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Regorafenib assessment in refractory advanced colorectal cancer: RegARd-C study protocol

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ABSTRACT

Introduction: Regorafenib was recently approved for patients with pretreated advanced colorectal cancer (aCRC), despite a moderate improvement of the patients' outcome, and significant toxicities. Based on previous studies showing that early fluorodeoxyglucose-positron emission tomography (FDG-PET)-based metabolic response assessment (MRA) might adequately select patients unlikely to benefit from treatment, the RegARd-C trial uses early MRA to identify likely non-responders to regorafenib in a population of patients with aCRC and guide a comprehensive evaluation of genomic and epigenetic determinants of resistance to treatment.

Methods and analysis: RegARd-C is a multicentric prospective study. Its primary objective is to identify non-benefitters from regorafenib given at 160 mg/day, 3 weeks out of 4 in a population of patients with pretreated aCRC. Baseline PET is repeated at day 14 of the first treatment course. MRA is blinded for the investigators. Overall survival (OS) is the primary end point and will be correlated with metabolic parameters and (epi)genetic alterations assessed from tumour and serial blood samples. A target sample size of 105 evaluable patients (70 as derivation set and 35 as validation set), is considered as sufficient to validate an expected HR for OS of metabolic responders compared to metabolic non-responders significantly <1 (with 80% power and 1-sided 5% α in case of a true HR$\leq$0.59 and a responders rate of 47%).

Ethics and dissemination: The study was approved by the Institut Jules Bordet's competent ethics committee and complies with the Helsinki declaration or the Belgian laws and regulations, whichever provides the greatest protection for the patient, and follows the International Conference on Harmonisation E 6 (R1) Guideline for Good Clinical Practice, reference number CPMP/ICH/135/95. The protocol and the trials results, even inconclusive, will be presented at international oncology congresses, and published in peer-reviewed journals. Genomic and epigenetic data will be made available in public open data sets.

Trial registration numbers: EudraCT number: 2012-005655-16; ClinicalTrials.gov number: NCT01929616.

Strengths and limitations of this study

- Prospective multicentric academic trial with a non-randomised design.
- Inclusion/exclusion criteria compatible with the study objectives (to determine biomarkers predictive of the patient's outcome under treatment by regorafenib monotherapy in metastatic colorectal cancer refractory to all known medications with fluorodeoxyglucose-positron emission tomography (FDG-PET)-assessable diseases).
- Imaging network: all PET-CT centres accredited according to European Association for Nuclear Medicine Research Limited (EARL), with central review and quality control by an Imaging Core laboratory of the FDG-PET/CT data.
- Prospective collection of biological specimens (frozen and paraffin-embedded tissue blocks, sequential frozen plasmatic samples for circulating tumour DNA (ctDNA) research, whole blood) for comprehensive genomic and epigenetic analysis guided by metabolic imaging definition of a responding/non-responding disease.
- Statistical hypothesis foreseeing an exploration set and a validation set and allowing the validation of a metabolic response hypothesis based on previous work taking into account the tumoral heterogeneity in response.

INTRODUCTION

Colorectal cancer

With a 35/100 000/year incidence rate in the developed world, colorectal cancer affects about 150 000 people per year in Western Europe.[1] About half of the patients will develop a metastatic disease, carrying a grim prognosis if unresectable with curative intent. Progress in chemotherapy has been substantial during the past decade, allowing rare but well-advertised secondary resections of primarily unresectable metastatic disease. In the palliative setting, chemotherapy aims essentially at extending survival and the use of all available drugs (fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, antiendothelial

growth factor receptor (EGFR) antibodies) either successively or concomitantly has increased the median OS of patients to more than 25 months.[2–6] However, no single drug or any combination is able to cure metastatic disease, and the tumour will eventually become resistant to all known medications, leading to the patient's death.

