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RADIO STEREO CAMPTO

"A PHASE II MULTICENTER CLINICAL AND RADIOBIOLOGICAL STUDY EVALUATING HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY WITH IRINOTECAN (CAMPTO™) CONCOMITANT IN THE TREATMENT OF INOPERATED OR RECURRING LIVER AND/OR LUNG METASTASES AFTER SURGERY, OF COLORECTAL CANCERS.

Eudrac: No. 2006-005440-87
Promoter reference: BRD 06/9-R
CPP WEST II: 2006/34
ANSM: A 61141-11

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SIGNATURE PAGE

DEVELOPER'S SIGNATURE

The sponsor undertakes to carry out this study in accordance with all legislative and regulatory provisions which the research may fall under and in accordance with the protocol.		
Name and function of the signing representative: *Dr. François Pein* *DRCI Manager* Western Cancer Institute (ICO) Institut de Cancérologie de l'Ouest	**Date :**	**Signature :**

INVESTIGATORS' SIGNATURE

I have read all the pages of the clinical trial protocol for which ICO René Gauducheau is the sponsor. I confirm that it contains all the information necessary to conduct the trial. I commit to participating in the trial in accordance with the protocol and the terms and conditions defined therein. I commit to participating in the trial in accordance with:

- the principles of the "Declaration of Helsinki",
- the international (ICH-E6) and French (good clinical practice rules and recommendations for biomedical research involving medicinal products for human use - decisions of November 24, 2006) guidelines and recommendations
- national legislation and regulations relating to clinical trials,
- compliance with the EU Clinical Trials Directive [2001/20/EC]

I also commit to ensuring that investigators and other qualified members of my team have access to copies of this protocol and documents relating to the conduct of the trial to enable them to work in accordance with the provisions contained in these documents.

Coordinating Investigator	**Name :** *Dr. Emmanuel Rio*	**Date :**	**Signature :**
Lead Investigator	**Name and establishment:**	**Date :**	**Signature :**

LIST OF ABBREVIATIONS

CTV	Clinical target volume
Gy	gray
HDV	histogram-dose-volume
ITV	internal target volume
OAR	organ at risk
PTV	planned target volume
RSHF	hypofractionated stereotactic radiotherapy
RT-CT	radio-chemotherapy

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1. GENERAL INFORMATION

A PHASE II MULTICENTER CLINICAL AND RADIOBIOLOGICAL STUDY EVALUATING HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY WITH IRINOTECAN (CAMPTO™) Concomitant in the treatment of inoperable or recurring liver and/or lung metastases from colorectal cancers

- *EUDRACT number:***No. 2006-005440-87**
- ***the CPP reference****(indicated when the CPP has issued its opinion)*
- *BRD internal number: BRD 06/9-R*
- *The name and contact details of the promoter: Institut de Cancérologie de l'Ouest represented by its Director General, Professor François Régis Bataille, René Gauducheau site, Bd Monod, 44805 Saint Herblain.*
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- ***the name, title and contact details of the person responsible for the research****at the level of the promoter: Professor François Régis Bataille, Director General, Western Cancer Institute,*
- ***the name and title of the investigator(s)****and the coordinates of the search location(s).*
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- **Composition of the independent oversight committee**:
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  - DOCTOR ETIENNE BARDET CRLCC NANTES
  - DOCTOR THIERRY LEVADE University Hospital of Toulouse

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH:

2.1. CLINICAL STUDY

With an incidence of over 30,000 new cases each year in France, colorectal cancer is the most common type of cancer (excluding skin cancers) and the second leading cause of cancer death after lung cancer in all sexes combined (1,2). Metastatic progression, primarily to the liver but also to the lungs, is extremely frequent. Twenty-five percent of patients present with liver metastases at diagnosis, and in 50% of cases, within 5 years of diagnosis (3-5). Surgical treatment, with or without chemotherapy, provides a therapeutic benefit, with a 5-year survival rate of around 30%.

However, 80% of patients will remain inoperable after one or more lines of chemotherapy, due to metastatic progression or contraindications to surgery (unresectability, anesthetic criteria, or patient refusal)(6). In cases of inoperability, radiofrequency ablation is the most frequently offered therapeutic alternative. For liver metastases, it provides 60% local control with median survival between 20 and 30 months (7,8). This technique remains invasive, whether performed laparoscopically or percutaneously. Furthermore, it is limited by anesthetic and anatomical constraints: metastases near large vessels, the bile ducts, or inaccessible via the probe. Finally, it cannot be combined with concomitant treatment. Stereotactic radiotherapy, on the other hand, provides 80% local control with median survival around 25 months in patients who have received multiple lines of chemotherapy.

Extracerebral hypofractionated stereotactic radiotherapy (HFRT) is an extremely well-tolerated treatment if dosimetric constraints are strictly adhered to. It yields encouraging results in the treatment of liver and lung metastases from colorectal cancer. According to initial data, a dose of 40 Gray (Gy) in four 10 Gy fractions appeared to be the best regimen for achieving an optimal benefit-to-tolerance ratio in combination with chemotherapy. 3. In light of published results on chemoradiotherapy, particularly with irinotecan, it seems reasonable to expect a therapeutic benefit by combining it with HFRT, without significantly increasing radiation toxicity. Based on available scientific and clinical data, we recommend weekly administration of irinotecan at 40 mg/m², 90 minutes before the first and third irradiation sessions (days 1-8).

More recently, in a series of 65 patients with liver metastases from colorectal cancer, a dose of 46 to 52 Gy in 3 fractions (54) was shown to achieve a 1-year local control rate > 90%. According to Kyle E (55) et al. (JCO 2009) (phase I/II - 47 patients), after a dose of 60 Gy in 3 fractions, the 1- and 2-year local control rates were 95% and 95%, respectively, with only one grade ≥3 toxicity.

Furthermore, the interim results of our study (56), based on 23 patients, confirm the good tolerability and encouraging results of the initial regimen (4 x 10 Gy on days 1-4-8-10 with irinotecan on days 1-8). No grade > 2 clinical or biological toxicities were noted, with 86% target control (including stable disease, partial or complete response) and one death related to biliary sclerosis in the context of locoregionally progressive cancer. In this context, to increase the therapeutic index, a new regimen of 4 fractions of 12 Gy (days 1-4-8-10) with irinotecan 40 mg/m² on days 1-8 is proposed.

Furthermore, in this context of recent technological development and modernization of the technical platforms of radiotherapy services, this multicenter study will allow us to acquire an area of expertise for extracerebral RSHF.

2.2. RADIOBIOLOGICAL STUDY

Hypofractionated stereotactic radiotherapy (HSRT) represents a therapeutic alternative to conventional radiotherapy because it allows for highly targeted irradiation of tumors at a high dose (4 x 15 Gy) while limiting radiotoxicity to healthy tissues (9). Due to the high radiation dose, the molecular and cellular mechanisms involved in tumor radiosensitivity may differ from those induced after fractionated radiotherapy with low radiation doses. Thus, while DNA damage and repair may still play an important role in understanding tumor radiosensitivity after HSRT, other molecular mechanisms occurring at the cell membrane level may also be involved. Indeed, our results have shown, in murine models, that a single dose of 15 Gy irradiation induces regression of fibrosarcoma or melanoma type tumors following apoptosis of the endothelial cell network in the tumor by a mechanism dependent on the generation of a membrane sphingolipid: ceramide (10).

A recent study by Sathishkumar et al. suggests that the efficacy of high-dose fractionated radiotherapy may be correlated with blood levels of ceramide and the enzyme involved in its synthesis: acid sphingomyelinase (11). In this study, eleven patients with large tumors of various origins (melanoma, sarcoma, and adenocarcinoma of the head and neck, pelvic pelvis, or abdomen) were irradiated with a high dose of 15 Gy followed by 30 fractions of 2 Gy. After the 15 Gy dose, a significant increase in blood ceramide levels was observed in 67% of patients who responded completely or partially to radiotherapy. Similarly, an increase in blood acid sphingomyelinase levels was observed in 38% of these same patients. The fact that blood levels of ceramide and acid sphingomyelinase were not elevated in the three patients who did not respond to radiotherapy suggests that there may be a correlation between these molecular events and therapeutic efficacy.

We believe it is essential to confirm these preliminary scientific data, which the present protocol should allow thanks to the radiation doses used. Indeed, it seems fundamental to define molecular factors measuring the effectiveness of hypofractionated stereotactic radiotherapy on tumors with poor prognoses, such as liver and/or lung metastases from colorectal cancer.

In this study, we propose to measure ceramide and the enzyme involved in its synthesis, acid sphingomyelinase, in patients with liver and/or lung metastases from colorectal cancer treated with hypofractionated stereotactic radiotherapy combined with the chemotherapeutic agent irinotecan. Ceramide and acid sphingomyelinase levels will be measured before the first radiotherapy session, 30 minutes to 24 hours after the second radiotherapy session (Day 3) (optional sampling), and 30 minutes to 24 hours after the last session (Day 10) (systematic sampling). The measurements will be performed in the laboratories of the Cancer Research Department – INSERM U601 and INSERM Unit U539.
This work will help to determine whether ceramide and acid sphingomyelinase can represent diagnostic and prognostic markers of the antitumor response after high-dose hypofractionated irradiation and chemotherapy treatment.

2.3. QUALITY OF LIFE ASSESSMENT

The assessment will be conducted using the EORTC-QLQC30 (version 3). This is a cancer-specific self-administered questionnaire (Aaronson NK, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst; 365-376. 1993). Internal validation of this 30-item questionnaire identified 15 dimensions and calculated 15 scores: 5 functional ability scores (physical capacity, ability to work or perform household tasks, cognitive ability, emotional state, social status), an overall quality of life score, a financial problems score, and 8 symptom scores (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, loss of appetite, constipation, diarrhea). Response options for the items range from 4 to 7 on a Likert-type scale. If at least half of the items for each score are completed, then the scores can be generated. Overall health and functional scores range from 0 (worst) to 100 (best), while symptom scores range from 100 (worst) to 0 (best). The average completion time is 10 minutes.

2.4. HEALTH ECONOMICS STUDY

A cost study will be conducted. It will be limited in scope from the community's perspective, focusing solely on estimating direct medical and non-medical costs, excluding indirect costs. These costs will be assessed prospectively, starting from the beginning of radiotherapy and continuing for one month after the end of treatment.

2.5. NAME AND DESCRIPTION OF THE EXPERIMENTAL DRUGS.

This protocol is based on the use of a cytotoxic molecule (irinotecan) combined with hypofractionated stereotactic radiotherapy.

2.5.1. Irinotecan

Irinotecan (INN) is a reference drug in the treatment of metastatic colorectal cancers.

