FFCD-1201

INTRA-ARTERIAL TREATMENT WITH IRINOTECAN (DEBIRI) LOADED MICROBEADS CONCOMITANTLY WITH FOLFOX SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH COLORECTAL CANCER WITH NON-RESECTABLE LIVER METASTASES - THE FIRST STUDY OF ITS KIND IN THE WORLD

PHASE II MULTICENTER NON RANDOMIZED

Eudract number: 2012-004166-18

COORDINATOR : Pr Julien TAIEB
Georges Pompidou European Hospital
Department of Gastroenterology
20 Rue Leblanc
75908 PARIS CEDEX 15
Tel: 01 56 09 50 42 - Fax: 01 56 09 35 29
E-mail : julien.taieb@egp.aphp.fr

SCIENTIFIC CO-LEADER :
Dr Simon PERNOT
Georges Pompidou European Hospital
Department of Gastroenterology
20 Rue Leblanc
75908 PARIS CEDEX 15
Tel: 01 56 09 50 42 - Fax: 01 56 09 35 29
E-mail : simon.pernot@gmail.com

Protocol Writing Committee:
Thierry Debaere, Boris Guiu, Karine Le Malicot, Come Lepage, Olivier Pellerin, Simon Pernot, Julien Taieb.

SPONSOR AND CENTER FOR RANDOMIZATION-MANAGEMENT-ANALYSIS (CRGA) :
Fédération Francophone de Cancérologie Digestive (FFCD), Faculty of Medicine, 7 Boulevard Jeanne d'Arc, BP 87900, 21079 Dijon Cedex, France

Francophone Federation of Digestive Oncology (FFCD) : **Cécile GIRAULT- Administrative Director**
Tel: 03 80 66 80 13 - Fax: 03 80 38 18 41
E-mail: cecile.girault@u-bourgogne.fr

Statistician : **Karine LE MALICOT**
Tel: 03 80 39 34 71- Fax: 03 80 38 18 41
E-mail: karine.le-malicot@u-bourgogne.fr

Project manager: **Martina SCHNEIDER**
Tel: 03 80 39 34 83- Fax: 03 80 38 18 41
E-mail : jeremie.bez@u-bourgogne.fr

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CONTACTS FFCD

Randomization + EIG declaration : Fax : 03 80 38 18 41 - Tel : 03 80 66 80 13

NAME	FUNCTION	PHONE	TELECOPIE
ADMINISTRATIVE MANAGEMENT			
Cécile GIRAULT	Administrative Director	03 80 39 33 87	03 80 38 18 41
Martina SCHNEIDER	Assistant Administrative Director	03 80 39 34 83	03 80 38 18 41
Aurélie DUBREU	Executive secretary	03 80 38 13 14	03 80 38 18 41
RANDOMIZATION CENTER - MANAGEMENT - ANALYSIS			
Karine LE MALICOT	Statistician	03 80 39 34 71	03 80 38 18 41
Emilie MAILLARD	Statistician	03 80 39 34 81	03 80 38 18 41
Marie MOREAU	Project Manager	03 80 39 34 04	03 80 38 18 41
Géraldine VAUDRIT	Assistant Project Manager	03 80 38 33 86	03 80 38 18 41
Jérémie BEZ	Project Manager	03 80 39 34 83	03 80 38 18 41
Jaïque CARIO	Assistant Project Manager	03 80 39 34 86	03 80 38 18 41
Gaëlle DELIGNETTE	Assistant Project Manager	03 80 39 34 86	03 80 38 18 41
Caroline CHOINE-POURRET	ARC Coordinator	04 69 18 19 02	09 74 44 22 47
Guillaume ARNOULD	ARC	06 30 73 42 78	03 80 38 18 41
Hicham FATTOUH	ARC	04 78 66 13 08	04 78 66 13 08
Florence GUILIANI-KPODOH	ARC	04 30 67 80 23	09 74 44 20 40
Nouredine LASMI	ARC	06 26 36 92 56	03 80 38 18 41
Nicolas LE PROVOST	ARC	05 33 05 62 21	05 56 05 03 59
Fadil MASSKOURI	Data Manager	03 80 39 34 05	03 80 38 18 41
Charles FUCHEY	Data Manager	03 80 39 34 81	03 80 38 18 41
Elodie GAUTIER	Data Manager	03 80 39 34 84	03 80 38 18 41
Carole MONTERYMARD	Data Manager	03 80 39 34 84	03 80 38 18 41

You can also contact the CRGA of the FFCD at: 03 80 66 80 13 (Monday to Friday from 9H00 to 18H00)

PROTOCOL AGREEMENT AND BPC

TRIAL FFCD-1201: INTRA ARTERIAL IRINOTECAN (DEBIRI) LOADED MICROBALLS IN COMBINATION WITH FOLFOX SYSTEMIC CHEMICAL THERAPY IN COLORECTAL CANCER PATIENTS WITH NON-RESCURABLE HEPATIC METASTASIS - NON RANDOMIZED MULTICENTRIC PHASE II

EudraCT No: 2012-004166-18

Version 1.2 of 28/07/2015

This version of the protocol is approved by :

The Promoter : Ms. Cecile GIRAULT Date: 07/28/2015Signature :

The Coordinator: Pr Julien TAIEB Date: 07/28/2015Signature:

I, the undersigned, Doctor

After having read the requirements of this research, the protocol and its annexes, I hereby certify that I will conduct this trial in accordance with Good Clinical Practice and in compliance with the applicable provisions of the Public Health Code.