Regorafenib

Regorafenib (BAY 73-4506) is a novel oral diphenylurea-based multikinase inhibitor, shown in preclinical studies as a potent inhibitor of several angiogenic and stromal receptor tyrosine kinases (RTKs), including a VEGFR-1, VEGFR-2, VEGFR-3, a PDGFR-β, a FGFR-1 and TIE2. In addition, regorafenib inhibits various oncogenic RTKs (c-KIT and RET) and intracellular signalling kinases (cRAF/RAF-1, B-RAF and B-RAF V600E mutant). The exact mode of action of regorafenib, however, remains unknown, even if it is probably associated with antiangiogenic and antiproliferative effects, mostly through RAF inhibition. Data from a phase I trial[7 8] has established the recommended dose at 160 mg/day 3 weeks out of 4. A recent phase III trial in aCRC, refractory to all known medications (CORRECT),[9] has randomised 760 patients between regorafenib (n=505) and placebo (n=255), showing a small but statistically significant advantage for OS (median 6.4 months vs 5 months, one-sided p value 0.005) and progression-free survival (PFS; median 1.9 months vs 1.7 months, one-sided p value <0.000001)) for regorafenib. This drug has the potential to become a standard therapy for the treatment of patients with mCRC who have been previously treated with all approved therapies. Nevertheless, the toxicity of this medication is important next to the palliative situation in which it was developed. Both the limited survival benefit and the clinically meaningful toxicity highlight the need to develop tools able to quickly identify the patients unlikely to benefit from the treatment in order to spare them from unnecessary side effects.

Early FDG PET-CT

Standard radiological response measurements (RECIST criteria, modified RECIST, WHO) rely entirely on measuring the size of the tumour with CT, ultrasound or MRI, and are only applicable under restrictive conditions (well-defined lesions, adequate minimum size, at least 6 weeks of chemotherapy). Response rates in advanced solid tumours correlate poorly with other patient outcomes, such as PFS and OS.[10 11] Several techniques with the potential to detect early response are emerging: serial FDG PET-CT, dynamic MRI (DCE-MRI) and diffusion MR techniques, and circulating tumour cells (CTCs). Among these, FDG PET-CT is the most studied and promising technique. It is widely available in Belgium, and its value in detecting early metabolic changes predictive of later outcome is currently being assessed.[12 13] Recent data suggest that use of serial FDG PET-CT imaging to assess tumour metabolism can reliably detect refractory disease. Our research group prospectively studied 41 patients with mCRC undergoing first-line or second-line chemotherapy.[13] Serial FDG PET-CT was performed at baseline and 14 days after the first cycle of chemotherapy. The metabolic changes were compared with the morphological response evaluated by CT according to RECIST criteria. A RECIST response was observed in 10/23 (43%) PET responding patients and in 0/17 (0%) PET non-responding patients (p=0.002). The metabolic assessment's predictive performance for RECIST response was 100% for sensitivity (95% CI 69% to 100%), 57% for specificity (95% CI 37% to 75%), 43% for positive predictive value (95% CI 23% to 66%) and 100% for negative predictive value (95% CI 80% to 100%). Comparing patients who had metabolic responses with those who did not, the HR was 0.28 (95% CI 0.10 to 0.76) for OS and 0.57 (95% CI 0.27 to 1.21) for PFS. This suggests that FDG PET-CT may be used for the early detection of non-responding patients. Additionally, we conducted another FDG PET-CT driven metabolic study with a similar design in 92 patients with advanced refractory CRC treated with a combination of sorafenib and capecitabine (SoMore study).[14] The aim of this metabolic study was to identify patients unlikely to benefit from the therapy. The metabolic analysis of this population will be used as a model for regorafenib. The most important finding related to this metabolic analysis was the identification of a prognostic value for early metabolic homogeneous response.[15] Indeed, among 79 patients who underwent baseline PET examination as well as day 14 examination, 37 patients (47%) were found responding homogeneously in all their lesions to treatment with combined sorafenib–capecitabine. These patients had prolonged survival after day 14 compared to all the other patients (HR=0.59, 95% CI 0.37 to 0.96, p=0.03).

Genomic and epigenomic assessments

Recent advances in next generation sequencing (NGS) technologies and data analysis have enabled patients' specific genomic/somatic alterations in their cancer genome to be explored in a relatively timely, costly and clinically efficient manner. The design of the RegARd-C study provides a unique opportunity to identify and characterise molecular factors that could predict PFS and OS for patients treated with regorafenib. Metabolic imaging could enable us to define the subpopulations of patients unlikely to benefit from this medication, thereby increasing the likelihood of finding determinants of resistance to therapy. Molecular translational research could also provide tools to distinguish patients who will or will not benefit from therapy, for instance by analysing the genetic and epigenetic differences between the metabolically non-responding patients and the remaining subpopulation.

