the investigator cannot collect the information from a visit, he must collect it from the doctor ensuring the follow-up of the participant.
If the study is stopped for other reason than the objective is reached (event driven trial), IMP is discontinued as a result of an event requiring immediate notification, the procedure described in section 8.4.1.5 is to be implemented.
The dispositions to be taken after the IMP discontinuation are described in section 6.5.

5.4.3. Lost to follow-up

When the investigator has no news of the participant, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones, etc.), to establish the reason for the discontinuation of IMP and to suggest the participant comes to a withdrawal visit. If all these attempts to contact the participant fail, the investigator can then declare the participant "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 centres will login to the IWRS at the beginning of each treatment cycle to record the current cycle number, record the patient's height (baseline visit only) and current weight for calculation of the patient's body surface area (BSA) to obtain the recommended S 95005 or capecitabine dosage. In addition, the IWRS will use the patient's weight to calculate the correct dosage of bevacizumab.

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

Study sites are required to use the BSA calculation provided by the IWRS when determining S 95005 or capecitabine doses.

Dose modifications and management of toxicities are described in section 8.3.

6.1.1. S 95005 plus bevacizumab arm

6.1.1.1. Treatment Regimen

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

- Days 1-5: S 95005 (35 mg/m^2/dose) orally twice daily; bevacizumab 5 mg/kg IV infusion on Day 1
- Days 6 -7: Rest
- Days 8-12: S 95005 (35mg/m^2/dose) orally twice daily
- Days 13-14: Rest
- Day 15: Bevacizumab 5 mg/kg/IV infusion on Day 15
- Days 16-28: Rest

6.1.1.2. S 95005 administration

S 95005 dosage is calculated according to body surface area (BSA). Table (6.1.1.2) 1 shows the number of tablets that are needed per calculated BSA.

- If at the beginning of the next treatment cycle, a patient's body weight decreases by ≥10% from baseline, the IWRS will recalculate the patient's BSA and provide the site with the adjusted S 95005 dosage.
- No increase in S 95005 dose due to increase in BSA is permitted.
- Study medication 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.
- Any missed doses reported by the patient should be recorded in the patient's diary.
- Extension of study treatment into Days 6 to7 or into the rest period (Days 13 through 28) is not permitted.

- S 95005 should be taken with a glass of water within 1 hour after completion of morning and evening meals.

Table (6.1.1.2) 1 - Number of tablets of S 95005 per dose

S 95005 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
35 mg/m^2	< 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)

6.1.1.3. Bevacizumab administration

Refer to the package insert for instructions regarding administration of bevacizumab.

6.1.2. Capecitabine plus bevacizumab arm

6.1.2.1. Treatment Regimen

Each treatment cycle will be 21 da ys in duration. One treatment cycle consists of the following:

- Days 1-14: Capecitabine (1250 mg/m^2/dose) orally twice daily; bevacizumab 7.5 mg/kg IV infusion on Day 1
- Days 15-21: Rest

Note: According to local clinical practice the starting dose of capecitabine could be reduced to 1000 mg/m² but could not be lower.

6.1.2.2. Capecitabine

Refer to the package insert for instructions regarding administration of capecitabine.

- If at the beginning of the next treatment cycle, a patient's body weight decreases by ≥10% from baseline, the IWRS will recalculate the patient's BSA and provide the site with the adjusted capecitabine dosage.
- No increase in capecitabine dose due to increase in BSA is permitted.
- Any missed doses reported by the patient should be recorded in the patient's diary.

6.1.2.3. Bevacizumab

Refer to the package insert for instructions regarding administration of bevacizumab.
At each visit, the IWRS will provide the site with the adjusted bevacizumab dosage based on the patient's actual weight.

6.2. IMPs dispensing

The treatment group will be allocated *via* IWRS using a balanced central randomization (1:1) to S 95005 + bevacizumab or capecitabine + bevacizumab with stratification by RAS status (wild-type, mutant type), ECOG performance status (0 vs. 1 vs. 2) and country.

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 an IMP label collection form or on the prescription form where the IMPs are dispensed by a pharmacist.

6.3. Previous and concomitant treatments

Collect all therapies and medications, prescription and over-the-counter, from the time of signed ICF through the withdrawal visit. Use of concomitant treatments should be documented in the patient's source documents.

At the Follow-Up Visit(s), collect any new anticancer therapy and the date of initiation.

6.3.1. Prohibited Medications and Therapies

Patients are not permitted to receive:

- Any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers (BRMs), or endocrine therapy during the study treatment period,
- Adjuvant treatment for CRC within the 6 months before the first study drug administration,
- Previous systemic anticancer therapy for unresectable metastatic CRC at any time before the randomisation,
- Treatment with sorivudine or its chemical related analogues are forbidden within 4 weeks prior to randomisation and during the study.

6.3.2. Concomitant Medications and Therapies

Caution is required when using drugs that are human thymidine kinase substrates, *e.g.*, zidovudine. Such drugs, if used concomitantly with S 95005, 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, zalcitabine, didanosine and abacavir.
Patient treated with oral anticoagulant treatment or heparins should be closely monitored especially in case of thrombopenia.

For precautions of use and interactions of concomitant treatment with capecitabine or bevacizumab please refer to the corresponding updated SmPC of the drugs (Appendix 7).

Palliative radiotherapy is permitted. As far as possible, the irradiation of target lesions must be avoided.

The following medications may be given concomitantly under the following guidelines:

Hematologic Support

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 American Society of Clinical Oncology (ASCO) 2006 Guidelines for Use of Hematopoietic Colony-Stimulating Factors, 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.

Management of Diarrhoea

Educate both patients and patients' families regarding the potential seriousness of chemotherapy-induced diarrhoea. Instruct patients to immediately contact the clinical site staff at the first sign of loose stool.

Provide patients with loperamide or other standard antidiarrheal therapy and instruct the patient on how to use it at the first sign of diarrhoea (Benson AB 3rd *et al.*, 2004)**.**

Monitor the patient's fluid and electrolyte balance, with appropriate intervention as clinically indicated with fluids and electrolyte replacement, antibiotics, and antiemetics.

Infection prophylaxis with oral antibiotics must be considered for patients with persistent diarrhoea beyond 24 hours, or coincident with Grade ≥3 neutropenia.

Administer prophylactic treatment for diarrhoea as clinically indicated.

If there are no institutional standards, refer to the guidelines published by Benson AB 3rd *et al.*, 2004.

Management of Nausea/Vomiting

Administer antiemetics as clinically indicated. If there are no institutional standards refer to the ASCO Guidelines for Antiemetics in Oncology (Kris MG *et al*., 2006)**.**

6.3.3. Effective contraception during study

Female patients who are considered not to be of childbearing potential must have a history of being postmenopausal (with a minimum of 1 year without menses without an alternative medical cause), bilateral salpingectomy, bilateral oophorectomy), or hysterectomy that is clearly documented in the patient's source documents.

Within the frame of this study, female participants of childbearing potential and male participants with partners of childbearing potential must agree to use a h ighly effective method of birth control (*i.e*., pregnancy rate of less than 1% per year) during the study and for 6 months after the discontinuation of study medication. Contraceptive methods that result in a low failure rate when used consistently and correctly include methods such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine hormone-releasing system (IUS), some intrauterine devices (IUDs), bilateral tubal occlusion, true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), or a female partner who is not of childbearing potential or a male partner who has had a vasectomy.