In particular, I agree to:

- comply with the protocol and any modifications notified to it by the promoter
- agree to supervise research in the center and to train collaborators in the conduct of research and provide a list of names
- have each patient sign a written consent after having read the information note intended for him/her, before any research is carried out
- Report serious adverse events or developments within 24 hours of learning of them, and as directed
- respect the inclusion and non-inclusion criteria, as well as the start and end dates of the study
- participate in the translational part of the study and send copies of the evaluation reports
- to complete all the items in the observation book, to ensure the quality of data collection, and the proper management of the products
- retain research data and documents for 15 years
- inform the sponsor of any conflict of interest situation that may affect its scientific independence in the context of the research
- inform the sponsor without delay of any action, whether amicable or contentious, brought by a person involved in the research or his or her beneficiaries, which may call into question the sponsor's liability
- accept periodic visits by the sponsor's representatives, and make available to them all source documents and materials related to the research in order to ensure quality control of the data recorded in the observation book. I accept control in the form of an audit by the sponsor and/or inspection by the health authorities
- respond by phone or mail to requests for corrections or clarifications regarding the data collection
- Allow time for the ARC FFCD to sign off on the forms, answer any questions, and take action.

Date: Signature:

STAMP of the CENTER :

Send the original to CRGA de la FFCD - 7 bd Jeanne d'Arc - BP 87900 - 21079 Dijon Cedex

SYNOPSIS

Essay title:	**Trial FFCD-1201: INTRA ARTERIAL IRINOTECAN (DEBIRI) LOADED MICROBALLS IN COMBINATION WITH FOLFOX SYSTEMIC CHEMICAL THERAPY IN COLORECTAL CANCER PATIENTS WITH NON-RESCURABLE HEPATIC METASTASIS - NON RANDOMIZED MULTICENTRIC PHASE II**
Trial number	FFCD- 1201
Developer	FFCD
Coordinator(s)	Pr. Julien Taïeb, Dr Simon Pernot
Rationale for the study	The treatment of patients with colorectal cancer with liver metastases is currently based on systemic chemotherapy. Triple therapy combining 5FU, oxaliplatin and irinotecan by IV route has been shown to be effective in terms of response and secondary resectability, however it is particularly toxic. Intra-arterial hepatic chemotherapy (IHC) has been studied in several studies. It has shown good efficacy with oxaliplatin and FUDR. However, it is a difficult procedure to implement and is reserved for expert centers. The aim of this protocol is to use triple therapy with 5FU, oxaliplatin, and irinotecan, the latter delivered intra-arterially to the liver, loaded on microbeads (DEBIRI). Moreover, the DEBIRI chemoembolization procedure is limited to 2 sessions for each lobe, and could be more easily generalized.
Objectives	**Principal:** Progression-free survival rate at 9 months according to RECIST 1.1. **Secondary:** Tolerance to treatment Response rate according to RECIST 1.1 criteria at 9 months Response rate according to EASL criteria at 9 months Hepatic progression-free survival according to RECIST 1.1 Overall survival Progression-free survival Secondary resection rate Evolution of tumor marker levels
Inclusion criteria	- Histologically proven colorectal adenocarcinoma, - Radiologically or histologically proven liver metastases - At least one measurable liver lesion according to RECIST v1.1 criteria - Age ≥ 18 years

	- WHO index≤ 2 - Life expectancy≥ 3 months - No extra-hepatic disease, except pulmonary nodules if number≤ 3 and size < 10 mm each - Hepatic Involvement < 60 - Primary tumor resected or in place - No prior chemotherapy for metastases (except peri-operative chemotherapy, if the last cycle was given at least 12 months ago) - Adjuvant chemotherapy after resection of the primary site allowed if the last cycle was administered at least 12 months ago - Normal liver function: total bilirubin ≤ 1.5N, AST≤ 5N, ALT ≤ 5N and PAL≤ 5N. - TP ≥ 60% - Adequate hematologic function: PNN ≥ 1500/mm^3 , platelets ≥ 100,000/mm^3 , Hb ≥ 9g/dL - Good renal function: creatinine clearance ≥ 60 mL/min - No cardiac dysfunction: no cardiovascular events in the past 6 months or no NYHA ≥ 2
Non-inclusion **criteria**	- Patient eligible for curative treatment (resection and/or radiofrequency ablation) according to a PCR (including the opinion of a liver surgeon) - Pregnant or breastfeeding women or patients of either sex of childbearing age who are not using an adequate method of contraception (see section V. 4) - Previous cancer, except for non-melanoma skin cancers and curatively treated cervical *in situ* cancers. Other curatively treated cancers are allowed provided they have not recurred for more than 5 years - Peripheral neuropathy - Inflammatory bowel diseases - Intestinal occlusion - Chronic liver disease (viral, alcoholic or metabolic) - Immunodeficiency syndromes (history of transplantation, HIV

