D6.1 First study subject approvals package

This document presents the REVERT First Subject Approvals Package that provides detailed information on the procedures that will be implemented for patient recruitment to the prospective clinical study protocol.

Following a revision process with the European Community Project Officers, on the 13th January the REVERT CRO, L.N.Age notified the Policlinico Tor Vergata (PTV) Ethics Committee that the REVERT protocol, EudraCT number: 2020-002533-14 has been prematurely terminated.

The REVERT study has been fully reconsidered as a “clinical investigation with MD (AI Class IIa)”. The reclassified protocol has not undergone any change from any point of view except the elimination of the pharmacological phase.

Hereafter, the new approval package includes:

1. Approval from Ethics Committee n° 4.22 P.U.D.– 26th January 2022
2. ClinicalTrials.gov PRS ID: NCT05396807.
3. Final version of REVERT study protocol.
4. Incidental Findings Policy (which is part of the study Protocol)

Since the start of the project on January 2020, both during the kick-off meeting and during the conference call meetings held in the lockdown period among the clinical partners, the optimal strategy to meet the protocol for the clinical study was defined. The main goal of the study is to validate and adjust a stratification tool that will be defined from the retrospective evaluation of mCRC patients’ outcomes and profiles in WP3 and 5. Data concerning already treated mCRC patients, will serve to build an AI-based profile capable to identify “good” or “poor” responders to therapy and to orient the clinician towards the best treatment option. Study protocol accurately describes inclusion and exclusion criteria, primary and secondary endpoints and methods of patients’ examination and follow up visits. All these parameters were thoroughly discussed among clinical partners and evaluated by the teams of each clinical partner.

Patients meeting the inclusion criteria will be asked to sign an Informed Consent, screened, examined while entering the clinical study and will be followed for at least 12 months at scheduled intervals and, in any case, at the first day of each chemotherapy cycle, before treatment start. During that time, primary and secondary endpoints will be followed and compared with those expected from the retrospective analysis.

The study protocol was discussed with CRO representatives on the 13th January and reclassified accordingly. On the 14th January a Request for Single Opinion to Clinical Investigation with Pre-market "early phase" Medical Device, No-Profit, Protocol Code: REVERT was presented at the PTV IRB for approval.

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 848098”.

The approved REVERT protocol is in the process of submission to the local Ethical Committees of the clinical partners and patients' recruitment will start in all participating centers.

The first patient of this clinical trial is scheduled on June 2022.

No critical issues are expected in this task accomplishment, since all the administered therapies employ approved-drugs (and their combination) as per standard good clinical practice.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848098".

FONDAZIONE PTV
POLICLINICO TOR VERGATA

Comitato Etico Indipendente
(D.M. 8 febbraio 2013)

PROTOCOLLO DI STUDIO REVERT
REGISTRO SPERIMENTAZIONI 4.22 P.U.D.

Roma, 15 febbraio 2022

Chiar.mo
Prof. Mario Roselli
UOSD Oncologia
Fondazione PTV
Policlinico Tor Vergata
SEDE

Spett.le
Dipartimento di Medicina dei Sistemi
Università degli Studi di Roma "Tor Vergata"
SEDE

Spett.le
L.N.AGE
SEDE

RIUNIONE DEL 26 GENNAIO 2022

MEMBRI PRESENTI:

Prof. Massimo ANDREONI
Prof. William ARCESE
Prof.ssa Maria Luisa BARBACCIA
Prof.ssa Livia BIANCONE
Prof.ssa Elena CAMPIONE
Dott.ssa Maria Grazia CELESTE
Prof. Carlo CHIARAMONTE
Dott.ssa Patrizia DANIELI
Prof. Roberto FLORIS
Prof. Claudio FRANCHINI
Prof.ssa Maria Luisa MANCA BITTI
Dott. M. Andrea MANTO
Prof.ssa Maria Grazia MARCIANI
Dott.ssa Marcella MARLETTA
Dott. Marco MATTEI
Prof. Saverio POTENZA
Prof. Mario ROSELLI
Prof.ssa Federica SANGIUOLO
Prof. Claudio SARTEA
Prof. Paolo SBRACCIA
Dott. Alessandro SILI
Prof. Umberto TARANTINO
Dott.ssa Antonella TOFI
Dott. Ercole VELLONE

ASSENTI GIUSTIFICATI:

Prof. Alfonso BELLIA
Dott.ssa Enrica CANTILLO

Il Comitato Etico si è riunito in modalità telematica, in data **26 gennaio 2022** per esprimere il proprio Parere etico motivato sul **Protocollo di Studio REVERT – taRgeted thErapy for adVanced coloRectal canceR paTients"; *"Terapia mirata per il trattamento dei pazienti con carcinoma metastatico del colon-retto"***
Sperimentatore: Prof. Mario Roselli, UOSD Oncologia
Promotore: Dipartimento di Medicina dei Sistemi, Università degli Studi di Roma Tor Vergata;
CRO: L.N.AGE S.r.L.

ESAMINATA

la documentazione presentata e in particolare:

- *Lettera d'Intenti della CRO in nome del Promotore no profit (atti prot.0001559/2022 del 24/01/2022);*
- *Delega del Promotore alla CRO L.N. AGE;*
- *Dichiarazione sulla natura No-Profit dello Studio;*
- *Protocollo di Studio (versione 4.0 del 07/01/2022);*
- *Sinossi in italiano (versione 4.0 del 07/01/2022);*
- *Foglio Informativo/Consenso Informato/Informativa e Manifestazione del Consenso al Trattamento dei Dati Personali (versione 1.0 del 07/01/2022);*
- *Lettera al Medico di Medicina generale (versione 1.0 del 07/01/2022);*
- *Polizza assicurativa (HDI GERLING 390-08297280-30022);*
- *Curriculum Vitae dello Sperimentatore Principale;*
- *Dichiarazione pubblica sul conflitto di interesse dello Sperimentatore Principale;*
- *Lista Centri (versione 1.0 del 29/06/2020);*
- *Notifica al Ministero della Salute (documentazione su dispositivo notificata);*
- *Proposta di Accordo tra le parti.*

RILEVATO CHE

il Protocollo presentato:

- è giustificato scientificamente ed eticamente quanto al razionale
- è giustificato quanto al disegno e al piano statistico per l'analisi dei dati
- è giustificato quanto ai soggetti in studio
- è conforme alle disposizioni di legge ed alle conseguenti raccomandazioni di questo Comitato Etico Indipendente, in materia di rispetto della privacy (ai sensi del D.Lgs.196 del 30.06.2003; GDPR 679/2016)
- è giustificato quanto alla qualificazione del ricercatore e/o delle strutture

ESPRIME PARERE FAVOREVOLE

Il Parere è stato espresso dal Comitato, all'unanimità dei votanti.
Assente al momento della votazione, il Prof. Mario Roselli.

Lo Studio potrà essere svolto presso il Centro clinico, solo a seguito della Delibera autorizzativa del Rappresentante legale dell'Azienda Ospedaliera Universitaria Policlinico Tor Vergata.

Si dichiara che questo Comitato è organizzato e opera nel rispetto delle norme di Buona Pratica Clinica (GCP-ICH) e secondo la normativa vigente sulle Sperimentazioni Cliniche e sull'istituzione e funzione dei Comitati Etici.

Il Presidente del Comitato Etico
Prof.ssa Maria Grazia Marciani

FONDAZIONE PTV
POLICLINICO TOR VERGATA

Comitato Etico Indipendente
(D.M. 8 febbraio 2013)

Presidente

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Dott.ssa Marcella MARLETTA (componente esterno)	***"Esperto in dispositivi medici"*** Direttore Generale - Direzione Generale dei Dispositivi Medici del Servizio farmaceutico e della sicurezza delle cure, Ministero della Salute
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Dott.ssa Antonella TOFI (componente esterno)	***"Medico di medicina generale territoriale"*** Medico Esperto in Medicina Generale
Dott. Ercole VELLONE (componente esterno)	***"Rappresentante dell'area professioni sanitarie"*** Ricercatore di Scienze infermieristiche generali cliniche e pediatriche Università degli Studi di Roma "Tor Vergata"

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Protocol Registration and Results System

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Email: mario.roselli@uniroma2.it [Update]

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New PRS Beta Home Page

Record List

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	Protocol ID	ClinicalTrials.gov ID	Brief Title	Record Status	Last Update	Responsible Party	Problems
Open PR	University Tor Vergata	NCT05396807	REVERT - taRgeted thErapy for adVanced colorEctal canceR paTients	Released	05/30/2022 03:48	Prof Mario Roselli mario.roselli@uniroma2.it	

KEY: R Results DR Delayed Results D Study Documents PR PRS Review
U XML Upload NP No longer public PRS Review Comments

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CLINICAL STUDY PROTOCOL

STUDY TITLE: **REVERT – taRgeted thErapy for adVanced colorEctal canceR paTients**

Sponsor: University Tor Vergata, Via Montpellier 1, 00133- Rome (Italy)

Clinical Phase: Premarket Medical Device "early phase"

Protocol Version Date: Version 5.0 of 26 April 2022

Coordinating Center: Medical Oncology Unit, Department of Oncohematology, Policlinico Tor Vergata, Viale Oxford 81, 00133-Rome (Italy)

Principal Investigator: Prof Mario Roselli, Medical Oncology Unit, Department of Oncohematology, Policlinico Tor Vergata, Viale Oxford 81, 00133- Rome (Italy)

CRO: L.N.Age srl.: Via Luigi Rizzo 62, 00136 Rome (Italy), Scientific Director Dr. Paolo Ferrazza