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

6.4. IMP compliance

The number of tablets (S 95005 and capecitabine) dispensed and the number of tablets (S 95005 and capecitabine) returned by the participant are to be counted by the pharmacist of the hospital or a d esignated person from his/her team and recorded in the eCRF and therapeutic tracking form.
If the participant did not bring back all blisters (S 95005 and capecitabine) dispensed at the previous visit, the investigator must estimate the number of IMP units taken by the participant since the previous visit, by questioning him/her.
Each participant must record all medications (S 95005 and capecitabine) taken together with corresponding times in a diary provided by the investigator.
The compliance will be assessed from the method described above and from the questioning of the participant.

6.5. Arrangements after the discontinuation of the IMP

After the discontinuation of the IMP, the participant will access to an appropriate medical care by his doctor; who will provide the best support care
Specific rules may be followed in some countries according to local regulation.

7. ASSESSMENT OF EFFICACY

The determination of antitumor efficacy will be based on objective tumour assessments made by the Investigator according to the revised RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3) of unidimensional evaluation. Treatment decisions by the Investigator will also be based on these criteria.

7.1. Efficacy measurements

Efficacy measurements performed during the study are indicated in Table (4.2.5) 1 and Table (4.2.5) 2.

7.2. Methods and measurement times

7.2.1. Tumour assessment

7.2.1.1. Method of Imaging

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded in metric notation using a ruler or calipers.
Contrast enhanced CT is the preferred method for tumour assessments. If contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and enhanced magnetic resonance imaging (MRI) of the abdomen (and pelvis if clinically indicated). Spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm. Images must be acquired of the chest and abdomen (and pelvis if clinically indicated or obtained at Baseline) at each time point. Preferably, CT and MRI will be used for tumour measurement.
Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.
Ultrasound should not be used to measure tumour lesions that are clinically not easily accessible for objective response evaluation (*e.g.*, visceral lesions). Ultrasound is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
An additional fluorodeoxyglucose positron emission tomography (FDG-PET) scan may help confirm the diagnosis of suspicious lymph nodes as needed. A “positive” FDG-PET scan lesion is one that is FDG avid “with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.” However, this scan is not mandatory. FDG-PET scan alone cannot replace a MRI or contrast-enhanced CT.
For additional guidance refer to revised RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3).

7.2.1.2. Tumour Definitions

Measurable Lesions:

- Measurable visceral lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥10 mm by CT scan if using slice thickness of 5 mm or less, or at least double the slice thickness of the CT or MRI scan if the slice thickness is >5 mm.
- Measurable pathological lymph nodes: A malignant lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥15 mm in the short axis when assessed by CT scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Only measurable lesions can be selected as target lesions.

Non-measurable Lesions: Non-measurable lesions include:

- Small visceral metastatic lesions that have a longest dimension less than 10 mm or if slice thickness is greater than 5 mm less than twice the slice thickness.
- Abnormal and suspected metastatic lymph nodes that are ≥10 mm to <15 mm in the short axis.
- Truly non-measurable lesions (*e.g.*, ascites and peritoneal carcinomatosis).

All non-measurable lesions can only be selected as non-target lesions.

Target Lesions:

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions.
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs/tissues, but in addition should be those that lend themselves to reproducible repeated measurements.
- When recording tumour measurements, the longest diameter will be measured for each non-nodal target lesion. For measurable pathological lymph nodes that may be identified as target lesions, the short axis measurement will be combined with the measurements of non-nodal (*i.e.*, visceral lesion) target lesions. Therefore, in cases of complete response (CR) when abnormal nodes have been used as target lesions, the sum of diameters will not reduce to a null value.
  - Target lesions will be followed up and measured at each subsequent time point.
  - The sum of the diameters for all target lesions will be calculated and recorded. The baseline sum will be used as a reference to further characterize any objective tumour assessment in the measurable dimension of the disease.
- Assign a measurement to all target lesions regardless of size. An option of 'too small to measure' will be provided if a measurement cannot be assigned. A value of zero should only be assigned in the case of a CR.
- An option of 'Not Assessable' for a lesion will apply only to lesions that cannot be read due to technical reasons, for example:
  - CT artefact.
  - Patient positioning where the lesions are obstructed or cannot be seen.
  - Lesions that may not be seen in their entirety due to CT slice thickness.

- In cases where a lesion divides into 2 l esions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases w here 2 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'.

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.
- Any equivocal lesion without clear diagnosis (*e.g.*, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.
- 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.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (*e.g.*, multiple enlarged pelvic lymph nodes or multiple liver metastases).

7.2.1.3. Response Criteria

On-site assessments will include the assessment of:

- Target and non-target tumour responses.
- Overall response.

The above assessments will be made as per the time points identified in section 4.2.6.1.15.

7.2.1.3.1. Target and Non-target Response Assessments

7.2.1.3.1.1. Criteria for Assessment of Tumour Response

Assessments will be based on the definitions below.

TARGET LESIONS

Lesions Response	Definition
Complete Response (CR)	The disappearance of all target 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.

NON-TARGET LESIONS

Lesions Response	Definition
Complete Response (CR)	The disappearance of all non-target lesions 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.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see definition below).

Progression in Non-target Disease:

There must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease (PD) for measurable disease; *i.e.*, an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion).

7.2.1.3.1.2. Additional Criteria to Consider When Assessing Tumour Response

When effusions are known to be a potential adverse effect of treatment, cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or SD is not mandatory, but might be performed to differentiate between response (or SD) and PD when substantial change of effusion and or ascites is noted.

For equivocal findings of progression (*e.g.*, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CEA will be followed with a dosage every 8 weeks (aligned on tumour assessments). The CEA assessments will be made as per the time points identified in section 4.2.6.1.14.

CEA alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit (<2.5ng/ml for an adult non-smoker and <5ng/ml for a smoker), however, they must normalise for a patient to be considered in complete response.

7.2.1.3.2. Overall Response Assessment

Assessments will be based on the definitions provided in Table (7.2.1.3) 1 below.

Table (7.2.1.3) 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

7.2.1.4. Best Overall Response Assessment

The confirmation of the response is required in this study.

The best overall response as per RECIST 1.1 (Eisenhauer EA *et al.*, 2009; Appendix 3) is the best confirmed response recorded from the start of the study treatment until the end of treatment. Complete or partial responses may be claimed only if the criteria for each are met at least 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3 of the RECIST 1.1.

7.2.2. Quality of Life

The EORTC Quality of Life Questionnaires – Core questionnaire (EORTC QLQ-C30) and CRC-specific module (QLQ-CR29) (Appendix 1) will be used in this study.
These 2 questionnaires should be filled in at the beginning of the visit prior to other study procedures. The investigator should explain to the patient how to complete the questionnaires but neither he/she nor the research staff can assist the patient with their completion. The patient should complete the questionnaires by him/herself in a quiet place. If the patient is unable to read, an impartial witness (independent of the research staff) can help the patient to fill in the questionnaires. The questionnaires are printed in duplicate on copy paper. The original of each questionnaire will be collected by the study monitor and the copy will stay on site.

8. ASSESSMENT OF SAFETY

8.1. Safety measurements

Safety measurements performed during the study are indicated in Table (4.2.5) 1 and Table (4.2.5) 2.

8.2. Methods and measurement times

8.2.1. Laboratory Evaluations

8.2.1.1. Reporting and Evaluation of Laboratory Test Results

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.