	infection) - Known contraindications to 5FU, oxaliplatin, folinic acid, irinotecan or contrast media - Patient with known contraindication to liver embolization procedures: Presence of bilio-digestive anastomoses or biliary prosthesis Cruciate or tumor thrombosis of the portal vein - Patient who for psychological, social, family or geographical reasons could not be followed regularly - Legal incapacity (persons deprived of liberty or under guardianship) - Patient not affiliated to a social security system - Concurrent participation in another study investigating the effect of a treatment until 4 weeks after the end of this study.
Study design and treatment **plan**	Microbeads (100-300µm), loaded with irinotecan (DEBIRI). The maximum dose per procedure is 100 mg of irinotecan, combined with intravenous FOLFOX. For patients with unilobar or bilobar liver involvement, DEBIRI will be injected at D17 and D45 (after the 2nd and 4th cycle of systemic chemotherapy with FOLFOX). Patients with bilobar involvement but for whom the investigator decides that the treatment will be unilobar and sequential, there will be 4 sessions. Thus, the right and left livers will be treated alternately. The DEBIRI administrations will then be performed at D17, D31, D45, D59, or in case of a shift in chemotherapy treatment, after the $2^{ème}$, $3^{ème}$, $4^{ème}$ and $5^{ème}$ cycle of FOLFOX. FOLFOX will be administered every 2 weeks until progression or unacceptable toxicity.
Statistical methods	A 1-step Fleming design will be used, with a one-sided α risk of 5% and a power (1-β) of 90%. The assumptions are: • H0: A proportion of patients living without progression of 55% during the first 9 months is uninteresting; • H1: A proportion of patients living without progression of more than 55% during the first 9 months would show the interest of the treatment; a proportion of 75% is hoped for.

	Total number: **48 evaluable patients** Taking into account a 20% rate of lost to follow-up or non-evaluable patients, **58 patients** should be included. **At the end of recruitment:** During analysis: - if 32 or fewer patients are alive without progression, then the treatment is considered ineffective - if 33 or more patients are alive without progression, then the treatment is considered effective The decision rule will be adjusted based on the actual number of evaluable patients.
Number of subjects needed	58
Associated translational studies	- **On lipid parameters:** The objective of this study will be to evaluate the impact of the different parameters of the lipid profile and the metabolism of lipoproteins on the response to treatment. - **On Pathology:** At the end of the study, if a sufficient number of patients have undergone secondary resections of liver metastases, a collection of surgical parts will be organized. An anatomopathological study of the tumor parenchyma and the healthy parenchyma resected after DEBIRI treatment will be performed.
Planned study period	Expected start date of inclusion: April 2013 Expected completion date of inclusion: April 2016 Expected completion date: July 2018

I. OBJECTIVES OF THE TRIAL

I.1 Main objective

Evaluate the investigator-assessed 9-month progression-free survival rate (according to RECIST 1.1 criteria).

I.2 Secondary objectives

Tolerance to treatment

Response rate according to RECIST 1.1 criteria at 9 months

Response rate according to EASL criteria, assessed at 9 months, by centralized review

Hepatic progression-free survival according to RECIST 1.1

Overall survival

Progression-free survival

Secondary resection rate

Evolution of tumor marker levels

II. PATIENT SELECTION

II.1 Inclusion criteria

Inclusion in the study requires that all of the inclusion criteria listed below be met:

- Histologically proven colorectal adenocarcinoma
- Radiologically or histologically proven liver metastases
- At least one measurable liver lesion according to RECIST v1.1 criteria
- Age ≥ 18 years
- WHO Index≤ 2
- Life expectancy≥ 3 months
- No extra-hepatic disease, except pulmonary nodules if number≤ 3 and size < 10 mm each
- Hepatic invasion < 60%.
- Primary tumor resected or in place
- No prior chemotherapy for metastases (except peri-operative chemotherapy, if the last cycle was given at least 12 months ago)
- Adjuvant chemotherapy after resection of the primary site allowed if the last cycle was administered at least 12 months ago
- Normal liver function: total bilirubin ≤ 1.5N, AST≤ 5N, ALT ≤ 5N and PAL≤ 5N.

- TP ≥ 60%
- Adequate hematologic function: PNN ≥ 1500/mm^3 , platelets ≥ 100,000/mm^3 , Hb ≥ 9g/dL
- Good renal function: creatinine clearance ≥ 60 mL/min
- No cardiac dysfunction: no cardiovascular events in the past 6 months or no NYHA ≥ 2.

II.2 Non-inclusion criteria

Inclusion in the study requires that none of the non-inclusion criteria listed below are present:

- Patient eligible for curative treatment (resection and/or radiofrequency ablation) as determined by the PCR (including the opinion of a liver surgeon)
- Pregnant or breastfeeding women or patients of either sex of childbearing age who are not using an adequate method of contraception (see section V. 4)
- Previous cancer, except for non-melanoma skin cancers and curatively treated cervical in situ cancers. Other curatively treated cancers are allowed provided they have not recurred for more than 5 years
- Peripheral neuropathy
- Inflammatory bowel diseases
- Intestinal occlusion
- Chronic liver disease (viral, alcoholic or metabolic)
- Immunodeficiency syndromes (transplant history, HIV infection)
- Known contraindications to 5FU, oxaliplatin, folinic acid, irinotecan or contrast media
- Patient with known contraindication to liver embolization procedures:
  - Presence of bilio-digestive anastomoses or biliary prosthesis
  - Cruciate or tumor thrombosis of the portal vein
- Patient who for psychological, social, family or geographical reasons could not be followed regularly
- Legal incapacity (persons deprived of liberty or under guardianship)
- Patient not affiliated with a social security plan.
- Concurrent participation in another study investigating the effect of a treatment until 4 weeks after the end of this study.