This clinical study will be conducted in accordance with the sponsor's Standard Operating Procedures (SOPs), current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonisation) Guidelines and EU Directives

Table of Contents

List of abbreviations

AE	Adverse Event
AI	Artificial Intelligence
AIOM	Italian Medical Oncology Association
ASCO	American Society of Clinical Oncology
CA 19-9	Carbohydrate Antigen 19-9
CEA	Carcinoembryonic Antigen
CR	Complete Response
EC	Ethics Committee
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EHRs	Electronic Health Records
ESMO	European Society for Medical Oncology
ETS	Early Tumour Shrinkage
FFPE	Formalin-Fixed Paraffin-Embedded
HER-2	Human Epidermal Growth Factor Receptor 2
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
KRAS	Kirsten rat sarcoma–RAS
MD	Medical Device
mCRC	metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
ML	Machine Learning
NCCN	National Comprehensive Cancer Network
NRAS	Neuroblastoma-RAS
OSPFS	Overall survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PS	Performance status
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response Rate
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolism

WT	Wild- type

1. PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Title of the study:
REVERT – taRgeted thErapy for adVanced colorEctal canceR paTients</td></tr>
<tr><td></td><td>Protocol code:
REVERT</td></tr>
<tr><td colspan="2">Sponsor: University Tor Vergata, Via Montpellier 1, 00133 - Rome (Italy)</td></tr>
<tr><td colspan="2">Study center(s):
A total number of 6 clinical sites located in Italy (3), Romania (2) and Spain (1) will take part in the trial. The coordinating site will be in Rome, Italy.</td></tr>
<tr><td>Planned study period:
March2022– March 2024 (12 months recruitment + 12 months of follow-up)</td><td>Phase of Development: Premarket Medical Device “early phase”</td></tr>
<tr><td colspan="2">Treatments in analysis: the best standard chemotherapy will be suggested among those considered equally efficacious as per good and current clinical practice and the best standard chemotherapy, evaluated on pre-defined algorithm, for individual patients with unresectable metastatic colorectal cancer (mCRC):

- XELOX
• Oxaliplatin 100 mg/sqm iv;
• Capecitabine 750 mg/sqm/bidiv.

- FOLFOX
• Oxaliplatin 85 mg/sqm iv;
• L-Leucovorin 200 mg/sqm iv;
• 5-fluorouracil 400 mg/sqmivbolus + 2400 mg/m² c.i.

- FOLFIRI
• Irinotecan 180 mg/m² iv;
• Levofolinate 200 mg/m² iv;
• 5-Fluorouracil 400 mg/m² ivbolus + 2400 mg/m² c.i..

- FOLFOXIRI
• Irinotecan 150 mg/sqm iv;
• Oxaliplatin 85 mg/sqm iv;
• L-Leucovorin 200 mg/sqm iv;
• 5-fluoruracil 2400 mg/sqmiv.

in Combinatorial Therapy with either:
• Bevacizumab 7.5 mg/kg iv;
• Cetuximab 400 mg/m2 initial dose (120-minute infusion), then 250 mg/m2 (60-minute infusion) thereafter once weekly;
• Panitumumab 6 mg/kg iv;
• Aflibercept 4 mg/kg iv (60- minute infusion) to be repeated every 2 weeks (only as second line treatment).

Artificial Intelligence is a software based on algorithm defined as Medical Device Class IIa.</td></tr>
</table>

Indication: unresectable metastatic colorectal cancer (mCRC)

Background and Rationale:

Colorectal cancer (CRC) is among the most frequent causes of cancer-related deaths. Around 50% of CRC patients with local or regional disease will develop distant metastases, while almost 21% of CRC patients present with metastases already at the time of diagnosis, with a 5-year survival of 13.8%. Selection of the optimal first line treatment thus represents a crucial step in the therapeutic pathway of metastatic CRC (mCRC) patients, allowing a significant improvement of both objective response rate (RR) and overall survival (OS) thanks to the development to already authorized new molecular drugs. Currently, one of the most pressing issues is finding more effective ways to canalize all efforts to select the right patients for the right therapy at the right time.

The REVERT clinical trial is a prospective study, inserted within a wider European Project. The clinical study will take advantage of the results of the retrospective evaluation of mCRC patients' outcomes and profiles, aimed at evaluate the efficacy of treatment strategies, that will performed during the early activities of the European Project. In such retrospective analysis Artificial Intelligence (AI) and Machine Learning (ML) will be instructed and used to derive predictive clinical data**,** after having analysed all possible variables including known mutational, biochemical and clinical features of samples from mCRC patients historically treated in the Oncology Units participating to the project and stored in partner Biobanks. AI and ML methodologies are based on Support Vector Machines and combine Multiple Kernel Learning and Random Optimization, incorporating already available large databases with new, potential prognostic/predictive biomarkers (e.g., gene mutations, epigenetic changes, gene expression profiling signatures). The emerging results will be used to help the choice of the best combinatorial therapy, for every prospectively enrolled mCRC patient. Sex and gender differences, also according to sidedness, will be analysed to evaluate their impact on survival and quality of life (QoL) in patients with mCRC.

Objectives:

Primary Objective

The primary objective of the study is to collect predictive preclinical data and integrate them with those derived by a retrospective study in mCRC patients, with the aim of using AI software to support physicians in choosing the most effective treatment.

Secondary Objectives:

1. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy evaluated by the overall survival (OS) in patients with mCRC.
2. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy evaluated by the clinical response to the treatment, achieving a complete (CR) or partial (PR) response, according to RECIST 1.1 criteria.
3. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy evaluated by the decrease in the sum of diameters of RECIST target lesions (Early Tumour Shrinkage).
4. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy on QoL, evaluated by the EORTC QLQ-C30 questionnaire.

Study design:

This is a clinical prospective, no-Profit, Interventional, Premarket Medical Device "early phase", multicentre, single-arm study, based on collecting data on predictive biomarkers of mCRC patients, integrate them with the results of the retrospective evaluation of outcomes and profiles of historical mCRC patients previously treated in the Oncology Units, in order to evaluate the efficacy of the best administered treatment. Results from the retrospective evaluation, will serve to build an AI-based profile capable to identify "good" or "poor" responders to therapy and to support the clinician towards the best treatment option. Following the first disease progression (PD), 2nd line therapy will be at Investigator's choice. The drugs under investigation are those commonly employed in mCRC patients as per usual standard of care. AI is a software based on algorithm defined as Medical Device Class IIa.

Planned number of patients:

A total of 106 consecutive patients (69 WT (wild type), 37 RAS mutated (mut), male and female, age ≥18 years), affected by mCRC.

Inclusion criteria:

1. Signed and dated Informed Consent.
2. Age ≥ 18 years at time of Informed Consent.
3. Histologically- or cytologically-confirmed mCRC.

4. Assessed tumour EGFR pathway mutational status (K-RAS, N-RAS), BRAF, HER-2 neu, MSI.
5. Sufficient amount of representative tumour specimen (primary or metastatic, archival or newly obtained for confirmatory central laboratory testing of BRAF and KRAS mutational status.
6. Dihydropyrimidine dehydrogenase (DPD) before 5-FU infusion.
7. Eligibility to receive bevacizumab, cetuximab or panitumumab per locally approved label with regard to tumour RAS status.
8. Recurrence of disease after primary radical surgery and adjuvant therapy carried out > 6 months prior the present trial.
9. Evidence of measurable or evaluable non-measurable disease as per RECIST, v1.1
10. ECOG PS of 0 or 1.
11. Adequate bone marrow function characterized by the following at screening:
    a) Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L;
    b) Platelets $\geq 100 \times 10^9$/L;
    c) Haemoglobin ≥ 9.0 g/dL.
12. Adequate renal function characterized by serum creatinine $\leq$ 1.5 × upper limit of normal (ULN), or creatinine clearance $\geq$ 50 mL/min.
13. Adequate hepatic function characterized by the following:

a. Serum total bilirubin $\leq 1.5 \times$ ULN and < 2 mg/dL;
b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN, or $\leq 5 \times$ULN in presence of liver metastases.

14. Female patients are either postmenopausal for at least 1 year, surgically sterile for at least 6 weeks, or must agree to take appropriate precautions to avoid pregnancy.
15. Males must agree to take appropriate precautions to avoid fathering a child from screening through follow-up.

Exclusion criteria:

1. Prior hypersensitivity or toxicity to chemotherapy drugs suggesting an inability to tolerate the proposed treatment.
2. Patients should not be candidate for upfront resection of metastatic disease.
3. Symptomatic brain metastasis.
4. Leptomeningeal disease.
5. Known history of acute or chronic pancreatitis.
6. History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery).
7. Impaired cardiovascular function or clinically significant cardiovascular diseases.
8. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure $\geq$ 150 mmHg or diastolic blood pressure $\geq$ 100 mmHg despite current therapy.
9. Impaired hepatic function, defined as Child-Pugh class B or C.
10. Concurrent or previous other malignancy.
11. History of thromboembolic or cerebrovascular events $\leq$ 6 months prior to starting study treatment.
12. Concurrent neuromuscular disorder associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
13. Known contraindication to receive antineoplastic treatment at the planned doses.
14. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study.
15. Pregnancy, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test result, or lactating.
16. Participation to other clinical trial studies.

Duration of study:
Study length is planned to be about 24 months.

Endpoints:
Primary endpoint: The primary endpoint of the trial will be **Progression Free Survival** (PFS), including PFS1

and PFS2, defined as the time from enrolment to the first documentation of objective disease progression or death due to any cause, whichever occurs first.