The laboratory must provide normal reference ranges.

Any laboratory abnormality that has a clinical impact on the patient, *e.g.*, results in delay of study medication 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 lab to a clinical diagnosis that is already reported as an AE. If there is a question or concern, please call the sponsor. All laboratory data will be analysed using NCI-CTCAE grade criteria (Version 4.03).

8.2.1.2. Repeat Testing

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.

8.2.2. Physical Examination and Performance Status

Perform physical examinations and performance status evaluations as described in the Study Procedures section of the protocol. If changes are observed, determine whether they meet the definition of an AE. Document all observations and evaluations.

8.2.3. Vital Signs and Body Weight

Verify and document vital signs and body weight. If a clinically significant change is observed, repeat the measurement as clinically indicated and evaluate for its clinical relevance and whether it meets the definition of an AE.

8.3. Management of toxicities and dose modifications

General notes regarding dose modifications.

For patients who have experienced a dosing delay for starting treatment cycle, 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 eCRF.

Before starting a n ew treatment cycle, toxicity must have resolved as specified in the following sections.

Treatment interruptions are regarded as lost treatment days and missed doses should not be replaced; the planned treatment schedule should be maintained.

8.3.1. S 95005

8.3.1.1. S 95005 dose reduction levels

S 95005 dose reductions to be applied in case of toxicity and the number of tablets for each calculated BSA are described in Table (8.3.1.1) 1.
Patients are permitted dose reduction(s) to a minimum dose of 20 mg/m^2 BID (40 mg/m^2/day) in 5 mg/m^2 steps.

Table (8.3.1.1) 1 - S 95005 dose reduction levels and number of tablets per dose

S 95005 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
Level 1 Dose reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 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/m^2 to 25 mg/m^2					
25 mg/m^2	< 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/m^2 to 20 mg/m^2					
20 mg/m^2	< 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 tablet in the morning and 2 x 15-mg tablets in the evening.
BSA=body surface area (calculate to 2 decimal places)

If dose modification fails to result in achieving minimal criteria to resume treatment, the Investigator should discontinue S 95005.

Should the toxicities that require S 95005 dose reduction recur after dose reduction to 20 mg/m^2, S 95005 should be discontinued.

Do not increase study medication dose after it has been reduced.

8.3.1.2. S 95005 dose modification in response to non-hematologic toxicities

Rules for S 95005 dosing modifications for treatment-related non-hematologic AEs are provided in Table (8.3.1.2) 1. ~~At the discretion of the Investigator, patients may continue on S 95005 at the same dose without reduction or interruption for drug-related AEs (irrespective of grade) considered unlikely to become serious or life-threatening (including, but not limited to, fatigue, alopecia, changes in libido, and dry skin).~~

Table (8.3.1.2) 1 - S 95005 dose modification criteria for non-hematologic toxicities

Grade[a]	Dose hold/Resumption within a 28-day treatment cycle	Dose adjustment for next cycle
Grade 1 or 2		
Any occurrence	Maintain treatment at the same dose level	None
Grade 3[a] or Higher		
1st, 2nd, or 3rd occurrence	Suspend treatment until Grade ~~0 or~~ 1 or baseline	Reduce by 1 dose level from the previous level
4th occurrence	Discontinue treatment	Discontinue treatment

[a] Except for Grade 3 nausea and/or vomiting controlled by ~~aggressive~~ antiemetic therapy or diarrhoea responsive to antidiarrheal medication.

If there is any uncertainty about continuing therapy or resuming therapy in a patient with Grade ≥3 non-hematologic drug-related AEs, the case must be discussed with the Sponsor's CRA prior to continuing therapy.

8.3.1.3. S 95005 dose modification in response to hematologic toxicities

Criteria for dose hold and resumption in response to hematologic toxicities related to myelosuppression are described in Table (8.3.1.3) 1 and Table (8.3.1.3) 2 respectively.

NOTE: For all patients with decreases in neutrophils and/or platelets, the next cycle of study treatment should not be started until the resumption criteria in Table (8.3.1.3) 2 are met even if the decreases did not meet the hold criteria.

Table (8.3.1.3) 1 - S 95005 dose hold criteria for hematologic toxicities related to myelosuppression

Parameter	Hold criteria	
	Conventional Units	**SI Units**
Neutrophils	<500/mm^3	<0.5 × 10^9/L
Platelets	<50,000/mm^3	<50 × 10^9/L

SI=International System

Table (8.3.1.3) 2 - S 95005 resumption criteria for hematologic toxicities related to myelosuppression

Parameter	Resumption criteria[a]	
	Conventional Units	SI Units
Neutrophils	≥1500/mm^3	≥1.5 × 10^9/L
Platelets	≥75,000/mm^3	≥75 × 10^9/L

[a]These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.
SI=International System

~~Criteria for S 95005 dose reduction in response to hematologic toxicities are as follows:~~
In case of febrile neutropenia, Grade 4 neutropenia that results in more than 1 week delay in start of next cycle or Grade 4 thrombocytopenia that results in more than 1 week delay in start of next cycle:

- Interrupt dosing until toxicity resolves to Grade 1 or baseline,
- When resuming dosing, decrease the dose level by 5 mg/m²/dose from the previous dose level (Table (8.3.1.1) 1).

For recommendation regarding use of G-CSF please refer to section 6.3.2.

~~Patients who experience complicated ≥Grade 3 neutropenia or thrombocytopenia should be considered for administration of hematopoietic growth factors, or for a dose reduction in the next cycle or both, dependent on the severity of the complication.~~

8.3.1.4. S 95005 dose resumption

If the patient recovers from toxicities requiring dose delay:

- during the 2-week treatment period of a cycle (treatment D1-5 and D8-12)
  - If no dose reduction is required, S 95005 may be resumed during that cycle.
  - If a dose reduction is required, S 95005 should be resumed at the start of the next cycle at the appropriate dose level as shown in Table (8.3.1.3) 2. Do not increase study medication dose after it has been reduced.
- during the recovery period (D13-28):
  - start the next cycle on schedule at the appropriate S 95005 dose level based on sections 8.3.1.2 and 8.3.1.3 above.

If the toxicities that are defined above do not recover during the treatment or rest period, the start of the next cycle can be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If resumption criteria are met by this maximum 28-day delay, start the next cycle, according to the planned treatment schedule, at the appropriate dose level.

Patients who require more than a 28-day delay in the scheduled start date of the next cycle will have S 95005 discontinued.

8.3.2. Capecitabine

Refer to the package insert for dose modification guidelines.

8.3.3. Bevacizumab

There are no recommended dose reductions for bevacizumab. Refer to the package insert for events requiring discontinuation or suspension of administration.

8.4. Adverse events

All adverse events and other situations relevant to the safety of the participants must be followed up and 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 trial.

8.4.1. Definitions

8.4.1.1. Adverse events

An adverse event 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 IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (*e.g*. run-in period) are also concerned).
An adverse event can therefore be:

- any unfavourable and unintended sign, including an abnormal finding from an additional examination (*e.g.* lab tests, X-rays, ECG)~~,~~ and 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 participant entered the study (increase in frequency and/or intensity), including the studied pathology, ~~and which is deemed clinically relevant by the investigator,~~

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

Of note:

- Any **hospitalisation for social reasons, educational purpose** (*e.g*. learning of diabetes management by the participant) or routine check-up should not be considered as an adverse event and should not be reported in the CRF.
- The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, should be reported in the specific page **"Procedures not subsequent to an adverse event"** of the CRF:
  - 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)~~.
  - ~~Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.~~
- ~~Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.~~

~~Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by t he tumour measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.~~

~~If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.~~

On the other hand, in the framework of this protocol, the following serious adverse events must not be notified immediately:

- any hospitalisation and/or surgical procedure planned before the entry of the participant in the study (without any worsening after entry in the study).
- hospitalisation for the administration of chemotherapy treatment or other care measures for cancer during the study and 100 days following last study drug intake.