III. PRE-INCLUSION ASSESSMENT

To be performed within 21 days prior to treatment and before inclusion:

- Thoracoabdomino-pelvic CT scan, documenting at least one measurable liver lesion
- Hepatic MRI
- PET scan strongly recommended before inclusion.

Remember to keep the radiology CDs in the patient's file; the ARC FFCD will make a copy of these imaging studies.

To be completed within 14 days prior to inclusion:

- Complete clinical examination including: weight, height, vital signs, WHO index, pain assessment (VAS)
- Medical history
- Description of the disease
- Biological workup consisting of measurements of hematological, nephrological and hepatic parameters: CBC/platelets, blood ionogram, creatinine, albumin, transaminases (AST, ALT), alkaline phosphatases (ALP), total and conjugated bilirubin, PT, APTT, fibrinogen level
- Determination of lipase
- ACE and CA 19-9 assay
- KRAS status will be determined at each center but not routinely at inclusion
- **Fasting** sample for patients participating in the 'lipid' translational study; don't forget to perform it (according to the corresponding section, p25).

IV. INCLUSION

After the patient has signed the clinical consent form (Appendix 1) and the results of the examinations necessary for inclusion in the study have been verified, the patient can be included. For centers participating in the associated 'lipid' study, the specific information and consent form (Appendix 2) must be proposed.

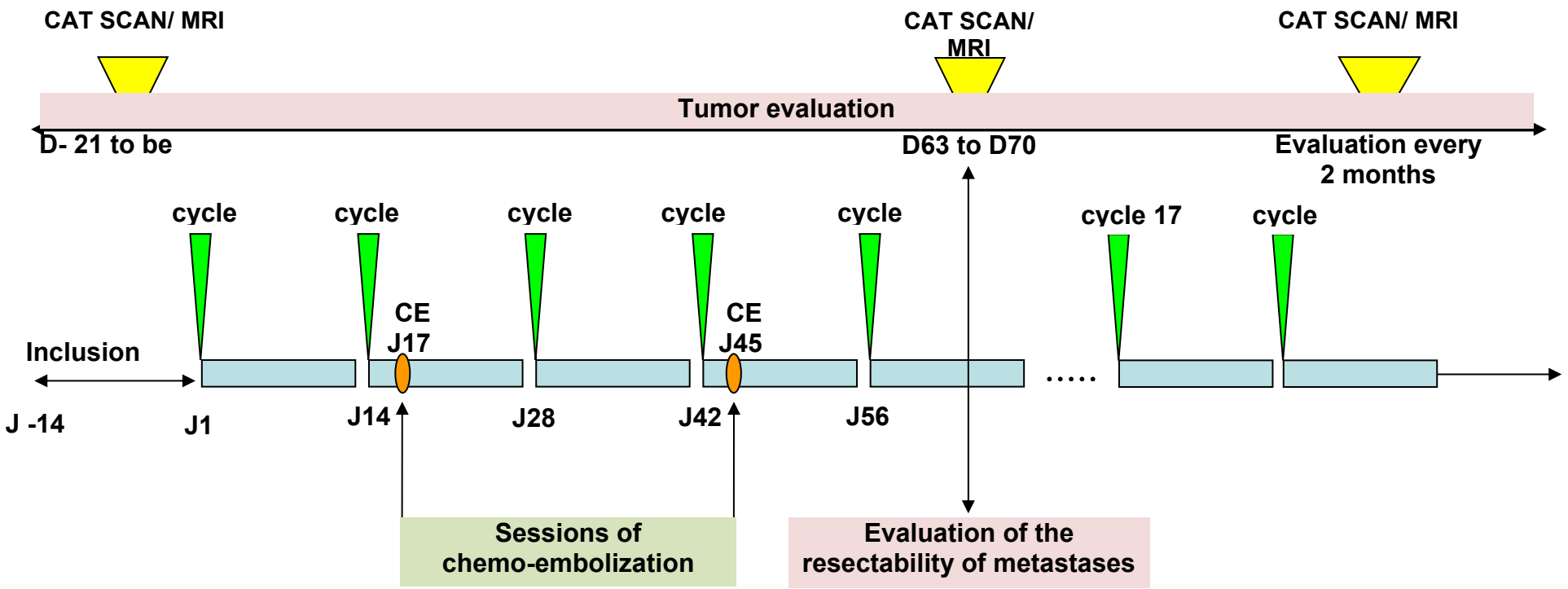
The patient's inclusion will be done directly via the eCRF; the inclusion confirmation and the inclusion number will be sent to you by email. For any help, the FFCD Randomization - Management - Analysis Center in Dijon is open from Monday to Friday from 9:00 am to 6:00 pm.

After inclusion in the study, treatment should begin within a maximum of 2 weeks.