Irinotecan will be administered by intravenous infusion over 30 to 90 minutes at a dose of 40 mg/m2 in 250ml of physiological saline (9‰ sodium chloride) or isotonic glucose on days 1 and 8 of radiotherapy.

The product used will be Campto, from Pfizer Laboratories. (Irinotecan hydrochloride trihydrate: 100 mg per vial, i.e., irinotecan) **86.65 mg/fl 5 ml)**

2.5.2. Radiotherapy

Hypofractionated stereotactic radiotherapy will be used. The total dose delivered will be 48 Gy, at a rate of 12 Gy per fraction, twice a week for 2 weeks (days 1-3-8-10).

2.6. SUMMARY OF THE RESULTS OF AVAILABLE AND RELEVANT CLINICAL AND NON-CLINICAL TRIALS IN RELATION TO THE BIOMEDICAL RESEARCH CONCERNED.

2.6.1. Stereotactic radiotherapy (SR)

2.6.1.1. From stereotactic cerebral radiotherapy to stereotactic extracerebral radiotherapy

Stereotactic cerebral radiotherapy is a technique that has been proven over many years (12-14). Thanks to precise immobilization and repositioning, RS allows for the delivery of a high dose (as a rule≥20 Gy), in one or a few fractions (generally > 6 Gy per fraction), unlike conventional irradiation (daily fractions of 2 Gy). The goal is to overcome any potential tumor radioresistance while protecting surrounding healthy tissues as much as possible. This therapeutic approach has led to improved local control in the treatment of brain metastases (15) while minimizing long-term neurological toxicity (16).

Over the past 10 years, technological advances have enabled the development of extracerebral stereotactic radiotherapy, primarily for the treatment of primary or secondary liver and lung tumors (17In these patients whose life expectancy remains limited, this type of non-invasive treatment should provide a therapeutic benefit without harming quality of life.

2.6.1.2. Target volume: definitions and dosimetric references

The dose must be delivered to a target volume that includes the macroscopic tumor (GTV = gross target volume) with any microscopic extensions (CTV = clinical target volume). In the case of metastases, their local development is considered sufficient to overlap the CTV with the GTV. Radiotherapy (RT) limits (on the order of millimeters) internal target movement (ITV) through its immobilization or dynamic organ movement tracking systems. Potential patient movement during treatment must also be considered to define a planning target volume (PTV = CTV + margins). Commonly accepted movement ranges are 5 mm laterally, 5 mm anteroposteriorly, and 5 to 10 mm craniocaudally, regardless of tumor location. The prescribed dose must cover 100% of the PTV.

According to the recommendations of the International Commission on Radiation Units and Measurement Standards (ICRU), the dose should be prescribed at the isocenter (ICRU point = center of the PTV), and 100% of the PTV should receive between 95% and 107% of the prescribed dose. These data are defined for conformal radiotherapy. They are not directly applicable to radiosurgery (RS), which requires stricter dosimetric constraints. Theoretically, 100% of the PTV should receive 100% of the prescribed dose. In this case, the dose prescribed at the isocenter will always be higher than the dose received by 100% of the PTV (example: 10 Gy covering the entire PTV with 12 Gy prescribed at the isocenter).

The doses shown in the following tables therefore correspond to doses covering 100% of the PTV.

2.6.1.3. *What dose, for what results?*

The total dose to be delivered to a metastasis to obtain the best therapeutic ratio is not formally defined. However, it is accepted that it must be at least 30 Gy in the case of hypofractionated treatment to obtain local control > 75% at 12 months (18,19).

Several teams have evaluated different irradiation regimens on extracerebral metastatic sites, the main results of which are summarized in the following table:

Table 1: Results of RS in the treatment of liver and lung metastases:

Author	*Location*	*Number of targets*	*Dose*	*Actuarial CL (%)*
Blomgren 1995 (20)	Liver Lung	16 5	15-45Gy 1-3fx	73%[2](median 8 months)
Blomgren 1998 (21)	Liver	21	30-37Gy 2-4fx	95%[2](median 9.6 months)
Herfarth 2001 (22)	Liver	66	11-21Gy 1fx	82% 12 months
Wulf 2003 (19)	Liver Lung	24 16	30Gy 3fx	76% 12 months 61% 24 months
Gunvén 2003 (23)	Post-liver hepatectomy	5	40-45Gy 2-3fx	80%[2](median 13 months)
Wulf 2004 (24)	Lung	51	30-37Gy 3fx	80% 12 months

1: Metastases are primarily of colorectal origin, 2: raw data, CL: local control; fx: fractions

2.6.1.4. *What dose, for what toxicity?*

- at the abdominal level

Regarding abdominal toxicity, Schefter et al (25) did not reach a toxic dose-limiting dose (defined as grade 3 hepatic or intestinal toxicity or any grade 4 toxicity, CTC-NCI criteria) after 60 Gy in 3 fractions to liver metastases. At the end of their study, they did not establish a maximum tolerated dose for hepatic remission.

Table 2 below summarizes the grade 3 side effects induced by hepatic RS.

Author	Number of patients	Median PTV cm3	Dose	Grade 3 toxicity (extremes)
Blomgren 1998	14	156 (21(2-1098)	30-37Gy 2-4fx	1/14 (gastric ulcer)
Wulf 2003	23	130 (19(42-772)	30Gy 3fx	1/23 (esophageal ulcer)
Herfarth 2001	37	ND	11-21Gy 1fx	0
Gunvén 2003	5	ND (23(8-485)	40-45Gy 2-3fx	0
Schefter 2005	18	41 (25(8-210)	36-60Gy 3fx	0

PTV: planned target volume; fx: fractions

The most frequent side effects are: fever (5-10%), nausea (20-30%), pain (5%); grade 1 or 2. At the biological level, cytolytic syndromes are infrequent (approximately 5%) and always grade 1. No author describes radiation-induced hepatitis.

Radiation-induced hepatitis is defined by the appearance of ascites, cytolysis, and/or cholestasis of grade≥3 within 3 months post-irradiation according to NCI criteria (19.26).

It is noted that the most recent studies have not shown any grade 3 toxicities despite the increased doses delivered. This is explained by the refinement of dosimetric constraints, particularly on surrounding organs.

- <u>at the thoracic level</u>

Regarding pulmonary RS, the toxic thoracic limiting dose (defined by grade 3 pulmonary or cardiomediastinal toxicity or any grade 4 toxicity, CTC-NCI criteria) is estimated at 60 Gy in 3 fractions (27).

However, for primary and secondary tumors, irradiated according to schemes comparable to hepatic RS, here again, the authors describe no major toxicity and no iatrogenic functional sequelae during the follow-up period.

Table 3 below summarizes the grade 3 side effects induced by pulmonary RS.

Author	Number of patients	Median PTV cm3 (extremes)	Dose	Grade 3 toxicity
Lee 2003	28	41 (30)	30-40Gy (4.4-230)	0 3-4fx
Uematsu 2003	50	ND (31)	30-76Gy 5-15fx	0
Wulf 2004	61	43a (24)	30-36Gy (including 51 meta) (2-260)	0 3fx
Nagata 2005	45	45 (30)	48Gy (6.6-101)	0 4fx

PTV: planned target volume, fx: fractions; a: median volume for metastases.

The most frequent side effects are: fever (10-30%), pain (10%) and esophagitis (in case of nearby lung lesions), always grade 1. Uematsu et al described 2/50 cases of vertebral compression fractures and Nagata et al 2/45 cases of reversible grade 2 radiation pneumopathy.

In all these studies, 90 to 100% of patients presented with grade 1 radiation pneumonitis in the irradiated volume on CT scan, without associated functional disorders.

- dosimetric constraints on healthy tissues (organs at risk = OAR)

Overall, hepatic and pulmonary RS induces few side effects insofar as the "histogram-dose-volume (HDV)" constraints of the OARs (target organs and neighboring organs) are perfectly defined and respected (26,27,30).

- target organs

Up to 80% of the liver volume can be amputated without functional sequelae (31). In the case of total liver irradiation, the maximum tolerated dose is 33 Gy in 22 fractions (32), i.e., a dose equivalent for late effects of 49.5 Gy3 to 2 Gy/fraction (ratio$\alpha/\beta$of 3 Gy, linear quadratic model not taking into account cell proliferation). Schefter et al (25) and Herfarth et al (22) did not describe toxicity greater than grade 2 (see table no. 2) after doses of 15 Gy in 3 fractions on no more than 35% of the liver and 7 Gy in a single dose on 50% of the liver.

The risk of respiratory functional sequelae appears beyond 25% of lungs irradiated at more than 20 Gy at 2 Gy/session x 5/week (V20) (33). This radiobiological constraint can be easily met by the RS. Indeed, according to Nagata et al (30), for a mean tumor volume (PTV) of 45 cm³, the mean equivalent V20 is 4.3% after 4 times 12 Gy, which is a biological equivalent for early effects at 105 Gy[10] at 2 Gy/fraction x 5/week (ratio$\alpha/\beta$of 10 Gy).

These "HDV" constraints are easily applicable insofar as the total volume of the PTV in each target organ (liver or lung) does not exceed 113 cm3 (corresponding to a total diameter of the metastasis or metastases of 6 cm).

- neighborhood bodies

The authors conclude that there is a risk of mediastinal irradiation if the dose per fraction exceeds 7 Gy on the trachea, main bronchi, pulmonary arteries and esophagus (20). For the heart, in the Takayama et al. study (34), only 3/5 patients who received between 5 and 10 Gy per fraction experienced grade 2 toxicity. No toxicity was reported at less than 5 Gy (31 patients).

Regarding abdominal irradiation, by limiting the gastric and small bowel dose to 12 Gy (Herfarth) and with a maximum point dose of 30 Gy (Schefter), the authors do not describe any major toxicity (≤grade 2).

2.6.1.5. Advantages of splitting

Recent technological advances (patient repositioning, respiratory control, tumor targeting) allow us to repeat sessions, and therefore to fractionate the dose; which induces radiobiological advantages on healthy and cancerous tissues.

- The liver and lungs are composed of independent functional subunits arranged in a so-called "parallel" architecture. Thanks to the large number of functional subunits spared by low-volume radiation therapy (LVT), there are few or no liver or lung dysfunctions. Furthermore, the rapid dose decay around the target volume allows stem cells in each irradiated subunit to regenerate healthy tissue between fractions, provided that the dose received at each session is not lethal.

- Fractionating the dose maintains a level of tumor radiosensitivity. Indeed, this radiosensitivity of cancer cells depends not only on their reoxygenation but also on their continued division between each fraction. This sustained cellular activity between sessions also allows for the incorporation of chemotherapy.

