Title:

Detection of Progressive Disease in Metastatic Colorectal Cancer Patients by NPY Methylation in Liquid Biopsies

LEAD-IN
FOLICOLOR TRIAL

Clinical Study Sponsor: Antwerp University Hospital
Drie Eikenstraat 655
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PROTOCOL SIGNATURE SHEET

Detection of Progressive Disease in Metastatic Colorectal Cancer Patients by *NPY* Methylation in Liquid Biopsies

LEAD-IN
FOLICOLOR Trial

Version: v.3.0 – Belgium (11 August 2020)

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC", and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Name + function	Site	Signature	Date (DD/MM/YYYY)
Principal Investigator Belgium			

PROTOCOL SYNOPSIS

Study title	LEAD-IN FOLICOLOR TRIAL: DETECTION OF PROGRESSIVE DISEASE IN METASTATIC COLORECTAL CANCER PATIENTS BY *NPY* METHYLATION IN LIQUID BIOPSIES
Type of study	Prospective, multicentric interventional study
Sponsor	Antwerp University Hospital (UZA)
Funding	Amgen
Indication	*RAS* and *BRAF* wild-type, unresectable, metastatic colorectal cancer, first-line treatment FOLFOX/FOLFIRI and panitumumab.
Study design	Prospective, multicentric interventional study to optimize the cutoff value of *NPY* methylation in liquid biopsies in metastatic colorectal cancer patients treated with first-line FOLFOX/FOLFIRI and panitumumab. Inclusion is possible after histologically or cytologically proven colorectal adenocarcinoma with metastatic lesions according to RECIST 1.1 at the start of first-line treatment using FOLFOX/FOLFIRI and panitumumab. Patient must have a proven *RAS* and *BRAF* wild-type tumor. Patients will be followed by study protocol up to and including the first CT scan following the last liquid biopsies taken, or when a follow-up period of 11 months is reached, until death, until metastasectomy, until lost to follow-up or until (consent) withdrawal.
Study objectives	**The primary objective** of this study is to optimize the cutoff value of *NPY* methylation in liquid biopsies (ctDNA) in metastatic colorectal cancer patients receiving first-line FOLFOX/ FOLFIRI and panitumumab. **The secondary objective** is to determine the progression free and 9-month survival of metastatic colorectal cancer patients. **Exploratory objectives** will include, but will not be limited to the following: • To explore and compare the use of ctDNA and CEA to predict progression; • Further exploration of ctDNA in liquid

	biopsies and searching for novel biomarkers; • To assess the quality of life and the patient experience of metastatic colorectal cancer patients with regard to the use of liquid biopsies for follow-up.
Included treatment	First-line FOLFOX/FOLFIRI and panitumumab.
Included dosing regimen and route	Chemotherapeutic agents will be given as an intravenous infusion at a dose and interval consistent with standard institutional practice.
Study population	Metastatic colorectal cancer patients starting first-line FOLFOX/FOLFIRI and panitumumab.
Main inclusion criteria	Key Inclusion Criteria (see 5.1 for complete list of inclusion criteria): • Man or woman ≥ 18 years of age at the time the informed consent is obtained • ECOG performance status of 0 or 1 • Histologically or cytologically confirmed adenocarcinoma of the colon or rectum in subjects with unresectable metastatic (M1) disease • At least 1 uni-dimensionally measurable lesion of at least 10 mm per RECIST 1.1 guidelines using conventional techniques (CT scan). Lesion must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation and prior to inclusion. All sites of disease must be evaluated ≤ 28 days prior to the start of first-line therapy • Wild-type *RAS* tumor status (of tumor tissue) • Wild-type *BRAF* tumor status (of tumor tissue) • Adequate hematologic, renal, hepatic and coagulation function • Starting a first-line treatment with a combination of FOLFOX/FOLFIRI and panitumumab
Main exclusion criteria	Key Exclusion Criteria (see 5.2 for complete list of exclusion criteria): • History of prior or concurrent central nervous system metastases • History of other malignancy, except: o Malignancy treated with curative intent and with no known active disease present for ≥ 3 years prior to start therapy and felt to be at low risk for recurrence by the treating physician o Adequately treated non-

	melanomatous skin cancer or lentigo maligna without evidence of disease ○ Adequately treated cervical carcinoma in situ without evidence of disease ○ Prostatic intraepithelial neoplasia without evidence of prostate cancer • Prior chemotherapy or other systemic anticancer therapy for the treatment of metastatic colorectal carcinoma including but not limited to bevacizumab and anti-EGFR therapy (e.g. cetuximab, panitumumab, erlotinib, gefitinib, lapatinib) • Prior adjuvant chemotherapy (including oxaliplatin therapy) or other adjuvant systemic anticancer therapy including but not limited to bevacizumab and anti-EGFR therapy (e.g. cetuximab, panitumumab, erlotinib, gefitinib, lapatinib) for the treatment of colorectal cancer ≤ 6 months prior to start therapy with the following exceptions: ○ Subjects may have received prior fluoropyrimidine therapy if administered solely for the purpose of radiosensitization for the adjuvant or neoadjuvant treatment of rectal cancer • Radiotherapy ≤ 14 days prior to start therapy. Subjects must have recovered from all radiotherapy-related toxicities. • Significant cardiovascular risk • History of interstitial lung disease (e.g., pneumonitis or pulmonary fibrosis) or evidence of interstitial lung disease on diagnostic CT scan • Active inflammatory bowel disease or other bowel disease causing chronic diarrhea (defined as ≥ CTC grade 2, [CTCAE version 5.0]) • Peripheral sensory neuropathy (≥ CTC grade 2 [CTCAE version 5.0]
Total sample size	The calculated sample size is 60 subjects

Planned study visits	**Screening period/eligibility check (Mb):**
	• Additional visit for CT scan if diagnostic CT scan is > 28 days before start of first-line therapy
	• 1 EDTA tube to check hematologic, renal, hepatic, metabolic, and coagulation function < 14 days before start of first-line therapy
	
	Inclusion
	• Questionnaire
	  ○ Quality of Life (EORTC QLQ-C30 & EORTC QLQ-CR29)
	
	Start first-line therapy (M0):
	• Start cycle 1 of first-line therapy (FOLFOX/FOLFIRI and panitumumab)
	• Liquid biopsy sampling:
	  ○ LB_0 to measure the ctDNA level
	  ○ LB_a and LB_b for further research
	
	Follow-up:
	• Biweekly liquid biopsy sampling up to and including 9 months after start first-line therapy
	• Every 8 weeks: CT scan combined with CEA up to and including the first CT scan following the last liquid biopsies taken
	• M9: Quality of Life (EORTC QLQ-C30 & EORTC QLQ-CR29) + patient experience
	
	End of Study (EOS):
	• Day on which the first CT scan is performed following the last liquid biopsies taken, or when 11 months of follow-up is reached.

Safety parameters	Clinical and laboratory events will be reported according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5.0).
Efficacy parameters	Progression will be assessed using standard imaging (CT scan) based on RECIST criteria 1.1. The level of ctDNA will be assessed through *NPY* methylation.
Laboratory parameters and biomarkers	ctDNA levels and standard laboratory parameters (hematology, biochemistry, liver function tests, TSH, urinalysis). Additional laboratory assessments as deemed necessary by the treating physician. CEA every 8 weeks (combined with CT scan and LB)
Imaging parameters	Computed tomography (CT)

Statistics	To determine the optimal cut-off value of the *NPY* methylation to discriminate between progressive and non-progressive disease (as determined by CT), we will develop a Receiver Operating Characteristic (ROC) curve with data of this lead-in study. ROC curves show the trade-off between sensitivity and specificity and the Area Under the Curve (AUC) is considered as an index of accuracy. In order to construct a 95% confidence interval for the AUC of width 0.2 and assuming an AUC of 0.9 we need a least a group of 27 patients with progressive disease and a group of 27 patients without progressive disease. Assuming a median PFS of 9 months, we would need to include 54 patients and follow them up for 9 months. However, it is expected that about 10-15% of the study population may become resectable by conversion therapy. Taking this into account, the total number of patients to be included is 60.

ABBREVIATION LIST

Abbreviation	Definition/Explanation
UZA	Antwerp University Hospital
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartaat-aminotransferase
cfDNA	Cell free DNA
CEA	Carcinoembryonic antigen
CMG	Centre of Medical Genetics
CNS	Central nervous system
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CSR	Clinical study report
CTC	Common terminology criteria
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor DNA
ddPCR	Digital droplet PCR
DICOM	Digital Imaging and Communications in Medicine
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
GDP	Guanosine 5'-diphosphate
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
GTP	Guanosine-5'-triphosphate
HCG	Human chorionic gonadotropin
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
ICF	Informed consent form

ICH	International conference on harmonization
ID	Identification number
INR	International normalized ratio
LB	Liquid biopsy
LDH	Lactate dehydrogenase
MAP	Mitogen-activated protein kinase
mCRC	Metastatic colorectal cancer
MSI	Microsatellite instability
NCI-CTCAE	National cancer institute – common terminology criteria for adverse events
PACS	Picture Archiving and Communication System
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PTT	Partial thromboplastin time
PTT	Partial thromboplastin time
QoL	Quality of life
RAF	Rapidly accelerated fibrosarcoma
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SD	Stable disease
TGF-α	Transforming growth factor alpha
TMG	Trial management group
TSH	Thyroid stimulating hormone
UPC	Urine protein creatinine
USA	United States of America
VPN	Virtual private network

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1 BACKGROUND AND RATIONALE

1.1 Disease and treatment

Colorectal cancer (CRC) is the third most common cancer in both men and women and a major cause of cancer related death. In 2018, there were approximately 1.8 million new cases of CRC worldwide and an estimated number of 881.000 deaths, accounting for 10% of all cancer related deaths. The incidence and mortality of CRC is still rising (1). Of newly diagnosed patients, 15% to 25% have metastatic disease at diagnosis and up to 50% of all patients eventually develop metastatic disease (2, 3).

As of 2009, three monoclonal antibodies have regulatory approval in multiple countries for the treatment of colorectal cancer (CRC): cetuximab (Erbitux®) and panitumumab (Vectibix®), both of which are directed against the epidermal growth factor receptor (EGFR), and bevacizumab (Avastin®), which is directed against vascular endothelial growth factor. The development of these three agents has provided additional therapeutic options for patients. However, metastatic colorectal cancer (mCRC) cannot be cured with the currently available chemotherapy regimens, and there is a continued need to improve the current treatment. The EGFR pathway has been shown to play an important role in carcinogenesis, and inhibiting this pathway with anti-EGFR antibodies has been shown to have clinical efficacy in the treatment of metastatic colorectal cancer in subjects whose tumors express wild-type *RAS* (4-6). Approximately 60% of subjects presenting with mCRC have tumors without activating *RAS* mutations (6). *RAS* mutation status may have prognostic significance and is predictive of response to cetuximab and panitumumab therapy in CRC (5-8). The addition of EGFR-targeted therapies to chemotherapy for the first-line treatment of wild-type (WT) *RAS* metastatic colorectal cancer has improved patient's objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) (9-12). For this reason, current guidelines recommend their use in combination with the most common backbone chemotherapeutic regimens such as FOLFOX [folinic acid, 5-fluorouracil, and oxaliplatin] or FOLFIRI [folinic acid, 5- fluorouracil, and irinotecan] (13).

1.2 Circulating Tumor DNA

In the past five years, liquid biopsies have been intensively studied as a new promising technique for the diagnosis and follow-up of CRC. Liquid biopsy is a technique in which non-solid biological tissues such as urine, stool or peripheral blood are sampled and analyzed (14). They are, for example, used for the detection of abnormally expressed biological markers manifested during carcinogenesis.

Circulating tumor DNA (ctDNA) originates from tumors as a result of cancer cells undergoing

apoptosis and necrosis, thereby releasing their DNA into the bloodstream. CtDNA liquid biopsies are very suitable for diagnosis as ctDNA can be detected in the plasma of even early-stage cancer patients. Moreover, ctDNA reflects the cumulative tumor burden as it is released in all regions of the tumor. This offers an advantage over traditional tissue biopsies, which contain only a minor part of the tumor and are not representative for tumor heterogeneity (15).

The use of liquid biopsies and the analysis of ctDNA in CRC patients is not new and has been performed in the past (16)(17-20). However, until now, a strong focus existed on the detection of tumor specific mutations, which has several limitations. First, tumor specific alterations need to be identified a priori by DNA sequencing of tumor biopsies, making it a costly and time-consuming practice. Second, since these somatic mutations can vary from case to case, a personal assay might have to be developed. Third, the amount of mutations that are found in a given primary tumor are highly variable. For some tumors, few mutations are present in the primary tumor, hence severely limiting sensitivity for plasma-based mutation detection markers. Several liquid biopsy tests have been proposed in the past (21), but all lack the sensitivity to have strong clinical utility.

In cont*RAS*t to genetic mutations, also epigenetic changes such as DNA hypermethylation of neuropeptide Y protein (*NPY*) have been described in CRC (16, 22, 23). Digital droplet PCR (ddPCR) allows to measure *NPY* methylation in a highly sensitive manner to determine the amount of ctDNA in plasma samples. In fact, *NPY* methylation is a surrogate marker for tumor burden in CRC patients. The main advantage of methylation assays is the applicability in almost every patient, while the use of mutation assays requires prior knowledge of mutations present in the tumor.

1.3 **Exploration of epigenetic methylation alterations in ctDNA**

Epigenetic changes in cancer have attracted great attention in the last years. It is widely accepted that the initiation and progression of cancer involve epigenetic abnormalities, such as DNA methylation. Changes in DNA methylation are considered an early event in carcinogenesis (24-26) and have already been proposed for early diagnosis of cancer. In CRC in particular, aberrant methylation has been observed, allowing non-invasive population screening using blood samples (23, 27-30) and follow-up during therapy (31-33).

Methylated ctDNA in liquid biopsies is valuable in cancer prognosis and tumor response. Therefore, it is of interest to further explore the use of DNA methylation in liquid biopsies in clinical practice.