8.4.1.2. 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 n ormal life, in other words leads to a p ersistent 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.

8.4.1.3. Adverse event of special interest

NA

8.4.1.4. Overdose

This refers to any intake of a quantity of IMP which is above the maximum dose recommended, (*i.e.*, 35 mg/m²/dose or > 160 mg/day for S 95005) in the study protocol, independently of the occurrence of any adverse event.
The quantity should be considered per administration or cumulatively regarding the recommended total dose in each cycle.
For capecitabine and bevacizumab: please refer to SmPC for overdose management information.

8.4.1.5. Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (*i.e.* **within 24 hours**) to the sponsor if it is:
- a serious adverse event,
- an adverse event of special interest,
- an overdose of the IMP even if asymptomatic,
- any intake of the IMP by a person around the participant,
- a pregnancy.

8.4.2. Responsibilities of the investigator

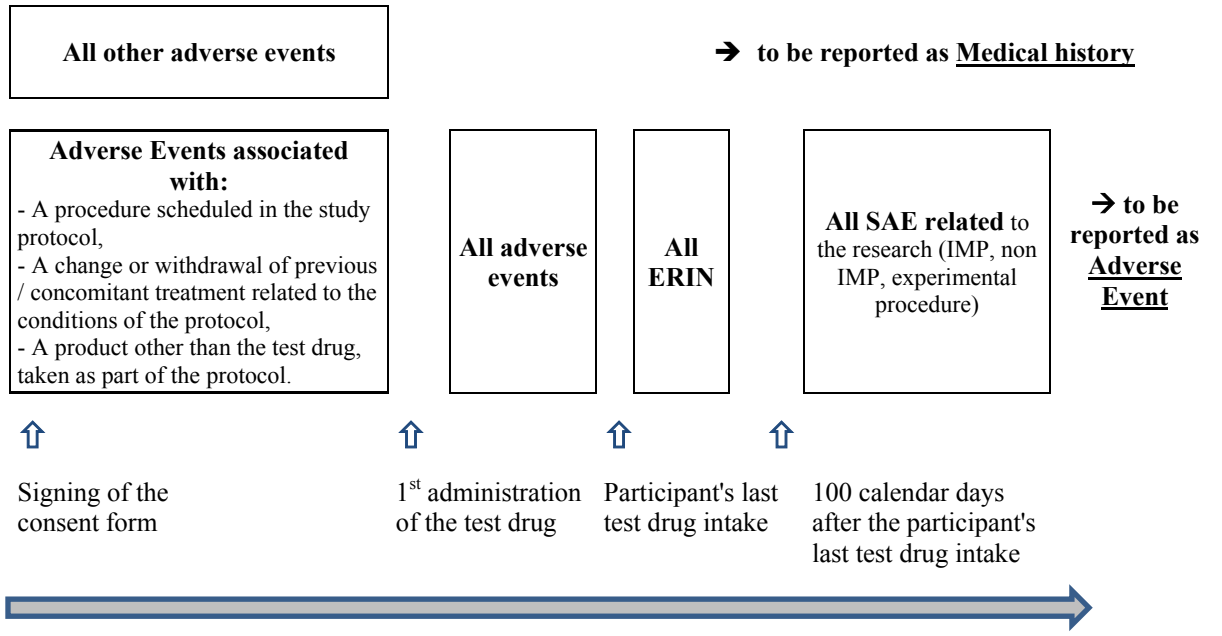
For any adverse event and special situation mentioned above the investigator must:
- **Note in the participant's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, …) and any other relevant information which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

8.4.2.1. Time frame for AE reporting

Any event meeting the above mentioned definitions (see section 8.4.1) must be reported to the sponsor on an adverse event form if it occurred:
- before the first intake of the test drug, **for event associated with any procedure/condition required by the study protocol**: procedure (MRI, etc.), change or withdrawal of previous/concomitant treatment relating to the conditions of the protocol.
- at any time after the first intake of the **test drug** up to the participant's last study drug intake for all events,
- after the participant's last study drug intake:
  - up to 100 calendar days after the participant's last test drug intake for all ERIN, regardless of the supposed role of the research (IMP, 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, or experimental procedure).

Of note, events occurring between the signature of the informed consent and the first administration of the test drug 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.



8.4.2.2. Evaluation of seriousness, intensity and causality

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 test drug. This evaluation must be assessed by the investigator and reported in the AE form.

The Seriousness should be evaluated according to international guidances (see definition in section 8.4.1.2 in accordance with ICH Topic E2A [ICH E2A, 1994] and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April [Directive 2001/20/EC, 2001]) .

The intensity of all AEs will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE 4.03) 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 test drug must be assessed when reporting the AE in the AE form. Only cases ticked "related" by the investigator or judged by the sponsor as having a

[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".

reasonable suspected causal relationship to the test drug will be considered as suspected Adverse Drug Reaction. In general, the expression reasonable causal relationship means to convey that there is evidence or arguments to suggest a causal relationship.

8.4.2.3. 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.

8.4.2.4. Follow-up of adverse events

The investigator must ensure that follow-up of the participant 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 adverse event 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 adverse event has not resolved at the participant's final visit in the study, the participant 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 participant is not done by the investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the participant.

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

Pregnancy

If a female participant in the study becomes pregnant, the investigator must:

- stop immediately the test drug (if the pregnancy is a non-selection/non-inclusion criterion),
- 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 participant 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 overdose, 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 participant

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.

8.4.2.6. Recording Methods in the e-CRF

Adverse events must be documented on the "Adverse Event" page of the e-CRF.
In case of chronic disease:

- if the disease is known when the participant 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 event which will clearly describe the diagnosis.

8.4.2.7. 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 **participant'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 serious (ERIN), 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 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.

8.4.3. Responsibilities of the sponsor

In accordance with international guidances, 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.
Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data to the appropriate Authorities and to all the investigators involved, according to the requirements stated in ICH Good Clinical Practice guidelines (ICH E6, 1996) and local regulations.

8.4.4. Responsibilities of Data Safety Monitoring Board

In accordance with the DSMB charter and the rules for DSMB functioning, the DSMB is responsible for reviewing the ~~efficacy (including disease-related events and~~ safety data on a regular basis (including disease-related events), and providing written recommendations to the International Coordinator and the Sponsor regarding the conduct of the study (modification or termination).

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Assessments related to selection/inclusion criteria.

Pregnancy test

9.2. Measurement of drug concentration

Not applicable

9.3. Biomarkers

9.3.1. Circulating biomarkers for genomic (circulating tumour DNA)

Blood samples for tumour genomic analysis on circulating DNA will be collected into EDTA tubes at C1D1 predose before test drugs administration. The plasma will be separated by centrifugation and stored at <-70°C in an appropriate labelled storage cryotube and sent on dry ice. DNA will be extracted from plasma sample and subjected to genomic analysis including KRAS, NRAS and BRAF mutation to identify genetic events that may be associated with response or resistance to S 95005 and/or bevacizumab, according to a separate protocol.
Their collections are mandatory for all patients in both arms. In addition, patients will be proposed to participate to an optional retrospective analysis. If the patient aggree by signing an separate ICF, backup DNA extracts may be retained up to 25 years after study closure in a storage repository for retrospective analysis according to local regulation.