2.6.2. Radiotherapy and concurrent chemotherapy

2.6.2.1. Target organ tolerance

➢ The lung

Concurrent radiochemotherapy (RT-CT) is the standard treatment for lung cancers, particularly for the most common form represented by locally advanced non-small cell lung cancer (35,36).

➢ The liver

Several authors have evaluated concurrent RT-CT in the treatment of liver metastases from colorectal cancer. Regardless of the irradiation or chemotherapy protocols, none reported any prohibitive toxicity. The main studies are summarized in Table 4 below:

Table 4 below summarizes the grade 3 side effects induced by hepatic RT-CT.

Author, number of patients, volume, RT-CT, toxicity, toxicity	*hematological clinic*
	Severe or grade≥3
Volberging 25 total liver 21Gy-7fx 5FU (IA) 8% ND 1982 (37) ADR (IV) 1 death (sepsis) MTX (IV)	
friedman 114 total liver 21Gy-7fx 5FU (IA/IV) 5% 8% 1988 (38) ADR (IV) 1 death TCM (IV)	
Robertson 22 partial liver 48-72Gy- FUdr (IA) 9% 9% 1995 (39) 30-44fx	
Mohuiddin 43 total liver 21Gy-7fx 5FU (IA/IV) 0% 16% 1996 (40) +/- overdose 33-60Gy +/- CDDP (IV)	
Dawson 43 partial liver 28-90Gy FUdr (IA) 2% ND 2000 (41) 30-60fx	

5FU: 5-fluorouracil; ADR: doxorubicin; MTX: methotrexate; MTC: mitomycin; Fudr: fluorodeoxyuridine; CDDP: cisplatin; IA: intra-arterial; IV: intravenous

Clinically, nausea and vomiting are the most frequent toxicities. Cases of fever and pain have been described (≤grade 2). Note that Robertson and Dawson each describe 3 cases of hemorrhagic gastritis occurring some time after treatment.

At the biological level, Dawson describes reversible grade 3 radiation-induced hepatitis, while Robertson notes 2/22 (9%) cases of grade 3 transient cholestatic syndromes. The hematological toxicity of chemotherapy appears to be potentiated more by the irradiated liver volume than by the total dose received (40).

2.6.2.2. Irinotecan and radiotherapy

Irinotecan is a reference drug in the treatment of metastatic colorectal cancers (42,43).

- Clinical data

Several phase I and II studies have evaluated the feasibility and efficacy of irinotecan-based radiochemotherapy (RT-CT) with or without other drugs in the treatment of rectal, esophageal and lung cancers.

In neoadjuvant treatment of rectal cancer, a phase I study (44) shows that concomitant weekly administration (J1-8-15) of irinotecan 90 mg/m2 is feasible with grade 3 digestive and hematological toxicities, respectively at 18% and 3%.
Three studies (45-47) using irinotecan at 40 or 50 mg/m2 weekly with continuous IV fluorouracil (2 phase II) or orally (capecitabine in phase I) concomitant, confirm the feasibility of the treatment.

Regarding mediastinal-pulmonary RT-CT, a phase II study (48) with 60 mg/m2 of weekly irinotecan combined with radiotherapy (60 Gy) in 24 patients with lung cancer, demonstrated its feasibility with 8% and 13% respectively of grade 3 esophagitis and radiation pneumonitis (in the irradiated volume). A phase I study (49The toxic dose-limiting drug (TDLD) of irinotecan 65 mg/m² combined with weekly cisplatin 30 mg/m² and concurrent irradiation of 50.4 Gy was evaluated in 19 patients with locally advanced esophageal cancer. This TDLD was established based on myelotoxicity (2/6 grade 3 at 85 mg/m²). No patient experienced grade 3 gastrointestinal toxicity; one patient (5%) experienced reversible grade 3 radiation pneumonitis.

The two phase II RT-CT studies on rectal cancer (47,49) conclude that there was a significant increase in the tumor response rate (> 70% including 32% and 22% complete histological responses, respectively).

- Radio awareness

In addition to its antitumor efficacy, numerous studies have demonstrated its radiosensitizing capabilities in vitro and in vivo (50-52Chen et al.53) describes the target enzyme of irinotecan (DNA-topoisomerase 1) as a mediator of cellular radiosensitization. It confirms that this radiosensitivity depends on the administration schedule (50,51(ideally before or during irradiation) and depends little on the concentration of the product (50).

2.7. SUMMARY OF FORESEEABLE AND KNOWN BENEFITS AND RISKS FOR INDIVIDUALS PARTICIPATING IN THE RESEARCH

2.7.1. Benefits

2.7.1.1. Individual benefit

In light of the published results on radiochemotherapy, particularly with irinotecan, it seems reasonable to expect a therapeutic benefit by combining it with high-frequency radiotherapy (HFRT), without significantly increasing the toxicity of the irradiation.

The protocol treatment is short (2 weeks) with only 4 trips without hospitalization (plus 1 to 2 preliminary trips for preparation for irradiation).

This data will be evaluated and collected by an EORTC quality of life test.

2.7.1.2. Collective benefit

This in vivo radiobiological study project is only possible thanks to the high dose delivered by the RSHF. It will improve fundamental knowledge about the radiosensitivity/radioresistance of malignant tumors.
The medico-economic study coupled with the project will allow us to assess for the first time the real cost of extra-cerebral RSHF.

2.7.2. Risks

2.7.2.1. Individual risk

- Physical risks and constraints

External beam radiotherapy is a painless treatment. However, it can induce immediate or delayed side effects depending on: the dose delivered (total and per session), the organ(s) irradiated, the volume irradiated, and the patient's intrinsic radiosensitivity. The probability and intensity of these side effects are listed in section 2.6.1.4. If these side effects occur, treatment is temporary and purely symptomatic.

Concurrent low-dose chemotherapy (CamptoTM) may increase the frequency of side effects without significantly worsening their intensity.

The irradiation technique with the ExacTract™ system requires the placement, under local anesthesia, of a permanent radiopaque implant near the tumor. This technique is comparable to image-guided (CT) needle biopsy of lung and liver lesions. The described complications are rare. In the lungs, the most frequent complication is pneumothorax, of which only 1/10 requires temporary symptomatic treatment (oxygen, drainage). In the liver, the most frequent complication is bleeding with an intravisceral hematoma..

- Psychological risks and constraints NA

- Socio-economic risks NA

- Research constraints

The patient must undergo:

- Before treatment: a blood test, completion of the EORTC-QLQC30 questionnaire, and placement of a permanent radiopaque implant (for centers using this technique). Implantation requires day hospitalization.
- The treatment will consist of four outpatient sessions over two weeks, including two half-days in the day hospital for chemotherapy administration (days 1 and 8). Blood tests will be performed between 30 minutes and 24 hours after the second radiation session (day 3).
- After treatment: a blood test (30 min to 24 hours after the last irradiation session), completing the EORTC-QLQC30 questionnaire (between the 6th and 8th week, then every 3 months for 1 year, then every 6 months until 48 months after the end of treatment).

From the 6th month onwards, the patient does not undergo any additional medical consultations or further examinations compared to a patient followed for the same pathology treated outside of the protocol.

2.7.2.2. Collective risk

N / A

2.7.3. Specify the expected adverse events and serious adverse events.

The expected adverse events and serious adverse events are described in Chapter 8.

2.8. DESCRIPTION AND JUSTIFICATION OF THE ROUTE OF ADMINISTRATION, DOSAGE, ADMINISTRATION SCHEDULE AND DURATION OF TREATMENT.

2.8.1. Radiotherapy

The total dose delivered is 48 Gy, at a rate of 12 Gy per fraction, twice a week for 2 weeks (J1-3-8-10).

2.8.2. Chemotherapy

Irinotecan will be administered by intravenous infusion over 30 to 90 minutes at a dose of 40 mg/m2 in 250ml of physiological saline (9‰ sodium chloride) or isotonic glucose on days 1 and 8 of radiotherapy.

2.9. A STATEMENT INDICATING THAT THE RESEARCH WILL BE CONDUCTED IN ACCORDANCE WITH THE PROTOCOL, GOOD CLINICAL PRACTICES, AND APPLICABLE LAWS AND REGULATIONS.

The sponsor and any investigator undertake to carry out this study in accordance with the recommendations of the Declaration of Helsinki, the provisions of European Directive 2001/20-EC as transposed into French law by Laws 2004-806 of 9 August 2004 relating to public health policy and 2004-800 of 6 August 2004 relating to bioethics and implementing decrees and orders, and to follow the recommendations of Good Clinical Practice (ICH, GCP).

They undertake to comply with all legislative and regulatory provisions that may apply to the research.

2.10. DESCRIPTION OF THE POPULATION TO BE STUDIED.

2.10.1. Population description

This is an open-label, multicenter phase II study to treat patients with inoperable or recurrent liver or lung metastases from colorectal cancer.

2.10.2. Description and number of subjects planned for the sample:

The plan is to include 48 patients over 3 years, using a two-stage methodology (Simon's optimal design). The calculation of the number of patients is detailed in § 9.2

Amendment of 21/01/14*Extension of inclusions until 19/06/2014 and inclusion of a total of 53 patients in order to take into account non-evaluable patients (included but not treated, …).*

Before the patient is included in the trial, the investigator will explain the study in full. An information sheet (Appendix 2) detailing the study will be provided to the patient for review at least 24 hours before the start of the study, and a copy will be kept for their records. After the patient has had time to consider this information and has been encouraged to ask questions, the investigator will ask them to provide written consent (Appendix 3) by writing the date and their name. The investigator will countersign and date this form and give the patient a copy of the consent form signed by both parties.

Consent forms bearing the patient's name must be checked on site. The original will be kept by the investigator in the study file.

Insofar as the patient does not wish to leave the study or if his colorectal cancer is not considered according to the terms of the study as a progressor, he cannot participate in any other therapeutic trial related to his disease.

Patients who are not informed of their diagnosis will not be included.

2.10.3. Recruitment procedures

Patient identification will take place during a pre-inclusion medical consultation following discussion of the case in a multidisciplinary digestive oncology meeting. Patients will be recruited during a consultation with the radiation oncologist or medical oncologist.

3. RESEARCH OBJECTIVES:

3.1. Main objective

Clinical: to achieve a gain in terms of response rate of the irradiated tumor site.

The main objective is to increase the tumor response rate after stereotactic radiotherapy, with a dose of 48 Gy in 4 fractions over 2 weeks in concomitant association with 40 mg/m2 of irinotecan (1st and 3rd irradiation session).

3.2. SECONDARY OBJECTIVES

Secondary objectives include evaluating: acute toxicity (within 90 days of treatment), late toxicity (after 90 days of treatment), quality of life until disease progression or death, local control rate, and overall survival.