1.4 **Rationale**

Many advances in systemic therapies have significantly improved the survival of patients with CRC (34). However, there is a high variability of therapeutic responses among patients and determining the optimal personalized treatment plan is challenging. Conventional monitoring of the therapy

response is based on imaging as suggested in RECIST 1.1 (35) and measurements of CEA and CA19.9 derived from plasma. However, radiological assessments are usually limited in frequency (radiation exposure, costs, logistics,…), have a detection limit, are not suited for small metastases and cannot describe intrinsic characteristics of each tumor. Therefore, other predictive biomarkers of treatment outcomes and disease progression are of great value to enable early therapy response evaluation and early change of therapy avoiding unnecessary side effects, enhancing efficacy and minimizing costs.

Quantification of ctDNA in real-time renders information on tumor characteristics and has been shown to be associated with treatment responses in mCRC (16, 36). Recently, our research group has shown that quantifying ctDNA through the methylation analysis of *NPY* in circulating DNA is a good marker for total tumor burden and can therefore be used for the follow-up of mCRC patients (22).

It could be demonstrated that the amount of ctDNA in plasma, measured using *NPY* ddPCR methylation assays, decreased immediately (14 days) after treatment start. The amount of ctDNA remained low or undetectable in patients undergoing curative metastasectomy, while the amount of ctDNA increased in patients showing progressive disease (22). As progressive disease might be detected earlier using liquid biopsies as compared to observations by radiographic evaluation, the use of liquid biopsies might be a promising tool to guide treatment options.

The aim of this study is to determine the optimal cutoff value of the liquid biopsy test (using a ROC curve based on the data of this study). This cutoff value will be used in a follow-up study to detect progressive disease in patients with metastatic colorectal cancer treated with first-line FOLFOX/FOLFIRI and panitumumab. Additionally, the follow-up trial will determine if ctDNA detects progression earlier than conventional used imaging techniques and will estimate the effect on progression-free survival in case therapy is guided by *NPY* methylation levels in liquid biopsy.

Furthermore, in the LEAD-IN FOLICOLOR Trial we will exploratively compare liquid biopsies to tumor markers (CEA and/or CA19.9) in their ability to predict progressive disease. This innovative study will add evidence to the clinical relevance of ctDNA during treatment.

2 OBJECTIVES

This is a prospective, multicenter interventional study designed to optimize the cutoff value of *NPY* methylation in liquid biopsies (ctDNA) in patients with metastatic colorectal cancer receiving first-line FOLFOX/FOLFIRI and panitumumab.

2.1 Primary objective

The primary objective of the LEAD-IN FOLICOLOR Trial is to optimize the cutoff value of *NPY* methylation in liquid biopsies (ctDNA) of patients with metastatic colorectal cancer receiving first-line FOLFOX/FOLFIRI and panitumumab.

2.2 Secondary objectives

The secondary objective is to determine the progression free and 9-month survival of *RAS* and *BRAF* wild-type metastatic colorectal cancer patients.

2.3 Exploratory objectives

The exploratory objectives will include, but will not be limited to the following:

- To compare the use of ctDNA and CEA to predict progression.
- Further exploration of ctDNA in liquid biopsies and searching for novel biomarkers.
- To explore the quality of life and the patient experience in this patient population with regard to the use of liquid biopsies for follow-up through questionnaires.
  This will include, but will not be limited to the following:
    - Burden of extra blood samples (extra blood samples during routine blood test)
    - Burden of CT scan with intravenous contrast
    - Confidence in liquid biopsy guided therapy (ctDNA analysis) compared to CT scan guided therapy
    - Preference between extra blood sample and CT scan (taking into account: burden, pain, time in the hospital, extra travel time to the hospital, confidence in technique…)

3 STUDY ENDPOINTS

3.1 Primary endpoint

Using the data of this LEAD-IN study, a Receiver Operating Characteristic (ROC) curve will be developed in order to determine the optimal cutoff value for *NPY* methylation in liquid biopsies to predict progression on CT scan.

3.2 Secondary endpoints

- To determine the progression free survival in patients with metastatic colorectal cancer defined as time from inclusion to the date of first disease progression among subjects with metastatic colorectal cancer per RECIST 1.1 criteria, or death.
- The 9-month survival will be determined as percentage surviving at 9 months after the start of first-line therapy.

3.3 Exploratory endpoints

- Explore and compare the use of *NPY* methylated ctDNA and CEA to predict progression
- Further exploration of ctDNA in liquid biopsies and searching for novel biomarkers.
- To assess the (health-related) quality of life in patients with colorectal cancer by the use of the following validated questionnaires: EORTC QLQ-C30 and EORTC QLQ-CR29 (cfr. Appendix 15.2 & 15.3).
- To assess the patient experience through a questionnaire (cfr. Appendix 15.4 & 15.5).

4 STUDY POPULATION

4.1 Number of centers

This study is a multicenter trial of which all mCRC patients will be recruited at approximately 10 hospitals in Belgium, including the Antwerp University Hospital.

5 SUBJECT ELIGIBILITY

Investigators will be expected to maintain a **screening log** of all potential study candidates that includes limited information about the potential candidate (date of birth), date of screening, and outcome of the screening process (e.g., enrolled into study, or reason for refusal to participate).

5.1 Inclusion Criteria

5.1.1 Disease related

- Histologically or cytologically confirmed adenocarcinoma of the colon or rectum in subjects with unresectable metastatic (M1) disease
- Starting first-line FOLFOX/FOLFIRI and panitumumab for metastatic colorectal cancer
- At least 1 uni-dimensionally measurable lesion of at least 10 mm per RECIST 1.1 guidelines (see Appendix 15.6) using conventional techniques (CT scan). Lesion must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation and prior to inclusion. All sites of disease must be evaluated ≤ 28 days prior to the start of first-line therapy.
- Wild-type *RAS* tumor status of the tumor tissue tested by the local hospital. This test must be performed during screening phase.
- Wild-type *BRAF* tumor status of the tumor tissue tested by the local hospital. This test must be performed during screening phase.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

5.1.2 Demographic

- Man or woman 18 years of age or older at the time the informed consent is obtained.

5.1.3 Laboratory

To be performed ≤ 14 days prior to the start of first-line therapy, unless otherwise specified:

5.1.3.1 Hematologic function within the following limits:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L (without platelet transfusion ≤ 14 days prior to start therapy)
- Hemoglobin (Hgb) ≥ 9.0 g/dL

5.1.3.2 Renal function within the following limits:

- Creatinine clearance (GFR) ≥ 50 mL/min calculated by the Cockcroft-Gault method as follows:
  - Male creatinine clearance = (140 – age in years) x (weight in kg) / (serum creatinine in mg/dL x 72)
  - Female creatinine clearance = (140 – age in years) x (weight in kg) x 0.85 / (serum creatinine in mg/dL x 72)
- Urinary protein ≤ 30 mg by urinalysis or ≤ 1+ by dipstick or urine protein creatinine (UPC) ratio ≤ 0.5 by urinalysis (unless excretion of < 1000 mg of protein per day as determined by 24-hour urine collection).

  Note: UPC ratio of spot urine is an estimation of the 24 urine protein excretion - a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formula:

  [urine protein]/[urine creatinine] - if both urine protein and creatinine are reported in mg/dL.

  [(urine protein) x0.088]/[urine creatinine] - if urine creatinine is reported in mmol/L.

5.1.3.3 Hepatic function within the following limits:

- Total bilirubin ≤ 1.5 x ULN
- Alkaline phosphatase ≤ 2.5 x ULN (if liver metastases, ≤ 5 x ULN)
- Aspartate aminotransferase (AST) ≤ 2.5 x ULN (if liver metastases, ≤ 5 x ULN)
- Alanine aminotransferase (ALT) ≤ 2.5 x ULN (if liver metastases, ≤ 5 x ULN)

5.1.3.4 Metabolic function within the following limits:

- Magnesium ≥ lower limit of normal

5.1.3.5 Coagulation function within the following limits:

- Partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤ 1.0 x ULN and international normalized ratio (INR) < 1.5, unless the subject is on therapeutic anticoagulation therapy. Patients on therapeutic anticoagulation are eligible if the following criteria are met:
  - The subject has an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or is on a stable dose of low molecular weight heparin.
  - The subject has no active bleeding or pathological condition that carries high risk of bleeding (e.g., tumor involving major vessels or known varices)

5.1.3.6 Negative pregnancy test

- Serum pregnancy test ≤ 14 days prior to start therapy (for women of childbearing potential only)

5.2 **Exclusion Criteria**

5.2.1 Disease Related

- History of prior or concurrent central nervous system (CNS) metastases
- History of other malignancy, except:
    - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years prior to the start of first-line therapy and felt to be at low risk for recurrence by the treating physician
    - Adequately treated non-melanomatous skin cancer or lentigo maligna without evidence of disease
    - Adequately treated cervical carcinoma in situ without evidence of disease
    - Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Cancer Therapy
    - Prior chemotherapy or other systemic anticancer therapy for the treatment of metastatic colorectal carcinoma including but not limited to bevacizumab and anti-EGFR therapy (e.g. cetuximab, panitumumab, erlotinib, gefitinib, lapatinib)
- Prior adjuvant chemotherapy (including oxaliplatin therapy) or other adjuvant systemic anticancer therapy including but not limited to bevacizumab and anti-EGFR therapy (e.g. cetuximab, panitumumab, erlotinib, gefitinib, lapatinib) for the treatment of colorectal cancer ≤ 6 months prior to the start of first-line therapy with the following exceptions:
    - Subjects may have received prior fluoropyrimidine therapy if administered solely for the purpose of radiosensitization for the adjuvant or neoadjuvant treatment of rectal cancer
- Radiotherapy ≤ 14 days prior to start therapy. Subjects must have recovered from all radiotherapy-related toxicities.
- Unresolved toxicities from prior anti-cancer therapy that, in the opinion of the investigator, excludes subject from participation

5.2.2 Other Medications

- Infection requiring a course of systemic anti-infectives that was completed ≤ 14 days before start therapy (exception can be made at the judgment of the investigator for oral treatment of an uncomplicated urinary tract infection (11))

5.2.3 General

- Significant cardiovascular risk:
    - Myocardial infarction, grade 2 or greater peripheral vascular disease**,** arterial thrombotic event, visceral arterial ischemia, cerebrovascular ischemia, transient ischemic attack, percutaneous transluminal coronary angioplasty/stent or unstable angina ≤ 24 weeks prior to start

therapy

- Symptomatic and/or serious uncontrolled cardiac arrhythmia
- Symptomatic congestive heart failure (New York Heart Association Class III or IV)
- Uncontrolled blood pressure defined as > 150 mmHg systole or > 90 mmHg diastole. Anti-hypertensive medications are allowed if hypertension is stably controlled at the time of start therapy.
- Pulmonary embolism, deep vein thrombosis, or other significant venous event ≤ 8 weeks before start therapy

- History of interstitial lung disease (e.g., pneumonitis or pulmonary fibrosis) or evidence of interstitial lung disease on baseline CT scan
- Active inflammatory bowel disease or other bowel disease causing chronic diarrhea (defined as ≥ CTC grade 2, [CTCAE version 5.0])
- Peripheral sensory neuropathy (≥ CTC grade 2 [CTCAE version 5.0]
- Any co-morbid disease or condition that could increase the risk of toxicity (such as clinically significant ascites)
- Subjects known to be human immunodeficiency virus (HIV) positive or known to have chronic or active hepatitis B or C infection
- Subject is currently enrolled in, or ≤ 30 days has passed since subject completed another investigational device or drug study(s), or subject is receiving other investigational agent(s)
- Women of child-bearing potential is evidently pregnant (e.g., positive HCG test) or is breast feeding
- Men and women of childbearing potential who do not consent to use adequate contraception during the course of the study. Adequate contraceptive precautions includes double barrier contraceptive methods (e.g., diaphragm and condom) or abstinence
- History of any medical or psychiatric condition or addictive disorder, or laboratory abnormality that, in the opinion of the investigator, may increase the risks associated with study participation or study drug administration or may interfere with the conduct of the study or interpretation of study results
- Subject has previously been included into this study
- Subject unwilling or unable to comply with study requirements (e.g., will not be available for follow-up assessment)
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures (except for subjects with a legally acceptable representative)

6 STUDY SCHEDULE AND PROCEDURES

6.1 Screening period/ eligibility check

The screening period is also referred to as 'M_b' (cfr. Appendix 15.1).

6.1.1 Pre-screening

The indications of eligibility (cfr. 5.1.1 & 5.1.2):

- Wild-type *RAS* tumor status (of tumor tissue)
- Wild-type *BRAF* tumor status (of tumor tissue)
- Unresectable mCRC
- First-line treatment: FOLFOX/FOLFIRI + panitumumab
- ECOG performance status of 0 or 1
- Man or woman 18 years of age or older at the time the informed consent is obtained
- Not meeting the exclusion criteria (cfr. 5.2)

Note[1]: Subjects that are determined not eligible after pre-screening must be listed as screen failure together with the reason for screen failure. Complete the eCRF 'End of Study Form'.

6.1.2 Signing of Informed Consent

Potentially eligible subjects (cfr. 6.1.1) are asked to sign the informed consent form (ICF). Only subjects who have signed the ICF will enter into the post-screening phase.

Note[1]: Subjects that are determined eligible after pre-screening, but who do not wish to participate should be listed as screen failure together with the reason for screen failure. Complete the eCRF 'End of Study Form'.

Note[2]: The ICF must be signed < 28 days before the start of the first-line therapy.

6.1.3 Post-screening

To check the hematologic, renal, hepatic, metabolic, and coagulation function of the patient (cfr. 5.1.3 Laboratory), 1 EDTA tube must be sampled within 14 days before the start of the first-line therapy. The EDTA tube will be analyzed in the local hospital, i.e. the hospital where the patient will be treated. If the laboratory criteria (as described in 5.1.3 Laboratory) are also met, the subject is eligible to include.

Note[1]: If the CT scan at diagnosis (CT_0) has been performed more than 28 days before the start of the first-line therapy, an additional CT scan needs to be performed < 28 days before the start of the first-line therapy.

