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FINAL STUDY REPORT

Full title of the trial:	**Cor**relating the tumoral metabolic progression **I**ndex measured by serial FDG PET-CT and apparent diffusion coefficient measured by MRI to patient's **O**utcome in advanced Co**l**orectal c**an**cer
Short title of the trial:	CORIOLAN
EudraCT Number:	2011-006280-21
Sponsor Protocol Number:	CORIOLAN1.0
ClinicalTrials.gov Number:	NCT01591590
Sponsor	Institut Jules Bordet Rue Meylemeersch 90, 1070 Anderlecht Belgique/België
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1. TRIAL INFORMATION

STUDY DESIGN	The study is designed as a single-arm prospective interventional non-therapeutic study to assess the value of FDG PET-CT in defining tumoral metabolic progression in advanced colorectal cancer subjects during a period without treatment
STUDY RATIONALE	We hypothesize that, in a population of patients with advanced colorectal cancer for which no known effective therapy is available, tumour growth rate is related to the patient's outcome, and that serial FDG PET-CT is able to measure it. If the hypothesis is verified, this finding could: • Allow to define therapeutic strategies according to the TMPI, assessed by serial pre-therapeutic FDG PET-CT. • Limit the need for randomization in the early drug development phases as each patient could be considered as his own control. • To stratify patients according to their baseline metabolic growth rate in RCT with OS as endpoint.
OBJECTIVES	Primary objective To assess the spontaneous evolution of tumoral metabolic progression index (TMPI) measured by serial FDG PET-CT without any intercurrent antitumor therapy as a prognostic factor for overall survival in patients with advanced colorectal cancer. Secondary objectives • To test TMPI as a prognostic marker for progression free survival. • To assess the prognostic value of baseline tumor FDG uptake on progression free survival and overall survival. • To compare TMPI to classical clinico-biologic assessment of prognosis (alkaline phosphatase, platelets count, LDH, tumor bulk) • To test the prognostic value of MRI based apparent diffusion coefficient (ADC) and variation of vADC based on voxel-based diffusion maps. • Translational research: o To identify and quantify tumor-specific rearrangements in plasma DNA using next-generation sequencing. o To characterize which of these tumor-specific rearrangements in plasma DNA form genomic and epigenetic determinants of tumoral metabolic progression guided by FDG-PET-CT metabolic imaging. o To identify these tumor-specific rearrangements in previous tumor tissue. o To analyze whether CTC levels correlate with tumoral metabolic progression guided by FDG PET-CT metabolic imaging. o To assess the prognostic value of CTCs on overall survival.
ENDPOINTS	• Primary: TMPI (delta SUVmx and Delta MV) • Secondary: o ADC (MRI-based apparent diffusion coefficient (ADC)) o Circulating DNA levels and delta
INCLUSION CRITERIA	• Participants must have histologically confirmed colorectal cancer that is metastatic or unresectable and for which standard treatments do not exist or are no longer effective. • Participants should be candidate for a Phase I study

	• The tumor should be refractory to all standard chemotherapy agents (fluoropyrimidines, irinotecan, and oxaliplatin) and anti-EGFR monoclonal antibodies in case of wild type K-ras (cetuximab or panitumumab) administered before study entry. Prior treatment with bevacizumab, regorafenib and/or aflibercept is allowed but not mandatory. • Age equal or over 18 years. • Life expectancy of greater than 12 weeks. • ECOG performance status ≤ 1. • Participants must have normal organ and marrow function as defined below: Total bilirubin within 2 × normal institutional upper limits AST/ALT/Alk Phosphatase levels < 5 × normal institutional upper limits Creatinine within 2 × normal institutional upper limits or creatinine clearance > 35mL/min • Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and during the assessment. For women of child-bearing potential a pregnancy test (urinary or serum) must be performed within 7 days prior to inclusion and it must be negative. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician within one month. • Signed written informed consent obtained prior to any study specific screening procedures.
EXCLUSION CRITERIA	Patients who exhibit any of the following conditions at screening will not be eligible for admission into the study: • Participants who have had chemotherapy or targeted therapy within 2 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier. • Participants who have had a major surgery or radiotherapy within 4 weeks prior to entering the study. • Patients receiving any experimental agents during the assessment time period. • Patients with uncontrolled brain metastases. • Bleeding diathesis, history of cardiovascular ischemic disease or cerebrovascular incident within the last six months. • Uncontrolled concurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, psychiatric illness or any significant disease which, in the investigator's opinion, would exclude the patient from the study. • Pregnancy or breast-feeding before the FDG PET-CT scan examinations • Uncontrolled diabetes. • Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer in situ, and basal cell or squamous cell carcinoma of the skin. • Medical, geographical, sociological, psychological or legal conditions that would not allow the patient to complete the study or sign informed consent.