Finally, the tumor response rate will be correlated with the initial level and post-therapeutic variations in levels of CEA and CA 19.9 (for tumors expressing the marker(s)).

3.3. Objective of ancillary studies, if applicable

3.3.1. Radiobiological: defining predictive factors of tumor response to radiotherapy.

Serum levels of ceramide and its enzyme, acid sphingomyelinase, will be correlated with the tumor response rate.

3.3.2. Health economics:

The studywill be based on calculating the cost associated with implementing this treatment.

4. RESEARCH DESIGN

4.1. EVALUATION CRITERIA

4.1.1. Main judgment criterion

The evaluation of the response to treatment of the irradiated site will be carried out according to the RECIST criteria (appendix 9) on the chest or liver CT scan by a review committee made up of the investigators.

- Evaluation between 6-8 weeks then at 3-6-9-12 months.
- Evaluation every 6 months after the 12-month period (M12), up to M48.

In this trial, the objective response encompasses the rate of complete and partial responses. Following the response assessment, the patient will be classified into one of the following eight categories:

1Complete answer (RC)
2Partial answer (PR)
3stable disease (ST)
4progression (PG)
5premature death from neoplastic causes (DCD K)
6Premature death from toxic causes (DCD Tox)
7premature death from other causes (DCD X)
8unknown (not evaluable, insufficient data) (I)

All patients meeting the eligibility criteria should be included in the primary response rate analysis. Groups 4 through 8 should be considered treatment failures.

4.1.2. Secondary judgment criteria

4.1.2.1. Toxicity assessment

Acute toxicity will be assessed according to the CTC-NCI 3.0 scale (Annex 7), late toxicity of radiotherapy will be assessed according to the RTOG scale (Annex 8).

4.1.2.2. Radiobiology study

Study of the role of endothelial membrane ceramide and acid sphingomyelinase as a determining factor associated with tumor response.

4.1.2.3. Quality of life

Quality of life assessment according to the EORTC-QLQC 30 questionnaire.

4.1.2.4. Socioeconomic,

Study of the overall cost of treatment.

4.2. RESEARCH METHODOLOGY

4.2.1. Experimental plan

This is a drug study (phase II), radiobiology, health economics; multicenter – national; non-randomized study; prospective study.

4.2.2. Clinical study procedure

The patient will be identified during a pre-inclusion medical consultation after discussion of the case in a multidisciplinary meeting.

	INVESTIGATIONS	***DEADLINE***
Pre-inclusion visit	Clinical examination (weight, WHO performance index) Information letter given to the patient	Within 15 days prior to inclusion
Hematology	NFS, platelets	Within 15 days before inclusion
Biochemistry	• Blood ionogram, serum creatinine, total bilirubin, liver transaminases, alkaline phosphatase, gamma-glutamyl transferase, PT1, aPTT1 • **1**10 ml tube (tube on sodium citrate) + 1 10 ml tube (dry tube) (radiobiological study)	Within 15 days before inclusion
Tumor markers	• ACE and CA 19-9	Within 15 days before inclusion
Respiratory function tests	• Optional depending on the irradiation technique	Within 21 days before inclusion
Imaging	• Thoraco-abdominal scan.	Within 21 days before inclusion

1: for centers that use a permanent implant

The images from the CT scans will be kept by the investigators (sheet or digital format) for the tumor response assessment study at the end of the first statistical stage.

An initial PET scan or liver MRI is recommended (possibly performed at the time of diagnosis of metastatic relapse). In this case, these examinations will be used for registration and fusion with the dosimetric CT scan.

Treatment should begin within three weeks of inclusion.

4.2.2.1. Radiotherapy

- Preparation for treatment:

The patient is positioned supine with arms raised or crossed. Extracranial stereotactic irradiation requires a system to limit internal movement. The patient is immobilized using a technique chosen by the center (respiratory gating and/or abdominal compression + or - vacuum mattress). Repositioning will be ensured using a stereotactic frame (such as the Elekta™ Body Frame) or by tracking markers previously implanted near the tumor (such as the ExacTract™).

Before treatment, at least two dosimetric CT scans are performed in fasting mode, at least one of which includes contrast injection (unless absolutely contraindicated) for liver metastases; contrast injection is optional for lung metastases. The scans are performed in contiguous slices no more than 3 mm thick, including the tumor volume and all organs at risk (OARs). To obtain high-quality images, the CT scan is performed while immobilizing the target volume (CTV) within the patient as much as possible: either during breath-holding (respiratory gating), with abdominal compression, or during free breathing if the scanner supports 4D imaging (CT reconstruction corresponding to a selected phase of the respiratory cycle).

- Volume delineation:

- CTV = metastasis(es) visible on the imaging assessment.
- ITV = CTV1∪CTV2 +/-∪CTV3. CTVs are defined based on dosimetric scanners #1-2 +/- 3
- The PTV = ITV + 3 mm minimum laterally, in the anteroposterior direction and + 5 mm minimum in the craniocaudal direction. The expansion of the PTV must be adapted according to the histogram-dose-volume (HDV) constraints of the neighboring OARs.
- The OARs (see table below) included in the irradiation field must be completely bypassed for the calculation of (HDV).

- Irradiation technique

The technique is chosen by the center: stereotaxic frame for extracranial localization (Elekta Body Frame) or automatic repositioning thanks to one or more markers implanted near the tumor (Brainlab Exactrac).

The total dose delivered is 48 Gy, at a rate of 12 Gy per fraction, twice a week for 2 weeks (J1-3-8-10).

A multibeam conformal technique or an arc therapy technique is recommended.

Intensity modulation may be used (if available at the center) when the lesion is close to an OAR (other than liver and lung) (see table below).

The energy of the photons must be≥6 MV.

- Quality control

The quality control procedure will be adapted according to the type of equipment used and the practices of each center. This quality control requires at least one image acquisition (scanner or imaging integrated into the treatment machine) during treatment to ensure correct patient repositioning and ITV (intravenous telemetry).

- Dosimetry based on planned target volume (PTV)

The prescribed dose is 48 Gy, corresponding to the 70-90% isodose, covering 100% of the PTV. Due to dose distribution heterogeneity, the tolerance margins are as follows: 100% of the PTV must be covered by at least the 43.2 Gy isodose; anything less constitutes a major protocol violation. Any isodose > 48 Gy must be within the PTV.

- Constraints on OARs

OAR	Maximum dose per fraction	Total dose /t volume
Lung	<4Gya over 40% of the volume on the treated side (right or left lung)	< 16Gy on 20% lung volume dt + left
Trachea-main bronchi	5Gyb	20Gy volume≤1 cm3
Heart	5Gyb	20Gy volume≤2 cm3
Pulmonary arteries	5Gyb	20Gy volume ≤1.5 cm3
Esophagus	5Gya	20Gy volume≤1 cm3
Stomach	8Gya	32Gy volume≤1 cm3
Liver	4.5Gyb	< 18Gy on 35% of total volume
Small intestine	8Gya	32Gy volume≤1 cm3
Kidneys	< 4.5Gyb over 50% of the volume on the treated side (right or left kidney)	< 16Gy on 35% of right and left kidney volume
Solitary functioning kidney or serum creatinine > 2ng/ml	< 2.5Gyb	< 10Gy on 10% volume
Spinal cord	< 6Gyb	<24Gy (maximum dose at a single point)

The constraints outlined in the table above are derived from data published in the various articles cited in the bibliography. They are established based on the toxicities described (≤RTOG grade 2) and dose equivalence calculation according to the linear quadratic model by taking a ratioα/βequal to 10 for early response tissues (a) and equal to 3 for late response tissues (b).

4.2.2.2. Chemotherapy

The number of previous chemotherapy regimens (including adjuvant therapy) will be recorded in the patient's chart. Similarly, it will be noted whether the patient has previously received irinotecan.

Irinotecan will be administered as a 30-minute intravenous infusion at a dose of 40 mg/m2 in 250ml of physiological saline (9‰ sodium chloride) or isotonic glucose on days 1 and 8 of radiotherapy.

The irradiation will start 60 to 90 minutes after the end of the infusion.

4.2.2.3. ***Associated treatments***

- Nausea and vomiting

Preventive treatment is strongly recommended before irinotecan administration and in cases of liver irradiation. Setrons are the drugs of choice in these indications.

- In case of liver irradiation

Corticosteroid therapy may be prescribed (such as predisone or predisolone at 0.5 mg/kg over 2 weeks)

- Cholinergic syndrome

It manifested as: sweating, hypersalivation, visual disturbances, abdominal cramps, and "early" diarrhea. Treatment of cholinergic syndrome is left to the investigator's discretion.

- Late diarrhea

In case of delayed diarrhea (more than 24 hours after irinotecan infusion), treatment with loperamide (Imodium) may be necessary.®) must be started, according to the recommendations provided in the appendix.

4.2.2.4. Other treatments

Any other symptomatic treatment necessary for the patient's comfort is permitted provided that the nature, dosage and duration of administration are specified in the data collection log.

The same applies to other specific treatments justified by a medical indication. Hematopoietic growth factors are authorized under the Marketing Authorisation.

4.2.2.5. Clinical study follow-up

The evaluation of the response to treatment of the irradiated target will be carried out according to the RECIST criteria (appendix 9) on the chest and/or liver CT scan by a review committee made up of the investigators.

- Evaluation between 6-8 weeks and then at 3-6-9-12 months
- Evaluation is conducted every 6 months after the initial 12-month period, until progression of the irradiated site(s) or until death, but not exceeding 48 months. Only in these two cases is the patient withdrawn from the study.

In parallel, in the event of continued locoregional progression or new metastatic location(s) other than the irradiated target, the patient will be treated according to the standard management of metastatic colorectal cancers, but it is still recommended to monitor them according to the imaging assessment recommended in the study.

A blood test (complete blood count, platelets, ionogram, total bilirubin, transaminases, alkaline phosphatases and gamma GT) will be performed on day 8 before the second Campto injection and between weeks 6 and 8 post-treatment.

A blood biological assessment (CBC, platelets, ionogram, urea, creatinine, total bilirubin, transaminases, alkaline phosphatases and gamma GT) and a measurement of tumor markers (CEA, CA19-9) will be carried out at M3, M6, M9, M12, then every 6 months until M48.

A clinical examination and toxicity assessment according to the CTC-NCI 3.0 scale will be performed between 6 and 8 weeks.

A clinical examination and assessment of late toxicity according to the RTOG scale will be carried out at M3, M6, M9, M12, then every 6 months until M48.

The EORTC QLC-C30 questionnaire (appendix 10) will be offered to patients from week 6 to 8, at M3, M6, M9, M12, then every 6 months until M48.