Note[2]: Subjects that are determined not eligible after post-screening must be listed as screen failure together with the reason for screen failure. Complete the eCRF 'End of Study Form'.

6.2 **Inclusion**

Subjects who meet all inclusion criteria during the pre- and post-screening phase are included in the trial. From now on, the patient's study identification number (ID) must be used to identify the subject throughout the entire clinical study. This unique study ID is automatically assigned by the Electronic Data Capture System "Castor EDC" (cfr. 7.4). The study ID consists of three parts: the trial ID (abbreviation of the trial 'LIFT'), followed by the center ID (abbreviation of the participating center) and the patient ID (three-digit number). The sponsor assigns the abbreviation of the participating center.

Note[1]: For example, an eligible patient in the Antwerp University Hospital could be assigned the study ID 'LIFT_UZA_001'.

As soon as the patient is officially included, the patient is asked to complete the Quality of Life questionnaire, including the EORTC QLQ-C30 and QLQ-CR29 (cfr. Appendix 15.2 & 15.3). This questionnaire must be completed by the day on which first-line therapy starts (M0) at the latest.

6.3 **Start first-line therapy**

Patients will receive FOLFOX/FOLFIRI and panitumumab with therapy guidance according to CT scans. The day on which the first-line therapy starts is named as 'M0'. First-line therapy (FOLFOX/FOLFIRI and panitumumab) is planned to be administered every 2 weeks (± 3 days) (not including the time to recover from toxicities). On the same day of, but <u>before</u> the administration of the first chemotherapy cycle, 3 liquid biopsies (LB_0, LB_a en LB_b) must be sampled. LB_0 will be used to measure the ctDNA level at baseline, and LB_a and LB_b will be used for further research. The 3 LB's must be transported to CMG Antwerp (cfr. 6.5.3).

6.4 **Follow-up**

LB sampling will occur biweekly (not taking into account the time to recover from toxicities, therapy pause or delay) **up to and including 9 months** after the start of first-line therapy. The collection of the liquid biopsy samples will move along with the first day of administration of a new chemotherapy cycle. Each time a next therapy cycle starts, three liquid biopsies should be collected <u>before</u> the therapy is administered. These three liquid biopsies include one Streck tube to measure the ctDNA level, and two Streck tubes that will be used for further research or, if necessary, as a

reserve sample. The LBs should be named after the applicable chemotherapy cycle; LB_2 for the 2nd chemotherapy cycle, LB_3 for the 3th chemotherapy cycle…). It is advised to combine the LB sampling with a routine blood test (standard of care).
When the last liquid biopsies have been collected (i.e. on the day of, but before the administration of the last therapy cycle that takes place in the 9 months after starting first-line therapy), the LB sampling stops. The patient has to complete the EORTC QLQ-C30, QLQ-CR29, and the patient experience questionnaire (cfr. Appendix 15.4 & 15.5). A time window of 7 days after M9 is allowed to complete the questionnaire.
After this, the treating physician will continue the patients' treatment conform the standard clinical practice.

Tumor response assessment will be performed by the local investigator per modification of RECIST 1.1 guidelines on bimonthly CT scans (not taking into account the time to recover from toxicities, therapy pause or delay) together with a CEA test, up to and including the next imaging (CT scan) that is performed after the collection of LBs has stopped. Thus, the CT scans will also move along with the administered chemotherapy cycles. In case of biweekly administration of therapy without delay or therapy pause, the bimonthly CT scans and CEA test correspond to the moments of evaluation of chemotherapy cycle 4, 8, 12, 16 and 20. Treatment is changed upon CT scan results (conform standard clinical practice).

With the exception of what is described in chapter 6.8, **the subjects will be followed (and thus the collection of follow-up data continues) until the next imaging (CT scan) that is performed after the collection of LBs has stopped, provided that this imaging is performed within 11 months of follow-up** (cfr. Appendix 15.1). The imaging refers to the CT scan that aims to evaluate the last administered chemotherapy cycle that was given within 9 months after the start of first-line therapy. If, for any reason, this CT scan will be performed > 11 months after the start of first-line therapy, or no CT scan will be performed after the last collection of LBs, the study ends when the subject has reached 11 months of follow-up.

Notes:

- In the event that **chemotherapy is delayed** due to poor blood results, and 3 liquid biopsies were already collected together with the routine blood test, 3 new liquid biopsies must be collected on the same day of, but before the administration of the newly scheduled chemotherapy cycle.
- No limitation is imposed on the duration of **therapy pause**. As soon as the therapy is restarted, the LB sampling continues as described in the protocol.

- If the **therapy changes** (i.e. stop FOLFOX/FOLFIRI and panitumumab) throughout the follow-up period, the follow-up procedure continues according to the protocol (i.e. LB-sampling on the first day of administration of the new therapy cycle up to and including 9 months after the start of the first-line therapy).
- If a **metastasectomy** is planned, 1 liquid biopsy must be taken on the day of, but before surgery. A second liquid biopsy must be collected within the next 2 days, excluding the day of surgery. After this, no more liquid biopsy samples need to be collected.
- After **progression** on CT scan, the patient will continue with standard of care as decided by the treating physician. The follow-up schedule is maintained. The LB sampling still continues up to and including 9 months after the start of first-line therapy but will then be linked/combined with the new therapy.
- If it is appropriate to perform a **MRI scan** during follow-up, this should be reported in the eCRF.

6.5 Sample collection

6.5.1 *RAS* and *BRAF* wild-type tumor status

The local hospital is responsible for analyzing the wild-type *RAS* and *BRAF* tumor status of the tumor tissue.

6.5.2 CEA level

The local hospital is responsible for analyzing the bimonthly CEA level, which has to be reported in the appropriate eCRF.

6.5.3 Liquid biopsies

The sponsor provides pre-prepared kits, each consisting of three Streck tubes for liquid biopsy sampling. The pre-prepared kit must be used when collecting the biweekly liquid biopsies. All samples will be transported to the Center for Medical Genetics (CMG) in Antwerp for *NPY* methylation analyses.

The local investigator (team) is responsible for registering the samples in a specific Excel-file, also provided by the sponsor, which has to be sent by e-mail to the CMG Antwerp. The samples are preferably sent on the day of collection (if not possible; no later than the following day) with a transport company to the CMG. Delivery is only possible on workdays (Monday to Friday) between 8:00 am and 4:30 pm. Samples that are collected on Friday and that cannot be sent the same day due to circumstances must be transported to the CMG next Monday. Until then, the liquid biopsy samples must be stored between 6°C and 37°C.

Note[1]: In the case of metastasectomy, 1 liquid biopsy must be taken on the day of, but before surgery. A second liquid biopsy must be collected within the next 2 days, excluding the day of surgery. However, both LB samples must be transported together to the CMG. Both samples are preferably sent on the day of collection of the second LB sample (if not possible; not later than the following day). If the second sample is collected on Friday and it is not possible to send both LBs the same day, the samples must be transported to the CMG next Monday.

*Note[2]: In the event that **chemotherapy is delayed** due to poor blood results, and 3 liquid biopsies were already collected together with the routine blood test, 3 new liquid biopsies must be collected on the same day of, but before the administration of the newly scheduled chemotherapy cycle. All LB samples (a total of 6 Streck tubes) must be transported together to the CMG.*

Note[3]:The Sponsor decides which transport company to work with.

6.6 **Questionnaire**

The questionnaire is available both on paper and digitally. The patient is free to choose which option he/she prefers. Paper questionnaires must be entered into the database Castor EDC by the local or central study team, and must be saved on site. Digital questionnaires are available via a web link, which Castor EDC automatically sends to the patient via email. Completed digital questionnaires are automatically imported into the patient record in Castor EDC. Completing the digital questionnaire is only possible if the patient explicitly indicates in the Informed Consent whether he/she agrees to share his/her email address with the Sponsor.

6.7 **Protocol compliance**

Protocol compliance will be checked after inclusion of the first 20 patients. This approach will guarantee that no important aspects are overlooked in order to follow the protocol faultless. The flow of collecting and transport of blood samples, communication of both blood results and CT evaluation, and completion of the eCRFs will be checked for unexpected barriers.

6.8 **End of study**

6.8.1 Study completion

The study is completed after performing the first imaging (CT scan) following the last collection of liquid biopsies according to the study protocol, provided that this imaging is performed within 11 months of follow-up. However, a maximum follow-up period of 11 months applies to all study

patients, regardless of whether or not the first imaging following the last collection of liquid biopsies has been performed. When study completion is reached, the collection of follow-up data stops. (S)AE reporting continues until 14 days after study completion.

Note[1]: In case of biweekly administration of therapy without delay or therapy pause, the moment of study completion corresponds to the 10th month of follow-up.

6.8.2 Changes in a patient's condition

This section refers to (1) changes in a patient's condition that renders the patient not suitable for further treatment/participation in the judgment of the investigator, or (2) major protocol violation or discovery of information that, if previously known, would have rendered the patient ineligible for study.

6.8.2.1 Before 9 months of follow-up

The collection of liquid biopsies stops.

The patient has to complete the 2nd questionnaire including the EORTC QLQ-C30, QLQ-CR29, and the patient experience questionnaire (cfr. Appendix 15.4 & 15.5). A time window of 7 days after end of study is allowed to complete the questionnaire.

The collection of follow-up data (i.e. (serious) adverse event reporting, chemotherapy information, response imaging and CEA level) continues until 11 months of follow-up (i.e. 11 months after M0) is reached.

6.8.2.2 After 9 months of follow-up

The collection of liquid biopsies has already stopped after M9.

The collection of follow-up data (i.e. (serious) adverse event reporting, chemotherapy information, response imaging and CEA level) continues until the next imaging (CT scan) that is performed after the collection of LBs has stopped (at M9). If, for any reason, this CT scan will not be performed, the collection of follow-up data continues until 11 months of follow-up is reached.

6.8.3 Metastasectomy

In the case that the patient will undergo metastasectomy, one liquid biopsy must be taken on the day of, but before surgery. A second liquid biopsy must be collected within the next 2 days, excluding the day of surgery.

6.8.3.1 Before 9 months of follow-up

The further collection of liquid biopsies stops.

The patient has to complete the 2nd questionnaire including the EORTC QLQ-C30, QLQ-CR29,

and the patient experience questionnaire (cfr. Appendix 15.4 & 15.5). A time window of 7 days after end of study is allowed to complete the questionnaire.

The collection of follow-up data (i.e. (serious) adverse event reporting, chemotherapy information, response imaging and CEA level) continues until 11 months of follow-up is reached.

6.8.3.2 After 9 months of follow-up

The further collection of liquid biopsies stops.

The collection of follow-up data (i.e. (serious) adverse event reporting, chemotherapy information, response imaging and CEA level) continues until the next imaging (CT scan) that is performed after the collection of LBs has stopped at 9 months of follow-up. If, for any reason, this CT scan will not be performed, the collection of follow-up data continues until 11 months of follow-up is reached.

6.8.4 Death

When a patient dies, all efforts should be made to complete and report the observations as thoroughly as possible.

6.8.5 Withdrawal of consent

Patients can leave the study at any time for any reason if they wish to do so without any consequences. Should a patient decide this by withdrawal of consent, all efforts will be made to complete and report the observations as thoroughly as possible. No further data (including the questionnaire) and liquid biopsies will be collected after the date of withdrawal from study. Data that was already collected will be stored and used for analysis. The Investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

6.8.6 Withdrawn consent with data withdrawal

Patient withdraws informed consent and requests to delete all of his/her previously collected data from the study. No further data (including the questionnaire) and liquid biopsies will be collected after the date of withdrawal from study.

6.8.7 Lost to follow-up

In the case of patients who miss scheduled visits, several attempts should be made by the site to contact these patients for follow-up information. The collection of follow-up data is extremely important regarding the reliable estimation of study endpoints, therefore at least 3 attempts within

a reasonable extent of time should be made to try to contact the patients if they do not attend clinic visits. If any of the trial patients are lost to follow-up, contact will initially be attempted through the trial research nurse or the lead investigator at each center. Where this attempt is unsuccessful, the patient's general practitioner will be contacted and asked to contact the patient or her/his family and provide follow-up information to the recruiting center. It is only after sufficient attempts at contacting the patient have been unsuccessful, that a patient may be declared "Lost to follow-up". The collection of follow-up data (i.e. (serious) adverse event reporting, chemotherapy information, response imaging and CEA level) stops as soon as the patient has been declared 'lost to follow-up'.

6.9 **Duration of the study**

Inclusion of patients in this trial starts when all necessary ethical approvals have been obtained, and the Clinical Trial Agreement has been signed. The subject accrual period runs until the predetermined number of study patients is reached (i.e. 60 subjects).
First-line therapy is administered at the start of the study (i.e. M0 or chemotherapy cycle n°1). The study ends for the patient when the first imaging (CT scan) is performed following the last collection of LBs according to the study protocol, when a follow-up period of 11 months is reached, after surgery (metastasectomy), after withdrawal of the written consent or when the patient dies (cfr. 6.8).

6.9.1 Early study termination

The Sponsor may terminate this study at any time. Reasons for termination may include, but are not limited to the following:

- Insufficient subject enrolment.
- Any information becoming available during the study that substantially changes the expected benefit of the study.

The subject accrual period stops immediately. However, the follow-up of previously enrolled subjects continues according to the protocol.
The collection of LBs stops as soon as 9 months of follow-up is reached (except for metastasectomy cfr. 6.8.3, and death). At M9, the patient has to complete the EORTC QLQ-C30, QLQ-CR29 and the patient experience questionnaire (cfr. Appendix 15.4 & 15.5). A time window of 7 days after M9 is allowed to complete the questionnaire. The collection of follow-up data (i.e. adverse event reporting, chemotherapy information, response imaging and CEA level) continues until the next imaging (CT scan) that is performed after the collection of LBs has stopped, or when 11 months of follow-up is reached.

7 METHODOLOGY

7.1 Study schedule

The complete schedule of assessments is outlined in Table 1.