INVESTIGATIONAL MEDICINAL PRODUCTS	Fluorodeoxyglucose (^{18}F), solution for injection, intravenous use Dose at each administration: 0.1 millicurie(s)/kilogram
INDICATION OF USE	Advanced colorectal cancer, refractory to all available medications
PARTICIPATING COUNTRY	Belgium
PARTICIPATING SITES NUMBER	1 participating site
LENGTH OF THE STUDY	• Actual start date of recruitment to the protocol: 27/06/2012 • Actual date stop date of recruitment to the protocol: 17/05/2018
INDEPENDENT DATA MONITORING COMMITTEE	No
ANALYSIS STAGE & DATE	Final Date of final analysis: 25/09/2021
DATE OF GLOBAL END OF TRIAL	25/09/2021

2. SUBJECT INFORMATION

2.1. General information

55 subjects were registered in the pilot phase, 47 subjects were enrolled and exposed to investigational medicinal product (IMP). 47 subjects were evaluable.

The actual number of subjects registered in each age range for the whole trial is specified in the table 1.

Age categorical characteristic	Number of subjects
In Utero	0
Preterm newborn-gestational age>37 week	0
Newborns (0-27 days)	0
Infants and toddlers (28 days – 23 months)	0
Children (2 – 11 years)	0
Adolescents (12 – 17 years)	0
Between 18 and 65 years	28
From 66 years to 84 years	27
85 years and over	0
TOTAL	**55**

The median of subjects 'age is 65 years (full range 38-82).

Amongst these 55 subjects, 26 were female and 29 were male.

2.2. Subject disposition

In total, 55 subjects were registered in the trial, 47 subjects completed the trial and 8 subjects did not complete the trial.

The reasons why some subjects did not complete the trial with the corresponding subjects' number are specified in the table 2.

Non-completion reasons	Number of subjects
Consent withdrawn by subject	3
Other: screen failure	3
Other:	2

Table 3: Non-completion reasons with corresponding subjects' number.

3. STATISTICAL ANALYSIS

Between June 2012 and May 2018, 55 subjects were enrolled in the study. Of these, 8 were excluded from the analysis due to ineligibility (n = 3), withdrawal of the informed consent (n = 3) and poor compliance with the study procedures (n = 2). Median age was 65 years (range 38–82), 64% of subjects had an ECOG performance status of 1, and the median number of prior treatments was 5 (range 2–8). Tumours of 57% and 0% of subjects were known to harbour RAS and BRAF mutations, respectively. In line with the study eligibility criteria, no subject received any cancer treatment between day 1 and 15. After day 15, 23 (49%) subjects were treated with investigational agents within the context of a phase I clinical trial (n = 10), a placebo-controlled clinical trial (n = 3), regorafenib (n = 8), trifluridine/tipiracil (n = 1) and capecitabine (n = 1). At the time of analysis, 45 deaths had been observed, of which 12 (26%) occurred within 12 weeks of study entry. The median OS was 6.3 months (range 0.4–4.3).

An 18F-FDG PET/CT scan was carried out on day 1 in 44 (94%) and on day 15 in 42 (89%) subjects. High WB-MATV both at baseline (n = 30/44, 68%) (4.2 versus 9.4 months; HR 3.1, 95% CI 1.5–6.4, p = 0.003) and on day 15 (n = 22/42, 52%) (4.7 versus 7.9 months; HR 2.2, 95% CI 1.0–4.6, p = 0.044) was associated with a worse OS. In 42 cases (89%), variations of WB-MATV between day 1 and day 15 were assessable. The median relative delta was +21%, and 3/14 (21%) low baseline WB-MATV subjects were observed to have high WB-MATV tumors two weeks later. Changes of WB-MATV did not predict OS, subjects with high TMPI having similar prognosis to those with low TMPI (7.0 versus 5.7 months; HR 1.3, 95% CI 0.71–2.6, p ≥ 0.383).