Secondary endpoint:

1. **Overall survival** (OS), defined as the time from enrolment to the date of death due to any cause. For patients still alive at the time of analysis, the OS time will be censored on the last date the patients were known to be alive.
2. **Response Rate** (RR), defined as the percentage of patients, relative to the total of enrolled subjects, achieving a complete (CR) or partial (PR) response, according to RECIST 1.1 criteria, during the phases of treatment. The determination of clinical response will be based on Investigator reported measurements.
3. **Early Tumour Shrinkage** (ETS), defined as the percentage of patients, relative to the total of the enrolled subjects, achieving a >20% decrease in the sum of diameters of RECIST target lesions at week 8 compared to baseline.
4. **Quality of Life** (QoL), will be measured using the EORTC QLQ-C30 questionnaire.

Statistics analysis plan(ning) and power calculation:

The prospective Medical Device study will follow an exact single-stage trial design. The retrospective algorithm-defining analysis will produce specific patient profile associated in particular to benefit of oxaliplatin vs irinotecan regardless of RAS/RAF mutational status, and to benefit of anti-VEGF vs anti-EGFR agents in RAS/RAF wild type patients. Assuming that 10-month-PFS rate in wild type (WT) patients is approximately 50% for conventionally chosen first-line regimens (historical control, P0), the phase II study will be looking for a 15% increase in the percentage of WT patients progression-free at 10 months when adopting the algorithm-driven treatment choice (i.e. improvement of 10-month PFS rate from 50% to 65%, P1). The hypothesis to be tested will be H0, $P < P0$ vs H1, $P > P1$, where P will be the actual 10-month PFS rate of enrolled WT patients. Accepting a false-positive rate (alpha) of 5% and a false-negative rate(beta) of 20%, H0 will be refused and H1 accepted with a statistical power of 80% if at least 42 WT patients out of a total sample size of 69 enrolled WT patients will remain progression-free at 10 months. A parallel study design has been conceived for RAS mutated (mut) patients. For mut patients the 8-month-PFS rate is approximately 50% in case of conventionally chosen first-line regimens (historical control, P0). The same phase II study will be looking for a 20% increase in the percentage of mut patients progression-free at 8 months with the algorithm-driven treatment choice (i.e. improvement of 8-month PFS rate from 50% to 70%, P1). For this subset of patients, the hypothesis to be tested will be H0, $P < P0$ vs H1, $P > P1$, where P will be the actual 8-month PFS rate of enrolled mut patients. Accepting a false-positive rate (alpha) of 5% and a false-negative rate (beta) of 20%, H0 will be refused and H1 accepted with a statistical power of 80%if at least 24 mut patients out of a total sample size of 37 enrolled mut patients will remain progression free at 8 months. In total, the study will therefore plan to enrol 106 patients.

Data documented in this study and the parameters measured will be evaluated and presented using descriptive statistics, i.e. arithmetic mean, SD, minimum, median and maximum values for quantitative variables, and absolute and relative (%) frequencies for qualitative variables. All analyzes will be verified with parametric and non-parametric tests and accompanied by a two-dimensional factorial ANOVA. The statistics will be reported by group.

FPFV: March 2022

LPFV: March 2023

LPLV: March 2024

1.1 Study Flow Chart

Visits (Day)	**Baseline (**within 28 days prior to first infusion) (±15 days)	**Day 1 Each Cycle (until PD)**	**Every 12 weeks from first day cycle** until PD	**End of study and after evidence of PD**
Informed Consent Signature	X			
Medical History	X			
Physical Examination (sex, weight, height)	X	X	X	X
Vital signs(blood pressure, heart rate)	X	X	X	X
Disease history	X			
ECOG PS	X	X	X	X
ECG	X			
Pregnancy test	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X
Inclusion/Exclusion Criteria	X			
Enrolment	X			
Blood count and differential	X	X	X	
Bilirubin total	X	X	X	
Bilirubin direct	X	X	X	
AST	X		X	
ALT	X		X	
Alkaline phosphatise	X		X	
Albumin	X		X	
LDH	X		X	

Serum creatinine	X	X	X	
Glucose	X		X	
Sodium	X		X	
Potassium	X	X	X	
Calcium	X	X	X	
Magnesium	X	X	X	
INR/APTT	X	X*	X	
CEA	X		X	
CA19.9	X		X	
EORTC QLQ-C30 questionnaire	X	X	X	**X**
Contrast-Enhanced chest and abdominal CT scan**	X		X	
Tissue specimen collection	X			
Blood sampling collection	X			
Plasma samples collection***	X			
Adverse Events	X	X	X	X

*Only for patients on anticoagulation therapy.

**Or Abdomen MRI and Chest CT if contrast-enhanced CT scan is contraindicated.

***Only during induction treatment, i.e after 4, 8 and 12 cycles of treatment, and at the time of PD)

2. INTRODUCTION

2.1 Premise

The present study is supported by EU Research and Innovation Union programme, Horizon 2020.

2.2 Study rationale

Colorectal cancer (CRC) is among the most frequent causes of cancer-related deaths. Around 50% of CRC patients with local or regional disease will develop distant metastases, while almost 21% of CRC patients present with metastases already at the time of diagnosis, with a 5-year survival of 13.8% [1]. Selection of the optimal first line treatment thus represents a crucial step in the therapeutic pathway of metastatic CRC (mCRC) patients, allowing a significant improvement of both objective response rate (RR) and overall survival (OS) thanks to the development and combination of different drugs, both cytotoxic (fluoropyrimidines, oxaliplatin, irinotecan) and biologic (cetuximab, panitumumab, bevacizumab). Among the combinatory regimens, those composed of oxaliplatin and irinotecan in combination with 5-FU led to the development of three cytotoxic doublet sand of the triplet chemotherapy regimen FOLFOXIRI, comprising all three cytotoxic drugs plus folinic acid [2]. In further support of mCRC first-line treatment, three molecularly targeted biologic agents were introduced: the anti-VEGF monoclonal antibody (mAb) bevacizumab [3] and the anti-EGFR mAbs cetuximab [4] and panitumumab [5]. These new drugs, together with others in more advanced metastatic settings, such as aflibercept, ramucirumab, regorafenib and TAS-102 have been shown to lead to a significant improvement in median survival in patients with unresectable mCRC. However, these new molecular target drugs, which are directed towards specific targets defined as "actionable", cause a heterogeneous tumour response, depending on the clinical characteristics and/or disease biology of the patient. Depending on the tumour mutational status, therapies able to specifically target dysregulated molecules are routinely used in combination. However, it is known that a percentage of KRAS or NRAS WT patients is not responsive to EGFR targeted therapy, leaving to hypothesize that additional mediators could be involved in the dysregulation of molecular mechanisms leading to tumour initiation and development. Indeed, results from a retrospective analysis of two randomized clinical trials showed that in patients with KRAS wild-type mCRC, those with left-sided tumours treated with targeted chemotherapies had markedly better progression-free survival (PFS), overall survival (OS), and objective response rates (ORR) than patients with right-sided primary tumours given the same treatments. Therefore, left- or right-sided malignancies are phenotypes of different molecular patterns.

Understanding the mechanism of sex-related biological factors in affecting the site of tumour formation, given that right-sided colon cancer is associated with a poorer prognosis and is more common in women than men, is of outmost importance in determining both the choice of the better screening and treatment protocols as well as the incidence, mortality, and survival rate of CRC. Age is also an important parameter to consider since the risk of proximal large polyp transformation increases with age and female sex.

Currently, one of the most pressing issues is finding more effective ways canalize all efforts to select the right patients for the right therapy at the right time [6].

All these findings have prompted an extensive search for prognostic biomarkers that may aid in selecting mCRC patients, who might potentially benefit from novel combinatorial therapy. Moreover, growing emphasis has been put on clinical decision support systems based on artificial intelligence, in general, and on machines learning techniques, in particular.

2.2.1 Artificial Intelligence

In recent years, the approach to medicine has substantially changed under the pressure of a growing availability of EHRs (digital Electronic Health Records) and the demand to provide precision medicine. Oncology is one of the fields mostly demanding for precision medicine in a "big data" world, as highlighted in the 2016 report of the Blue Ribbon Panel of the Cancer Moonshot initiative that recommended to mine past patient data for predicting future patient outcomes and for minimizing cancer treatment's debilitating side effects [7]. However, the general problem of precision medicine is represented by the huge amount of clinical variables to consider in order to extract knowledge from the growing volumes of digital data and highlights the urgent need for a new generation of computational theories and tools [8].
In this context, it was recently hypothesized that AI would be a solid instrument to build a predictive tool for VTE (Venous Thromboembolism) risk assessment in chemotherapy-treated cancer outpatients. Thus, a combined approach of Kernel Machine Learning (KML) and Random Optimization (RO) techniques was applied to design and validate a set of VTE predictors capable of exploiting significant patterns in routinely collected demographic, clinical and biochemical data. The algorithm was devised using a training set, and a testing set was used to compute the final performance of our risk predictors [9]. Moreover, a validation set was used to internally validate the approach used [10]. Customized and evidence-based management of patients on the basis of computerized systems, could provide a real-time VTE risk calculation guiding clinicians in the decision making process [11]. Besides, in the application of predictive analysis techniques in health sectors, the use of Big Data sources represents a relevant factor in terms of effectiveness and cost-efficacy towards a personalized medicine-based approach [12; 13]. The creation of a platform for mining knowledge and of learning health systems capable of delivering informative clinical evidence will ensure predictive models of quality are obtained [13].