Moreover, as tumour cells liberate naked DNA (circulating tumour DNA, ctDNA) into the bloodstream after necrosis or apoptosis, we will investigate whether tumour-specific rearrangements can be detected in

plasma, which will be used as 'liquid biopsy'. Although 'liquid biopsies' are minimally invasive and may represent a molecular assessment of the overall cancer, the detection of ctDNA still has some difficulties that we will take into account: the distinction between ctDNA and cell-free DNA and the very low proportion of ctDNA which may hinder its exact quantification.

Aim of the study

RegARd-C aims at identifying, in a population of patients bearing advanced, refractory CRC, those who draw no benefit from treatment with regorafenib. OS will be used as a primary end point. Covariates that will be analysed in relationship to OS will be metabolic parameters obtained at baseline and very early following treatment initiation as well as genetic, epigenetic and molecular aberrations (before and after treatment) assessed from tumour biopsies and serial blood samples, in addition to known clinical and pathological factors. The molecular aberrations will be investigated using gene expression profiling, RNA and exome sequencing, and methylation profiling of the tumour biopsies and repeated blood samples taken during therapy.

METHODS AND ANALYSIS

Study design

The study was designed as a single-arm, prospective, non-randomised, non-comparative, open label phase II trial, with all patients being accrued in one stage. No early stopping rules are used. Written informed consent has to be obtained by an investigator from the patient before any screening and inclusion procedure. An FDG PET-CT will be performed at baseline (D-7-D0) and repeated after 14–17 days from start of the first cycle. The clinicians will remain blinded to the assessment of FDG PET-CT response. Clinical and biological evaluation will be made every cycle, starting at day 28 of the second cycle. RECIST 1.1-based radiological assessment (CT or MRI) will be made every two cycles, starting at day 28 of the second cycle. Treatment will be continued until disease progression, unacceptable toxicity or any other reason (study withdrawal, loss to follow-up, death…; see figure 1 for an overview of the study design).

Study organisation-role of the coordinating centre

The role of the coordinating centre (CC) is to coordinate the trial in all participating centres and to work with all study investigators and research staff:

- To collect and clean clinical trial data.
- To monitor the safety and timely study progress.

The CC is responsible for the clinical trial administration, trial progress, data management including database design and data cleaning, statistical analysis, safety handling, IT support, drug supply, sample collection and manuscript preparation.

The CC includes the principal investigator (AH), the principal coinvestigator (AD), the nuclear medicine principal investigator (PF), the research administration staff, the biostatistician (MPa), programmers, the study leader (RH), the data manager (AK), consultants, the research nurse (FH), the administrative support staff (JV) and the monitor (SJ).

For RegARd-C, there is no end point adjudication committee or steering committee.

Objectives

To identify in a population of patients bearing advanced, refractory CRC those unlikely to draw a substantial benefit from treatment with regorafenib. OS will be used as the primary end point.

Secondary objectives are to (1) analyse PFS and response rate (RR) in relationship to the same covariates as for OS, (2) assess regorafenib efficacy (OS, PFS, RR) and safety profile in this study population, (3) assess the disease control rate (DCR=Complete response (CR) + partial response (PR) + stable disease (SD)), (4) compare the relative benefit (OS, PFS) of regorafenib according to the history of treatment with bevacizumab and (5) validate the relationship that was found, in a previous study[14] conducted in the same patient population treated with sorafenib and capecitabine, between OS and early metabolic consistent response in all the patient's lesions.