9.3.2. Circulating biomarkers for proteomic

Blood samples for circulating proteins biomarkers analysis including thymidine kinase (TK1) and thymidine phosphorylase (TP) levels will be collected at C1D1 predose before test drugs administration and at withdrawal visit. After centrifugation, samples will be aliquoted and stored at < -70°C and sent on dr y ice. These samples will be processed for analysis of predictive and resistance biomarkers for S 95005 and/or bevacizumab response or biological activity, according to a separate protocol.
Their collection is mandatory for all patients in both arms. Biological samples will be destroyed after analysis.

9.3.3. Archived biopsy (if available)

Archived tumour samples, collected at metastatic stage diagnosis, will be analysed to identify biomarkers that may predict response to S 95005 and capecitabine in combination with bevacizumab. Samples will be analysed to assess g enomic and proteomic expression including microsatellite instability. The analysis will be described in a separate analysis protocol.

9.3.4. Transfer of results

Results will be transferred to Data Management according to section 14.2.

10. STATISTICS

10.1. Statistical analysis

Statistical analysis will be performed using SAS® software by a Contract Research Organisation under the responsibility of the Pole of Expertise Methodology and Data Valorisation of I.R.I.S.

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. Endpoints

10.1.1.1. Efficacy endpoints

The efficacy endpoints are defined according to guidelines (ICH E9, 1998; EMEA Guidelines, 2005).

10.1.1.1.1. Primary efficacy endpoint

Progression free survival (PFS) is defined as the time from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who are alive with no disease progression as of the analysis cut-off date will be censored at the date of the last evaluable tumour assessment. Patients who receive non-study cancer treatment before disease progression will be censored at the date of the last evaluable tumour assessment before the non-study cancer treatment is initiated. D etailed censoring rules are outlined in the SAP. The PFS cut-off date used for the primary analysis will be based on the observation of the 100th event (PD or death) in the study.

10.1.1.1.2. Secondary efficacy endpoints

- **Disease Control Rate (DCR):** The assessment of DCR will be based on Investigator review of the images. DCR is defined as the proportion of patients with objective evidence of confirmed CR or PR, or SD.
- **Objective Response Rate (ORR):** The assessment of ORR will be based on Investigator review of the images. ORR is defined as the proportion of patients with objective evidence of confirmed CR or PR.
  At the analysis stage, the best overall response will be assigned for each patient as the best confirmed response recorded from the start of the study treatment until the end of treatment. If applicable, responses recorded after disease progression or initiation of non-study cancer treatment will be excluded. A patient's best response assignment of SD needs to be maintained for at least 6 weeks after study randomization. The minimum time requirement for response confirmation is 4 weeks.
- **Duration of response (DR)** is derived for those patients with objective evidence of PR or CR. DR is defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumour progression or death due to any cause. Patients alive and progression free as of the analysis cut-off date are censored at their last evaluable tumour response assessment prior to initiation of any non-study cancer treatment.

- **Overall Survival (OS)** is defined as the time from the date of randomization to the date of death. In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time will be censored at the date of last study follow-up, or the cut-off date, whichever is earlier. Patients will be followed for OS until the end of the study (last visit of the last patient).

10.1.1.2. Safety endpoints

The safety endpoints are:
- Adverse events (AE)
    - Serious adverse events (SAE) during the study, according to the investigator or sponsor opinion
    - Emergent adverse event (EAE) under treatment
- Clinical laboratory evaluation
    - Biochemistry, haematology, coagulation parameters
    - Urinalysis parameters
- Physical examination and performance status (ECOG),
- Vital signs,
- ECG parameters

10.1.1.3. Other endpoints

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30, incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.

The colorectal cancer module (QLQ-CR29) is meant for use among colorectal cancer patients varying in disease stage and treatment modality.

10.1.2. Analysis sets

10.1.2.1. Analysis sets

- **Non Included Set (NIS)**: All enrolled patients not selected or not included.
- **Randomised Set (RS)**: All patients to whom a therapeutic unit was randomly assigned using IWRS.
- **Full Analysis Set (FAS):** All randomized patients who have taken at least one dose of IMP will be included in the FAS. Based on the intention-to-treat principle, patients in the FAS will be analysed in the arm they were assigned by randomization.
- **Per Protocol Set (PPS):** All patients of the FAS without relevant deviation(s), which could affect the evaluation of the IMP effect on the primary efficacy endpoint.
- **Tumour Response (TR) Population:** All patients in the PPS with measurable disease (at least one target lesion) at baseline and with at least one tumour evaluation while on treatment (with the same method of measurement as baseline). Patients who have a cancer-

related death prior to their first tumour evaluation will also be considered evaluable with PD as best overall response.

- **Safety Set (SS):** This set will correspond to patients who received at least one dose of IMP. Patients will be analysed according to the treatment actually received. Each patient will be classified into and analysed consistently within one (and only one) treatment group.
- **Quality of Life Set (QLS):** To be included in the QLS for the QLQ-C30 questionnaire, patients should have completed at least two third (i.e. at least 20 questions) of the questions of the baseline QLQ-C30 questionnaire, and at least two third of the questions of a QLQ-C30 questionnaire during the study period. Same conditions for the QLQ-CR29 questionnaires.

The determination of the analysis sets will be finalised before the database lock.

10.1.3. Statistical methods

10.1.3.1. General considerations

10.1.3.1.1. Statistical elements

10.1.3.1.1.1. Descriptive statistics

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): total number of patients, total number and percentage of patients having an event overall, number of patients at risk, number of patients with censored data, number of patients with event of interest.

10.1.3.2. Study patients: Disposition, baseline characteristics and follow-up

The patients'disposition and baseline characteristics will be described in the RS by group 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 at baseline, including reasons for discontinuation and protocol deviations.

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.

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 (delay, reduction, interruption).

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

The number, type, and extent of use of 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.

10.1.3.3. Efficacy analysis

All efficacy analyses will be performed in the FAS, unless otherwise specified.

10.1.3.3.1. Primary efficacy endpoint

10.1.3.3.1.1. Primary analysis

For the primary efficacy endpoint, PFS, the hazard ratio and the corresponding 2-sided 80% and 2-sided 95% CIs for TAS-102 + bevacizumab versus capecitabine + bevacizumab will be estimated using a Cox proportional hazard model adjusting for the stratification factor 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 6, 12, 18, a nd 24 months along with the corresponding 2-sided 80% and 2-sided 95% CI for the estimates.

The primary analysis will be conducted in the FAS.

10.1.3.3.1.2. Secondary analyses

Sensitivity PFS Analyses

As a secondary analysis, the primary analysis of PFS will be repeated in the PPS.

In order to assess the consistency of the primary analysis of PFS, another sensitivity analysis taking into account the further anti-cancer therapy as an event will be carried out both in the FAS and the PPS.

Exploratory PFS Analyses

Additional exploratory analyses for PFS will investigate the effect of specific factors either in a multivariate analysis setting (Cox regression model) or as the marginal effect in specific subgroups. These factors will include, but are not limited to, region, ECOG performance status, gender, age (<75, ≥75 years), prior adjuvant treatment, location of primary disease, surgical resection, number of metastatic sites (1, ≥2), presence of liver metastasis, RAS and BRAF status. Additional exploratory analyses will be defined in the SAP.