Artificial Intelligence (AI) and Machine Learning (ML) have been used to diagnose and classify cancer for nearly 20 years, but only a few studies have investigated their relevance in cancer prognosis [14]. In particular, ML or semi-supervised learning techniques was recently applied to develop models for breast cancer (BC) progression and survivability. Was recently demonstrated the potential of a semi-explainable decision support system (DSS), based on Multiple Kernel Learning (MKL) [15], that can be adapted to different medical problems [9;16] and gives the possibility to inspect the learned model. The model combines a support vector machine (SVM) [17, 18, 19] algorithm and random optimization (RO) [20]. Hence, it can offer an explanation on how routinely collected demographic, clinical and biochemical data are important in predictions.

2.2.2 REVERT-AI

In the context of developing predictive models, REVERT-AI is based on Multiple Kernel Learning (MKL) and combines Support Vector Machines (SVM) and Random Optimization (RO). The model is built on the standardized Machine Learning Platform KELP. Moreover, REVERT will include other Machine Learning Systems: WEKA for all the algorithms and PyToch for Deep Learning. REVERT-AI is capable of exploiting significant patterns in routinely collected demographic, clinical and biochemical data and allowed the design of a clinical decision support system (DSS). The results from the retrospective analysis of all data concerning already treated mCRC patients, will serve to build an AI-based profile capable to identify "good" or "poor"

responders to therapy. The availability of both solid and liquid tumour biopsies will allow to perform NGS analysis to achieve the biomolecular fingerprint of individual patients. These two important pieces of information – the clinical data and the biomolecular fingerprint – will be used to build a mCRC dedicated ML model based on the already available RISK model, possibly capable of identifying those patients who may not benefit from first line therapy, with the double benefit of being both prognostic and predictive of a worst clinical outcome. The allocation to the best treatment option will be performed following the indication of each patient's profile as emerged from the computational framework platform based on AI, and developed by other Operative Units involved in the REVERT study in its whole. The information retrieved with the ML approach, will be used to early identify those molecular patterns that could play an active role in mCRC management.

In the global context of the European REVERT project, the main objective is to develop an improved and innovative model of combinatorial therapy – based on personalised medicine – that identifies the most efficient and cost-effective therapeutic intervention for patients with unresectable metastatic colorectal cancer (mCRC). The specific objectives are:

- To build a sophisticated computational framework based on AI to predict patient responses to combinatorial therapies for unresectable mCRC care, based on the analysis of new, potential prognostic biomarkers (e.g., gene mutations, epigenetic changes, gene expression profiling signatures) as molecular predictors of therapeutic response, treatment resistance or disease outcome, in comparison with established therapeutic interventions;
- To assess the significance of biomarkers and molecular predictors of therapeutic response or disease outcome in subjects with unresectable mCRC using an innovative AI-model;
- To screen and characterize molecular mechanisms of already approved drugs as potential novel candidates for combination therapy to effectively target metastatic cancer by using patient tumour-derived organoids models;
- To validate the health, economic and social impact of the model.

As requested by the European call itself, the REVERT project has been designed to analyses the response to already authorized standard of care chemotherapy and associated molecular drugs, to treat patients with mCRC. These combinatorial therapies are equally efficacious. We can reassure that no other regimen, other than the standard one, will be employed. The AI-driven decision will consist in identifying those patients in which a particular feature, emerged from the AI evaluation, might be better treated with a certain sequence rather than another. The Investigator in this way can use the capability of the AI to take into account all the variables to permit him/her to choose the best combinatorial therapy and decide in this way to enroll or not in the study.

2.3 Risks and benefits

2.3.1 Risks

No critical issues are expected in the study, since all the administered therapies employ already authorized drugs (and their combination) as per standard good clinical practice and according to AIOM, ESMO, NCCN and ASCO guidelines.

2.3.2 Benefits

Clinical evidence demonstrates the benefits of AI that may add significant and sustained benefits to personalized medicine at no additional cost to the health system. Oncology is a field that could significantly benefit from a precision medicine-based approach, both in the development of targeted therapies, which represent a key to successful patient treatment, and in other clinical contests, in order to improve treatment delivery and clinical outcome.

Given the above mentioned considerations, the risk-benefit profile for the conduct of this study appears to be favourable.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to collect predictive preclinical data and integrate them with those derived by a retrospective study in mCRC patients with the aim of using AI software to support physicians in choosing the most effective treatment.

3.2 Secondary Objectives

The secondary objectives are:

1. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy evaluated by the overall survival (OS) in patients with mCRC.
2. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy evaluated by the clinical response to the treatment, achieving a complete (CR) or partial (PR) response, according to RECIST 1.1 criteria.
3. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy evaluated by the decrease in the sum of diameters of RECIST target lesions (Early Tumour Shrinkage).
4. The assessment of the efficacy of predictive clinical data, in choosing the best approved combinatorial therapy on QoL, evaluated by the EORTC QLQ-C30 questionnaire.

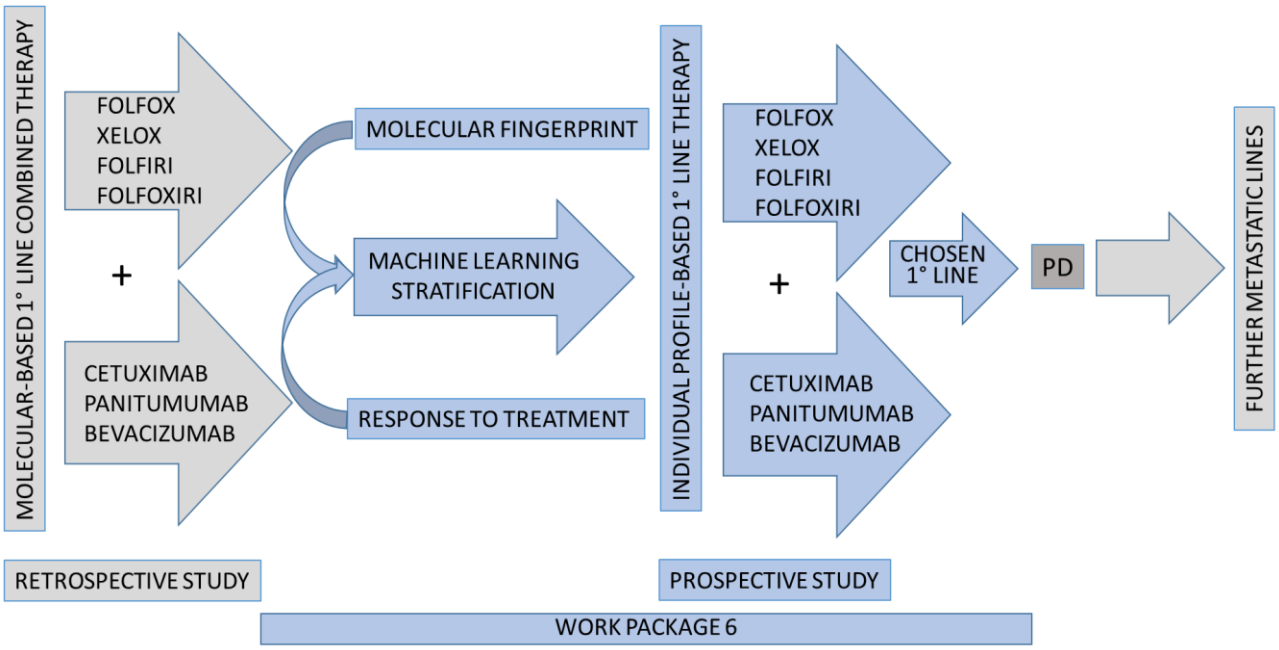
4. STUDY DESIGN

4.1 Study overview and plan

This is a clinical prospective, no- Profit, Interventional, Premarket Medical Device “early phase”, multicentre, single-arm study, based on collecting data on predictive biomarkers of mCRC patients, integrate them with the results of the retrospective evaluation of outcomes and profiles of historical mCRC patients previously treated in the Oncology Units in order to evaluate the efficacy of the best administered treatment. Results from retrospective evaluation, will serve to build an AI-based profile capable to identify “good” or “poor” responders to therapy. The Investigator in this way can use the capability of the AI to take into account all the variables to permit him/her to choose the best combinatorial therapy and decide in this way to enroll or not in the study.

All the administered therapies employ already authorized drugs (and their combination) as per usual standard of care and according to AIOM, ESMO, NCCN and ASCO guidelines. Following the first disease

progression (PD), 2nd line therapy will be at Investigator's choice. AI model is a software based on algorithm defined as Medical Device Class IIa, no CE Marked.



The Principal Investigator's site will be located in Italy, the other involved study sites are indicated in the Site List provided separately from the present document. The number of patients to be included is 106 (69 WT (wild type), 37 RAS mutated (mut), male and female, age ≥18 years, affected by mCRC.

Study length is planned to be about 24 months. The end of study is defined as the time when all enrolled patients will have experienced evidence of disease progression or will be out of treatment as per protocol, toxicity, medical decision or patient's withdrawal.
The study consists of the following Visits:
- VISIT: Baseline Visit (within 28 days prior to first infusion, ±15 days);
- VISIT: Day 1 of Each Cycle until the end of the study;
- VISIT: Every 12 weeks from first day of cycle until the end of the study;
- VISIT: At the end of the study and after the evidence of PD.