Patient selection criteria

Inclusion criteria

Participants must

- Have histologically proven adenocarcinoma of the colon or the rectum that is metastatic or unresectable and for which standard treatments do not exist or are no longer effective. The tumour should be refractory to all standard chemotherapy agents (fluoropyrimidines, irinotecan and oxaliplatin) and anti-EGFR monoclonal antibodies in case of RAS wild type (cetuximab or panitumumab) administered before study entry. Patients treated with oxaliplatin in an adjuvant setting should have progressed during adjuvant therapy or within 6 months of completion of this treatment. Patients who do not strictly meet these criteria but for whom further treatment with oxaliplatin would be prohibited (for instance, allergic reaction, residual neurotoxicity grade ≥2) are allowed for inclusion. Prior treatment with bevacizumab and/or aflibercept is allowed but not mandatory;
- Have signed written informed consent (approved by an Independent Ethics Committee (IEC) and obtained prior to any study specific screening procedures);
- Be aged 18 or older;
- Have a life expectancy of greater than 12 weeks;
- Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤1;
- Have normal organ and bone marrow function as defined below: leucocytes > 3000/µL, with an absolute neutrophil count >1500/µL, platelets >100 000/µL, haemoglobin≥9 g/dL, total bilirubin ≤1.5×institutional

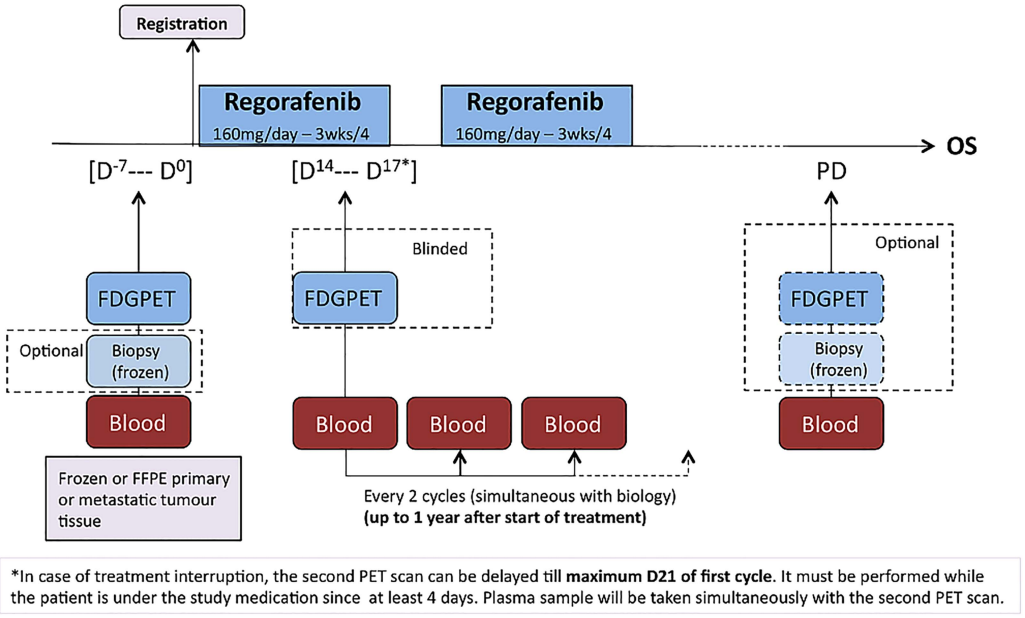

Figure 1 Study design. FDG PET, fluorodeoxyglucose positron emission tomography; FFPE, formalin fixed paraffin embedded; OS, overall survival; PD, disease progression.

upper limit of the normal (ULN), aspartate aminotransferase/alanine transaminase/alkaline phosphatases (P-Alk) levels ≤2.5×institutional ULN (≤5× institutional ULN in case of liver metastatic involvement), P-Alk levels ≤5×institutional ULN, international normalised ratio of prothrombin time (INR) ≤1.5×institutional ULN, creatinine within 1.5×normal institutional upper limits or creatinine clearance >30 mL/min;

- Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately;
- Presence of a previously collected frozen or formalin fixed paraffin embedded (FFPE) primary or metastatic tumour. Frozen tissue from the primitive tumour is preferred. If no archived tissue is available for the patient, the tissue should be collected freshly in the primary (preferentially) or a metastatic lesion before study entry;
- Presence of at least one metabolically measurable tumoral lesion on FDG PET-CT fulfilling the following criteria: Size ≥1.5 cm and FDG uptake above the background liver uptake.