Additional assessments, such as urinalysis or other laboratory assessments, can always be performed by the treating physician if deemed necessary. Additional CT scans can also be made, for example when the treating physician has clinical indications for progression. Results from additional tests or data from additional visits (for example if requested by the patient) will be collected for the study. Study visits in the hospital will take place in the treating hospital of the patient.

Table 1. Schedule of assessments

	Pre-screening	Post-screening	Start first-line therapy - M0	M0 + every 2 weeks◂ (up to and including M9)	M0 + every 8 weeks	EOS: study completion (i.e. first CT scan after last LB collection$^{\Delta}$)	EOS: metastasectomy, changes in patient's condition	EOS : withdrawal, death, lost to follow-up
Inclusion/exclusion criteria	X	X						
Informed consent		X						
Demographics	X	X						
ECOG	X					X	X	X$^{¤}$
Medical history	X							
Pregnancy test▪		X						
Laboratory assessments		X		X$^{\pi}$	X$^{\pi}$			
CT scan		X*			X	X$^{\Delta}$		
Blood sample for LB_a and LB_b			X_2					
Blood sample for LB_x			X_1	X_3	X_3		X_2**	
CEA level		X			X	X$^{\Delta}$		
Therapy information	X		X	X	X	X		

Quality of Life Questionnaire (EORTC QLQ-C30 + QLQ-CR29			X∞	X♦			X¥	
Patient Experience Questionnaire				X♦			X¥	
(S)AE's			Continuously					
Documentation + reason end of study						X	X	X

∞ To be completed as soon as the patient is included, and by the day on which first-line therapy starts (M0) at the latest
¥ To be completed only if < 9 months follow-up
▲ At the start of, but before the administration of each chemotherapy cycle (cfr. 6.4. Follow-up, Notes)
▪ Serum pregnancy test; to be performed ≤ 14 days prior to start therapy (for women of childbearing potential only)
♦ To be completed only after reaching 9 months of follow-up (i.e. last collection of LBs)
Δ If, for any reason, no CT scan will be performed after the collection of LBs have stopped, study completion is reached after 11 months of follow-up
π It is advised to combine the LB sampling with a routine blood test (standard of care)
¤ ECOG should not be determined in case of death
* Only if diagnostic CT scan is performed > 28 days before the start of the first-line therapy
** Only in the case of metastasectomy: collection of one LB sample on the day of surgery but before the operation, and a second LB sample within the next 2 days, excluding the day of surgery
1 Only one blood sample (Streck tube) is needed
2 Two blood samples (Streck tubes) are needed
3 Three blood samples (Streck tubes) are needed

7.2 **Assessments and study visits**

7.2.1 Screening period (Mb)

Pre-screening

- Eligibility check (inclusion/exclusion criteria) including *BRAF* and *RAS* WT
- Demographics (age)
- ECOG
- Medical history
- Therapy information

Written informed consent should be obtained prior to enrolment in the post-screening phase:

- Demographics (age, sex, ethnic origin)
- Therapy information
- Serum pregnancy test ≤ 14 days prior to start therapy (for women of childbearing potential

only)

- Laboratory assessments:
  hematology (erythrocytes/haematocrit, hemoglobin, neutrophils, thrombocytes, leukocytes, leukocyte formula), biochemistry (creatinine, creatinine clearance, ureum, sodium, potassium, chloride, bicarbonate, calcium, phosphor, magnesium, uric acid, CRP, total protein, albumin, glucose (serum), LDH, AST(GOT), ALT(GPT), alkaline phosphatase, GGT, amylase, bilirubin + fractions, cholesterol, triglycerides), liver function tests (PTT, aPTT, INR), TSH, urinalysis (urinary protein or UPC)
- CT scan → only if diagnostic CT scan is performed > 28 days before the start of first-line therapy
- CEA level at baseline

7.2.2 Start first-line therapy (M0)

- Streck tubes for LB_0, LB_a and LB_b
- Questionnaire (EORTC QLQ-C30 + QLQ-CR29): to be completed as soon as the patient is included, and by the day on which first-line therapy starts (M0) at the latest
- Therapy information
- If applicable: (S)AE reporting

7.2.3 M0 + every 2 weeks (up to and including M9)

Note: Biweekly LB sampling is only applicable if there is no therapy pause or delay; LB sampling will move along with the start of a new chemotherapy cycle.

- Chemotherapy cycle 2, 3, 4, ..., 19
- Laboratory assessments: routine blood test
- The routine blood test should include, but will not be limited to the following:
  - Hematology
  - Erythrocytes/hematocrit
  - Hemoglobin
  - Neutrophils
  - Thrombocytes
  - Leukocytes
  - Leukocyte formula
- Collection of liquid biopsies
  - Streck tube for LB_x

- Extra Streck tubes for further research
- Therapy information
- Questionnaire: Quality of Life (QLQ-C30 + QLQ-CR29) & Patient Experience: to be completed when reaching 9 months of follow-up (i.e. last collection of LBs)
- If applicable: (S)AE reporting

7.2.4 M0 + every 8 weeks

Note: Bimonthly CT scan is only applicable if there is no therapy pause or delay; CT scans will move along with the administered chemotherapy cycles.

- Laboratory assessments: routine blood test (cfr. 7.2.3)
- CT scan (last imaging to be performed is the next CT scan following the last LBs that have been collected at M9)
- CEA level (up to and including the next CT scan following the last LBs that have been collected at M9)
- Collection of liquid biopsies
  - Streck tube for LB_x (up to and including M9)
  - Extra Streck tubes for further research (up to and including M9)
- Therapy information
- If applicable: (S)AE reporting

7.2.5 End of study [EOS] in case of study completion

- EOS is reached after performing the next imaging (CT scan) following the last liquid biopsies that have been collected at M9
  - CT scan
  - CEA level
- ECOG
- Therapy information
- If applicable: (S)AE reporting until 14 days after EOS
- Confirmation and documentation reason for end of study

Note: If, for any reason, no CT scan will be performed after the collection of LBs have stopped, study completion is reached after 11 months of follow-up.

7.2.6 End of study in case of metastasectomy

- Collection of liquid biopsies
  - One Streck tube on the day of surgery but before the operation
  - Second Streck tube within the next 2 days, excluding the day of surgery
- ECOG
- Therapy information
- Questionnaire: Quality of Life (QLQ-C30 + QLQ-CR29) & Patient Experience: to be completed if metastasectomy takes place before 9 months of follow-up
- If applicable: (S)AE reporting until 14 days after EOS
- Confirmation and documentation reason for end of study

7.2.7 End of study in case of changes in a patient's condition

- ECOG
- Therapy information
- Questionnaire: Quality of Life (QLQ-C30 + QLQ-CR29) & Patient Experience: to be completed if metastasectomy takes place before 9 months of follow-up
- If applicable: (S)AE reporting until 14 days after EOS
- Confirmation and documentation reason for end of study

7.2.8 End of study in case of withdrawal

- ECOG
- Confirmation end of study + documentation reason of withdrawal

7.2.9 End of study in case of lost to follow-up

- ECOG
- Confirmation end of study + documentation of lost to follow-up

7.2.10 End of study in case of death

- Confirmation end of study + documentation reason of death

7.3 Summary of study procedures

7.3.1 Summary of study specific procedures

The procedures listed and described in this section are specific to the study and are not part of standard clinical care.

- Screening period
  - Informed Consent Form
  - eCRF completion
  - Specific laboratory assessments (cfr. 5.1.3) < 14 days before start therapy
  - Serum pregnancy test (if applicable)
  - Additional CT scan if the CT scan at diagnosis (CT_0) is performed > 28 days before start therapy
  - Quality of Life questionnaire

- Start first-line therapy
  - Collection of liquid biopsies (LB)
  - Transportation of LBs to CMG Antwerp
  - eCRF completion

- Follow-up
  - Biweekly collection of liquid biopsies(3 samples) up to and including M9
    - Exceptions: delay of therapy (cfr. 6.4. Notes) and metastasectomy (cfr. 6.8.3)
  - Transportation of LBs to CMG Antwerp
  - Bimonthly CEA test up to and including the next imaging (CT scan) following the last LBs that have been collected at M9
  - eCRF completion
  - M9: Quality of Life and Patient Experience questionnaire

7.3.2 Summary of standard of care study procedures

- Screening period
  - CEA level at baseline

- Start first-line therapy
  - First-line therapy FOLFOX/FOLFIRI and panitumumab planned to be administered every 2 weeks (± 3 days)
  - Bimonthly CT scan

- Follow-up
  - Routine blood test before the start of new chemotherapy cycle
  - Tumor response assessment per modification of RECIST 1.1 guidelines on bimonthly CT scan
  - Decision of the treating physician to change therapy according to the outcome of the bimonthly CT scan
  - Decision of the treating physician to delay chemotherapy
  - Decision of the treating physician to perform a metastasectomy

7.4 Data collection and data storage encoding

Clinical information about the patients, collected at the study visits in the hospital or by the external partner will be encoded and put in an eCRF of the Electronic Data Capture System “Castor EDC”. The management of this central database is performed by the Multidisciplinary Oncology Centre Antwerp (MOCA) of the Antwerp University Hospital in Edegem, Belgium. UZA is owner of the database and the information will be kept for at least 30 years after study termination.
Patient reported outcomes are collected through questionnaires on a web-based customized survey (created in Castor EDC) meeting the requirements of the privacy commission. The results from the analysis of liquid biopsies will be collected in the eCRFs in Castor EDC, as well as in an encrypted Excel-file on a shared IT-platform of UZA. Only investigators of CMG Antwerp and MOCA will have access to this encrypted document. All individual patient documentation is stored encoded and the same code is used in both the central database with CRFs and the web-based survey. All liquid biopsies will be stored at the biobank of UZA. Biobank specimens and the patient’s associated clinical data will be stored for 30 years. The management of intellectual property rights and the ownership of the data is discussed in detail in the contract documents.

7.5 Evaluation of data

7.5.1 Tumor response evaluation

CT scan: Image analysis will be performed locally and also the decision about progression will be made in the treating center.

7.5.2 ctDNA analysis

As described, liquid biopsies contain, except for ctDNA, circulating DNA originating from non-malignant cells. One can differentiate ctDNA from non-malignant DNA by selecting on a base of *NPY* methylation (22). The blood samples will be centrifuged according to protocol (two-step high speed). Hereafter, the plasma fraction and cell pellet will be stored and analyzed separately. To enable an objective analysis, the CMG Antwerp is blinded and will therefore not be aware of the disease status of the study patients during the course of the study. The results of the *NPY* methylation analyses will be reported to the central study coordinator of the Antwerp University Hospital.

8 STATISTICAL CONSIDERATIONS

8.1 Sample size calculation

The primary endpoint is the optimal cutoff value of *NPY* methylation to discriminate between

progressive and non-progressive disease (as determined by CT). For the sample size calculation, we have based ourselves on the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curve using *NPY* methylation. In order to construct a 95% confidence interval for the AUC of width 0.2 and assuming an AUC of 0.9 we need at least a group of 27 patients with progressive disease and a group of 27 patients without progressive disease. Assuming a median PFS of 9 months, we will need to include 54 patients and follow them up for 9 months. However, it is expected that about 10-15% of the study population (*RAS* and *BRAF* WT unresectable mCRC) may become resectable by conversion therapy (FOLFOX/FOLFIRI and panitumumab) (37-39). Taking this into account, the total number of patients to be included is **60**.

8.2 Primary analysis

To determine the optimal cutoff value of the *NPY* methylation to discriminate between progressive and non-progressive disease (as determined by CT), we will develop a Receiver Operating Characteristic (ROC) curve with data of this lead-in study. ROC curves show the trade-off between sensitivity and specificity and the Area Under the Curve (AUC) is considered as an index of accuracy. The AUC will be calculated, and the optimal cutoff will be determined.

8.3 Secondary analysis

- In the primary analysis we compare *NPY* methylation values and progression status (as determined by CT) taken at the same time point. As a secondary analysis we will study if *NPY* methylation values at earlier time points can predict progression status later on. For this also ROC-curves will be used.
- A logistic regression model predicting progressive disease using *NPY* methylation values as a predictor will be considered. This model will allow correction for other variables (e.g. age).
- To determine the progression free survival in patients with metastatic colorectal cancer defined as time from inclusion to the date of first disease progression among subjects with metastatic colorectal cancer per RECIST 1.1 criteria, or death. Progression free survival will be presented with a Kaplan-Meier curve and median progression free survival with corresponding 95% confidence interval will be reported.
- For the 9-month survival the percentage alive at 9 months after start of first-line therapy will be reported with corresponding 95% confidence interval.

8.4 Exploratory analysis

- In this study, we will exploratively compare the use of ctDNA and CEA to predict progression, through logistic regression models. To compare these two methods, we will take sensitivity,

specificity, negative predictive value and positive predictive value into account. This study will result in useful preliminary data that can be further studied in future projects. Moreover, this data might lead to more correct determination of effect sizes, which can be used for power calculations for future studies.

- The further exploration of ctDNA in liquid biopsies and search for novel biomarkers can result in important leads that can be systematically studied in deeper extent in further projects.
- We will exploratively study patient experience through short questionnaires. The results of these questionnaires can lead to interesting qualitative information which can be used to optimize patient care and/or the protocol of the next (randomized) phase of the FOLICOLOR trial.
- The quality of life and the patient experience measured by the questionnaires will be reported with descriptive statistics.

9 SAFETY REPORTING

9.1 Ethical Committee

The investigator will inform the subjects and the reviewing accredited Ethical Committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited Ethical Committee, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 Adverse events

9.2.1 Definition Adverse Event (AE)

Adverse events are defined as any undesirable experience occurring to a subject during the study that need not be related to treatment. An adverse event is any unfavorable, unintended diagnosis, symptom, sign (including abnormal laboratory finding), syndrome, or disease that occurs during the study, having been absent at baseline, or –if present at baseline- appears to worsen. All adverse events, including chemotherapy toxicities of all grades, reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Definition Unexpected Adverse Event (UAE)

An unexpected adverse event is defined as an adverse event that is not mentioned in the protocol or consent documents, or an AE that has not been seen before. Additionally, unexpected AEs in this study can be considered as unanticipated problems involving risks to study participants and others as an event that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (i.e. the incident, experience, or outcome may have been caused by the procedures involved in the research).