5. STUDY POPULATION

5.1 Number of Patients

The eligibility criteria described in this study protocol are designed to identify patients for whom study treatment is considered appropriate. All relevant medical conditions should be considered when deciding whether a patient is suitable for enrolment in the study. Selection of patients' best treatment will be performed on the basis and in accordance with the profiles generated and elaborated by the AI platform. To this aim, 106 (69 WT, 37 RAS mut) unresectable mCRC patients afferent to the Oncology Clinical Units

involved in the study, who gave their signed informed consent to participate to the project, will be consecutively enrolled and a therapeutic strategy will be designed based on the choice of the best treatment defined by each individual's profile.

In WT patients, the 10-month-PFS rate is approximately 50% for conventionally chosen first-line regimens. The study will be looking for a 15% increase in the percentage of WT patients progression-free at 10 months when adopting the algorithm-driven treatment choice (i.e. improvement of 10-month PFS rate from 50% to 65%).

For RAS mut patients the 8- month-PFS rate is approximately 50% in case of conventionally chosen first-line regimens. The study will be looking for a 20% increase in the percentage of mut patients progression-free at 8 months with the algorithm-driven treatment choice (i.e. improvement of 8-month PFS rate from 50% to 70%).

5.2 Inclusion Criteria

All the following inclusion criteria must be met for a patient to be included in the study:

1. Signed and dated Informed Consent.
2. Age ≥ 18 years at time of Informed Consent.
3. Histologically- or cytologically-confirmed mCRC.
4. Assessed tumour EGFR pathway mutational status (K-RAS, N-RAS), BRAF, HER-2 neu, MSI.
5. Sufficient amount of representative tumour specimen (primary or metastatic, archival or newly obtained for confirmatory central laboratory testing of BRAF and KRAS mutational status.
6. Dihydropyrimidine dehydrogenase (DPD)before 5-FU infusion.
7. Eligibility to receive bevacizumab, cetuximab or panitumumab per locally approved label with regard to tumour RAS status.
8. Recurrence of disease after primary radical surgery and adjuvant therapy carried out > 6 months prior the present trial.
9. Evidence of measurable or evaluable non-measurable disease as per RECIST, v1.1
10. ECOG PS of 0 or 1.
11. Adequate bone marrow function characterized by the following at screening:
    a) Absolute neutrophil count (ANC) ≥ 1.5×10^9/L;
    b) Platelets ≥ 100×10^9/L;
    c) Haemoglobin ≥ 9.0 g/dL.
12. Adequate renal function characterized by serum creatinine ≤ 1.5 × upper limit of normal (ULN), or creatinine clearance ≥ 50 mL/min.
13. Adequate hepatic function characterized by the following:
    a) Serum total bilirubin ≤ 1.5 × ULN and < 2 mg/dL;
    b) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 × ULN, or ≤ 5 ×ULN in presence of liver metastases.
14. Female patients are either postmenopausal for at least 1 year, surgically sterile for at least 6 weeks, or must agree to take appropriate precautions to avoid pregnancy.
15. Males must agree to take appropriate precautions to avoid fathering a child from screening through follow-up.

5.3 Exclusion Criteria

Patients meeting any of the following criteria at screening will not be included in the study:

1. Prior hypersensitivity or toxicity to chemotherapy drugs suggesting an inability to tolerate the proposed treatment.
2. Patients should not be candidate for upfront resection of metastatic disease.
3. Symptomatic brain metastasis.
4. Leptomeningeal disease.
5. Known history of acute or chronic pancreatitis.
6. History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery).
7. Impaired cardiovascular function or clinically significant cardiovascular diseases.
8. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy.
9. Impaired hepatic function, defined as Child-Pugh class B or C.
10. Concurrent or previous other malignancy.
11. History of thromboembolic or cerebrovascular events ≤ 6 months prior to starting study treatment.
12. Concurrent neuromuscular disorder associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
13. Known contraindication to receive antineoplastic treatment at the planned doses.
14. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study.
15. Pregnancy, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test result, or lactating.
16. Participation to other clinical trial studies.

6. CRITERIA AND PROCEDURE FOR RANDOMIZATION

6.1 Treatment allocation

A therapeutic strategy will be designed based on the choice of the best treatment defined by each individual profile. The allocation to the best treatment option will be performed following the indication of each patient's profile as emerged from the computational framework platform based on AI, as developed in the retrospective analysis of the European REVERT project in its whole, in accordance with the results of new and enriched profiles common to patients defined either as "good" or "poor responders" as elaborated by a platform.

The platform allows the stratification of patients at risk according to their individual response to a treatment with already approved drugs. This will set the basis for developing a decision-support system that identifies relevant signatures within the molecular and clinical data of the patient.

The pre-clinical validation of the AI predictors performs retrospective-only case approaches on a) traditional clinical and biomolecular data, and b) innovative biomarkers analysed on selected collection of biological

samples obtained from "good" or "poor" responders and already available from the network of biobanks from participating clinical centres.

6.2 Randomization
Not applicable

6.3 Blinding
Not applicable

7. STUDY CONDUCT

7.1 Study Duration
Study length is planned to be about 24 months, starting after the tasks of other Units involved in the EUROPEAN REVERT study have been completed. The end of study is defined as the time when all enrolled patients will have experienced evidence of disease progression or will be out of treatment as per protocol, toxicity, medical decision or patient's withdrawal. A detailed list of the study assessments and related timeframes is reported in sections 7.2 (Detailed study plan) and 1.1 (Study Flow Chart). All the tests, procedures and exams will be performed as per usual standard of care.

7.2 Detailed Study Plan

7.2.1 VISIT: Baseline Visit (within 28 days prior to first infusion, ±15 days)
During the Baseline Visit, fulfilment of eligibility criteria will be verified. The following tests and procedures will be performed:

1. Informed Consent review and signature;
2. Medical history;
3. Physical examination (sex, weight, height);
4. Vital signs (blood pressure, heart rate);
5. Previous and concomitant treatments;
6. Disease history;
7. ECOG PS;
8. ECG;
9. Pregnancy test (when relevant);
10. Previous and Concomitant Treatments;
11. Inclusion/Exclusion Criteria;
12. Enrolment;
13. Complete blood examination as per current clinical procedure: blood count and differential, bilirubin (total and direct), AST, ALT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium, magnesium), International normalized ratio (INR)/Activated partial Thromboplastin Time (APTT), CEA, CA19.9;
14. EORTC QLQ-C30 questionnaire;
15. Contrast-Enhanced chest and abdominal CT scan, or Abdomen MRI and Chest CT if contrast enhanced CT scan is contraindicated;

16. Collection of a paraffin-embedded block of the primary tumour and/or metastases, or 10 slides5 μm-thick for immunohistochemistry and 10 slides 8 μm-thick;
17. Collection of blood and plasma samples.

7.2.2 **VISIT:** Day 1 of Each Cycle until the end of the study

The Visit have to be performed on day 1 of each Cycle, and to be repeated every 2/3 weeks depending by the therapy. The Cycles will be performed for all the duration of the study until the end of study defined as the time when all enrolled patients will have experienced evidence of disease progression or will be out of treatment as per protocol, toxicity, medical decision or patient's withdrawal. The following tests and procedures will be performed:

1. Partial blood examination: Blood count and differential, bilirubin (total and direct), serum creatinine, electrolytes (potassium, magnesium, calcium), INR/APTT (only for patients on anticoagulation therapy);
2. Physical examination (sex, weight, height);
3. Vital signs (blood pressure, heart rate);
4. ECOG PS;
5. EORTC QLQ-C30 questionnaire;
6. Report eventual Adverse Events and treatment toxicity.

7.2.3 **VISIT:** Every 12 weeks from first day of Cycle until the end of the study

The following tests and procedures will be performed:

1. Complete blood examination: Blood count and differential, bilirubin (total and direct), AST, ALT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium, magnesium), INR/APTT(only for patients on anticoagulation therapy); CEA, CA19.9;
2. Physical examination (sex, weight, height);
3. Vital signs (blood pressure, heart rate);
4. ECOG PS;
5. EORTC QLQ-C30 questionnaire;
6. Contrast-Enhanced chest and abdominal CT scan, or Abdomen MRI and Chest CT if contrast enhanced CT scan is contraindicated (the same technique used in the baseline assessment);
7. Collection of plasma samples (only during induction treatment, i.e. after 4, 8 and 12 cycles of treatment, and at the time of disease progression);
8. Report eventual Adverse Events and treatment toxicity.

7.2.4 **VISIT:** End of the study and after the evidence of PD

The following tests and procedures will be performed:

1. Physical examination (sex, weight, height);
2. Vital signs (blood pressure, heart rate);
3. ECOG PS;
4. EORTC QLQ-C30 questionnaire;

5. Report eventual Adverse Events.

8. TRIAL PROCEDURES AND ASSESSMENTS

8.1 Physical examination and vital signs

A comprehensive physical examination inclusive of vital signs measurements at rest (height, weight, blood pressure, heart rate) will be performed during all the study.

8.2 Electrocardiogram

An ECG, will be performed at Baseline Visit.

The electrodes will have to be placed in their usual positions, and any effort should be done in order to prevent the subject from moving during the acquisition.

8.3 ECOG Scale of Performance Status (ECOG PS)

The ECOG PS will be performed during all the study.

These scales and criteria are used by physicians and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
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.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
5	Dead.

8.4 Tumour assessments

Tumour assessments must include Contrast-Enhanced chest and abdominal CT scans (with oral/IV contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. If a CT scan for tumour assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. Tumour assessment will be performed at Baseline Visit, and at VISIT-Every 12 weeks from first day of cycle until the end of the study.

8.5 Tissue specimen collection

Will be performed at Baseline Visit. Patient is asked to provide an archival specimen from the Hospital in which he/she received surgery for his/her disease.