V. TREATMENT

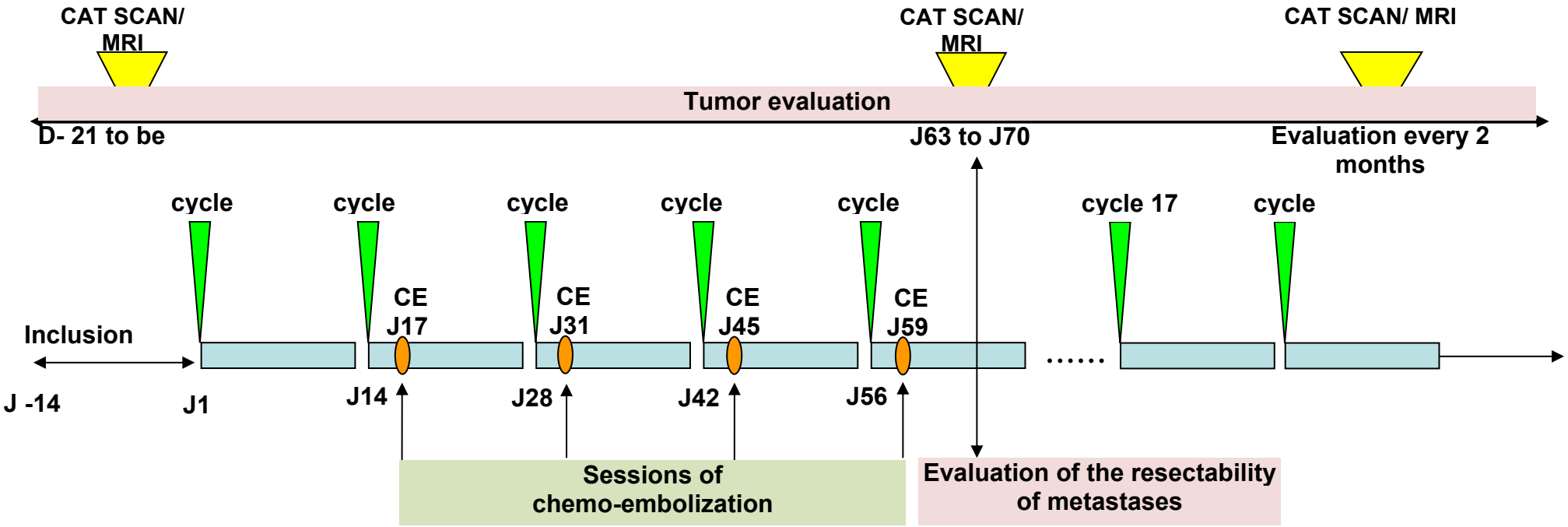
V.1 Treatment scheme:

Bilobar treatment in 2 sessions:



Following this initial treatment plan, all patients will receive FOLFOX chemotherapy every 2 weeks according to the usual schedule until progression or unacceptable toxicity.

Sequential unilobar treatment in 4 sessions:



The chemoembolization treatment can, at the investigator's choice, be administered in a unilobar and sequential manner, in 4 sessions. Thus, the right and left livers will be treated alternately. The administrations of DEBIRI will then be performed at D17, D31, D45, D59 (+/- 2 days), or in case of delayed chemotherapy treatment, 3 days (+/- 2 days) after C2, C3, C4 and C5 of FOLFOX. After this initial treatment plan, all patients will receive FOLFOX chemotherapy every 2 weeks according to the usual schedule until progression or unacceptable toxicity.

V.2 Chemoembolization

V.2.1 Scheduled irinotecan dose

Each vial of DC Bead is loaded with 100 mg of irinotecan. It is intended to use the contents of one vial per lobe. For unilobar disease, there will be 1 vial loaded with 100 mg of irinotecan and for bilobar disease, 2 vials loaded with 200 mg, if the treatment is done in one session.

V.2.2 Microbead size

Microbeads with a size of 100-300µm will be used in this study and provided by the sponsor.

V.2.3 Precautions and instructions for loading the medication:

Instructions for loading the beads will be provided in the investigator's binder and the pharmacy bag.

V.2.4 Dilution of the loaded microbeads with a contrast agent

Remove the excess supernatant of the irinotecan solution from the vial containing the loaded microbeads before mixing with the contrast agent. A non-ionic contrast agent should be used. It is recommended that the microbeads be diluted prior to injection with a volume of at least 5-10 mL of contrast agent per mL of microbeads (i.e., 10-20 mL of contrast per vial of microbeads). A good suspension of the microbeads in the contrast must be obtained before administration.

V.2.5 Conservation of loaded microbeads:

Irinotecan-loaded microbeads can be stored for up to 24 hours in a refrigerator at 2°C to 8°C or for up to 4 hours at room temperature, with or without a non-ionic contrast agent.

V.2.6 Pre-administration assessment:

Prior to each chemoembolization procedure, the patient should be ensured to have adequate liver and hematologic function (total bilirubin ≤ 1.5N, ALT, ASAT, and PAL ≤ 5N, albumin ≥ 2.5g/dL; PNN ≥ 1500/mm^3 , platelets ≥ 100,000/mm^3 , INR <1.5) and a patent portal trunk.

V.2.7 Procedure

The DEBIRI procedure will begin with a 4 or 5Fr peripheral arterial approach at the operator's convenience.

The operator will first proceed to a diagnostic phase. Successively, he will catheterize the superior mesenteric artery and the celiac trunk. During these angiographies, the operator will identify the disposition of the hepatic arterial vascularization, the permeability of the portal trunk and the vascular topography of the lesions. The operator may be required to perform selective angiography of the phrenic, inferior epigastric, and internal mammary arteries when peripheral hepatic tumors have been identified.

After this diagnostic phase, **lobar administration** will be used whenever possible. The operator will catheterize the right and left hepatic arteries with a maximum 3Fr microcatheter. Prior to DEBIRI injection, the operator will place the microcatheter on the right downstream of the cystic artery, and on the left downstream of the right gastric artery. The right gastric artery may be prophylactically embolized if the operator deems it necessary.

Each vial of irinotecan-loaded microbeads (DEBIRI) will be mixed with at least 10-20 mL of non-ionic iodinated contrast medium (e.g. Imeron 350, Omnipaque 350).