9.2.3 Recording of AEs

All AEs, reported spontaneously by the subject or observed by the investigator or his staff will be recorded on the AE form of the CRF with the following information:

1. The severity grade according to the NCI-CTCAE version 5.0, published November 27, 2017 (The complete document can be reviewed and downloaded from the following internet site:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (1=mild, 2=moderate, 3=severe, 4=life threatening)

2. Whether it constitutes an UAE or SAE

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); chemotherapy temporarily interrupted; chemotherapy permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the AE CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changed in severity, the interventions required to treat it, and the outcome.

9.2.4 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.3 Serious Adverse Events

9.3.1 Definition Serious Adverse Event

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death
- is life threatening (at the time of the event)
- requires hospitalization or prolongation of existing patients' hospitalization
- results in persistent or significant disability or incapacity

*Note: In this study, admission for diagnosis or treatment of recurrences are **not** considered a SAE*

9.3.2 Recording of SAEs

All SAEs must be reported initially in Castor EDC. The PI must sign the completed SAE report electronically in Castor EDC as soon as possible but no later than one working day from the time the local investigator has first knowledge of the SAE. Castor EDC will automatically send a notification to the central study coordinator when the SAE report has been created. The central Ethics Committee of UZA will inform the Medical Ethics Committee(s) of the participating centers.

The (S)AE report must be updated after initial submission in Castor EDC as soon as final data related to the (S)AE is available.

9.4 **(Suspected) Unexpected (Serious) Adverse Reactions**

Since the LEAD-IN FOLICOLOR Trial is a prospective interventional study in which there is no investigational product, (S)U(S)AR reporting does not apply.

9.5 **Annual report**

The sponsor will submit once a year throughout the clinical trial an annual report to the central ethical committee of the UZA for distribution to all ethical advisory boards of participating hospitals.

This annual report consists of:

- A status update of the trial, including but not limited to the following: date of EC approval, date of inclusion of first study patient, total number of patients included, total number of patients who discontinued their participation (end of study);
- An aggregated summary table of all serious adverse events, ordered by organ system.

10 ADMINISTRATION PROCEDURES AND PUBLICATION

10.1 Regulatory Approval

As required by local regulations, the sponsor will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

10.2 Publication Policy

The sponsor encourages acknowledgement of all individuals/organizations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.
The results of this study may be published or communicated to scientific meetings by the investigators involved in the study.

10.3 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study.

10.4 Insurance, Indemnity and Compensation

The sponsor has a liability insurance which will be annually renewed.

11 MONITORING

Monitoring in Belgium will be done according to ICH-GCP E6 Guideline and by medically qualified personnel. The LEAD-IN FOLICOLOR Trial is classified as a low-risk trial and therefore minimal monitoring is required. The purposes of trial monitoring are to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

Objective of on-site monitoring:

- To identify procedural errors in the execution of the research

Central monitoring:

- Detection of missing, late and inaccurate research

Source Data Verification:

- Monitoring will be performed according to the Data Monitoring Plan, which can be consulted in the Trial Master File that is saved in the Antwerp University Hospital.

11.1 Overview of data collection

Demographics	- Sex - Age - Language - Race - Date of birth - Weight
Inclusion criteria	- Cfr. 5.1
Exclusion criteria	- Cfr. 5.2
Baseline	- Location of tumor - Relevant medical history - Recent blood transfusion
Follow-up	- Chemotherapy information: name, dose, (date of) administration - Imaging: imaging technique, date of imaging - Report of target lesions: sum of diameters, general evolution - Report of non-target lesions: sum of diameters, general evolution - Assessment of new lesions: type, location - CEA: level, date
Adverse Events	- According to the NCI-CTCAE version 5.0, published November 27, 2017 - System organ code - AE term

	- Start date - Outcome - End date - Severity - Relation to therapy - Relation to liquid biopsy sampling - Action with (chemo)therapy - Treatment of AE (incl. medications) - Unexpected AE
Serious Adverse Events	- Patient initials - System organ code - SAE term - Description of the SAE incident - Onset period & date - Severity - Category - Outcome - Date of recovery - Relation to therapy - Relation to liquid biopsy sampling - Action with (chemo)therapy - Treatment of SAE (incl. surgery, medications) - Relevant medical history - Contact person (name, e-mail address, telephone number)
Death	- Date of death - Autopsy (report) - Cause of death
End of Study	- Last date in study - ECOG - Reason for end of study - Date of metastasectomy
Questionnaire	- Dutch: cfr. Appendix 15.2 & 15.3 - French: cfr. Appendix 15.4 & 15.5
Liquid Biopsy Sampling	- Confirmation LB collection - Date of collection - Reason for missing LBs - Confirmation shipment of LBs

11.2 Mandatory data

Castor EDC visualizes which data is mandatory, and which data can be entered without obligation.

11.3 Data entry & monitoring guidelines

The guidelines for data entry and monitoring in Castor EDC can be consulted in the Data Entry Manual.

12 STUDY ADMINISTRATION

12.1 Coordinating Study Team

The Coordinating Study Team will govern the conduct of the study. The Coordinating Study Team will be composed of the Chief Investigator, the central study coordinator of UZA, representatives of CMG Antwerp, representatives of the UZA Biobank, and representatives of Amgen.

13 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

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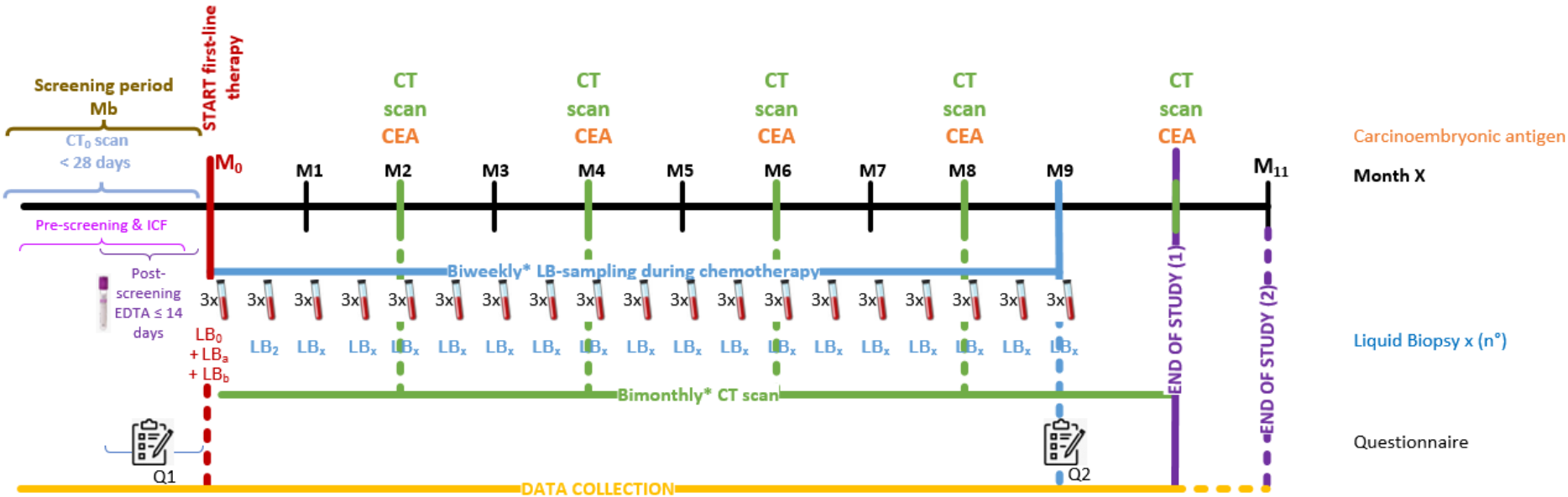
15 APPENDIX

15.1 Follow-Up Scheme



- Post-screening is only possible after signing the ICF
- *Biweekly LB-sampling is only applicable if the time to recover from toxicities, therapy pause or delay are not taken into account. LB sampling and imaging will move along with the administered chemotherapy cycles.
- CT_0: If CT scan at diagnosis has been performed more than 28 days before the start of the therapy, an additional CT scan needs to be performed before start therapy
- The LB samples must be collected on the same day of, but before the administration of the chemotherapy (thus, the collection of the LB samples will move along with the first day of administration of the new chemotherapy cycle).
- If applicable, it is advised to combine the LB sampling with a routine blood test (standard of care).
- In the event that chemotherapy is delayed due to poor blood results, and 3 LB samples were already collected together with the routine blood test, 3 new LB samples must be collected before the newly scheduled chemotherapy is administered
- If a metastasectomy is planned, a LB sample must be taken on the day of surgery, but before the operation. A second LB sample must be collected within the next 2 days, excluding the day of surgery.
- Q1: EORTC QLQ-C30 + CR29
- Q2: EORTC QLQ-C30 + CR29 + patient experience
- End of Study is reached when the first imaging (CT scan) following the last liquid biopsies taken is performed (1). If, for any reason, no CT scan will be performed after the collection of LBs have stopped, study completion is reached after 11 months of follow-up (2).

15.2 Questionnaire 1 (Dutch version)

Meetmoment vragenlijst: start eerstelijnstherapie

Mijn geboortedatum (ter controle): __ __ / __ __ / __ __ __ __ (Dag/Maand/ Jaar)

Datum van vandaag: __ __ / __ __ / __ __ __ __ (Dag/Maand/ Jaar)

Mijn geslacht: ☐ Man ☐ Vrouw

EORTC QLQ-C30 – Kwaliteit van leven

Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is? Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

	Helemaal niet	Een beetje	Nogal	Heel erg
1. Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
2. Heeft u moeite met het maken van een lange wandeling?	1	2	3	4
3. Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
4. Moet u overdag in bed of in een stoel blijven?	1	2	3	4
5. Heeft u hulp nodig met eten, aankleden, u zelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
6. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
7. Was u beperkt in het uitoefenen van uw hobby's of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
8. Was u kortademig?	1	2	3	4
9. Heeft u pijn gehad?	1	2	3	4
10. Had u behoefte om te rusten?	1	2	3	4

Volgende pagina, a.u.b.

11. Heeft u moeite met slapen gehad?	1	2	3	4
12. Heeft u zich slap gevoeld?	1	2	3	4
13. Heeft u gebrek aan eetlust gehad?	1	2	3	4
14. Heeft u zich misselijk gevoeld?	1	2	3	4

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
15. Heeft u overgegeven?	1	2	3	4
16. Had u last van obstipatie? (Was u verstopt?)	1	2	3	4
17. Had u diarree?	1	2	3	4
18. Was u moe?	1	2	3	4
19. Heeft pijn u gehinderd in uw dagelijkse bezigheden?	1	2	3	4
20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
21. Voelde u zich gespannen?	1	2	3	4
22. Maakte u zich zorgen?	1	2	3	4
23. Voelde u zich prikkelbaar?	1	2	3	4
24. Voelde u zich neerslachtig?	1	2	3	4
25. Heeft u moeite gehad met het herinneren van dingen?	1	2	3	4
26. Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?	1	2	3	4
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?	1	2	3	4
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Volgende pagina, a.u.b.

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is:

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

EORTC QLQ-CR29 – Ziekte-specifieke levenskwaliteit

Soms zeggen patiënten dat ze de volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze klachten of problemen gedurende de afgelopen week heeft ervaren? Wilt u de vragen beantwoorden door het vakje aan te kruisen dat het meest op u van toepassing is?

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
31. Heeft u overdag meer dan gewoonlijk geplast?	1	2	3	4
32. Heeft u 's nachts meer dan gewoonlijk geplast?	1	2	3	4
33. Heeft u ongewild urine verloren?	1	2	3	4
34. Heeft u pijn gehad bij het plassen?	1	2	3	4
35. Heeft u buikpijn gehad?	1	2	3	4
36. Heeft u pijn gehad in uw zitvlak of bij uw anus?	1	2	3	4
37. Heeft u een opgeblazen gevoel gehad in uw buik?	1	2	3	4
38. Heeft u bloed in uw ontlasting gehad?	1	2	3	4

Volgende pagina, a.u.b.

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
39. Heeft u slijm in uw ontlasting gehad?	1	2	3	4
40. Heeft u een droge mond gehad?	1	2	3	4
41. Heeft u haaruitval gehad ten gevolge van uw behandeling?	1	2	3	4
42. Heeft u problemen met uw smaak gehad?	1	2	3	4
43. Heeft u zich zorgen gemaakt over uw gezondheid in de toekomst?	1	2	3	4
44. Heeft u zich zorgen gemaakt over uw gewicht(sverlies)?	1	2	3	4
45. Voelde u zich lichamelijk minder aantrekkelijk ten gevolge van uw ziekte of behandeling?	1	2	3	4
46. Voelde u zich minder vrouwelijk/mannelijk ten gevolge van uw ziekte of behandeling?	1	2	3	4
47. Was u ontevreden met uw lichaam?	1	2	3	4

48. Heeft u een stoma? (dunnedarm-stoma of dikkedarm-stoma)
    - ☐ Ja
    - ☐ Nee

Beantwoord deze vragen (vraag 49 tot en met 55) ALLEEN ALS U <u>EEN STOMA</u> HEEFT, zo niet, ga dan naar vraag 56.

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
49. Heeft u last gehad van het ongewild vrijkomen van gas (winderigheid) uit uw stoma?	1	2	3	4
50. Was er lekkage van ontlasting uit uw stomazakje?	1	2	3	4
51. Heeft u een pijnlijke huid gehad rond uw stoma?	1	2	3	4
52. Heeft u <u>overdag</u> vaak het stomazakje moeten vervangen?	1	2	3	4
53. Heeft u <u>'s nachts</u> vaak het stomazakje moeten vervangen?	1	2	3	4
54. Voelde u zich ongemakkelijk/opgelaten door uw stoma?	1	2	3	4
55. Heeft u problemen gehad met de verzorging van uw stoma?	1	2	3	4

Volgende pagina, a.u.b.