The collection of tissue specimens is mandatory for study entry. If tumour tissues will become available during the course of the study (metastasis biopsies), they will be collected too.

Blood and plasma sampling collection

Will be performed at Baseline Visit and at VISIT: every 12 weeks from first day of cycle until the end of the study.

Two 3ml EDTA tubes, one 3ml sodium citrate tube and two serum tubes will be collected at baseline, at re-evaluation and at the end of study. They will be labelled as REVERT - Patient Code- date and will be stored at -20°C until shipment to the Coordinating Centre.

Three 3ml EDTA tubes will be collected at any time during the treatment. They will be labelled as REVERT - Patient Code – Blood SNPs and will be stored at -20°C until shipment to the Coordinating Centre.

Blood and tumor samples will be stored and checked by the REVERT project partners at:

- BioBIM, Biobanca Interistituzionale Multidisciplinare, San Raffaele Pisana, Via della Pisana 235, 00166 Roma.
- IBBL, Integrated Bank of Luxemburg, 1, rue Louis Rech • L-3555, 3531 Dudelange, Lussemburgo.

8.6 EORTC QLQ-C30 Questionnaire

The EORTC QLQC30 will be performed during all the study.

It includes 5 functional scales (physical, role, emotional, social, and cognitive functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms (dyspnoea, sleep disturbances, constipation, and diarrhoea), and perceived financial impact. For the majority of the EORTC QLQ-C30 items a 4-point Likert-type response scale is used. The only exception is the global health status/QoL scale in which a 7-point Likert type scale is used. For ease of interpretation, all scales and individual item responses are linearly converted to a 0 to 100 scale. EORTC QLQ-C30 scores reported during the treatment will be also expressed as percentage of the scores reported at baseline.

9. TREATMENTS IN OBSERVATION

9.1 Treatments dosage and administration

The following non investigational medicinal products are those commonly employed in mCRC patients as per usual standard of care and according to AIOM, ESMO, NCCN and ASCO guidelines.

Eligible patients will receive either:

XELOX

- Oxaliplatin 100 mg/sqm iv over 2 hours, day 1;
- Capecitabine 750 mg/sqm/bid, day 2 to 15; if toxicities grade ≥2 do not occur, patients may subsequently receive capecitabine 1000 mg/sqm/bid, day 2 to 15 starting the second cycle based on investigator's choice; to be repeated every 3 weeks (21 days), for a maximum of 12 cycles, followed by maintenance with Capecitabine only.

FOLFOX

- Oxaliplatin 85 mg/sqm iv over 2 hours, day 1 in two-way with
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1 followed by
- 5-fluorouracil 400 mg/sqm iv bolus, day 1 followed by 5-fluoruracil 2400 mg/sqm 48h continuous infusion, starting on day 1; to be repeated every 2 weeks for a maximum of 12 cycles, followed by maintenance with 5-fluorouracil only.

FOLFIRI

- - Irinotecan, IV Infusion, 180 mg/m² in 90 min. day 1
- - Levofolinate, IV infusion, 200 mg/m² day 1
- - 5-Fluorouracil (5-FU) 400 mg/m² bolus followed by a 2400 mg/m² continuous infusion for 46 hours, cycles repeated every 2 weeks.

FOLFOXIRI

- Irinotecan 150 mg/sqm iv over 60 minutes day 1, followed by
- Oxaliplatin 85 mg/sqm iv over 2 hours day 1, in two-way with
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1 followed by
- 5-fluoruracil 2400 mg/sqm 48 h-continuous infusion, starting on day 1; to be repeated every 2 weeks for a maximum of 12 cycles followed by maintenance with 5-fluorouracil only.

In **Combinatorial Therapy** with either:

- Bevacizumab 7.5 mg/kg iv over 90 minutes, day 1; if the first infusion is tolerated, then subsequent infusions may be administered in 30 minutes;
- Cetuximab 400 mg/m2 initial dose (120-minute infusion), then 250 mg/m2 (60-minutes infusion) thereafter once weekly;
- Panitumumab 6 mg/kg iv over 60 minutes, day 1 (if the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes);
- Aflibercept 4 mg/kg iv (60- minutes infusion) to be repeated every 2 weeks but only as second metastatic line treatment.

Artificial Intelligence is a software based on algorithm defined as Pre-market Medical Device Class IIa.

9.2 Labelling and storage conditions

Not applicable.

9.3 Accountability/dispensing treatment And Compliance

Not applicable.

9.4 Concomitant medications

9.4.1. Allowed medications

Any medications (other than those excluded by the clinical protocol in the section 9.4.2 below) that are considered necessary for the patients' well-being and will not interfere with the trial medication may be prescribed during the study at Investigator's discretion.

The Investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of Informed Consent, in the appropriate section of the eCRF.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration and indication of each drug.

Hormonal contraceptives for females of childbearing potential are permitted.

9.4.2. Not allowed medications

The use of any of the medications listed above is not permitted during the study: Refer to the applicable SmPCs.

10. SAFETY AND MDVIGILANCE

A Comprehensive assessment of any apparent toxicity experienced by the participants will be performed throughout the course of the trial, from the time of the patient's signature of Informed Consent to the end of the observational period. Trial site personnel will report any Adverse Event (AE), whether observed by the Investigator or reported by the patient.

Adverse events will be recorded after the subject has signed the study Informed Consent to the end of the observational period.

All relevant details are provided in the following sections 10.1 – 10.5.

10.1 Adverse Event definition

An Adverse Event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as Adverse Events. Abnormal results of diagnostic procedures are considered to be Adverse Events if the abnormality:

- results in study withdrawal;
- is associated with a serious Adverse Event;
- is associated with clinical signs or symptoms;
- leads to additional treatment or to further diagnostic tests;
- is considered by the Investigator to be of clinical significance.

Adverse device effect (ADE): adverse event related to the use of an investigational medical device. In addition, this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

10.2 Serious Adverse Event

Adverse Events are classified as serious or non-serious. A Serious Adverse Event is any AE that is:

- fatal;

- life-threatening;
- requires or prolongs hospital stay;
- results in persistent or significant disability or incapacity;
- a congenital anomaly or birth defect.

All Adverse Events that do not meet any of the criteria for serious should be regarded as non-serious Adverse Events.

Serious adverse device effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance will be considered as device deficiency.
NOTE: Device deficiencies will also include device malfunctions, user errors, and inadequate labeling.

Unanticipated serious adverse device effect (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Note: All risks mentioned in the protocol and in the Informed Consent form are considered anticipated.

AE/ADE severity: For all AEs/ADEs including SAEs/SADEs in clinical trials, severity (or intensity) should be assessed and recorded. The assessment of severity is based on the investigator's clinical judgement. The CTCAE guideline displays Grades 1 through 5 with unique clinical descriptions of severity for each AE:

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

10.3 Adverse Event Reporting Period

The study period during which Adverse Events/ Adverse Device Effects must be reported is normally defined as the period from the initiation of any study procedures to the end of the study.
The Investigator/coordinator must report all AEs/ ADEs that occur throughout the study according to the appropriate procedures listed below. If the Investigator becomes aware of any possible Serious Adverse Event (SAE)/ Serious Adverse Device Effect (SADE), including death, he/she must report this event by phone and fax/email the SAE/SADE form to the study Sponsor within 24 hours of notification of the event.

10.4 Recording of Adverse Events

At each contact with the subject, the Investigator must seek information on AEs/ADEs by specific questioning and, as appropriate, by examination. Information on all AEs/ADEs should be recorded immediately in the source document, and also in the appropriate AE/ADE module of the appropriate e-CRF form. All clearly related signs, symptoms, and abnormal diagnostic procedures results should record in the source document, though should be grouped under one diagnosis.
All AEs/ADEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs/SADEs that are still ongoing at the end of the study period must be

followed up to determine the final outcome. Any SAE/SADE that occurs after the study period and is considered to be possibly related to the study should be recorded and reported immediately.

10.5 Reporting of Serious Adverse Events

The Pharmacovigilance will be under the control of Prof Mario Roselli, telephone number: +39 0620908190. A SAE/SADE form must be completed by the Investigator and faxed/emailed to the Study Sponsor within 24 hours. The Investigator will keep a copy of this SAE/SADE form on file at the study site. Report SAEs/SADEs by fax/email to:

FAX: +39 06 20903806
email: mario.roselli@ptvonline.it; mario.roselli@uniroma2.it

At the time of the initial report, the following information should be provided:

1. Study identifier;
2. Study Centre;
3. Patient number;
4. A description of the event;
5. Data of onset;
6. Current status.

Within the following 48 hours, the investigator must provide further information on the SAE/SADE in the form of a written narrative. This should include a copy of the completed SAE/SADE form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing SAEs/SADEs should be provided promptly to the Study Sponsor.

10.6 Contraception Requirements

All subjects of childbearing potential must practice effective contraception during the study. For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy.
- Post-hysterectomy.

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g. bilateral tubal ligation); intrauterine contraception/device; hormonal contraception, or any 2 barrier (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap).
-

For males:

- Effective male contraception includes a vasectomy with negative semen analysis at follow up or the use of condoms with spermicide.

11. STATISTICAL METHODOLOGY

11.1 Statistics analysis plan(ning) and power calculation

The prospective Premarket MD study will follow an exact single-stage trial design [21]. The retrospective algorithm-defining analysis will produce specific patient profile associated in particular to benefit of oxaliplatin vs irinotecan regardless of RAS/RAF mutational status, and to benefit of anti-VEGF vs anti-EGFR agents in RAS/RAF wild type patients.