10.1.3.3.2. Secondary efficacy endpoints

Analysis of OS will use the same population and analytical methods as described for PFS in the section 10.1.3.3.1.

Analysis of DR will also use similar analytical methods but based on the TR Population.

DCR and ORR based on the TR Population will be evaluated in each arms with their 2-sided 95% Clopper-Pearson CIs.

10.1.3.4. Safety analysis

All patients included in the Safety set (SS) will be evaluated by treatment arm in the safety analysis, unless otherwise specified.

10.1.3.4.1. Adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and the severity of the toxicities will be graded according to the NCI CTCAE criteria, v4.03, where applicable. Concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHODD).

Number of events, number and percentage of patients reporting at least one event, presented by primary system organ class, and preferred term, will be provided for serious adverse events and emergent adverse events over the treatment periods.

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

In addition, separate summaries of SAEs and Grade 3 and 4 AEs will be presented.

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.

10.1.3.4.2. Clinical laboratory evaluation

Haematological and chemistry laboratory parameters will be graded according to the NCI CTCAE v.4.03 criteria, where applicable. Absolute values and changes from baseline will be summarized by cycle. In addition, worst severity grade, time to event, and time to resolution will also be summarized.

In order to examine the evolution of toxicities the worst grade will be analysed in relation to the grade presented by the patient at baseline.

Urinalysis abnormalities will be described.

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

10.1.3.4.3.1. 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.

10.1.3.4.3.2. 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).

10.1.3.4.3.3. Quality of life analysis

EORTC QLQ-C30 and QLQ-CR29 questionnaire responses will be described separately in each arm using descriptive statistics.

The Global Scale as well as the Functional Scales in Physical, Role, Emotional, Cognitive and Social dimensions as well as the 9 symptom scales: Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties of the QLQ-C30 will be assessed at each time point in the QLS.

The EORTC QLQ-CR29 and its symptom and functional scales will be assessed in a similar manner as that described for the QLQ-C30.

10.1.3.5. Biomarker analysis

Exploratory analyses for PFS will investigate the effect of potential predictive biomarkers (RAS, BRAF and others) in a multivariate analysis setting (Cox regression model). The interaction between each biomarker and the treatment will be investigated.

For other biomarkers, descriptive statistics will be provided.

10.2. Determination of sample size

A screening design approach has been utilized, where sample size considerations are based on estimating the PFS hazard ratio with certain precision in order to optimize a future Phase 3 confirmatory design. The primary analysis will be conducted after 100 PFS events (progression of disease or death) are observed in approximately 150 patients randomized in the study, based on 1:1 randomization. The corresponding upper limit of the 2-sided 80% CI for an observed PFS HR of 0.77 would just exclude 1. The corresponding HR critical value for a 2-sided 95% CI would be 0.67. Additional confidence interval approximations for varying observed hazard ratios are shown in the table below:

	Approximate confidence limits	
Observed HR	**95% CI**	**80% CI**
0.55	0.37 - 0.81	0.43 - 0.71
0.60	0.41 - 0.89	0.46 - 0.78
0.65	0.44 - 0.96	0.50 - 0.84
0.67	0.45 - 0.99	0.52 - 0.86
0.70	0.47 - 1.04	0.54 - 0.90
0.75	0.51 - 1.11	0.58 - 0.97
0.77	0.52 - 1.14	0.60 - 1.00
0.80	0.54 - 1.18	0.62 - 1.03

An accrual period of approximately 24 months and a 20%/year loss to PFS follow-up rate has been assumed to account for patients that discontinue treatment for reasons other than disease progression and a follow-up scan that confirms progression has not been obtained (e.g., patient discontinues study treatment due to toxicity and new therapy is initiated prior to documentation of disease progression). Assuming a median PFS time in the capecitabine + bevacizumab arm of approximately 9 months, if the observed PFS HR is 0.77, the primary PFS analysis target events milestone is projected at approximately 12 months after the last patient is randomized in the study (projected total study duration of 36 months until the PFS primary analysis milestone).

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 Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

12.1.1. Before the study

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

12.1.2. During the study

The investigator will allow the monitor to:
- inspect the site, the facilities and the material used for the study,
- meet all members of his/her team involved in the study,
- consult all of the documents relevant to the study,
- have access to the electronic case report forms (i.e. access to an analogic phone line or his/her computer)
- check that the electronic case report forms have been filled out correctly,
- directly access source documents for comparison of data therein with the data in the electronic case report forms
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study 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 participants 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 participants. 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 participants 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 participants.
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 participants. 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 or an equivalent document...).

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 Competent Authorities may also carry out an inspection in the facilities of the sponsor and/or the study centre(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 Competent Authorities 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 of 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 participants 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 Competent Authorities and persons responsible for the audit to the computerised medical files of all participants,
- 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

An independent Data Safety Monitoring Board (DSMB) will be set-up in order to monitor safety data during the study.
The DSMB is independent from the sponsor and is responsible for reviewing on a regular basis strictly confidential data related to the safety of the patients during the study. At any time if necessary the Committee may ask for any supplementary information. The DSMB will make appropriate recommendations to the Sponsor concerning the conduct of the study: continuation, amendment or suspension.

The detailed composition, role, and organization of the DSMB will be specified in a separate and specific charter.

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 document, the insurance documents, the SmPC of administered IMP will be submitted to (an) 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 5).

13.3. Participant information and informed consent

In any case, the participant 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 to collect written consent from each participant before his/her participation in the study. Prior to this, the investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs.
The participant 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.
Two original information and consent forms must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.
If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. The participant 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 participant will be given one signed original information and consent form, the second 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 Competent Authorities.
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, with the exception of an amendment required to eliminate an immediate risk to the study participants.

Each participant affected by the amendment or an independent witness must complete, date and sign two originals of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the information and consent form.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

An electronic data capture system is going to be used for this study. An electronic case report form (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. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor or the CRO.
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 participant'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 participant visit, and all other documents provided by the sponsor (*e.g.* documents relating to the IMP management).
The e-CRF should be completed within a reasonable time after the visit of participant and before the next scheduled visit. Data recorded directly on e-CRF and considered as source data (see section 4.6) must be collected immediately in the e-CRF.
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 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.
The monitor must make certain that data are completed on the e-CRF.
Key data subject to monitor's verification are defined in the monitoring guide. 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 participant, 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 will receive a CD-ROM containing participant data of his/her centre for the study file.

14.2. Data management

Data are collected via a CRF and stored in a secured database.
For data collected on the e-CRF, the Data & Clinical Logistics 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 centralisators, the Data & Clinical Logistics of I.R.I.S. is responsible for data transfer: IWRS, centralised laboratory, provide(s) 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, procedures and other specific panels using MedDRA,
- medications using WHO-DD.

The coding process is described in a specification manual.
When data validation is achieved, a review of 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 made available for data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 15 years after the end of the study, or more if specified by the local regulation.
At the end of the study, the investigator will be provided with a copy of each participant's data on a CD-ROM support. These data include the completed e-CRF, all electronic CRF comments, history of all queries, all signature history and the full audit trail reports.

15. INSURANCE

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as sponsor of clinical trials on a worldwide basis.
Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.
All relevant insurance documentation are included in the file submitted to any authorities' approval of which is required.