4.2.3. Radiobiology Study

Two 10 ml blood samples (one in a dry tube, one in a tube containing sodium citrate) will be taken before the first radiotherapy session, from 30 minutes to 24 hours after the second radiotherapy session (Day 3), and from 30 minutes to 24 hours after the last radiotherapy session (Day 10). Each tube will be authenticated and marked with the date and time of collection.

The tubes will be stored for a maximum of 30 minutes at 4°C before being centrifuged at 4°C for 15 minutes at 1000 g. The plasma (tube containing sodium citrate) and serum (dry tube) will be collected and immediately frozen at -80°C. These plasma and serum samples will allow for the quantification of ceramide and its enzyme, acid sphingomyelinase, in the patients' blood. The tubes will be centralized at the ICO, René Gauducheau site, and the assays will be performed in the laboratories of the Cancer Research Department-Inserm U 601 and Inserm Unit U 539.

If the patients have given their consent (Annex 4), these tubes may, on the one hand, be used for other research for scientific purposes related to the pathology and, on the other hand, be kept for 15 years in the ICO serum bank, René Gauducheau site for subsequent use, again for scientific purposes related to the pathology.

4.2.3.1. Ceramide quantification

The method for quantifying ceramide will first be based on the extraction of serum or plasma lipids. These lipids will then be separated by thin-layer chromatography on silica plates. The bands corresponding to ceramide will be extracted from the silica plate and then analyzed by gas chromatography. This method will allow both the quantification of ceramide and the assessment of the carbon chain composition of the different ceramides present in the patients' blood.

4.2.3.2. Acid sphingomyelinase activity assay

Acid sphingomyelinase activity will be measured by the ability of this plasma or serum enzyme to convert exogenous sphingomyelin coupled to the fluorochrome BODIPY into fluorescent ceramide-BODIPY. The assay will be performed for 1 hour at 37°C. The ceramide-BODIPY will then be separated by thin-layer chromatography on silica plates, and the fluorescence will be quantified using the Typhoon fluorescence analyzer (Amersham).

4.2.4. Health economics study

4.2.4.1. Type of costs taken into account

The cost study will be limited from the community's point of view, focusing on estimating direct medical and non-medical costs, while excluding indirect costs.

- *direct medical costs*

  - treatment phase: irradiation (preparation, sessions, quality controls), day hospitalization.
  - hospital follow-up phase: possible hospitalization for complications up to 1 month following treatment.

- *direct non-medical costs*

  - transportation to get to the treatment location.

These costs will be assessed prospectively, from the start of radiotherapy and over a period of one month following the end of treatment.

4.2.4.2. Specifications regarding cost calculation

Cost estimation will utilize the micro-costing method, which relies on detailed observation for each patient of all the resources consumed by them.

- *Treatment phase*

The data collected will follow the different stages of radiotherapy as well as those of chemotherapy treatment. For each patient, the following phases will be identified and documented:

- **radiotherapy**

- treatment preparation (immobilization system, CT image acquisition, treatment planning and data transfer to the accelerator).
- irradiation sessions.
- machine quality control.
- patient quality control.

The main cost elements that will be taken into account for each of these phases are as follows:

- costs in medical and paramedical staff
- equipment depreciation costs
- equipment maintenance costs
- costs of consumables used

Resource consumption related to each of these phases will be recorded and quantified for each patient, along with clinical data, based on economic questions integrated into the observation log and documented by clinical research assistants (CRAs):

- time spent by each category of medical and non-medical staff

- consumables used
- type of equipment and downtime

The unit costs used to value this data will be obtained from a specific questionnaire completed by each of the centers:

- Specification of the type of equipment used, including purchase price, lifespan, and actual annual hours of use.
- annual maintenance cost
- average annual number of treatments initiated with the equipment regardless of the irradiation technique.

- **chemotherapy**

The cost of this treatment will be assessed for each patient, based on:

- the number of chemotherapy treatments and the quantity of product used.
- of the day hospitalization package.

➢ *Follow-up phase*

All hospitalizations for treatment-related complications will be recorded by the Clinical Research Associate (CRA) in the observation log:
- Reason and duration of hospitalization.
- procedures performed during hospitalization.

This follow-up will take place for up to 1 month after the end of treatment.

➢ *Transportation*

The CRAs will be responsible for interviewing patients about:
- the type of vehicle used.
- the number of round trips between home and the treatment location.

The monetary valuation will be based on the current social security reimbursement rate.

STUDY TIMETABLE

The protocol will proceed according to the summary table below. Before day 8 of treatment (concomitant administration of the second dose of irinotecan with radiotherapy), tolerance and toxicity will be assessed, and continuation of treatment, adjustment of irinotecan doses, or discontinuation of treatment will be carried out according to the pre-established criteria in chapter 6.1.1.3.

	INCLUSION ASSESSMENT	**TREATMENT a**				**MONITORING**					
	J0	**J1** Campto + 12 Gy	**D3** 12 Gy	**J8** Campto + 12 Gy	**J10** 12 Gy	**Weeks 6-8**	**3 months**	**6 months**	**9 months**	**12 months**	**Every 6 months (g)**
Eligibility criteria	X										
Informed consent, dated and signed	X										
Clinical examination	X					X	X	X	X	X	X
Thoraco-abdominal CT scan	X[b]					X	X	X	X	X	X
PET scan and/or liver MRI recommended	X										
NFS-platelets	X[c]			X[e]		X	X	X	X	x	x
Biochemistry	X[c]			X[e]		X	x	x	x	x	x
ACE, CA 19-9 Assay	X[c]						X	X	X	X	X
Blood sample for radiobiological study	X[c]		X[d]		X[d]						
Evaluation of response according to RECIST criteria						X	X	X	X	X	X
Quality of life assessment EORTC QLQ-C30	X					X	X	X	X	X	X
Acute toxicity assessment according to the CTC-NCI scale						X					
Late toxicity assessment according to the RTOG scale							X	X	X	X	X
Health economics study						X					

a: treatment should begin as soon as possible, but not more than 3 weeks after inclusion.
b: examination carried out less than 3 weeks before inclusion.
c: examinations carried out less than 2 weeks before inclusion.
d: sample taken within 30 minutes to 24 hours after irradiation.
e: sample to be taken before treatment
f: sample to be taken 30 minutes to 24 hours after irradiation.
g: up to a maximum of 48 months

4.3. EXPECTED DURATION OF PARTICIPATION OF PERSONS AND DESCRIPTION OF THE CHRONOLOGY AND DURATION OF ALL TRIAL PERIODS, INCLUDING FOLLOW-UP, IF APPLICABLE.

- Radiotherapy:

The total dose delivered is 48 Gy, at a rate of 12 Gy per fraction, twice a week for 2 weeks (J1-3-8-10).

- Chemotherapy:

Irinotecan will be administered as a 30-minute intravenous infusion at a dose of 40 mg/m2 in 250ml of physiological saline (9‰ sodium chloride) or isotonic glucose on days 1 and 8 of radiotherapy.

From the last day of their treatment, patients will be monitored until progression, until death, but not exceeding 48 months.

4.4. DESCRIPTION OF THE RULES FOR PERMANENT OR TEMPORARY SHUTDOWN

4.4.1. Criteria for prematurely ending a person's participation in research

If a patient permanently stops treatment, the reasons for this stoppage will be recorded in the observation log.
These reasons could be:

- Decision of the investigator or sponsor
- Withdrawal of consent or refusal of treatment by the patient.
- Occurrence of grade 4 toxicity during treatment.
- Tumor progression
- Patient's inability to continue the study (inability to comply with respiratory gating requirements (for centers that use it), intercurrent illness, significant deterioration of general condition)
- Loss of follow-up of the patient
- Death

Study withdrawals are only effective after confirmation by the investigator and the sponsor. These withdrawals are always final. An evaluation report corresponding to the semi-annual review will be conducted at the time of withdrawal.

Once a patient has left the study, no further data concerning them will be collected.

In the event of continued loco-regional progression or new metastatic localization, the patient may be treated according to the standard management procedures for metastatic colorectal cancers.

4.4.2. Criteria for definitively or temporarily halting part or all of the research

The end date of the research will be the date of the end of follow-up (48 months after the end of treatment) for the last patient followed in the study. However, the research may be stopped early due to (ANSM decision, monitoring committee, ineffectiveness, toxicity, etc.)

4.5. MEASURES IMPLEMENTED TO MAINTAIN ANONYMITY AND PROCEDURES FOR LIFTING ANONYMITY, WHERE APPLICABLE.

Not applicable

4.6. IDENTIFICATION OF ALL DATA TO BE COLLECTED DIRECTLY IN THE OBSERVATION NOTEBOOKS, WHICH WILL BE CONSIDERED AS SOURCE DATA.

All data will be documented in a source document.

5. SELECTION AND EXCLUSION OF INDIVIDUALS FROM THE RESEARCH:

5.1. PRE-INCLUSION CRITERIA (IF APPLICABLE)

Not applicable

5.2. INCLUSION CRITERIA FOR PEOPLE WHO PARTICIPATE IN THE RESEARCH.

1) Age≥18 years old
2) Social insurance
3) Performance index < 2 (WHO) (Annex 2)
4) Life expectancy > 6 months
5) Histologically proven colorectal adenocarcinoma
6) Metastases (inoperable or recurrent after surgery) from colorectal cancer, with liver and/or lung involvement (up to 3 if only one organ is metastatic, or 3 in total if both organs are metastatic). The largest diameter of the single metastasis will be≤6cm for the liver,≤6 cm for the lung. If there are multiple metastases, the sum of their maximum diameters will be≤6cm for the liver,≤6 cm for the lung.
7) Measurable or assessable lesion(s)
8) Thoraco-abdominal CT scan less than 3 weeks old
9) Patients must have received at least one line of 5FU-based chemotherapy.
10) Patients may have received one or more lines of chemotherapy, including irinotecan.
11) Bilirubinemia < 1.5 x ULN
12) ASAT and ALAT < 5x LSN
13) Neutrophil count > 1.5 x 10^9/L, platelet count > 100 x 10^9/L, hemoglobin > 9 g/dL
14) TP, TCA Normal (only for patients treated with a permanent implant)
15) Informed consent signed.

5.3. CRITERIA FOR EXCLUDING PEOPLE WHO PARTICIPATE IN THE RESEARCH.

1) Absolute contraindication to the administration of irinotecan.
2) A history of radiotherapy to the thoraco-abdominal region contraindicates further irradiation.
3) History of other invasive cancer treated within the last 5 years (excluding basal cell carcinoma and non-invasive cervical carcinoma)
4) Diffuse metastatic disease or more than three metastases in the liver and/or lung during the natural history of the disease (effectively excluding any patient with a complete radiological response on several*metastases even if 1to 3 residual after medical treatment(s)).*
5) Tumor location(s) = CTV within 12 mm laterally or within 15 mm craniocaudally of the stomach, small intestine, esophagus, trachea, right and left main bronchi and right and left pulmonary arteries.
6) Pregnancy or breastfeeding.