The goal of the procedure is to deliver the entire dose of irinotecan. It is important to maintain anterograde flow in the vessel during the procedure.

DEBIRI should be injected slowly, at a rate of 1 mL of solution per minute.

When the near stasis point is observed prior to the full dose of irinotecan, the injection of DEBIRI is discontinued regardless of the volume of beads delivered at that time. Therefore, some patients may not receive the entire contents of the prepared vial and may receive a total dose of less than 100 or 200 mg, respectively, in cases of lobar or bilobar involvement. The operator will make sure to respect these recommendations to prevent an inappropriate reflux of DEBIRI that would cause ischemia or necrosis of non-targeted territories.

When the planned dose of irinotecan is administered before the near-stasis point is reached, no additional embolization should be performed with products such as gelfoam, lipiodol or microspheres.

The operator will take care to avoid sedimentation of the beads in the syringe during the procedure by performing gentle rotations or using a three-way valve to keep the beads suspended in the solution.

Extrahepatic vessels may be embolized prophylactically, at the discretion of the interventional radiologist, to minimize extrahepatic infusion of irinotecan beads.

For multifocal or bilobar disease, embolization of each lobe will be performed, at the investigator's discretion, either during the same session or in a unilobar and sequential manner, in 2 sessions. If the treatment is done in one session, the catheter will be placed in the

right and then left hepatic artery and a maximum of one vial of DEBIRI will be administered in each lobe.

Catheter removal and hemostasis at the puncture site will be accomplished by manual compression or by placement of a percutaneous puncture site closure device (e.g., Angioceal™).

Patients will need to be hospitalized overnight following the procedure. After the chemoembolization procedure, vital signs, femoral access point, pain management and hydration will be observed in all patients.

The amount of contrast material delivered to the patient during the procedure, the radiation dose, and the fluoroscopy exposure time should be recorded. The embolized vessels and the amount of embolic agent will be recorded.

All treatments used during the procedure, including analgesic treatments, should be recorded.

Any unused irinotecan-loaded microbeads will be discarded.

V.2.8 Peri-chemoembolization treatment recommendations/pre-medication for chemoembolization:

Primary prophylaxis with G-CSF should be used until all chemoembolization procedures have been completed and then left to the discretion of the investigator thereafter. The choice of G-CSF is left to the discretion of the investigator.

The following prophylactic treatments are recommended:

- **Prophylactic treatment to prevent renal failure:** IV hydration started the day before chemoembolization and continued until day 2, with a 2,000-mL bag per day (1,000 mL of saline + 1,000 mL of 5% glucose).
- **Prophylactic treatment of gastric toxicities:** esomeprazole 80 mg at D0, D1 and D2, infusion (oral possible for D1 and 2).
- **Prophylactic treatment of nausea and vomiting**: ondansetron 8 mg or granisetron 3 mg, before chemoembolization and 8 mg 6h after (at D0) and prednisolone 40 mg twice a day at D0, D1; then 40 mg/d at D2, D3, D4, D5
- **Prophylactic treatment of pain:**
  Ideally, self-administration of level 3 analgesics by PCA (Patient Control Analgesia) is implemented. The injected preparation is oxycodone 2 mg, injected by a pump with a

refractory period of 3 min and with a maximum dose of 20 mg per 4h. This PCA will be maintained for 12 hours after chemoembolization.

Otherwise, 5 to 10 mg of morphine, 30 minutes before and 6 hours after chemoembolization. This prophylaxis is given as an indication and can be modified at the investigator's discretion.

Intra-arterial infusion of 1-3 mL of 1% lidocaine immediately prior to chemoembolization with DEBIRI.

- **Prophylactic treatment of infections:** 2000 mg of cefazolin twice a day, at D0, D1 and D2.

V.3 Simplified FOLFOX 4 treatment

Simplified FOLFOX 4 administered IV every 2 weeks:

- Oxaliplatin 85 mg/m^2 in 2h in 250 mL of G5% (H + 0)
- Folinic acid 400 mg/m^2 in 2h in 250 mL of G5% (H + 0)
- 5FU 400 mg/m^2 in 10 min in 100 mL of G5% (H + 2H)
- 5FU 2400 mg/m^2 as a continuous infusion over 46 hours in G5% in a portable infuser (qsp 230 mL, 5mL/h), pump, or portable syringe pump

Patients with uni- or bilobar involvement will have chemoembolization and FOLFOX administrations at the following visits:
Or in a bilobar treatment in 2 sessions

Visit n°	FOLFOX cycle number	Chemoembolization cycle number	Time (days)
1	1		T=0
2	2		T+14
3		1	T+17
4	3		T+28
5	4		T+42
6		2	T+45
7	5		T+56

Either in a unilobar treatment in 4 sessions

Visit n°	FOLFOX cycle number	Chemoembolization cycle number	Time (days)
1	1		T=0
2	2		T+14
3		1	T+17
4	3		T+28
5		2	T+31
6	4		T+42
7		3	T+45
8	5		T+56
9		4	T+59

No targeted therapy is proposed in this protocol for the first line (neither anti-EGFR nor anti-VEGF).