Assuming that 10-month-PFS rate WT patients is approximately 50% for conventionally chosen first-line regimens (historical control, P0) [22], the phase II study will be looking for a 15% increase in the percentage of WT patients progression-free at 10 months when adopting the algorithm-driven treatment choice (i.e. improvement of 10-month PFS rate from 50% to 65%, P1).

The hypothesis to be tested will be H0, P < P0 vs H1, P > P1, where P will be the actual 10-month PFS rate of enrolled WT patients. Accepting a false-positive rate (alpha) of 5% and a false-negative rate(beta) of 20%, H0 will be refused and H1 accepted with a statistical power of 80% if at least 42 WT patients out of a total sample size of 69 enrolled WT patients will remain progression-free at 10 months.

A parallel study design has been conceived for RAS mut patients. For mut patients the 8- month- PFS rate is approximately 50% in case of conventionally chosen first-line regimens (historical control, P0) [23]. The same phase II study will be looking for a 20% increase in the percentage of mut patients progression-free at 8 months with the algorithm-driven treatment choice (i.e. improvement of 8-month PFS rate from 50% to 70%, P1).

For this subset of patients, the hypothesis to be tested will be H0, P < P0 vs H1, P > P1, where P will be the actual 8-month PFS rate of enrolled mut patients. Accepting a false-positive rate (alpha) of 5% and a false-negative rate (beta) of 20%, H0 will be refused and H1 accepted with a statistical power of 80% if at least 24 mut patients out of a total sample size of 37 enrolled mut patients will remain progression free at 8 months.

In total, the study will therefore plan to enrol 106 patients.

PFS, RR, OS and QoL will be described by Kaplan-Mayer curves and compared by log rank test. Data documented in this study and the parameters measured will be evaluated and presented using descriptive statistics, i.e. arithmetic mean, SD, minimum, median and maximum values for quantitative variables, and absolute and relative (%) frequencies for qualitative variables. All analyzes will be verified with parametric and non-parametric tests and accompanied by a two-dimensional factorial ANOVA. The statistics will be reported by group.

11.2 Study endpoints

11.2.1 Primary endpoint

The primary endpoint of the trial will be Progression Free Survival (PFS), including PFS1 and PFS2, defined as the time from enrolment to the first documentation of objective disease progression or death due to any cause, whichever occurs first. Documentation of disease progressive disease is defined as per RECIST 1.1 criteria based on investigator assessment. PFS will be censored on the date of the last evaluable on study tumour assessment documenting absence of progressive disease for patients who are alive, on study and progression free at the time of the analysis.

11.2.2 Secondary endpoints

1. Overall survival (OS), defined as the time from enrolment to the date of death due to any cause. For patients still alive at the time of analysis, the OS time will be censored on the last date the patients were known to be alive.
2. Response Rate (RR), defined as the percentage of patients, relative to the total of enrolled subjects, achieving a complete (CR) or partial (PR) response, according to RECIST 1.1 criteria, during the phases of treatment. The determination of clinical response will be based on Investigator reported measurements.
3. Early Tumour Shrinkage (ETS), defined as the percentage of patients, relative to the total of the enrolled subjects, achieving a >20% decrease in the sum of diameters of RECIST target lesions.
4. Quality of Life (QoL), will be measured using the EORTC QLQ-C30 questionnaire.

Data documented in this study and the parameters measured will be evaluated and presented using descriptive statistics, i.e. arithmetic mean, SD, minimum, median and maximum values for quantitative variables, and absolute and relative (%) frequencies for qualitative variables. The statistics will be reported by group.
Statistical analysis is performed in accordance to statistical principles for clinical trials (CPMP/ICH/363/96).

12. REGULATORY AND ETHICAL ISSUES

12.1 Compliance with Regulations Applicable To Clinical Trials

The study will be conducted according to the laws, regulations and administrative provisions relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medical device, as applicable by national legislation and EU Directives. The Investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with:

- The clinical trial protocol;
- The ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996);
- The National Comprehensive Cancer Network (NCCN) guidelines for colon-rectal cancer treatment;
- European Society of Medical Oncology guidelines on gastrointestinal cancers;
- Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo, 4 April 1997) (Oviedo Bioethics Convention);
- Guidelines for Good Pharmacoepidemiology Practices from ISPE, Good Practices for Outcomes Research from ISPOR or Good Epidemiological Practice from IEA;
- Applicable regulatory requirements.

In particular, the Investigator must ensure that only subjects whose written Informed Consent has been properly given are included into the trial.

12.2 Informed Consent Form

An unconditional prerequisite for a subject's participation in the Study is the countersignature of the written Informed Consent form by the patient. The written Informed Consent to participate in the Study must be given before any Study-related activities carried out.

Adequate information must therefore be given to the patient by the Investigator before Informed Consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language will be provided by the Sponsor for the purpose of obtaining Informed Consent. In addition to providing this written information to a potential subject, the Investigators will inform the subject verbally of all pertinent aspects of the Study (the language used in doing so must be chosen so that the information can be fully and readily understood by laypersons).

The Informed Consent Form must be signed and personally dated by the participant and the Investigator. The signed and dated declaration of Informed Consent will remain at the Investigator's site, and must be safely archived by the Investigator. A copy of the signed and dated information and consent form should be provided to the participant prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favourable opinion. The agreed, revised information will be forwarded to each patient enrolled in the Study. The Investigator will explain the changes to the previous version.

12.3 Criteria for patient's withdrawal

Participants will be free to discontinue the trial at any time without giving their reasons. A participant must be withdrawn in the event of any of the following:

- withdrawal of the subject's consent.
- discovery of ineligibility
- administrative reasons

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible. In case of premature withdrawal from the trial, the Investigations scheduled for the last visit should be performed, if possible, with focus on the most relevant assessments. In any case, the appropriate eCRF section must be completed.

12.4 Withdrawal from the Investigational Medicinal Product

Not applicable.

12.5 Premature discontinuation of the trial

The whole trial may be discontinued prematurely in the event of any of the following:

- Progression disease;
- Out of treatment as per protocol;
- Toxicity;
- Investigator's decision
- Patient's withdrawal.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations. The whole trial may be terminated or suspended upon request of Health Authorities.

12.6 Definition of end of the trial

The study will terminate once all the enrolled participants will have performed the VISIT- End of the study and after the evidence of PD.

12.7 Regulatory Authorities and Ethics Committee (EC)

Before starting with the study operations, the clinical protocol must be authorized/approved in writing by an appropriate Regulatory Authority/ ECs. Any amendments to the Protocol or subsequent changes to the Informed Consent as a result of changes to the Protocol, must be approved by the Regulatory Authority/ ECs. Records of the EC review and approval of all documents pertaining to this study must be kept on file by the Investigator and are subject to Regulatory Authorities inspection during or after completion of the study. Unexpected and associated SAEs/SADEs must also be reported to the EC.

12.8 Protocol Amendments

Changes to the Protocol should only be made by an approved protocol amendment. Protocol amendments must be approved by the Sponsor, Regulatory Authority, Coordinator EC and/or each respective site's EC (if applicable), prior to implementation.

12.9 Patient Confidentiality

The REVERT software system will ensure the integrity of data and privacy management in respect to national rules, the EU's GDPR (Reg. EU 2016/679) and the EU Charter of Fundamental Rights. The Sponsor is concerned about the individual patient's privacy and, therefore, all patient data will be identified only by a subject identification number. The data will be blinded correspondingly in all data analysis.
However, it is required that the Investigator will permit, after receiving patient's approval, the study monitor, independent auditor or regulatory agency personnel (with or without the Investigator) to review that portion of the patient's medical record that is directly related to the study.

12.10 Clinical Trial Insurance

Adequate insurance coverage for all subjects of all countries participating in the trial will be supplied by the Sponsor. Insurance conditions will meet the relevant local laws and regulations.

13. DOCUMENTATION

13.1 Site Documents Required

Prior to the initiation of the study, the following items must be received by the Sponsor:

1. Letter of EC approval for the Protocol, amendments (if applicable), Informed Consent, advertisements (if applicable), Membership list;
2. A signed copy of the Protocol, amendments and notifications (if applicable);
3. The Investigator's Curriculum Vitae as well as the Curriculum Vitae of any Co-Investigator(s);
4. A list of the persons involved with the study and their signatures;
5. Study site agreement(s);
6. Health regulatory approval (where applicable);
7. Local laboratory certification and normal ranges (if applicable).

13.2 Site Documents Supplied by the Sponsor

Prior to the initiation of the study, the Sponsor will supply the Investigator with the following items in addition to the Protocol:

1. Procedure and credential for the access to the electronic Case Report Forms;
2. REVERT Platform;
3. Operations Manual (inclusive of e-CRF manual);
4. Model of Informed Consent;
5. Current version of the RCPs.

13.3 Maintenance And Retention Of Records

The Study will be conducted according to Good Clinical Practices. It is the responsibility of the Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. All original subject files (medical records) must be stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator will be instructed to consult with the Sponsor before disposal of any study record and to notify the Sponsor of any change in the location, disposition or custody of the study files.