7) Lack of access to, or refusal to use, effective means of contraception for men or women of reproductive age.
8) Any other concomitant experimental treatment.
9) Any other concomitant anticancer treatment, immunotherapy or hormone therapy.
10) Follow-up is impossible due to psychological or sociological issues, or due to geographical distance.

5.4. PROCEDURE FOR PREMATURE CESSATION OF TREATMENT AND PROCEDURE FOR EXCLUSION FROM RESEARCH

5.4.1. Criteria and procedures for premature termination of treatment or exclusion of a person from research;

If a patient permanently stops treatment, the reasons for this stoppage will be recorded in the observation log.

These reasons could be:

- Decision of the investigator or sponsor
- Withdrawal of consent or refusal of treatment by the patient.
- Occurrence of grade 4 toxicity during treatment, imposing it.
- Tumor progression
- Patient's inability to continue the study (inability to comply with respiratory gating requirements (for centers that use it), intercurrent illness, significant deterioration of general condition)
- Loss of follow-up of the patient
- Death

5.4.2. Methods and schedule for collecting this data;

All data will be collected in a clinical-physical observation notebook.

5.4.3. Arrangements for replacing these persons, if applicable;

The end of the first statistical stage will be validated from the**16th patient included evaluable (on their tumor response rate) at 6 months post-treatment.**

The study will be closed from the**48th patient included evaluable (on their tumor response rate) at 6 months post-treatment.**

5.4.4. Methods for monitoring these individuals

Statistical analysis of each included patient will not be performed before the first stage of evaluating the tumor response rate at 6 months post-treatment.

6. TREATMENTS ADMINISTERED TO PEOPLE WHO PARTICIPATE IN RESEARCH

6.1. DESCRIPTION OF THE TREATMENT(S) NECESSARY TO CARRY OUT THE RESEARCH AND METHODS OF ADMINISTRATION.

6.1.1. Investigational drug(s) / comparator

6.1.1.1. Identification of treatments:

Irinotecan (INN) is a reference drug in the treatment of metastatic colorectal cancers.

The product used will be Campto, from Pfizer laboratories. (Irinotecan hydrochloride trihydrate: 40 mg per vial, i.e., irinotecan**86.65 mg/fl 5 ml**)

6.1.1.2. Administration

Irinotecan will be administered by intravenous infusion over 30 to 90 minutes at a dose of 40 mg/m2 in 250ml of physiological saline (9‰ sodium chloride) or isotonic glucose on days 1 and 8 of radiotherapy.

6.1.1.3. Dosage adjustment

- **Adapting radiotherapy according to toxicity**

Radiation-induced toxicity will be assessed on day 8 according to CTC-NCI criteria (appendix 3):

- Any toxicity grade>2, requires the cancellation of the session and the postponement of the administration of irinotecan to the following irradiation session (J10) according to the criteria defined § 1.2 (table n°2) below.
- Any grade 4 toxicity (other than that induced by irinotecan, see table below) requires the permanent cessation of all treatment.

- **Chemotherapy doses are adjusted according to toxicity.**

Table No. 1: Toxicity present on day 8 (before the second administration of irinotecan)

Toxicity on the scheduled day of treatment		CTC-NCI Grade	**Adaptation**
Diarrhea	increase≥2-3 bowel movements/day	≥1	**Reduce the irinotecan dose to 30 mg/m2**
Neutropenia	Between 1.0 and 1.5×109/L	2	
Thrombocytopenia	<100×109/L	≥1	
Neutropenia	Between 0.5 and 1.0×109/L	3	**Postpone to day 10* and reduce the irinotecan dose to 30 mg/m2**
Transaminases Or Alkaline phosphatases	Between 5 and 20 x LSN Between 2.5 and 20 x LSN	2-3	**Postpone to day 10* and reduce the irinotecan dose to 30 mg/m2**
Total bilirubin	Between 1.5 and 3 x LSN	2	**Postpone to day 10* and reduce the irinotecan dose to 30 mg/m2**
Total bilirubin	Between 3 and 10 x LSN	3	**Stopping chemotherapy**
Any grade 4 toxicity on the elements listed above			**Stopping chemotherapy**

**: if hematological conditions are required*

Table No. 2: Toxicity present on day 10 (before the second administration of irinotecan)

Toxicity on the scheduled day of treatment		CTC-NCI Grade	**Adaptation**
Diarrhea	increase≥2-3 bowel movements/day	≥1	**Reduce the irinotecan dose to 30 mg/m2**
Neutropenia	Between 1.0 and 1.5×109/L	2	
Thrombocytopenia	<100×109/L	≥1	
Neutropenia	Between 0.5 and 1.0×109/L	3	**Reduce the irinotecan dose to 30 mg/m2**
Transaminases Or Alkaline phosphatases	Between 5 and 20 x LSN Between 2.5 and 20 x LSN	2-3	**Reduce the irinotecan dose to 30 mg/m2**
Total bilirubin	Between 1.5 and 3 x LSN	2	**Reduce the irinotecan dose to 30 mg/m2**
Total bilirubin	Between 3 and 10 x LSN	3	**Stopping chemotherapy**

Any grade 4 toxicity on the elements listed above	**Stopping chemotherapy**

Dose reductions for other clinical reasons are at the investigator's discretion, but the reason must be stated.

6.1.2. Other medications in the protocol:

Not applicable

6.2. MEDICATIONS AND TREATMENTS PERMITTED AND PROHIBITED UNDER THE PROTOCOL, INCLUDING RESCUE MEDICATIONS.

6.2.1. Authorized treatments

- Nausea and vomiting

Preventive treatment is strongly recommended before irinotecan administration and in cases of liver irradiation. Setrons are the drugs of choice for this indication.

- Corticosteroid therapy in cases of liver irradiation

A treatment such as prednisone or prednisolone at 1mg/kg/day for 2 weeks is possible.

- Cholinergic syndrome

Sweating, hypersalivation, visual disturbances, abdominal cramps, "early" diarrhea. Treatment of cholinergic syndrome is left to the investigator's discretion.

- Late diarrhea

In case of delayed diarrhea (more than 24 hours after irinotecan infusion), treatment with loperamide (Imodium) may be necessary.®) must be started, according to the recommendations provided in the appendix.

- Other treatments

All symptomatic treatments necessary for the patient's comfort are permitted provided that their nature, dosage and duration of administration are specified in the data collection log.
The same applies to other specific treatments justified by a medical indication. Hematopoietic growth factors are authorized under the Marketing Authorisation.

6.2.2. Unauthorized treatments

Irinotecan should not be administered concomitantly with potent inhibitors of cytochrome CYP450 3A4 (such as ketoconazole) or inducers (such as rifampicin, carbamazepine, phenobarbital,

phenytoin, or St. John's wort). Furthermore, investigational treatments and any antineoplastic therapy are not authorized.

Any other concomitant experimental treatment.

6.2.3. Emergency treatment

N / A

6.3. METHODS FOR MONITORING TREATMENT ADHERENCE.

The irinotecan vials used will be kept by the investigator department or by the investigator facility's pharmacy for accounting purposes during monitoring visits.
The destruction of the vials will only be authorized after written agreement from the promoter.
A certificate of destruction must be provided in return.

6.4. STORAGE CONDITIONS FOR EXPERIMENTAL DRUGS.

6.4.1. Description of pharmacy storage

Irinotecan will be provided free of charge by the sponsor. It will be delivered to the investigator sites via a service provider. Supplies will be delivered after each patient enrollment.

6.4.2. Description of storage in the service, if applicable

Store away from light.
Since irinotecan solution does not contain a preservative, it must be used immediately after dilution. However, if the dilution is performed under strict aseptic conditions, the irinotecan infusion solution, stored at room temperature, can be used (including the infusion time) within 12 hours of preparation, or within 24 hours of preparation if stored in a refrigerator (+2°C at +8°C).

6.4.3. Description of storage at the patient's home, if applicable

Not applicable

7. EVALUATION OF EFFICACY AND TOLERABILITY

7.1. DESCRIPTION OF EVALUATION PARAMETERS.

The evaluation of the response to treatment of the irradiated tumor site will be carried out according to the RECIST criteria (appendix 9) on the thoracic or hepatic CT scan by a review committee made up of the investigators.

7.2. PLANNED METHODS AND SCHEDULE FOR MEASURING, COLLECTING AND ANALYZING EFFECTIVENESS EVALUATION PARAMETERS.

- Evaluation between 6-8 weeks then at 3-6-9-12 months.
- Evaluation every 6 months after the 12-month period, up to M48.

In this trial, the objective response encompasses the rate of complete and partial responses. Following the response assessment, the patient will be classified into one of the following eight categories:

1Complete answer (RC)
2Partial answer (PR)
3stable disease (ST)
4progression (PG)
5premature death from neoplastic causes (DCD K)
6Premature death from toxic causes (DCD Tox)
7premature death from other causes (DCD X)
8unknown (not evaluable, insufficient data) (I)

All patients meeting the eligibility criteria should be included in the primary response rate analysis. Groups 4 through 8 should be considered treatment failures.

8. SAFETY ASSESSMENT:

8.1. DEFINITIONS

8.1.1. Adverse events

An adverse event is defined as any harmful manifestation in a patient or a participant in a clinical trial, and which is not necessarily related to the treatment planned in the clinical trial.

All adverse events encountered during the study, whether observed by the physician or reported by the patient, will be recorded in the observation log in the section provided for this purpose.

All adverse events (AEs) must be reported in the eCRF, from inclusion until the initiation of a new treatment.

The severity of adverse events will be rated according to the criteria chosen when drafting the protocol (the chosen evaluation criteria should be included in the appendix). For any event not listed in the chosen classification, the rating will be as follows:

1 = benign
2 = moderate
3 = severe
4 = involving a life-threatening situation

8.1.2. Side Effects

An adverse event is considered suspected for any adverse event for which a causal link, regardless of its importance (doubtful, plausible, possible, certain), can be envisaged either with the treatment under investigation or with the comparator or protocol.

8.1.3. Serious events or adverse effects

An adverse event (AE) is considered a serious adverse event (SAE) when it:

* results in death,
* puts life at risk,
* results in temporary or permanent incapacity or disability,
* requires or prolongs the patient's hospitalization,
* causes a congenital or neonatal anomaly,
* is medically important (meaning: requires management to prevent progression to one of the above stages).

8.1.4. Expected serious adverse effects or events

An expected serious adverse event (SAE A) is an event already mentioned in the most recent version of the investigator's brochure or in the most recent summary of product characteristics (SmPC) for drugs already having a marketing authorization.
These expected serious adverse effects or events will be reported by the sponsor to the relevant authorities on a deferred basis.