Preventive treatments related to FOLFOX

Prophylaxis for FOLFOX administration is at the discretion of the investigator. However, the following prophylactic regimens are recommended:

- Prevention of chemo-induced nausea and vomiting (AFSOS recommendations):
  - Before chemotherapy (D1):
  - Anti-5-HT3: Odensetron (Zophren) IV 8 to 16 mg, 30 minutes before, respecting cardiac contraindications (congenital long QT syndrome, uncorrected hypokalemia or hypomagnesemia)
  - Aprepitant (Emend): per os, 125 mg, 1h before
  - Dexamethasone: IV 8 to 16 mg before
  - After chemotherapy:
  - Aprepitant per os: 80 mg in the morning of D2 and D3

- Prevention of mucositis (based on AFSOS recommendations):
  - Mouthwash prescriptions:
    - Sodium bicarbonate 1.4% pure, no other product added
    - As often as possible, minimum 8-10 times a day
    - In gargle
    - Away from meals
  - Oral hygiene tips (soft toothbrush)

- Prevention of neutropenia: G-CSF prophylaxis should be used until all chemoembolization procedures have been completed and then left to the discretion of the investigator thereafter.

- Prevention of neuropathy:
  - calcium gluconate (1g) and magnesium sulfate (1g) in 30 minutes IV before and after oxaliplatin at D1

To know all the other authorized and contraindicated treatments, please refer to the different RCP (see annex 7).

V.4 Precautions to take:

Women and men of childbearing age who participate in this trial must use effective contraception throughout their participation in the trial and for 12 months afterwards. Effective contraceptives may be hormonal (e.g., birth control pills, injections, or implants) or mechanical (e.g., condoms, IUDs, diaphragms, or other devices). For women using mechanical contraceptives, it is strongly recommended to combine 2 methods of mechanical contraception (such as condom, IUD, diaphragm or other device). Women who use hormonal contraceptives are advised to use a mechanical method of contraception at the same time.

VI. EXPECTED TOXICITIES AND DOSE ADJUSTMENT

Chemotherapy toxicities will be assessed using the NCI-CTC v4 scale (Appendix 5).

VI.1 FOLFOX

The expected toxicities with FOLFOX are mainly:

For oxaliplatin:

- allergic reactions
- cramps, dysesthesias (aggravated by cold)
- moderately emetogenic
- laryngeal spasm (reversible)
- peripheral sensory neuropathies

For 5-FU:

- mucositis
- diarrhea
- hand-foot syndrome
- weakly emetogenic
- hematological toxicity

Dose adaptations for guidance only:

Persistent paresthesias between 2 treatments (grade 2)	Reduce oxaliplatin to 65 mg/m^2
Painful paresthesias or with functional discomfort (grade 3)	Stopping oxaliplatin
Dermal toxicity grade > 2	Reduce bolus 5-FU to 300 mg/m^2 Reduce continuous 5-FU to 1800 mg/m^2.
Neutropenia < 1000/mm^3 (> grade 2) or thrombocytopenia < 50,000/mm^3 (> grade 2)	Stop bolus 5-FU and reduce oxaliplatin to 65 mg/m^2 if thrombocytopenia
Diarrhea, mucositis or other toxicity grade > 2	Reduce oxaliplatin to 65 mg/m^2. Reduce bolus 5-FU to 300 mg/m^2 Reduce continuous 5-FU to 1800 mg/m^2.
Grade 3-4 cardiac, cerebellar or allergy toxicity	discontinuation of chemotherapy

Wait for resolution of toxicities in case of grade 3 or 4 before resuming the cycle.

On the day of the resumption of the cycle D1: 1,500 PNN/mm^3 and 100,000 platelets/mm^3 are needed to resume the cycle.

VI.2 Chemoembolization

The main adverse effects expected with chemoembolization are:

- Unwanted reflux or passage of microbeads into normal arteries adjacent to the targeted lesion or through the lesion to other arteries or arterial beds
- Non-targeted embolization
- Pulmonary embolization
- Capillary bed saturation and tissue damage
- Ischemic stroke or ischemic infarction
- Rupture of a vessel or lesion and hemorrhage
- Neurological deficits including cranial nerve palsy
- Vasospasm
- Repermeabilization
- Foreign body reactions requiring medical intervention
- Infection requiring medical intervention
- Catheter tip clot formation and subsequent mobilization
- Deaths

Expected effects for the embolization procedure (from CNIHM anticancer files November 2008):

- Fever, right upper liver quadrant pain, vomiting
- Transient thrombocytopenia and liver dysfunction
- Increased transaminases (cytolysis)
- Local ischemic and septic manifestations (cholecystitis, hepatic infarction, hepatic abscess, digestive hemorrhage)
- Renal insufficiency

Adaptations for chemoembolization:

- **The chemoembolization procedure will be stopped in case of:**
  - Inability to catheterize the hepatic artery
  - Dissection of the hepatic artery
  - Anaphylactic shock to contrast medium
  - Per-procedural discovery of portal vein occlusion or arteriovenous shunt
  - near-stasis (stop-flow) observed prior to the full dose of irinotecan
- If the following grade 3 or 4 toxicities occur as a result of chemoembolization, no additional session will be performed (but FOLFOX will be continued).

- Arteritis
- Grade 3 or 4 hepatic impairment
- Local ischemic and septic manifestations (cholecystitis, hepatic infarction, hepatic abscess, digestive hemorrhage) of grade 3 or 4
- Grade 3 or 4 renal insufficiency

- **The interval between chemoembolization sessions may be extended to allow for recovery of liver function.**
- No dose adjustment of irinotecan is planned for chemoembolization sessions.
- In case of hematological toxicity, FOLFOX dose adjustment rules **will be applied and chemoembolization will be continued.**

In case of doubt, do not hesitate to ask for advice from the study's referring radiologist, Dr. Olivier Pellerin, through the FFCD.