16. OWNERSHIP OF THE RESULTS - PUBLICATION POLICY

I.R.I.S., acting as the study sponsor, assumes full responsibility relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit. In order to allow this information to be used effectively, it is essential that the study results be communicated to the sponsor as soon as possible.

As the study is a multicentre one, the first publication must be performed only with data collected from several centres and analysed under the responsibility of the Pole of Expertise Methodology and Data Valorisation of I.R.I.S. 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 sponsor has been provided

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 at least 30 days for a publication and 15 days for an abstract before the forecasted date of communication and/or submission for a publication. The sponsor shall make comments on the project within 15 days for a publication and 7 days for an abstract, of receipt of the project. The investigator, who submitted the project, shall take the sponsor's comments into due consideration. In any case, should the investigator who submitted the project decide not to modify the project according to the sponsor's comments, it shall provide the sponsor with the grounds of its decision in writing.

However, in the case where the sponsor is in the process of filing a patent application on the results of the study, the sponsor will be able to delay its authorisation for publication or communication of the results of the study until the date of international registration of the patent.

Authorship rules for trial

- Authorship will follow the guidelines for the target journal. This especially considering the maximum number of authors permitted for the target journal.
- The maximum number of authors will usually be included.
- The Coordinator will be the last author. The first author on the main publication will be the highest recruiter. All other authors will be listed between the first and last author according to recruitment.
- Company Representative authors should not outnumber non-Company Representative authors and usually should not exceed 4.
- Company Representative authors should not be first author.
- Per centre, a total of 4 authors (depending on the maximum number permitted by the target journal) may be included in the authors list.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

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.

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 the coordinators 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, with the exception of a measure required to eliminate an immediate risk to the study participants.

When the submission is performed by the investigator or the 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 Competent Authorities in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by the Biometry Department in compliance with I.R.I.S. standard operating procedure.

The sponsor's representative and *the coordinators* must mutually agree on the final version. One copy of the final report must be dated and signed by *the coordinators* and the Director of the Innovation Therapeutic Pole.

17.2. Concerning the sponsor

The sponsor undertakes to:

- supply the investigator with adequate and sufficient information concerning the IMP(s) administered during the study to enable him/her to carry out the study,
- supply the investigator with investigator's brochure if the test drug is not marketed,
- supply the investigator with SmPC, 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 IMP(s) administered that may be required by the local authorities before the beginning of the study,
- provide the coordinators annually, 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).

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 S 95005 (TAS-102) and study CL2-95005-002 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 any personal data by applying to the study monitor.
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 participants. 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., except to the representatives of the Competent Authorities, and only at their request. In the latter case, the investigator commits himself to informing I.R.I.S. prior to disclosure of information to these authorities.
A participant screening log and a full identification and enrolment list of each participant will be completed and kept by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.
The participant screening log must be completed from the moment the investigator checks that a participant could potentially take part in the study (by assessment of participant 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 (*e.g.* co-investigator, nurse) and any other person involved in the study for this centre (*e.g.* 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 centre.

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 l ocal regulation (e.g. Food & Drug Administration 1572 form),
- 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 participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

The investigator must send an e-mail to the Sponsor within 24 working hours to inform about the last follow-up of last participant (or the last contact attempt if the last participant is declared lost to follow-up) in the centre.

18. REFERENCES

Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, Lyman GH, Pettengell R, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C; European Organisation for Research and Treatment of Cancer. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011 Jan;47(1):8-32

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, 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. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76

Benson AB 3rd, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, McCallum R, Mitchell EP, O'Dorisio TM, Vokes EE, Wadler S. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004 Jul 15;22(14):2918-26.

Coghlin C, Murray G. Biomarkers of colorectal cancer: recent advances and future challenges. Proteomics Clin Appl. 2015 Feb;9(1-2):64-71

Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, Jonker D, Osborne S, Andre N, Waterkamp D, Saunders MP; AVEX study investigators. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1077-85

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), (2011/C 172/01)

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).

Du Bois D, Du Bois EF (Jun 1916). "A formula to estimate the approximate surface area if height and weight be known". Archives of Internal Medicine 17 (6): 863-71. PMID 2520314. Retrieved 2012-09-09.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47

EMEA "Guideline on evaluation of anticancer medicinal products in man". CPMP/EWP/205/95 rev.3-December 2005.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013 Apr;49(6):1374-403

Gonzales-Pons M, Cruz-Correa M. Colorectal Cancer Biomarkers: Where Are We Now? BioMed Research InternationalVolume 2015; Article ID 149014 2015

ICH Topic E6 – Guideline for Good Clinical Practice: Consolidated guideline finalised (step 4) in June 1996. Adopted by CPMP, July 96, issued as CPMP/ICH/135/95/step 5, post step errata, July 2002.

ICH Topic E9 – Statistical Principles for Clinical Trials: Adopted by CPMP, March 1998, issued as CPMP/ICH/363/96/step 5.

ICH Topic E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, issued as CPMP/ICH/377/95.1994

Kalia M. Biomarkers of Colorectal CancerJ Cancer Biol Res 3(1) 2015: 1058

Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM. American Society of Clinical Oncology guideline for antiemetics in oncology: update. J Clin Oncol. 2006 Jun 20;24(18):2932-47.

Kuboki Y, Nishina T, Shinozaki E, Yamazaki K, Shitara K, OkamotoW, Kajiwara T, Matsumoto T, Tsushima T, Mochizuki N, Fukutani M, Nakamoto M, Hasegawa H, Sugama A, Nomura S, Sato A, Ohtsu A, Yoshino T. An investigator initiated multicenter phase I/II study of TAS-102 with bevacizumab for metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE). J Clin Oncol., ASCO Annual Meeting (May 29 - June 2, 2015).Vol 33, No 15_suppl (May 20 Supplement), 2015: 3544

Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909-19.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Colon Cancer-Version 3. 2015

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Rectal Cancer-Version 3. 2015

Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; Vol. 31: 103-115

Price TJ, Zannino D, Wilson K, Simes RJ, Cassidy J, Van Hazel GA, Robinson BA, Broad A, Ganju V, Ackland SP, Tebbutt NC. Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of Capecitabine, Bevacizumab and Mitomycin C. Ann Oncol. 2012 Jun;23(6):1531-6

Tebbutt NC, Wilson K, Gebski VJ, Cummins MM, Zannino D, van Hazel GA, Robinson B, Broad A, Ganju V, Ackland SP, Forgeson G, Cunningham D, Saunders MP, Stockler MR, Chua Y, Zalcberg JR, Simes RJ, Price TJ. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J Clin Oncol. 2010 Jul 1;28(19):3191-8

Tsukihara H, Nakagawa F, Sakamoto K, Ishida K, Tanaka N, Okabe H, Uchida J, Matsuo K, Takechi T. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, together with bevacizumab, cetuximab, or panitumumab on human colorectal cancer xenografts. Oncol Rep. 2015 May;33(5):2135-42

Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, on behalf of the ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2014;25 (Supplement 3): iii1–iii9

Label of LONSURF (trifluridine and tipiracil) tablets, for oral use - Initial USA Approval. Sept 2015.

Product Information of LONSURF (trifluridine and tipiracil) tablets, for oral use - Initial EU Approval. April 2016.

19. APPENDICES

Appendix 1: Quality of life questionnaires

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.