Forty-three (91%), 46 (98%) and 30 (64%) subjects were assessable for CEA, cfDNA and CTC, respectively, at baseline. High CEA (4.4 versus 7.0 months; HR 1.9, 95% CI 1.0–3.5, p = 0.053), high cfDNA (n = 21, 46%) (4.7 versus 7.0 months; HR 2.2, 95% CI 1.2–4.3, p = 0.015) and a high CTC count (n = 10, 33%) (3.3 versus 7.5 months; HR 6.5, 95% CI 2.4–17.0, p < 0.001) predicted worse OS. Variations of CEA, cfDNA and CTC count between day 1 and day 15 were assessable for 35 (74%), 42 (89%) and 22 (34%) subjects, respectively, with the median relative delta for each of the same biomarkers being +16.3%, +6%, and +100%. In no case, these variations were associated with OS (CEA: HR 1.9, 95% CI 0.94–3.8, p = 0.073; cfDNA: HR 1.6, 95% CI 0.86–3.1, p = 0.133; CTC count: HR 1.2, 95% CI 0.49–2.9, p = 0.703).

Other Prognostic Factors at Baseline Among the other baseline prognostic factors analyzed, low Hb (HR 2.2, 95% CI 1.2–4.0, p = 0.017), high neutrophil/lymphocyte ratio (HR 2.4, 95% CI 1.3–4.5, p = 0.006), high ALP (HR 3.5, 95% CI 1.7–7.5, p < 0.001), and high CRP (HR 3.5, 95% CI 1.8-6.7, p < 0.001) predicted poor OS. Forty-three subjects (91%) could be scored using to the Colon Life nomogram. The median estimated probability of death at 3 months was 30% (range 10–94%). In subjects with lower Colon Life scores, median OS was 6.9 months (range 1.7–12.5 months), while in those with higher Colon Life scores median OS was 4.7 months (range 0.4–14.3 months) (HR 1.2, 95% CI: 0.6–2.2, p = 0.648). Receiving further treatment after completion of the trial was associated with a numerically, but not statistically significantly, longer OS (median OS 7.1 versus 3.5 months; HR 0.66, 95% CI 0.36–1.2, p = 0.17).

4. SAFETY ANALYSIS

4.1. General information

In this trial, only adverse events related to FDG tracer occurring during the study conduct and up to 24 hours after the last injection of FDG tracer had to be reported.

Regarding the serious adverse events (SAEs) reporting, SAEs caused by a protocol mandated intervention during the period from informed consent signature until 1st FDG PET-CT) and all SAEs related to FDG tracer occurring be during the study conduct and up to 24 hours after the last injection of FDG tracer had to reported.

4.2. Serious Adverse Events overview

No serious adverse events as defined in the protocol were reported.

4.3. Non-Serious Adverse Events overview

No non-serious adverse events as defined in the protocol were reported.

5. ADDITIONAL INFORMATION

5.1. Global substantial protocol amendments

The global substantial amendments to the protocol are summarised in the below table.

Amendment date	Description
13/02/2013	• Development of the translational research (collection of plasma for genomic analysis and blood for circulating tumour cell enumeration at day 1 and day 15) • Suppression of CT examination and contrast used for FDG PET-CT • Precision regarding the evaluability criteria for FDG PET-CT • Statistical part (recruitment, study duration and analysis)
02/12/2014	• Making the DW-MRI optional • Adding the definition of End of trial • Sample Size justification • Deletion of one exclusion criterion • Update in the Quality control: study monitoring • Clarification and update in Quality control and quality assurance • Clarification and update in Data handling and records keeping

Amendment date	Description
03/11/2015	• Clarification on the AE/SAE reporting • Clarification in the data handling and records keeping (CRF) • Clarification in some inclusion and exclusion criteria

5.2. Global interruption(s) and restarts

Not applicable

5.3. Limitations and caveats

There were no limitations and caveats applicable to this summary of the results.