Exclusion criteria

Excluded from the study are patients identified with any of the following conditions or characteristics:

- Prior treatment with sorafenib or regorafenib.
- Participants with previous cancer who are not disease-free for at least 5 years prior to registration, EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumours (Ta (Non-invasive tumour), Tis (Carcinoma in situ) and T1 (tumour invades the lamina propria)).
- Participants who have had chemotherapy or targeted therapy within 2 weeks prior to entering the study.
- Participants who have had a major surgery or radiotherapy within 4 weeks prior to entering the study.
- Unresolved toxicity higher than NCI-CTCAE (V.4.0) Grade 1 attributed to any prior therapy/procedure excluding alopecia and oxaliplatin-induced neurotoxicity ≤Grade 2.
- Participants receiving any experimental agents.
- Participants with known brain metastases.
- Bleeding diathesis, history of cardiovascular ischaemic disease or cerebrovascular incident within the past 6 months.
- Any haemorrhage or bleeding event NCI-CTCAE v.4 Grade ≥3 within 4 weeks prior to the start of study medication.
- Uncontrolled concurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure (New York Heart Association (NYHA) class ≥2), unstable angina pectoris (defined by angina symptoms at rest or new-onset angina started within the past 3 months), cardiac arrhythmia requiring antiarrhythmic therapy (β-blockers or digoxin are permitted).
- Uncontrolled hypertension (defined by systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg despite optimal medical management).
- Patients with phaeochromocytoma.
- Patients with seizure disorder requiring medication.
- Any history of organ allograft.
- Pleural effusion or ascites affecting respiration (NCI CTCAEv.4 Grade ≥2 dyspnoea).
- Uncontrolled diabetes.

- Non-healing wound, ulcer or bone fracture.
- Known history of HIV infection, or active hepatitis B or C or chronic hepatitis B or C requiring treatment with antiviral therapy.
- Interstitial lung disease with ongoing signs and symptoms.
- Renal failure requiring haemodialysis or peritoneal dialysis.
- Dehydration NCI-CTCAE v.4 grade>1.
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's ability to understand informed consent and participation in the study or evaluation of the study results.
- Known hypersensitivity to the study drug or excipients in the formulation.
- Any illness or medical conditions that are unstable or could jeopardise the safety of the patient and his/her compliance in the study.
- Pregnant or lactating women.
- Participants unable to swallow oral medications.
- Participants with thrombotic, embolic, venous or arterial events, such as cerebrovascular accident (including transient ischaemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of study treatment within 6 months of informed consent.
- Persistent proteinuria >Grade 3 NCI-CTCAE v4.0 (>3.5 g/24 h, measured by urine protein:creatinine ratio on a random urine sample).

Intervention to be measured

FDG-PET/CT imaging

Increased glycolysis is one of the hallmarks of cancer. FDG, an analogue of glucose labelled with a positron-emitting isotope of Fluor (F^{18}), is actively taken up in cancer cells of many tumour types. The positrons emitted by the FDG are detected by a dedicated camera, enabling the visualisation of cellular glycolytic activity.[16] The criteria listed below define the minimal requirements for metabolic imaging assessment of tumour response:

- Blood glucose <150 mg/dL at the time of FDG administration. Insulin or oral antidiabetic medication is not allowed on the days of FDG-PET/CT imaging.
- Delay between the first FDG-PET/CT imaging and the start of regorafenib ≤7 days. The second FDG-PET/CT imaging is performed on day 14 (ideal range: day 14–17). In case of treatment interruption, the second PET scan can be delayed until maximum day 21 of the first cycle. It must be performed while the patient is under study medication since at least 4 days.

All participating FDG-PET/CT centres were required to obtain the FDG-PET/CT's EARL accreditation and keep it for the whole duration of the study.[17] All images are centralised by an imaging core lab with central quality control by an imaging expert and central review by two independent reviewers. The results of the metabolic assessment remains blinded for the clinical investigator, and will follow a predetermined 3-step methodology previously described.[13 15]