Beantwoord deze vragen (vraag 56 tot en met 61) ALLEEN ALS U GEEN STOMA HEEFT.

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
56. Heeft u last gehad van het ongewild vrijkomen van gas (winderigheid)?	1	2	3	4
57. Heeft u ongewild ontlasting verloren?	1	2	3	4
58. Heeft u een pijnlijke huid gehad rondom uw anus?	1	2	3	4
59. Heeft u overdag vaak ontlasting gehad?	1	2	3	4
60. Heeft u 's nachts vaak ontlasting gehad?	1	2	3	4
61. Voelde u zich ongemakkelijk/opgelaten door uw ontlastingspatroon?	1	2	3	4

Gedurende de afgelopen 4 weken: (alleen voor MANNEN)

	Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
62. In hoeverre had u zin in seks?	1	2	3	4
63. Indien u seksueel actief was (met of zonder geslachtsgemeenschap): had u moeite met het stijf worden of blijven van uw penis?	1	2	3	4

Gedurende de afgelopen 4 weken: (alleen voor VROUWEN)

	Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
64. In hoeverre had u zin in seks?	1	2	3	4
65. Indien u geslachtsgemeenschap heeft gehad: had u pijn of ongemak tijdens de gemeenschap?	1	2	3	4

Bedankt voor het invullen van deze vragenlijst!

Het FOLICOLOR Lead-In onderzoeksteam

15.3 Questionnaire 1 (French version)

Questionnaire à remplir après 9 mois de suivi ou fin d'étude prématuré

Ma date de naissance (pour vérification): __ __ / __ __ / __ __ __ __ (Jour/Mois/ Année)

Date d'aujourd'hui: __ __ / __ __ / __ __ __ __ (Jour/Mois/ Année)

Sexe: ☐ Masculin ☐ Féminin (marquer d'une croix la bonne case)

EORTC QLQ-C30 – Qualité de vie

Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.

	Pas du tout	Un peu	Assez	Beaucoup
66. Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provisions chargé ou une valise?	1	2	3	4
67. Avez-vous des difficultés à faire une longue promenade ?	1	2	3	4
68. Avez-vous des difficultés à faire un petit tour dehors?	1	2	3	4
69. Etes-vous obligée de rester au lit ou dans un fauteuil pendant la journée?	1	2	3	4
70. Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux toilettes?	1	2	3	4

Au cours de la semaine passée:	Pas du tout	Un peu	Assez	Beaucoup
71. Avez- vous été gênée pour faire votre travail ou vos activités de tous les jours?	1	2	3	4
72. Avez-vous été gênée dans vos activités de loisirs?	1	2	3	4
73. Avez-vous eu le souffle court?	1	2	3	4
74. Avez-vous ressenti de la douleur?	1	2	3	4
75. Avez-vous eu besoin de repos?	1	2	3	4

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
76. Avez-vous eu des difficultés pour dormir?	1	2	3	4
77. Vous êtes-vous sentie faible?	1	2	3	4
78. Avez-vous manqué d'appétit?	1	2	3	4
79. Avez-vous eu des nausées (mal au coeur)?	1	2	3	4
80. Avez-vous vomi?	1	2	3	4
81. Avez-vous été constipée?	1	2	3	4
82. Avez-vous eu de la diarrhée?	1	2	3	4
83. Etiez-vous fatiguée?	1	2	3	4
84. Des douleurs ont-elles perturbé vos activités quotidiennes?	1	2	3	4
85. Avez-vous eu des difficultés à vous concentrer sur certaines choses par exemple pour lire le journal ou regarder la télévision?	1	2	3	4
86. Vous êtes-vous sentie tendue?	1	2	3	4
87. Vous êtes-vous fait du souci?	1	2	3	4
88. Vous êtes-vous sentie irritable?	1	2	3	4
89. Vous êtes-vous sentie déprimée?	1	2	3	4
90. Avez-vous eu des difficultés pour vous souvenir de certaines choses?	1	2	3	4
91. Votre état physique ou votre traitement médical vous ont-ils gênée dans votre vie familiale?	1	2	3	4
92. Votre état physique ou votre traitement médical vous ont-ils gênée dans vos activités sociales (par exemple, sortir avec des amis, aller au cinéma…)?	1	2	3	4
93. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers?	1	2	3	4

Voir page suivante S.V.P.

Veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation:

94. Comment évalueriez-vous votre <u>état de santé</u> au cours de la semaine passée?

1	2	3	4	5	6	7
Très mauvais						Excellent

95. Comment évalueriez-vous l'ensemble de votre <u>qualité de vie</u> au cours de la semaine passée?

1	2	3	4	5	6	7
Très mauvaise						Excellente

EORTC QLQ-CR29 – Qualité de vie spécifique à la maladie

Les patients rapportent parfois les symptômes ou problèmes suivants. Pourriez-vous indiquer, s'il vous plaît, si, durant la semaine passée, vous avez été affecté(e) par l'un de ces symptômes ou problèmes. Entourez, s'il vous plaît, le chiffre qui correspond le mieux à votre situation.

<u>Au cours de la semaine passée:</u>	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
96. Avez-vous fréquemment uriné dans la journée?	1	2	3	4
97. Avez-vous fréquemment uriné pendant la nuit?	1	2	3	4
98. Avez-vous eu des fuites urinaires?	1	2	3	4
99. Avez-vous eu des douleurs en urinant?	1	2	3	4
100. Avez-vous eu mal au ventre?	1	2	3	4
101. Avez-vous ressenti des douleurs au niveau de la région anale?	1	2	3	4
102. Vous êtes-vous senti(e) ballonné(e)?	1	2	3	4
103. Avez-vous vu du sang dans vos selles?	1	2	3	4

<u>Voir page suivante S.V.P.</u>

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
104. Avez-vous constaté des glaires dans vos selles?	1	2	3	4
105. Avez-vous eu la bouche sèche?	1	2	3	4
106. Avez-vous perdu des cheveux du fait de votre traitement?	1	2	3	4
107. Les aliments avaient-ils un goût inhabituel ?	1	2	3	4
108. Vous êtes-vous inquiété(e) de votre santé pour l'avenir?	1	2	3	4
109. Vous êtes-vous inquiété(e) de votre poids?	1	2	3	4
110. Vous êtes-vous senti(e) moins attirant(e) du fait de votre maladie ou de votre traitement ?	1	2	3	4
111. Vous êtes-vous senti(e) moins femme/homme du fait de votre maladie ou de votre traitement ?	1	2	3	4
112. Votre corps vous a-t-il déplu?	1	2	3	4

113. Avez-vous un anus artificiel (stomie)?
- ☐ Oui
- ☐ Non

Ne répondez aux questions 49 – 55 que SI <u>VOUS AVEZ</u> UN ANUS ARTIFICIEL. Dans le cas contraire, passez directement à la série de questions 58 - 63.

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
114. Avez-vous eu des fuites de gaz par votre anus artificiel (stomie)?	1	2	3	4
115. Avez-vous eu des fuites de matières fécales en dehors de votre poche de stomie?	1	2	3	4
116. La peau entourant votre anus artificiel (stomie) vous a-t-elle fait souffrir?	1	2	3	4
117. Avez-vous dû souvent changer votre poche de stomie au cours de la journée?	1	2	3	4
118. Avez-vous dû souvent changer votre poche de stomie au cours de la nuit?	1	2	3	4
119. Vous êtes-vous senti(e) gêné(e) à cause de votre poche?	1	2	3	4
120. Les soins de votre poche de stomie vous ont-ils posé des problèmes?	1	2	3	4

Ne répondez aux questions 56 – 61 que SI <u>VOUS N'AVEZ PAS</u> D'ANUS ARTIFICIEL.

<u>Au cours de la semaine passée:</u>	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
121. Avez-vous eu des fuites de gaz involontaires par l'anus?	1	2	3	4
122. Avez-vous eu des fuites de matières fécales par l'anus?	1	2	3	4
123. La peau entourant votre anus vous a-t-elle fait souffrir?	1	2	3	4
124. Avez-vous dû fréquemment aller à la selle au cours de la journée?	1	2	3	4
125. Avez-vous dû fréquemment aller à la selle au cours de la nuit?	1	2	3	4
126. Vous êtes-vous senti(e) gêné(e) lorsque vous alliez à la selle?	1	2	3	4

<u>Au cours des 4 dernières semaines:</u>

Pour les HOMMES uniquement:

	Pas du tout	**Un peu**	**Assez**	**Beaucoup**
127. Dans quelle mesure vous êtes-vous intéressé à la sexualité?	1	2	3	4
128. Avez-vous eu des difficultés à avoir une érection ou à rester en érection?	1	2	3	4

<u>Au cours des 4 dernières semaines:</u>

Pour les FEMMES uniquement:

	Pas du tout	**Un peu**	**Assez**	**Beaucoup**
129. Dans quelle mesure vous êtes-vous intéressée à la sexualité?	1	2	3	4
130. Avez-vous ressenti des douleurs ou une gêne lors des rapports sexuels?	1	2	3	4

<u>Merci d'avoir rempli ce questionnaire !</u>
<u>L'équipe de recherche de LEAD-IN FOLICOLOR Trial</u>

15.4 Questionnaire 2 (Dutch version)

In te vullen na 9 maanden follow-up of bij vroegtijdig beëindigen van de studie

Mijn geboortedatum (ter controle): __ __ / __ __ / __ __ __ __ (Dag/Maand/ Jaar)

Dag van vandaag: __ __ / __ __ / __ __ __ __ (Dag/Maand/ Jaar)

Mijn geslacht: ☐ Man ☐ Vrouw

EORTC QLQ-C30 – Kwaliteit van leven

Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is? Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

	Helemaal niet	Een beetje	Nogal	Heel erg
131. Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
132. Heeft u moeite met het maken van een lange wandeling?	1	2	3	4
133. Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
134. Moet u overdag in bed of in een stoel blijven?	1	2	3	4
135. Heeft u hulp nodig met eten, aankleden, u zelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
136. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
137. Was u beperkt in het uitoefenen van uw hobbies of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
138. Was u kortademig?	1	2	3	4
139. Heeft u pijn gehad?	1	2	3	4
140. Had u behoefte om te rusten?	1	2	3	4

141.	Heeft u moeite met slapen gehad?	1	2	3	4
142.	Heeft u zich slap gevoeld?	1	2	3	4
143.	Heeft u gebrek aan eetlust gehad?	1	2	3	4
144.	Heeft u zich misselijk gevoeld?	1	2	3	4

Gedurende de afgelopen week:		**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
145.	Heeft u overgegeven?	1	2	3	4
146.	Had u last van obstipatie? (Was u verstopt?)	1	2	3	4
147.	Had u diarree?	1	2	3	4
148.	Was u moe?	1	2	3	4
149.	Heeft pijn u gehinderd in uw dagelijkse bezigheden?	1	2	3	4
150.	Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
151.	Voelde u zich gespannen?	1	2	3	4
152.	Maakte u zich zorgen?	1	2	3	4
153.	Voelde u zich prikkelbaar?	1	2	3	4
154.	Voelde u zich neerslachtig?	1	2	3	4
155.	Heeft u moeite gehad met het herinneren van dingen?	1	2	3	4
156.	Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?	1	2	3	4
157.	Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?	1	2	3	4
158.	Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Volgende pagina, a.u.b.

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is:

159. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

160. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

EORTC QLQ-CR29 – Ziekte-specifieke levenskwaliteit

Soms zeggen patiënten dat ze de volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze klachten of problemen gedurende de afgelopen week heeft ervaren? Wilt u de vragen beantwoorden door het vakje aan te kruisen dat het meest op u van toepassing is?

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
161. Heeft u overdag meer dan gewoonlijk geplast?	1	2	3	4
162. Heeft u 's nachts meer dan gewoonlijk geplast?	1	2	3	4
163. Heeft u ongewild urine verloren?	1	2	3	4
164. Heeft u pijn gehad bij het plassen?	1	2	3	4
165. Heeft u buikpijn gehad?	1	2	3	4
166. Heeft u pijn gehad in uw zitvlak of bij uw anus?	1	2	3	4
167. Heeft u een opgeblazen gevoel gehad in uw buik?	1	2	3	4
168. Heeft u bloed in uw ontlasting gehad?	1	2	3	4

Volgende pagina, a.u.b.

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
169. Heeft u slijm in uw ontlasting gehad?	1	2	3	4
170. Heeft u een droge mond gehad?	1	2	3	4
171. Heeft u haaruitval gehad ten gevolge van uw behandeling?	1	2	3	4
172. Heeft u problemen met uw smaak gehad?	1	2	3	4
173. Heeft u zich zorgen gemaakt over uw gezondheid in de toekomst?	1	2	3	4
174. Heeft u zich zorgen gemaakt over uw gewicht(sverlies)?	1	2	3	4
175. Voelde u zich lichamelijk minder aantrekkelijk ten gevolge van uw ziekte of behandeling?	1	2	3	4
176. Voelde u zich minder vrouwelijk/mannelijk ten gevolge van uw ziekte of behandeling?	1	2	3	4
177. Was u ontevreden met uw lichaam?	1	2	3	4

178. Heeft u een stoma? (dunnedarm-stoma of dikkedarm-stoma)
- ☐ Ja
- ☐ Nee

Beantwoord deze vragen (vraag 49 tot en met 55) ALLEEN ALS U <u>EEN STOMA</u> HEEFT, zo niet, ga dan naar vraag 58.

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
179. Heeft u last gehad van het ongewild vrijkomen van gas (winderigheid) uit uw stoma?	1	2	3	4
180. Was er lekkage van ontlasting uit uw stomazakje?	1	2	3	4
181. Heeft u een pijnlijke huid gehad rond uw stoma?	1	2	3	4
182. Heeft u <u>overdag</u> vaak het stomazakje moeten vervangen?	1	2	3	4
183. Heeft u <u>'s nachts</u> vaak het stomazakje moeten vervangen?	1	2	3	4
184. Voelde u zich ongemakkelijk/opgelaten door uw stoma?	1	2	3	4
185. Heeft u problemen gehad met de verzorging van uw stoma?	1	2	3	4

Beantwoord deze vragen (vraag 56 tot en met 61) ALLEEN ALS U GEEN STOMA HEEFT.