Within the framework of this protocol, the expected adverse events are:

8.1.4.1. Regarding Irononotecan

Gastrointestinal disorders:

- As monotherapy:

Severe diarrhea was observed in 20% of patients who followed the diarrhea management guidelines.
Severe diarrhea was found in 14% of evaluable cycles.
The median time to onset of the first loose stool is 5 days after Campto infusion.
Rare cases of pseudomembranous colitis have been reported, including one case with bacteriological documentation (Clostridium difficile).

- Dehydration:

Episodes of dehydration, generally associated with diarrhea and/or vomiting, have been reported.
Rare cases of renal failure, hypotension, or cardiovascular collapse have been observed in patients who experienced episodes of dehydration associated with diarrhea and/or vomiting.

- Other gastrointestinal events:

Rare cases of intestinal obstruction, ileus or gastrointestinal bleeding, and rare cases of colitis, including typhlitis, ischemic and ulcerative colitis, have been reported.
Rare cases of intestinal perforations have been reported.
Rare cases of symptomatic or asymptomatic pancreatitis related to irinotecan treatment have been observed.

Hematological disorders:

- As monotherapy:

Neutropenia is observed in 78.7% of patients and is severe (neutrophil count < 500/mm³).[3]) in 22.6% of cases. Among the evaluable cycles, 18% were complicated by neutropenia < 1000/mm³[3], including 7.6% with neutropenia < 500/mm³[3]Full recovery is usually achieved by the 22nd.[e]day.
Fever accompanied by severe neutropenia is reported in 6.2% of patients and in 1.7% of cycles.
Infectious episodes occurred in approximately 10.3% of patients (2.5% of cycles), were associated with severe neutropenia in approximately 5.3% of patients (1.1% of cycles), and resulted in 2 deaths.
Anemia was reported in approximately 58.7% of patients (8% with hemoglobin < 8 g/dl and 0.9% with hemoglobin < 6.5 g/dl).
Thrombocytopenia (< 100,000/mm³)[3]) was observed in 7.4% of patients and 1.8% of cycles, including 0.9% of patients with platelets <= 50,000/mm³[3]that is 0.2% of cycles.
Almost all patients had normalized their platelet count by the 22nd[e]day.
One case of peripheral thrombocytopenia with antiplatelet antibodies is reported in post-marketing clinical experience.

Infection :

- Rare cases of renal failure, hypotension or cardiovascular collapse have been observed in patients with severe systemic infection.

General side effects:

- Acute cholinergic syndrome:
  An acute, transient, and severe cholinergic-like syndrome is observed in 9% of patients treated with monotherapy and in 1.4% of patients treated with combination therapy. The main symptoms are defined by early diarrhea and a range of symptoms such as abdominal cramps, conjunctivitis, rhinitis, hypotension, vasodilation, hyperhidrosis, chills, malaise, dizziness, visual disturbances, miosis, lacrimation, and hypersalivation occurring during or within 24 hours of Campto administration. The symptoms resolve with atropine administration (see Warnings/Precautions).

- Cardiovascular disorders: rare cases of hypertension during or following the infusion have been reported.
- Respiratory disorders: Cases of interstitial lung disease with pulmonary infiltrates are rare with Campto. Early effects, such as dyspnea, have been reported (see Warnings/Precautions for Use).
- Immune system disorders: Infrequent and moderately severe allergic reactions and rare cases of anaphylactic/anaphylactoid-type reactions have been reported.

Biological tests:

In monotherapy, a minor to moderate transient increase in serum levels of either transaminases, alkaline phosphatases, or bilirubin is observed in 9.2%, 8.1%, and 1.8% of patients, respectively, in the absence of progression of liver metastases. A minor to moderate transient increase in serum creatinine levels is observed in 7.3% of patients.
In association, a transient serum elevation (grade 1 and 2) of ALT, AST, alkaline phosphatase, or bilirubin was observed in 15%, 11%, 11%, and 10% of patients, respectively, in the absence of progression of liver metastases. Transient grade 3 elevations were observed in 0%, 0%, 0%, and 1% of patients, respectively. No grade 4 elevations were observed.
In very rare cases, an elevation of serum amylase and/or serum lipase has been reported.
Rare cases of hypokalemia and hyponatremia, mainly related to diarrhea and vomiting, have been reported.

Nervous system disorders:

Very rare cases of transient speech disorders associated with Campto infusions have been reported.

8.1.4.2. Regarding radiotherapy

- Esophageal ulceration causing bleeding (less than 1% of cases).

- Severe spasmodic cough resistant to treatment.

- Gastro-duodenal ulceration causing bleeding (less than 2% of cases).

- Inflammatory colitis with more than 7 bowel movements per day.

- Febrile syndrome > 40°C occurring after tumor necrosis, and requiring hospitalization for investigation.

8.1.4.3. Regarding the protocol

Percutaneous placement of radiopaque implants can be complicated by:

-at the pulmonary level: pneumothorax resolving spontaneously (10% of cases), pneumothorax requiring drainage or oxygen therapy (less than 2% of cases), hemoptysis (3% of cases), gas embolism (less than 1% of cases).

- at the liver level: visceral hemorrhage requiring a blood transfusion.

8.1.4.4. Regarding the pathology

The life expectancy of a patient being treated for metastatic cancer is lower than that of a control population. There is a risk of: diffuse metastatic progression, local progression, and paraneoplastic metabolic complications leading to organ failure and potentially life-threatening conditions.

8.1.5. Unexpected serious side effects

An unexpected serious adverse event (SAE I) is an event whose nature, severity, frequency or course is inconsistent with the information in the most recent investigator's brochure or the most recent summary of product characteristics for drugs with a marketing authorization.

These unexpected serious adverse events will be reported to the relevant authorities within 7 or 15 days of their being become known to the sponsor.

8.2. DESCRIPTION OF THE SECURITY ASSESSMENT PARAMETERS.

Each patient will benefit from clinical monitoring, regular assessment of side effects (according to standardized scales) and biological monitoring according to a pre-established schedule.

8.3. PLANNED METHODS AND SCHEDULE FOR MEASURING, COLLECTING AND ANALYZING SAFETY ASSESSMENT PARAMETERS.

Any event related to the study will be reported to the sponsor by the investigators. Similarly, the sponsor will implement quality control of the records through monitoring visits.

8.4. PROCEDURES PUT IN PLACE FOR THE RECORDING AND NOTIFICATION OF ADVERSE EVENTS.

8.4.1. Notification of EIGs

Any adverse event (AE) that meets the definition of a serious adverse event (SAE) requires the completion of an SAE declaration form, whether expected or not. The investigator must verify that the information entered on this form is accurate and clear (do not use abbreviations).

The EIG must be reported immediately (within 24 hours of its discovery by the investigator) to the sponsor by fax (DRCI – ICO René Gauducheau. Fax 02 40 67 97 87).

Adverse events must be reported to the sponsor of enrollment up to 1 month after the end of the study treatment.

8.4.2. Declaration to the competent authorities

Upon receiving notification of a serious adverse event (SAE), the sponsor assesses whether the SAE was expected or unexpected. The sponsor undertakes to transmit first-order SAEs (I) to the relevant authorities (EMEA, ANSM, etc.) within 7 days for deaths and life-threatening serious adverse events (with a further 7 days to submit any additional information) and within 15 days for other unexpected serious adverse events, according to the applicable format.

A new fact relevant to the research or the product being researched is likely to change the benefit/risk assessment and have an impact on the safety of subjects participating in the trial.
These new facts must be notified to the promoter and will be reported to the competent authorities within 15 calendar days of receipt by the promoter.

The sponsor will send a summary table of SAE I every six months to the CPP and the trial investigators.

EIG A events will be recorded and kept by the sponsor for reporting via the annual safety report.

The protocol, the patient information sheet and the consent form may be amended if new safety information is updated.

8.4.3. Independent Oversight Committee

The independent monitoring committee may be convened at the request of an investigator in the event of a recurrence of serious adverse events (see 8.1.4). This committee will be composed of: Professor Eric Gamelin (CRLC of Angers), Dr. Thierry Levade (University Hospital of Toulouse), and Dr. Etienne Bardet (CRLC of Nantes). This committee may review the patient's entire medical file, their technical file concerning the irradiation, and all care documents.
Therefore, it can help in making difficult decisions during the trial period where independent judgment is desirable. It can provide advice in the following circumstances:
Opinion on a premature termination of the trial (due to toxicity or because the trial is no longer feasible).
Advice on major changes to the protocol that have become necessary due to recruitment or trial monitoring, or to take into account new scientific data;
Interim analysis: interpretation of the results of the analysis, request for additional analyses or data from the test.
The Independent Committee's opinion is transmitted in writing to the sponsor and investigators of the study.

8.4.4. Annual Security Report (RAS)

A safety report is produced annually on the anniversary date of the clinical trial authorization (CTA) issued by the competent authority.
This report consists of three parts: patient safety report, line-listing of adverse events and overall summary table.

The report is prepared by the research sponsor in collaboration with the coordinating investigator. The sponsor has 60 days (from the anniversary date of the AEC) to submit this document to the relevant authorities.

Similarly, a summary table of EIG I will be sent to the CPP every six months.

8.5. METHODS AND DURATION OF FOLLOW-UP OF INDIVIDUALS AFTER THE OCCURRENCE OF ADVERSE EVENTS.

Every patient included in the protocol, whether they have withdrawn from the study or are a long-term survivor (beyond 48 months after the end of treatment), will be followed up regularly at their referring center, just like any other patient treated for metastatic colorectal cancer. The frequency of follow-up depends on the medical practices of each center.

9. STATISTICS:

This multicenter study will include patients treated at the ICO (René Gauducheau site) in Nantes, the Léon Bérard Center in Lyon, the Orléans Hospital Center and the Oscar Lambret Center in Lille, the Eugène Marquis Center in Rennes, and the University Hospital of Bordeaux, representing approximately fifteen patients per year. The study is planned for an initial duration of three years and will include 48 patients.

***Amendment of 21/01/14**: Extension of inclusions until 19/06/2014 and inclusion of a total of 53 patients in order to take into account non-evaluable patients (included but not treated, …).*

9.1. STATISTICAL ANALYSES

9.1.1. Subgroup analyses planned (optional)

Not applicable

9.1.2. Planned interim analyses (optional)

An interim analysis is planned for the 16th evaluable patient (see chapter 9.2).

9.1.3. Responsible(s) for statistical analyses

The statistical analysis will be carried out under the responsibility of Dr Loïc Campion with the help of SAS 9.1 software.