Translational research genomic analysis

Blood samples for plasma preparation (2×9 mL for each time point) will be collected (and frozen) at baseline (D-7↔D0) and simultaneously with the second PET. An extra 9 mL whole blood sample will be collected at baseline in order to distinguish somatic from germline mutations. Plasma samples will also be obtained every two cycles, starting from the first cycle and (simultaneously with biology) up to 1 year after the start of therapy. Moreover, a final plasma sample will be obtained at disease progression (see figure 2 for overview of sample collection). Optional fresh frozen tumour tissue from an FDG PET targetable metastatic or primary lesion will be obtained before study entry and at disease progression. Previously collected frozen or FFPE primary or metastatic tumour needs to be available at the study entry. The translational research group will study the genetic and epigenetic aberrations that are associated with the patient's outcome (PFS, OS) and with metabolic response after treatment with regorafenib. The molecular aberrations will be investigated using gene expression profiling, RNA and exome sequencing, and methylation profiling of the tumour biopsies and repeated blood samples taken during therapy.

Follow-up

Follow-up procedures, performed every 2 months, will include physical examination, vital signs and ECOG performance status, laboratory tests and blood samples for translational research analysis, as well as radiological assessment of the tumours.

According to the European Union (EU) Clinical Trial Directive for each participating EU country, the end of the study will be reached when the last visit under treatment protocol of the last subject for all centres has occurred. The patients will continue to be followed afterwards every 2 months till disease progression or death or refusal, whichever occurs first. Patients may be offered any further treatment available, at the investigator's discretion.

Statistical considerations

Analyses will be carried out looking at constructing signatures that are prognostic for OS as well as PFS and RR. Baseline data will be used for some models and all eligible patients (intent-to-treat population) will be included in these analyses. Models integrating data in the short follow-up after treatment will also be developed. In that latter situation, only patients having undergone the necessary examinations will be included in the analyses. Time zero for measuring time to event variables will be adapted and will be dependent on the timing of further examinations. Analyses will be adjusted

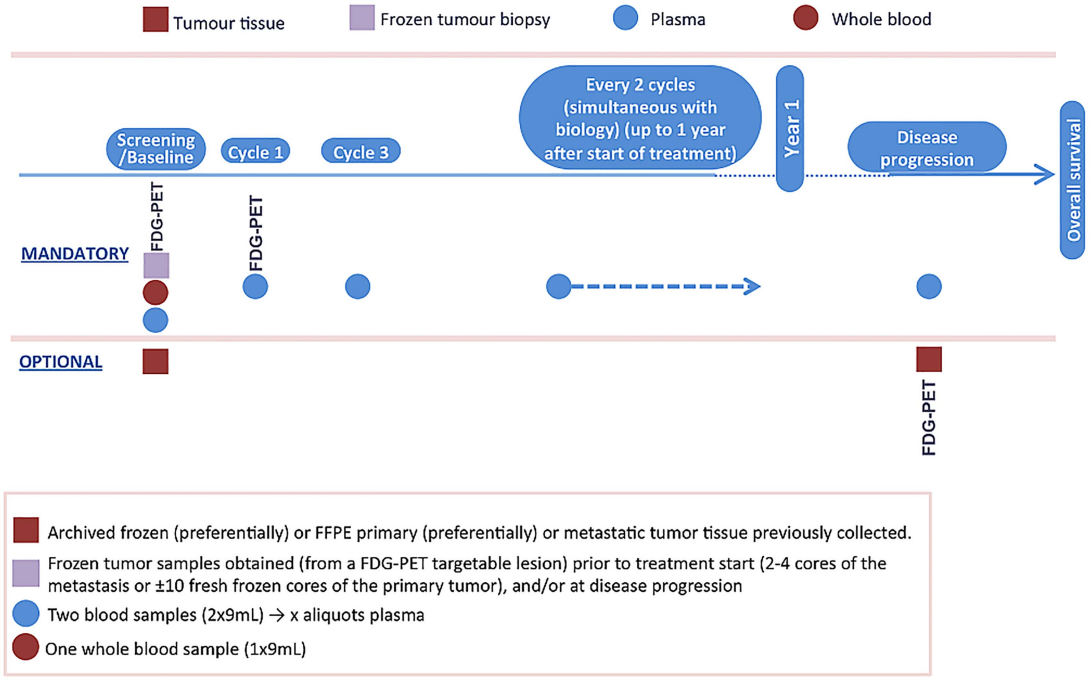

Figure 2 Schedule of assessments. FDG PET, fluorodeoxyglucose positron emission tomography; FFPE, formalin fixed paraffin embedded.