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
186. Heeft u last gehad van het ongewild vrijkomen van gas (winderigheid)?	1	2	3	4
187. Heeft u ongewild ontlasting verloren?	1	2	3	4
188. Heeft u een pijnlijke huid gehad rondom uw anus?	1	2	3	4
189. Heeft u overdag vaak ontlasting gehad?	1	2	3	4
190. Heeft u 's nachts vaak ontlasting gehad?	1	2	3	4
191. Voelde u zich ongemakkelijk/opgelaten door uw ontlastingspatroon?	1	2	3	4

Gedurende de afgelopen 4 weken:

Alleen voor MANNEN:

	Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
192. In hoeverre had u zin in seks?	1	2	3	4
193. Indien u seksueel actief was (met of zonder geslachtsgemeenschap): had u moeite met het stijf worden of blijven van uw penis?	1	2	3	4

Gedurende de afgelopen 4 weken:

Alleen voor VROUWEN:

	Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
194. In hoeverre had u zin in seks?	1	2	3	4
195. Indien u geslachtsgemeenschap heeft gehad: had u pijn of ongemak tijdens de gemeenschap?	1	2	3	4

Volgende pagina, a.u.b.

Vragenlijst m.b.t. ervaring van patiënten

Beste patiënt,

Uw mening telt.

Om de zorg voor patiënten met darmkanker te verbeteren, doen we onderzoek naar opvolgingsmethodes voor darmkanker. In deze korte vragenlijst willen we peilen naar uw ervaring met de verschillende opvolgingsmethodes. Deze vragenlijst wordt anoniem verwerkt.

Alvast bedankt voor uw deelname.

Het FOLICOLOR LEAD-IN onderzoeksteam

Vraag 1

Wanneer u terugdenkt aan uw ervaring tijdens de CT-scan met toediening van contrastvloeistof (via een infuus), kunt u aangeven in hoeverre u de volgende ongemakken ervaarde: *Omcirkel het getal dat het meest op u van toepassing is (maximaal één antwoord mogelijk)*

	Helemaal niet	Nauwelijks	In redelijke mate	In hoge mate	In zeer hoge mate
1. Pijn bij plaatsen van het infuus	1	2	3	4	5
2. Warm gevoel, gevoel dat je moet plassen na toediening van contrast	1	2	3	4	5
3. Onwel gevoel na toediening van contrast	1	2	3	4	5
4. Onaangename smaak na toediening van contrast	1	2	3	4	5
5. Angst in de scan	1	2	3	4	5
6. Claustrofobisch gevoel in de CT-scan	1	2	3	4	5

Volgende pagina, a.u.b.

	Helemaal niet	Nauwelijks	In redelijke mate	In hoge mate	In zeer hoge mate
7. Gevoel van isolatie, alleen te zijn tijdens de scan	1	2	3	4	5
8. Oncomfortabele positie in de CT-scan	1	2	3	4	5
9. Ongemak ten gevolge van te lange duurtijd van de scan	1	2	3	4	5
10. Andere, namelijk:	1	2	3	4	5

……

……

……

<u>Vraag 2</u>

Wanneer u terugdenkt aan uw ervaring tijdens de afname van de twee extra bloedtubes voor deze studie bovenop uw standaard bloedafname, kunt u aangeven in hoeverre u de volgende ongemakken ervaarde:

Omcirkel het getal dat het meest op u van toepassing is (maximaal één antwoord mogelijk):

	Helemaal niet	Nauwelijks	In redelijke mate	In hoge mate	In zeer hoge mate
1. Angst tijdens bloedafname	1	2	3	4	5
2. Pijn tijdens bloedafname	1	2	3	4	5
3. Andere, namelijk:	1	2	3	4	5

……

……

<u>Volgende pagina, a.u.b.</u>

Vraag 3

Stel dat zowel de opvolging op basis van een CT-scan als de opvolging op basis van een bloedafname allebei bewezen evenwaardige en even doeltreffende opvolgingsmethoden voor patiënten met darmkanker zijn, welke van deze methoden zou dan uw voorkeur genieten? *Kruis het hokje aan van uw keuze (maximaal één antwoord mogelijk).*

- ☐ Opvolging van uw ziekte op basis van een CT-scan met toediening van contrastvloeistof via een infuus en dit om de 8 weken *(dit is de huidige standaardzorg)*,
- ☐ Opvolging van uw ziekte op basis van een bloedafname en dit om de **2** weken.

Vraag 4

Stel dat zowel de opvolging op basis van een CT-scan als de opvolging op basis van een bloedafname allebei bewezen evenwaardige en even doeltreffende opvolgingsmethoden voor patiënten met darmkanker zijn, welke van deze methoden zou dan uw voorkeur genieten? *Kruis het hokje aan van uw keuze (maximaal één antwoord mogelijk).*

- ☐ Opvolging van uw ziekte op basis van een CT-scan met toediening van contrastvloeistof via een infuus en dit om de 8 weken *(dit is de huidige standaardzorg)*,
- ☐ Opvolging van uw ziekte op basis van een bloedafname en dit om de **4** weken.

Vraag 5

Stel dat zowel de opvolging op basis van een CT-scan als de opvolging op basis van een bloedafname allebei bewezen evenwaardige en even doeltreffende opvolgingsmethoden voor patiënten met darmkanker zijn, welke van deze methoden zou dan uw voorkeur genieten? *Kruis het hokje aan van uw keuze (maximaal één antwoord mogelijk).*

- ☐ Opvolging van uw ziekte op basis van een CT-scan met toediening van contrastvloeistof via een infuus en dit om de 8 weken *(dit is de huidige standaardzorg)*,
- ☐ Opvolging van uw ziekte op basis van een bloedafname en dit om de **8** weken.

Vraag 6

Stel dat zowel de opvolging op basis van een CT-scan als de opvolging op basis van een bloedafname allebei bewezen evenwaardige en even doeltreffende opvolgingsmethoden voor patiënten met darmkanker zijn, welke van deze methoden zou dan uw voorkeur genieten? (maximaal é*én antwoord mogelijk)*

- ☐ Opvolging van uw ziekte op basis van een CT-scan met toediening van contrastvloeistof via een infuus, **ongeacht de frequentie** ➔ *ga naar vraag 7*
- ☐ Opvolging van uw ziekte op basis van een bloedafname, **ongeacht de frequentie** ➔ *ga naar vraag 8*

Volgende pagina, a.u.b.

Vraag 7

Waarom kiest u ervoor om zich in dat geval toch te laten opvolgen aan de hand van een CT-scan met contrasttoediening? *(meerdere antwoorden zijn mogelijk)*

- ☐ Ik ervaar minder angst voor dit onderzoek
- ☐ Ik vind dat dit onderzoek minder pijnlijk is
- ☐ Ik vind dit een meer aangename, meer comfortabele methode
- ☐ Ik heb meer vertrouwen in deze methode
- ☐ Ik vind dat ik mij dan minder moet verplaatsen naar het ziekenhuis
- ☐ Ik vind dat ik dan minder tijd moet doorbrengen in het ziekenhuis
- ☐ Andere:

  ……
  ……

Vraag 8

Waarom kiest u ervoor om zich in dat geval toch te laten opvolgen aan de hand van regelmatige bloedafnames? *(meerdere antwoorden zijn mogelijk)*

- ☐ Ik ervaar minder angst voor dit onderzoek
- ☐ Ik vind dat dit onderzoek minder pijnlijk is
- ☐ Ik vind dit een meer aangename, meer comfortabele methode
- ☐ Ik heb meer vertrouwen in deze methode
- ☐ Ik vind dat ik mij dan minder moet verplaatsen naar het ziekenhuis
- ☐ Ik vind dat ik dan minder tijd moet doorbrengen in het ziekenhuis
- ☐ Andere:

  ……
  ……
  ……

Heeft u nog opmerkingen? Noteer deze hier:

……

……

……

……

Bedankt voor het invullen van deze vragenlijst!

Het FOLICOLOR Lead-In onderzoeksteam

15.5 Questionnaire 2 (French version)

Questionnaire à remplir après 9 mois de suivi ou fin d'étude prématuré

Ma date de naissance (pour vérification): __ __ / __ __ / __ __ __ __ (Jour/Mois/ Année)

Date d'aujourd'hui: __ __ / __ __ / __ __ __ __ (Jour/Mois/ Année)

Sexe: ☐ Masculin ☐ Féminin (marquer d'une croix la bonne case)

EORTC QLQ-C30 – Qualité de vie

Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.

	Pas du tout	Un peu	Assez	Beaucoup
196. Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provisions chargé ou une valise?	1	2	3	4
197. Avez-vous des difficultés à faire une longue promenade ?	1	2	3	4
198. Avez-vous des difficultés à faire un petit tour dehors?	1	2	3	4
199. Etes-vous obligée de rester au lit ou dans un fauteuil pendant la journée?	1	2	3	4
200. Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux toilettes?	1	2	3	4

Au cours de la semaine passée:	Pas du tout	Un peu	Assez	Beaucoup
201. Avez- vous été gênée pour faire votre travail ou vos activités de tous les jours?	1	2	3	4
202. Avez-vous été gênée dans vos activités de loisirs?	1	2	3	4
203. Avez-vous eu le souffle court?	1	2	3	4
204. Avez-vous ressenti de la douleur?	1	2	3	4
205. Avez-vous eu besoin de repos?	1	2	3	4

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
206. Avez-vous eu des difficultés pour dormir?	1	2	3	4
207. Vous êtes-vous sentie faible?	1	2	3	4
208. Avez-vous manqué d'appétit?	1	2	3	4
209. Avez-vous eu des nausées (mal au coeur)?	1	2	3	4
210. Avez-vous vomi?	1	2	3	4
211. Avez-vous été constipée?	1	2	3	4
212. Avez-vous eu de la diarrhée?	1	2	3	4
213. Etiez-vous fatiguée?	1	2	3	4
214. Des douleurs ont-elles perturbé vos activités quotidiennes?	1	2	3	4
215. Avez-vous eu des difficultés à vous concentrer sur certaines choses par exemple pour lire le journal ou regarder la télévision?	1	2	3	4
216. Vous êtes-vous sentie tendue?	1	2	3	4
217. Vous êtes-vous fait du souci?	1	2	3	4
218. Vous êtes-vous sentie irritable?	1	2	3	4
219. Vous êtes-vous sentie déprimée?	1	2	3	4
220. Avez-vous eu des difficultés pour vous souvenir de certaines choses?	1	2	3	4
221. Votre état physique ou votre traitement médical vous ont-ils gênée dans votre vie familiale?	1	2	3	4
222. Votre état physique ou votre traitement médical vous ont-ils gênée dans vos activités sociales (par exemple, sortir avec des amis, aller au cinéma…)?	1	2	3	4
223. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers?	1	2	3	4

Veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation:

224. Comment évalueriez-vous votre état de santé au cours de la semaine passée?

1	2	3	4	5	6	7
Très mauvais						Excellent

225. Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée?

1	2	3	4	5	6	7
Très mauvaise						Excellente

EORTC QLQ-CR29 – Qualité de vie spécifique à la maladie

Les patients rapportent parfois les symptômes ou problèmes suivants. Pourriez-vous indiquer, s'il vous plaît, si, durant la semaine passée, vous avez été affecté(e) par l'un de ces symptômes ou problèmes. Entourez, s'il vous plaît, le chiffre qui correspond le mieux à votre situation.

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
226. Avez-vous fréquemment uriné dans la journée?	1	2	3	4
227. Avez-vous fréquemment uriné pendant la nuit?	1	2	3	4
228. Avez-vous eu des fuites urinaires?	1	2	3	4
229. Avez-vous eu des douleurs en urinant?	1	2	3	4
230. Avez-vous eu mal au ventre?	1	2	3	4
231. Avez-vous ressenti des douleurs au niveau de la région anale?	1	2	3	4
232. Vous êtes-vous senti(e) ballonné(e)?	1	2	3	4
233. Avez-vous vu du sang dans vos selles?	1	2	3	4

Voir page suivante S.V.P.

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
234. Avez-vous constaté des glaires dans vos selles?	1	2	3	4
235. Avez-vous eu la bouche sèche?	1	2	3	4
236. Avez-vous perdu des cheveux du fait de votre traitement?	1	2	3	4
237. Les aliments avaient-ils un goût inhabituel ?	1	2	3	4
238. Vous êtes-vous inquiété(e) de votre santé pour l'avenir?	1	2	3	4
239. Vous êtes-vous inquiété(e) de votre poids?	1	2	3	4
240. Vous êtes-vous senti(e) moins attirant(e) du fait de votre maladie ou de votre traitement ?	1	2	3	4
241. Vous êtes-vous senti(e) moins femme/homme du fait de votre maladie ou de votre traitement ?	1	2	3	4
242. Votre corps vous a-t-il déplu?	1	2	3	4

243. Avez-vous un anus artificiel (stomie)?
- ☐ Oui
- ☐ Non

Ne répondez aux questions 49 – 55 que SI <u>VOUS AVEZ</u> UN ANUS ARTIFICIEL. Dans le cas contraire, passez directement à la série de questions 58 - 63.

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
244. Avez-vous eu des fuites de gaz par votre anus artificiel (stomie)?	1	2	3	4
245. Avez-vous eu des fuites de matières fécales en dehors de votre poche de stomie?	1	2	3	4
246. La peau entourant votre anus artificiel (stomie) vous a-t-elle fait souffrir?	1	2	3	4
247. Avez-vous dû souvent changer votre poche de stomie au cours de la journée?	1	2	3	4
248. Avez-vous dû souvent changer votre poche de stomie au cours de la nuit?	1	2	3	4
249. Vous êtes-vous senti(e) gêné(e) à cause de votre poche?	1	2	3	4
250. Les soins de votre poche de stomie vous ont-ils posé des problèmes?	1	2	3	4

Ne répondez aux questions 56 – 61 que SI <u>VOUS N'AVEZ PAS</u> D'ANUS ARTIFICIEL.