13.4 Data management plan

A data management plan has been created within the EUROPEAN REVERT Study before data collection begins, describing all functions, processes, and specifications for data collection, cleaning, and validation. An ICT framework for data integration will also be implemented. The common knowledge representation model will be based on an ontological approach that will help to define and implement the conceptual model used to govern the common knowledge base. Innovative methodologies of ML, Natural Language Processing (NLP), Information Extraction (IE), Sentiment Analysis, Text Summarization, Classification, will be implemented to obtain methods for extracting information. Data anonymization and privacy management will be put into action with respect to the EU values and the Charter of Fundamental Rights of the European Union. The integrity of data entered in the database will be ensured and the tools (Keys, Indexes, Constraints and Triggers) to implement data integrity will be developed. In addition, customized software scripts to connect different database formats and automatically collect the data will be built and ran periodically.

High data quality standards will be maintained and processes and procedures will be utilised to repeatedly ensure that data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. Datasets and analytic programs will be kept on a secure server and archived according to each Centre's record retention procedures. The name of patients will not be recorded; a sequential identification number will be attributed to each patient registered in the trial. This number only will identify the patient and will be included in all electronic Databases. In order to avoid identification errors, patients' initials (maximum of 2 letters) and date of birth will also be reported on the Database. Investigators will guarantee, by means of a Confidentiality Agreement preventing the unauthorized disclosure of Confidential Information, that all persons involved in this study will respect the confidentiality of any information concerning the trial subject. All parties involved in this clinical trial will maintain the strict confidentiality to assure that neither the person nor the family privacy of the patient participating in the trial is violated; appropriate measures shall be taken to avoid the access of non authorized persons to the trial data. The processing of the personal data of patients taking part in the trial, and in particular regarding data concerning consent, shall comply with the MS local laws of each participating Medical Oncology Centre on privacy (e.g.

the Italian LD 127/2001) and with the European Directive on the Privacy of data (95/46/EC). The patient can withdraw consent whenever he wants and further data will not be collected, even if the already collected data will be used for the study's analyses.

13.5 Case Report Form (CRF)

Electronic CRFs (eCRFs) for individual patients will be used in the frame of this study. eCRFs are used to record study date and are an integral part of the study and subsequent reports. It is the Investigator's responsibility to ensure the accuracy and completeness of the data entered in the eCRFs. The data will be entered into a validated database. Database lock will occur once quality control procedure, and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

Source documents for this study such as the clinic chart or tests are to be maintained in a study binder. eCRFs, source documents and copies of test results must be available at all times for inspection by the study monitor, Sponsor, CRO and Regulatory Authority.

13.6 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's and parents' (or tutor's) full name,
- Date of birth,
- Sex,
- Height,
- Weight,
- Medical history and concomitant diseases,
- Prior and concomitant therapies (including changes during the trial),
- Trial identification (Sponsor's trial number according to clinical trial protocol),
- Date of subject's inclusion into the trial (i.e. date of giving Informed Consent),
- Subject number in the trial,
- Dates of the subject's visits to the site,
- Any medical examinations and clinical findings predefined in the clinical trial protocol,
- All Adverse Events/ Adverse Device Effects observed in the subject,
- Date of subject's end of trial,
- Date of and reason for early withdrawal of the subject from the trial.

It must be possible to identify each subject by using this subject file. Additionally, any other documents containing source data must be filed (e.g., ECG trace and report, completed scales and questionnaires). Such documents must bear at least the subject number and the date when the procedure was performed.

13.7 Monitoring

The study monitor will be responsible for coordinating the activities of the study monitoring team to ensure adherence to ICH guidelines and the Standard Operating Procedures. Experienced Monitors from CRO will

be trained to monitor the study. The Monitors will be trained on ICH GCP Guidelines, trial-specific SOPs, study protocol and the study monitoring convention.

These visits are for the purposes of verifying adherence to the Protocol and the completeness and exactness of data entered on the eCRF. The study monitor will verify eCRF entries by comparing them with the primary source document which will be made available for this purpose. The Monitor will review the progress of the study with the Investigator and other site personnel on a regular basis. At the end of the study, a Closure Monitoring Visit will be performed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the Monitor to review CRFs and relevant source documents. The Coordinator and/or Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits will be made available by the Investigator.

13.8 Protocol Modifications

The procedures defined in the Protocol and in the e-CRFs will be carefully reviewed to ensure that all parties involved with the study fully understand the Protocol. In order to ensure the validity of the data, with minimal exceptions, no deviations from the Protocol may be made unless waived by the Sponsor depending upon the magnitude of the deviation. If the issue is broad enough to warrant revision of the Protocol, such revisions must be submitted to and have approval in writing from the Sponsor, and the EC prior to implementation at the site.

13.9 Audit/Inspection

The study may be inspected by regulatory agencies. These inspections may take place at any time during or after the study and are based on the local regulations. The purpose of the Audit is to determine whether or not the study is being conducted and monitored in compliance with recognized GCP guidelines or laws and study protocol.

14. USE OF INFORMATION AND PUBLICATION

14.1 Confidential Information

Confidential information refers to any information provided by the Sponsor. This includes, but is not limited to, the clinical protocol (and protocol amendments, if any), eCRFs, assay or study methods and basic scientific data. Any data collected during the study should also be considered as confidential.

14.2 Clinical Trial Report

After completion of the trial, a clinical trial report according to MDRD will be written by the Sponsor.

14.3 Publication policy

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor and by the Coordinator of the REVERT project, as per EU agreements.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

15. INVESTIGATOR'S AGREEMENT

I have carefully read the foregoing Protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this Protocol and will attempt to complete the Study within the time designated.
I will provide copies of the Protocol and all other information to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drugs and conduct of the study.
I agree to keep records on all subject information (CRFs, shipment and drugs return forms and all other information collected during the study) in accordance with GCP and local regulations.

_____	_____
Investigator's signature	Sponsor signature
Date: _____	Date: _____
Name _____	Name_____
(please use capital letters or stamp)	(please use capital letters or stamp)

PROTOCOL TITLE
REVERT – taRgeted thErapy for adVanced colorEctal canceR paTients

16. LIST OF APPENDICES

16.1 Declaration of Helsinki

16.2 EORTC QLQC30 Questionnaire

16.3 ECOG PS

17. REFERENCE

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INCIDENTAL FINDINGS

1. Regarding the incidental findings in the retrospective study, the communication, the subsequent approach and the diagnostic/therapeutic decisions are regulated according to the paragraph included in the Informed Consent, which the patient agrees and signs before being recruited into the study. This is in accordance with the regulation for Patient Rights.

2. Concerning the prospective study, a specific Incidental Policy has been defined and agreed upon by all Consortium partners. Based on that, the informed consent form will require patients to sign whether:

- I agree to receive information about clinically relevant incidental findings not related to colorectal cancer disease.
- I agree to my GP/treating physician being contacted in relation to these clinically relevant incidental findings not related to colorectal cancer disease.

The document is herein attached.

Incidental Findings Policy

I. SCOPE

This Policy sets forth REVERT policy with respect to planning for and handling incidental findings during the course of the research protocol conducted by REVERT investigators that include biological sample evaluation and imaging procedures.

II. BACKGROUND

For purposes of this Policy, an incidental finding (IF) is a finding concerning an individual research subject that has potential health importance and is discovered in the course of conducting research, but is beyond the aims of the study.

Advances in technologies have produced new diagnostic capabilities with improved accuracy and potential new treatment mechanisms. As a result, there has been an increased use of both genetic and imaging techniques in human subjects research. In the course of the REVERT project, investigators may gather information about a subject that is not pertinent to the research study, but may have important clinical implications for the subject. The incidence of IFs is widely variable, depending on a number of factors.

An IF may be discovered not only in collecting and analyzing research samples and data during a study, but also in screening procedures to determine whether a potential subject qualifies for inclusion in the study population or in collecting baseline physiological information.

III. POLICY

This Policy applies only to the REVERT protocol investigators in which the genetic and biological analyses and the imaging procedures produce results that provide anatomic or physiological data of the type that is used in clinical diagnosis or treatment. High density images include MRI scans, CT scans, PET scans and Xrays.

An IF of Clinical Significance in the context of this Policy is either a Class A IF or a Class B IF. A Class A IF is one that reveals a condition that is likely to be life-threatening or severe, while a Class B IF is not necessarily immediately life threatening or severe, but is likely to be deemed by a subject to be important to his/her health. All Ifs will be notified to the PI as soon as possible but no later than two weeks following receipt of the analysis/imaging result.

Communication with the subject is the responsibility of the PI. However, if the PI is not a physician or is otherwise not qualified to discuss the IF with the subject, such communication should include a medical professional (including a resident or fellow) who is knowledgeable about the type of IF found and who is experienced in communicating sensitive medical information. Communication may be initially verbal, followed by a written communication. The subject should have the opportunity to have questions answered. The time frame of the initial communication with the subject should be consistent with the suspected severity of the finding. Investigators should obtain appropriate contact information for the subject. If an IF of Clinical Significance is found, the subject will decide whether to proceed with further examinations, tests, and/or treatments and the subject or his/her insurer will bear any costs of such further examinations, tests or treatments. At the time of an IF of Clinical Significance has been reported to the PI, the PI should provide the IRB with the following information: the subject's study number, the date of the finding and a description of the IF of Clinical Significance. In addition, the PI should indicate the date of communication with the subject and the outcome, if known, for each IF of Clinical Significance.

IV. IF Management Plan:

• Incidental Findings will be addressed specifically in consent forms with disclosure of a pathway for follow up and cost of handling this finding

• It is the responsibility of the research team to make the subject aware of a potential finding

• The subject or surrogate is first in line for disclosure of an incidental finding. Incidental findings will be discussed by the PI.

• Relevant study documentation will be provided to a care provider if elected by the subject.

• Verbal communication of an incidental finding should be done in a timely fashion, and documented in writing by a letter that draws on the informed consent language.