for multiplicity. As no formal hypothesis can be performed on the discriminating value of genomic biomarkers, it was decided to target a sample size of 105 evaluable patients and to use the first 70 patients as the derivation set and the 35 last patients as the validation set. It should be stressed, however, that the total sample size of 105 evaluable patients is sufficient to validate the hypothesis generated by the SoMore study.[14] We will use a binary assessment of PET metabolic response based on previous results obtained from SoMore, sharing the same inclusion criteria. We will define OS and PFS from the time of the second PET and analyse the relationship with PET metabolic response with univariate and multivariate Cox regression models. To detect in a validation series that the HR for responders compared to non-responders is significantly <1 (with a power of 80% in case of a true HR≤0.59 and a 1-sided α level of 5% and a rate of responders of 47%), we need to observe 89 events. We then plan to carry out a validation comparison between early homogeneous responders and the other patients once we will have reached 89 events for these 105 evaluable patients. For this validation comparison, there will be no split of the total sample. In order to reach this number of evaluable patients, the overall sample size of registered patients will be adapted during the study accrual. Taking into account an expected 20–25% dropout rate between registration and the time of further examinations, between 124 and 140 patients will be accrued. The analyses for derivation will be carried out when at least 80% of events (deaths) will have been observed. The analyses for validation will also occur when 80% of events will be reached. The study is designed as a single-arm study, with all patients being accrued in one stage. No early stopping rules will be used. The clinicians will remain blinded to the assessment of FDG PET-CT response and of the whole molecular analyses.

ETHICS AND DISSEMINATION

Ethical considerations

Patient protection

The principal investigator ensures that this study conforms to the Declaration of Helsinki (available at http://www.wma.net/en/30publications/10policies/b3/) or the laws and regulations of the country, whichever provides the greater protection to the patient. The study follows the International Conference on Harmonisation E 6 (R1) Guideline for Good Clinical Practice, reference number CPMP/ICH/135/95 (available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf).

Dissemination

The protocol and the trial results, even inconclusive, will be presented at international oncology congresses, and published in peer-reviewed journals. Genomic and epigenetic data will be made available in public open data sets.

Trial sponsorship, financing and insurance

This study is supported by an unrestricted grant from Bayer Healthcare Pharmaceutical, which provided regorafenib but played no further role in this study design, data collection and study management, and will play no role in results analysis and interpretation of data; nor in the writing of the report; nor in the decision to submit

the report for publication, and has no kind of authority over any of these activities.

DISCUSSION AND CONCLUSIONS

Regorafenib, an oral multikinase inhibitor that shares with sorafenib several targets involved in tumour angiogenesis, oncogenesis and tumour microenvironment, improves the patients' outcome, but at the cost of significant toxicities, underscoring the need to identify those who will benefit from therapy. A previous study (SoMore trial) showed that early FDG PET-based metabolic response assessment may adequately discriminate patients with chemorefractory aCRC unlikely to benefit from a sorafenib-capecitabine combination. RegARd-C aims to explore early FDG PET-based metabolic response assessment in patients treated with regorafenib (1) as a clinical tool to spare them from needless toxicity from a drug that gives them little or no benefit and (2) as a translational tool able to guide comprehensive genomic and epigenetic research on the determinants of drug resistance. This translational research will be conducted on fresh or archived tumoral tissues and on serial blood samples looking for free ctDNA. For a subset of patients, fresh frozen tumoral tissues taken by PET-guided biopsy procedures on metabolically resistant lesions will be available.

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Contributors AH, AD, NC, MP contributed to protocol writing; manuscript design; trial set-up; manuscript writing. CV participated in protocol writing; manuscript design; manuscript writing. TG took part in protocol writing; trial set-up; coordination of PET imaging network. CG and PF participated in protocol writing; manuscript design; trial set-up; manuscript writing; coordination of PET imaging network.

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Competing interests None.

Ethics approval Institut Jules Bordet Ethical Committee acting as the central ethical committee for this study, and the ethical committee of every clinical centre involved in this trial (17 Belgian centres).

Provenance and peer review Not commissioned; externally peer reviewed.

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