<u>Au cours de la semaine passée:</u>	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
251. Avez-vous eu des fuites de gaz involontaires par l'anus?	1	2	3	4
252. Avez-vous eu des fuites de matières fécales par l'anus?	1	2	3	4
253. La peau entourant votre anus vous a-t-elle fait souffrir?	1	2	3	4
254. Avez-vous dû fréquemment aller à la selle au cours de la journée?	1	2	3	4
255. Avez-vous dû fréquemment aller à la selle au cours de la nuit?	1	2	3	4
256. Vous êtes-vous senti(e) gêné(e) lorsque vous alliez à la selle?	1	2	3	4

<u>Au cours des 4 dernières semaines:</u>

Pour les HOMMES uniquement:

	Pas du tout	**Un peu**	**Assez**	**Beaucoup**
257. Dans quelle mesure vous êtes-vous intéressé à la sexualité?	1	2	3	4
258. Avez-vous eu des difficultés à avoir une érection ou à rester en érection?	1	2	3	4

<u>Au cours des 4 dernières semaines:</u>

Pour les FEMMES uniquement:

	Pas du tout	**Un peu**	**Assez**	**Beaucoup**
259. Dans quelle mesure vous êtes-vous intéressée à la sexualité?	1	2	3	4
260. Avez-vous ressenti des douleurs ou une gêne lors des rapports sexuels?	1	2	3	4

<u>Voir page suivante S.V.P.</u>

Questionnaire concernant l'expérience du patient

Cher patient,

Votre avis compte.
Pour améliorer les soins aux patients atteints d'un cancer du côlon, nous recherchons des différentes méthodes de suivi. Par ce questionnaire nous voulons évaluer votre expérience avec ces différentes méthodes. Ce questionnaire est traité de manière anonyme.

Merci pour votre participation.

L'équipe de recherche de LEAD-IN FOLICOLOR Trial

Question 1

Lorsque vous repensez au scanner (avec administration d'un produit de contraste par perfusion) que vous avez passé, pouvez-vous indiquer avec quelle intensité vous avez ressenti les inconvénients suivants:

Encerclez le nombre qui correspond le plus à votre ressenti (une seule réponse possible):

	Aucun(e)	Léger (légère)	Modéré(e)	Fort(e)	Très fort(e)
11. Douleur lors de la pose de la perfusion	1	2	3	4	5
12. Sensation de chaleur, d'envie d'uriner après l'administration du produit de contraste	1	2	3	4	5
13. Sensation générale de malaise après l'administration du produit de contraste	1	2	3	4	5
14. Goût désagréable après l'administration du produit de contraste	1	2	3	4	5
15. Anxiété lors du scan	1	2	3	4	5

Voir page suivante S.V.P.

	Aucun(e)	Léger (légère)	Modéré(e)	Fort(e)	Très fort(e)
16. Sensation de claustrophobie dans le scanner	1	2	3	4	5
17. Sentiment d'isolement, d'être seul lors du scan	1	2	3	4	5
18. Position inconfortable dans le scanner	1	2	3	4	5
19. Inconfort du fait de la durée trop longue du scan	1	2	3	4	5
20. Autre, à *préciser S.V.P.*:	1	2	3	4	5

……

……

……

Question 2

Lorsque vous vous souvenez de votre expérience de la prise des deux tubes de sang supplémentaires pour cette étude en plus de votre test sanguin standard, pouvez-vous indiquer avec quelle intensité vous avez ressenti les inconvénients suivants:

Encerclez le nombre qui correspond le plus à votre ressenti (une seule réponse possible):

	Aucun(e)	Léger (légère)	Modéré(e)	Fort(e)	Très fort(e)
4. Aanxiété lors de la prise de sang	1	2	3	4	5
5. Douleur lors de la prise de sang	1	2	3	4	5
6. Autre, à *préciser S.V.P.*:	1	2	3	4	5

……

……

Voir page suivante S.V.P.

Question 3

Supposons que les méthodes de suivi reprises ci-dessous soient équivalentes et tout aussi efficaces, laquelle choisiriez-vous?
Cochez la case de votre choix (une seule réponse possible).

- ☐ Suivi de votre maladie sur base d'une tomodensitométrie (CT-scan) avec administration d'un produit de contraste par perfusion toutes les 8 semaines *(ce qui est le traitement de référence actuel)*
- ☐ Suivi de votre maladie sur la base d'un prélèvement sanguin toutes les **2** semaines

Question 4

Supposons que les méthodes de suivi reprises ci-dessous soient équivalentes et tout aussi efficaces, laquelle choisiriez-vous?
Cochez la case de votre choix (une seule réponse possible).

- ☐ Suivi de votre maladie sur base d'une tomodensitométrie (CT-scan) avec administration d'un produit de contraste par perfusion toutes les 8 semaines *(cequi est le traitement de référence actuel)*
- ☐ Suivi de votre maladie sur la base d'un prélèvement sanguin toutes les **4** semaines

Question 5

Supposons que les méthodes de suivi reprises ci-dessous soient équivalentes et tout aussi efficaces, laquelle choisiriez-vous?
Cochez la case de votre choix (une seule réponse possible).

- ☐ Suivi de votre maladie sur base d'une tomodensitométrie (CT-scan) avec administration d'un produit de contraste par perfusion toutes les 8 semaines *(cequi est le traitement de référence actuel)*
- ☐ Suivi de votre maladie sur la base d'un prélèvement sanguin toutes les **8** semaines

Question 6

Supposons qu'un suivi par tomodensitométrie (CT-scan) et un suivi par prélèvement sanguin soient deux méthodes de suivi équivalentes et que l'une soit aussi efficace que l'autre pour les patients atteints d'un cancer colorectal, laquelle préféreriez-vous?
Cochez la case de votre choix (une seule réponse possible).

- ☐ Suivi de votre maladie sur la base d'un CT-scan avec administration d'un produit de contraste par perfusion, **quelle que soit la fréquence** ➔ *passez à la question 7*
- ☐ Suivi de votre maladie sur la base d'un prélèvement sanguin, **quelle que soit la fréquence** ➔ *passez à la question 8*

Voir page suivante S.V.P.

Question 7

Pourquoi choisissez-vous d'être suivi par tomodensitométrie (CT-scan) avec administration d'un produit de contraste par perfusion? *Vous pouvez cocher plusieurs réponses.*

- ☐ Cette méthode me fait moins peur
- ☐ Cette méthode est moins douloureuse
- ☐ Je trouve cette méthode plus agréable et plus confortable
- ☐ Cette méthode m'inspire plus confiance
- ☐ Je devrai me rendre souvent à l'hôpital
- ☐ Je devrai passer moins de temps à l'hôpital
- ☐ Autre, à *préciser S.V.P*.:

  ……

  ……

Question 8

Pourquoi choisissez-vous d'être suivi par prélèvements sanguins réguliers?
Vous pouvez cocher plusieurs réponses.

- ☐ Cette méthode me fait moins peur
- ☐ Cette méthode est moins douloureuse
- ☐ Je trouve cette méthode plus agréable et plus confortable
- ☐ Cette méthode m'inspire plus confiance
- ☐ Je devrai me rendre moins souvent à l'hôpital
- ☐ Je devrai passer moins de temps à l'hôpital
- ☐ Autre, à *préciser S.V.P*.:

  ……

  ……

Si vous avez des remarques, vous pouvez nous en faire part ci-dessous?

……

……

……

……

Merci d'avoir rempli ce questionnaire!

L'équipe de recherche de LEAD-IN FOLICOLOR Trial

15.6 RECIST guideline (version 1.1)

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed:* based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a short axis of ⩾15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

Future work: A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

1. Background

1.1. History of RECIST criteria

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evidence of anti-tumour effect is supported by years of evidence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (reviewed in [1–4]). At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were published in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

1.2. Why update RECIST?

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three-dimensional)-based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imaging technologies such as FDG-PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non-cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

1.3. Process of RECIST 1.1 development

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co-authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression-free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co-authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

1.4. What about volumetric or functional assessment?

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F-fluorodeoxyglucose positron emission tomographic (FDG-PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is *not* intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of tumour at baseline

3.1. Definitions

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

3.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ⩾15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

3.1.2. *Non-measurable*

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

3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:.

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2. *Specifications by methods of measurements*

3.2.1. *Measurement of lesions*

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ⩾10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.[19]

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4. Tumour response evaluation

4.1. *Assessment of overall tumour burden and measurable disease*

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2. *Baseline documentation of 'target' and 'non-target' lesions*

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3. *Response criteria*

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

4.3.1. *Evaluation of target lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2. *Special notes on the assessment of target lesions*

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. As noted in Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3. *Evaluation of non-target lesions*

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

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

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

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

4.3.4. *Special notes on assessment of progression of non-target disease*

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

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic

disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5. *New lesions*

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
   If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. *Time point response*

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

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

4.4.2. *Missing assessments and inevaluable designation*

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

4.4.3. *Best overall response: all time points*

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

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

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

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

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

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

CR = complete response, PD = progressive disease, and NE = inevaluable.

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

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

4.4.4. *Special notes on response assessment*

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

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

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

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

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

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

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

needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

4.5. *Frequency of tumour re-evaluation*

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

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

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2. *Duration of overall response*

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

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

4.7. *Progression-free survival/proportion progression-free*

4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.[20]). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, all *eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti-tumour activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary endpoint for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measurable lesion.

In those many cases where response is a secondary endpoint and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre-specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all randomised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpretation of the RECIST guidelines (for example, reducing the number of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[35]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[35]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]

		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

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Conflict of interest statement

None declared.

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Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

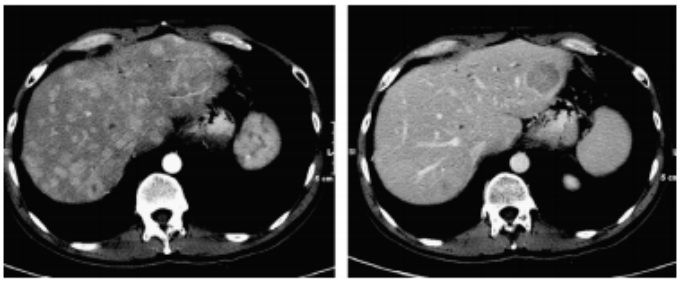

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

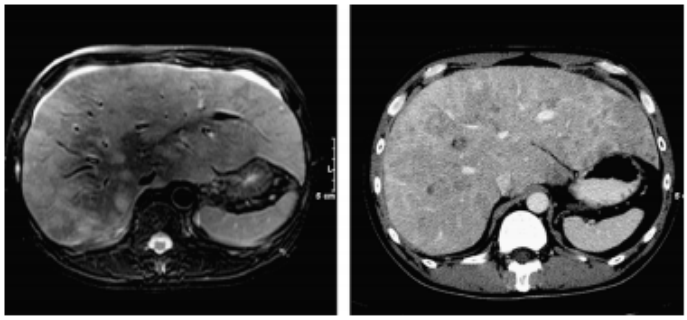

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials.*

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

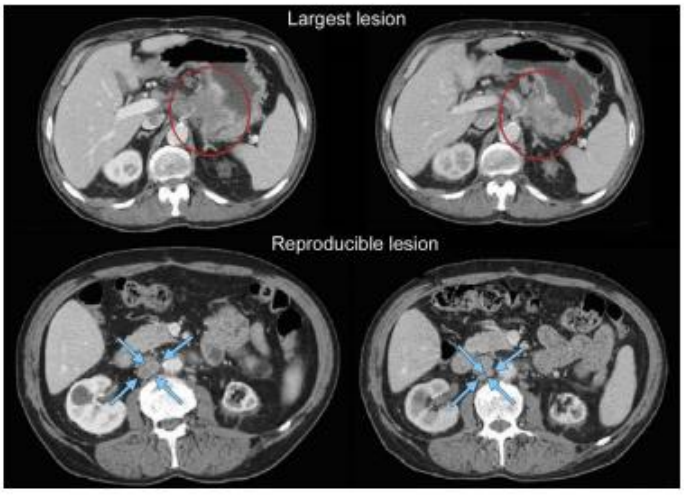

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

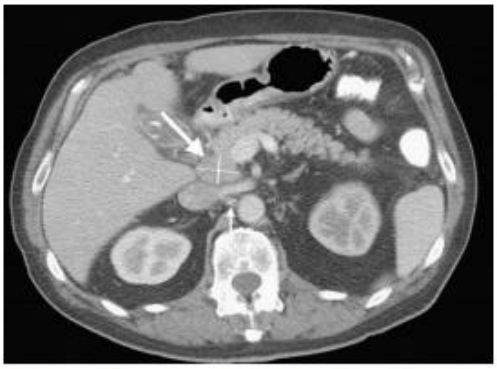

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

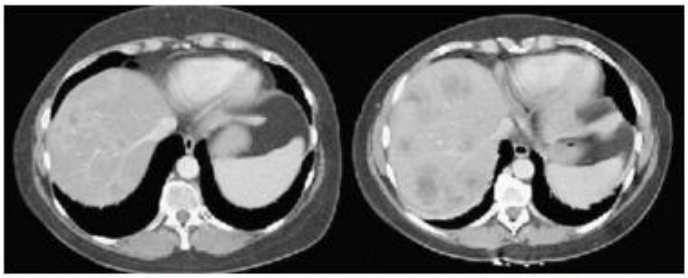

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

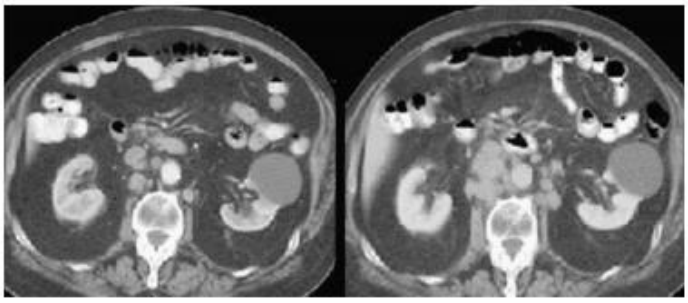

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients…in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(continued on next page)

Appendix III – continued

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

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