9.2. EXPECTED NUMBER OF PEOPLE TO BE INCLUDED IN THE RESEARCH, AND EXPECTED NUMBER OF PEOPLE AT EACH RESEARCH SITE WITH ITS STATISTICAL JUSTIFICATION.

Given the pathology and the context of the study, it is assumed that this new treatment will not be beneficial in the future if the response rate is not greater than 75% (Null Hypothesis H0: $p \leq p0 = 75\%$); we also accept a response rate of 90% or more (Alternative Hypothesis H1: $p \geq p1 = 90\%$) would be of definite interest in these patients.

- The null hypothesis (H0: $p \leq p0 = 75\%$) is therefore compared to the alternative hypothesis (H1: $p \geq p1 = 90\%$).
- If we fix the risk α (risk of accepting a new, insufficient treatment) at 10% and the risk β (risk of rejecting a promising new treatment) at 10%, calculating the number of subjects needed using Simon's two-step optimum design test (1) gives the following results:

- The first stage includes 16 patients; at the end of the stage:
  - If we get 12 or fewer responses (75%), we stop the trial: the percentage of effectiveness is less than 90% (Rejection H1).
  - If we obtain 13 or more responses, we continue the trial by including 32 additional patients.

- At the end of stage 2, out of the 48 patientsassessable:
  - -if we observe 39 or less than 39 responses (81.25%), we conclude that the response rate is less than 90% (Rejection H1).
  - -if we observe 40 or more of 40 responses (83.33%), we conclude that the response rate is significantly greater than 75% (Rejection H0).

Bibliographic reference: (1) Simon R. Optimal two-stage designs for phase II clinical trials. Control. Clin. Trials 1989, 10: 1-10.

9.3. EXPECTED DEGREE OF STATISTICAL SIGNIFICANCE.

See chapter 9.2

9.4. STATISTICAL CRITERIA FOR STOPPING THE SEARCH.

See chapter 9.2

9.5. METHOD FOR TAKING INTO ACCOUNT MISSING, UNUSED OR INVALID DATA.

The primary objective of the study is to evaluate the tumor response rate at the irradiated site. Therefore, any patient lost to follow-up before 6 months post-treatment will not be analyzed and will not be included in the statistical analysis (see section 5.4.3).

9.6. SELECTION OF INDIVIDUALS TO INCLUDE IN THE ANALYSES.

See chapter 9.5.

9.7. MANAGING CHANGES MADE TO THE INITIAL STRATEGY ANALYSIS PLAN.

The interim statistical analysis will be based on the tumor response rate in the irradiated site from the 16th evaluable patient (see chapter 9.2).

If the number of evaluable patients (at 6 months post-treatment) compared to the number of patients initially included is low, due to the frequency of serious adverse events, the monitoring committee will meet to assess whether or not to continue the study.

10. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS.

Each patient's medical data will only be transmitted to the sponsor or any person duly authorized by the sponsor, and, where appropriate, to the authorized health authorities, under conditions guaranteeing their confidentiality.

The sponsor and the supervisory authorities may request direct access to the medical file for verification of the procedures and/or data of the clinical trial, without violating confidentiality and within the limits authorized by laws and regulations.

11. QUALITY CONTROL AND ASSURANCE.

11.1. TRIAL MONITORING

Monitoring will be carried out by the Clinical Research Promotion Unit. A Clinical Research Associate (CRA) will visit each site regularly to perform quality control checks on the data reported in the case report forms. The CRA will ensure that the forms contain all the required information and verify their compliance with the protocol and applicable regulations.

Each patient's observation log must be consistent with the source documents (i.e., patient file). The Clinical Research Associate (CRA) must have easy access to these documents. The CRA is bound by confidentiality regarding the information they access.

The frequency of visits will depend on the number of patients included, the rate of inclusions and the difficulties encountered during the conduct of the study and will be defined by the study sponsor.

Site monitoring visits will be scheduled by appointment with the investigator. CRAs must be able to consult:

- the patient data collection notebooks included,
- the patients' medical and nursing records,
- the investigator's binder.

Basic monitoring will check the following 5 points:

- the presence of signed informed consent forms,
- compliance with inclusion criteria,
- the main criterion for judgment,
- monitoring and reporting of adverse events,
- the reporting of new facts,

The protocol was classified according to the estimated risk level for the patient participating in the research. It will be followed as follows:
Class II: Risk close to usual care (50% of cases to be monitored at 100%)

11.2. INSPECTION / AUDIT

As part of this study, an inspection or audit may take place at one of the investigating centers.

An inspection is an official control carried out by the supervisory authorities with the aim of assessing the admissibility of clinical data, verifying compliance with legislation and the absence of fraud.
Inspectors verify documents, logistical resources, records and any other resources that the authorities consider to be associated with the clinical trial and that may be located at the trial site itself, at the

sponsor's premises and/or at the premises of the contract research organization (CRO) or at other establishments deemed relevant.

An audit is a quality control of the trial; it can be conducted by representatives of the sponsor or a company duly mandated by the sponsor.

12. ETHICAL CONSIDERATIONS.

12.1. WRITTEN INFORMED CONSENT

The investigator undertakes to inform the patient clearly and fairly about the protocol and to obtain their informed and written consent (information letter and consent form attached). The investigator will provide the patient with a copy of the information leaflet and a consent form. The patient can only be included in the study after having read the information leaflet and signed and dated the consent form. The investigator must also sign and date the consent form. Both documents will be provided in duplicate so that the patient and the investigator can each keep a copy. The investigator's original will be filed in the investigator's binder.

12.2. COMMITTEE FOR THE PROTECTION OF PERSONS

The sponsor undertakes to submit the study project for prior authorization by an Ethics Committee (CPP). The information provided relates, on the one hand, to the methods and nature of the research and, on the other hand, to the safeguards provided for patients participating in this trial.

12.3. AMENDMENTS TO THE PROTOCOL

Requests for substantial modifications will be submitted by the promoter for authorization or information to the ANSM and/or the relevant ethics committee in accordance with Law 2004-806 of August 9, 2004 and its implementing decrees.

The modified protocol will need to be updated with a date.
The patient information and consent forms will need to be modified if necessary.

12.4. DECLARATION TO THE COMPETENT AUTHORITIES

This protocol will be submitted for authorization to the ANSM.

12.5. PATIENT ANONYMITY

By signing this protocol, the principal investigator and all co-investigators agree to maintain the confidentiality of the identities of the patients who participated in the study. The first letter of the last name, the first letter of the first name, and the date of birth will be the only information recorded in the case report form (CRF) and will allow the CRF to be linked to the patient in retrospect.

The sponsor is also required to anonymize all documents in their possession (examination reports, imaging, biology, etc.) that would be attached to the CRF.

12.6. COMPUTERIZED DATA

The computer file used to conduct this research by recording patient data has been the subject of an authorization request to the CNIL (National Commission for Information Technology and Freedoms), in accordance with the "Data Protection Act".

12.7. FILE OF INDIVIDUALS PARTICIPATING IN BIOMEDICAL RESEARCH

N / A

13. DATA PROCESSING AND STORAGE OF DOCUMENTS AND DATA RELATING TO RESEARCH.

13.1. DATA COLLECTION

A case report form (CRF) will be created for each patient. All information required by the protocol must be provided in the CRF. It will document the various stages of the patient's care as outlined in the protocol. It must include the data necessary to confirm adherence to the protocol and to identify any major deviations from it.

- paper observation notebook:

According to the center, the investigator or a clinical research associate will keep the CRFs up to date.

The data must be copied in a clear and legible manner.
Missing data will be notified by the entry DM (missing data).
Incorrect data will be clearly crossed out and new data copied next to it with the date and the corrector's initials.
The anonymity of the subjects will be ensured according to the rules defined in 12.5. All personal data will be erased.

The notebooks will be dated and signed when the patient has finished the trial in order to validate the data.

- If electronic observation log

Not applicable

13.2. DATA PROCESSING

The collection of clinical data will be based on the establishment of a clinical database and the creation of data entry templates similar to the observation logbook, in accordance with the protocol and regulations currently in force.
The database structure and data entry screens will be approved by the trial sponsor.

13.3. DATA ARCHIVING

All notebooks and study documents must be kept in a locked cabinet.for 15 years.
This information must be kept by the sponsor and the investigator.

14. FINANCING AND INSURANCE, IF THESE POINTS ARE NOT COVERED BY A SEPARATE DOCUMENT (E.G., CONTRACT OR AGREEMENT).

The sponsor covers any additional costs related to specific supplies or examinations required by the research protocol or for its implementation. Funding is provided by a PHRC grant and support from Pfizer.

This funding will cover the following costs:

- Supply of Irinotecan
- promotion (administrative management of the trial, monitoring)
- insurance subscription
- submission fees to the CPP and the ANSM
- data entry
- data analysis
- Pharmacovigilance
- Health economics study
- Radiobiology study
- The tests considered as an additional cost for the investigator sites

In accordance with Article L.1121-10 of Chapter I of Title II of Book I of Part One of the CSP, the promoter assumes responsibility for compensating the harmful consequences of biomedical research for the person who participates in it and for their beneficiaries, unless it proves that the damage is not attributable to its fault or to that of any other party involved, without the fact of a third party or the voluntary withdrawal of the person who initially consented to participate in the research being able to be used as a defense.
The sponsor, the Western Cancer Institute, declares that it has taken out an insurance policy guaranteeing, according to the terms of the contract and within the limits of the sums stipulated, the financial consequences of its civil liability as defined by Article L 1121-10 of the Public Health Code. The sponsor's taking out such a policy does not preclude it from exercising its rights of recourse against the aforementioned parties in the event of their negligence.

15. RULES RELATING TO PUBLICATION.

One year after the end of the study, the final report will be submitted to the sponsor who will send a summary to the supervisory authorities.

A copy of the publication will be provided to the ICO, the study sponsor, which will be duly cited. Apart from the coordinating investigators, authors will be assigned proportionally to the number of patients included.

The protocol has been declared in the American public database: clinicaltrial.gov.

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ANNEXES

- Appendix 1: Study Summary
- Appendix 2: Newsletter
- Appendix 3: Patient Consent Collection Form
- Appendix 4: Consent form for the storage and use of blood samples during and at the end of biomedical research
- Appendix 5: List of investigators (identity, function, specialty, place of practice = establishment & department, registration number with the medical board, full contact details)
- Annex 6: PERFORMANCE INDEX (WHO SCALE)
- Appendix 7: NCI-CTC 3.0 TOXICITY CRITERIA
- Appendix 8: RTOG/EORTC Radiotherapy Late Morbidity Score
- Appendix 9: RECIST Criteria
- Appendix 10: Quality of Life Questionnaire
- Appendix 11: CRF follow-up of the study
- Appendix 12: Medical and Economic CRF