Today's date (Day, Month, Year): |_|_|_|_|_|_|_|_|

	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

ENGLISH

EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

ENGLISH

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

Appendix 2: 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 Response Evaluation Criteria in Solid Tumours: Revised RECIST 1.1 (Eisenhauer EA *et al.*, 2009)

Measurability of tumour at baseline

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable

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 (CT-scan slice thickness no greater than 5 mm),
10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable),
20 mm by chest X-ray.
Malignant lymph nodes: 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 recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

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.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:
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 usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Tumour response evaluation

Assessment of overall tumour burden and measurable disease
To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements.
Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-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 (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).
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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm

should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.
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 as noted above, 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.

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 and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria
This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

Evaluation of target lesions:
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions
Lymph nodes. 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. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. 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'. When this occurs it is important that a value 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 (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. 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'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, 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. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: *i.e.* an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

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. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of

progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
Negative FDG-PET at baseline, with a positive FDG-PET (a 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) at follow-up is a sign of PD based on a new lesion.
No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1: Time point response: patients with target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not 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	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Not evaluable

When patients have non-measurable disease only (therefore non-target), Table 2 is to be used.

Table 2: Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = Not evaluable.

1 = 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response **is not** required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on

last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response **is** required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3: Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Not evaluable.

1 = If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a m easurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (*e.g.* very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to

an event' (*e.g.* time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Confirmatory measurement/duration of response

Confirmation
In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, *i.e.* in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.
In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response
The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).
The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease
Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).
The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.
Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency

should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix 4: 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 5: 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 i ntervention 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 6: Substantial amendment No. 1 to the clinical study protocol

FINAL VERSION DATE: 17/March/2016

COUNTRIES CONCERNED: Italy

CENTRES CONCERNED All

NATURE OF AMENDMENT

STUDY SUMMARY SHEET
12. Has adequate organ function as defined by the following laboratory values obtained within 5 days prior to first day of study drug administration: 12.5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5xULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5xULN. 12.6. Serum creatinine ~~of ≤1.5 mg/dL~~ clearance ≥ 50 ml/min (using Cockcroft formula).
Non-inclusion criteria related to administration of S 95005 23. Has previously received S 95005 or history of allergic reactions attributed to compounds of similar ~~or biologic~~ composition to S 95005 or any of its excipients. *Non-inclusion criteria related to administration of bevacizumab* 24. History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients. 25. History of hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies. *Non-inclusion criteria related to administration of capecitabine* 26. History of allergic reactions or hypersensitivity to capecitabine or any of its excipients fluorouracil 27. History of severe and unexpected reaction to fluoropyrimidine therapy. 28. Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. 29. Treatment with sorivudine or its chemical related analogues, such as brivudine, within 4 weeks before the first study drug intake
"4. STUDY DESIGN"
Section "4.2.1. Study plan"
• **Treatment period:** Randomised patients should receive the first dose of study treatment (Day 1 of Cycle 1) no later than 3 days after randomisation. Each patient should receive at least 28 days of combination of S 95005+ bevacizumab or at least 21 days of combination of capecitabine + bevacizumab except in case of safety concerns. ~~The maximum number of cycles is at the discretion of the investigator.~~ Patients will be treated by the assigned combined regimen until they meet a discontinuation criterion as described in section 5.4.1. Patients will be considered to be on t reatment as long as either component of the combination regimen continues to be administered. The estimated median PFS is 11.7 months in the S 95005 + bevacizumab group and 9 months in the capecitabine + bevacizumab group (please refer to section 10 for more details).

Section "5. SELECTION AND WITHDRAWAL OF PARTICIPANTS"

Section "5.1. Inclusion Criteria"

Section "5.1.4. Medical and therapeutic criteria"

12. Has adequate organ function as defined by the following laboratory values obtained within 5 days prior to first day of study drug administration:

12.5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5xULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5xULN.

12.6. Serum creatinine ~~of ≤1.5 mg/dL~~ clearance ≥ 50 ml/min (using Cockcroft formula).

Section "5.2. Non-inclusion criteria"

Section "5.2.2. Medical and therapeutic criteria"

Non-inclusion criteria related to administration of S 95005

23. Has previously received S 95005 or history of allergic reactions attributed to compounds of similar ~~or biologic~~ composition to S 95005 or any of its excipients.

Non-inclusion criteria related to administration of bevacizumab

24. History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients.

25. History of hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.

Non-inclusion criteria related to administration of capecitabine

26. History of allergic reactions or hypersensitivity to capecitabine or any of its excipients or fluorouracil.

27. History of severe and unexpected reaction to fluoropyrimidine therapy.

28. Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.

29. Treatment with sorivudine or its chemical related analogues, such as brivudine, within 4 weeks before the first study drug intake

Section "5.4.1. Withdrawal criteria"

Information to be collected during the last visit of these patients is given in Section 4.2.6.2.10. These follow-up modalities are used to ensure the efficacy and safety evaluation of all participants who received the IMP.

The reasons for premature discontinuation of IMP are:

[…]

- Refer to the bevacizumab and to the capecitabine ~~package insert~~ SmPC (Appendix 6) for events requiring discontinuation of treatment.

Section "6. TREATMENT OF PARTICIPANTS"
Section "6.3.1. Prohibited Medication and Therapies"
Patients are not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers (BRMs), or endocrine therapy during the study treatment period. Palliative radiotherapy is not permitted while the patient is receiving study treatment. Treatment with sorivudine or its chemical related analogues, such as brivudine, are forbidden during the study and within 4 weeks before the first study drug intake.
Section "6.3.2. Concomitant Medication and Therapies"
Caution is required when using drugs that are human thymidine kinase substrates, *e.g.*, zidovudine. […]. Patient treated with oral anticoagulant treatment or heparins should be closely monitored especially in case of thrombopenia. For precautions for use and interactions of concomitant treatments with capecitabine or bevacizumab please refer to the corresponding SmPC of the drugs (Appendix 6).
Addition of Appendix 6 "Capecitabine and bevacizumab SmPC"
Capecitabine SmPC is available here: Link to European Medicines Agency (EMA) website Bevacizumab SmPC is available here: Link to European Medicines Agency (EMA) website

Appendix 7: Capecitabine and bevacizumab SmPC

Capecitabine SmPC is available here:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000316/human_med_001157.jsp&mid=WC0b01ac058001d124

Bevacizumab SmPC is available here:
http://www.ema.europa.eu/ema/index.jsp%3Fcurl=pages/medicines/human/medicines/000582/human_med_000663.jsp

Appendix 8: Substantial amendment No. 3 to the clinical study protocol

FINAL VERSION DATE: 30th August 2016

COUNTRIES CONCERNED: Germany

CENTRES CONCERNED All

NATURE OF AMENDMENT:

Initial text	**Amended text**
Section "8.4.1.1 Adverse events"	
"An adverse event 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 IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (e.g. run-in period) are also concerned). An adverse event can therefore be: - any unfavourable and unintended sign, including an abnormal finding from an additional examination (lab tests, X-rays, ECG, …), - any symptom or disease, - any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity), including the studied pathology, and which is deemed clinically relevant by the investigator, detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in participant's diary or safety evaluation scale)."	"An adverse event 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 IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (e.g. run-in period) are also concerned). An adverse event can therefore be: - any unfavourable and unintended sign, including an abnormal finding from an additional examination (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 participant entered the study (increase in frequency and/or intensity), including the studied pathology, ~~and which is deemed clinically relevant by the investigator~~, detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in participant's diary or safety evaluation scale)."