VII. PATIENT MONITORING DURING TREATMENT AND AFTER WITHDRAWAL OF TREATMENT

Monitoring during treatment:

- **Before each cycle of FOLFOX:**
  - Complete clinical examination including: weight, vital signs, WHO, pain assessment (VAS)
  - Biological check-up: CBC/platelets
  - Adverse event evaluations according to NCI CTC version 4.0

- **Before each chemoembolization session**
  - Complete clinical examination including: weight, vital signs, WHO, pain assessment (VAS)
  - Biological workup consisting of measurements of hematological, nephrological and hepatic parameters: CBC/platelets, blood ionogram, creatinine, albumin, transaminases (AST, ALT), alkaline phosphatases (ALP), total and conjugated bilirubin, PT
  - Adverse event evaluations according to NCI CTC version 4.0

CEA and CA 19-9 assays, as well as thoracoabdomino-pelvic CT and liver MRI will be performed at an initial evaluation between D63 and D70 and then every 2 months after the start of treatment.

For patients participating in the associated 'lipid' translational study, please remember to perform the **fasting** sample and then technician the sample.

After the chemoembolization treatment period:

All patients will receive chemotherapy with FOLFOX every 2 weeks according to the usual regimen until progression or unacceptable toxicity.

VIII. STOP PROCESSING THE STUDY

The processing of the study will be stopped in case of:

- Investigator's decision
- Major toxicity requiring discontinuation of treatment (despite protocol adaptations)
- Serious or unexpected event requiring discontinuation of protocol treatment
- Progression of the disease
- Patient refusal or withdrawal of consent

In all cases of treatment discontinuation, the patient remains in the analysis for intention-to-treat and overall survival, and for 30 days after the last study treatment for toxicity.
There is no exclusion period for a subsequent therapeutic trial.

IX. CENTRALIZED READING OF CT SCANS AND MRI

Responses will be evaluated according to RECIST version 1.1 criteria (Appendix 3) and will be reviewed by a panel of independent radiologists according to RECIST version 1.1 criteria and EASL criteria (Appendix 4).
Don't forget to keep the CDs and the report of the CT and MRI evaluation in the patient's file; the FFCD CRA will make a copy of these imaging assessments to centralize them at the CRGA on the 'FFCD Images' platform using a secure transmission via the company ETIAM.

X. MANAGEMENT OF SERIOUS ADVERSE EVENTS (SIA)

Safety will be assessed by evaluating the general, clinical and biological status of patients at the time of scheduled visits and by collecting events occurring between visits. Toxicities will be assessed using the NCI-CTC Toxicity Scale version 4.0 (Appendix 5).

X.1 Definitions

Adverse Event (AE)

An adverse event is a harmful occurrence in a person who is a subject of biomedical research, whether or not the occurrence is related to the research or the product being investigated.
All adverse events will be recorded in the observation book on the pages provided.

Serious Adverse Event (SAE)

A serious adverse event is any event that meets at least one of the following criteria:

- Resulting in death,
- Life-threatening,
- Leading to hospitalization or prolonged hospitalization,
- Causing permanent disability or severe temporary incapacity,
- Causing a birth defect, fetal malformation or abortion,
- Medically significant (examples: overdoses, second cancers, pregnancies and new developments may be considered medically significant)

Pregnancy is an exclusion criterion in this trial.
However, if a pregnancy is discovered after inclusion, the patient must be excluded from the trial. The sponsor should be informed immediately via the Serious Adverse Event Reporting Form (no severity criteria should be checked). The patient should be followed until the outcome of the pregnancy and this outcome, whatever it may be, should be reported to the sponsor.
Hospitalizations included in the protocol will not be considered an SAE.

Undesirable Effect

Any noxious and undesired response to an investigational drug at any dose or to any investigational component. The adverse reaction is serious if it meets the severity criteria (see above).

Unexpected Serious Adverse Effect

An unexpected serious adverse reaction is an event that is not mentioned, or is different in nature, intensity, or evolution from the product reference document.

In this essay the reference documents will be:

- For irinotecan-loaded beads (DEBIRI): the Investigator's Brochure
- For FOLFOX: the Summaries of Product Characteristics for oxaliplatin, 5-fluorouracil, folinic acid (Appendix 7)

The versions of the PCRs used for the definition of expected or unexpected will be the latest available on the anniversary date of the start of the trial.

X.2 Course of action

The investigator informs the sponsor of all Serious Adverse Events (Expected and Unexpected), whether or not attributable to the research, that occur during treatment and within 30 days of the last treatment administration.

All Delayed Serious Adverse Events (occurring after this 30-day period) considered reasonably related to the protocol treatment(s) or research should be reported without time limitation.

The report is made by faxing the "notification of a serious adverse event" form (Appendix 8), documented as precisely as possible, dated and signed, within 24 working hours of their discovery to the FFCD's Randomization Management Analysis Center (CRGA): by fax to 03 80 38 18 41.

Modalities and duration of follow-up of individuals following the occurrence of adverse events.

The investigator is responsible for appropriate medical follow-up of patients until resolution or stabilization of the effect or until the patient's death. This may sometimes mean that this follow-up extends beyond the patient's discharge from the trial.

He/she transmits the additional information to the sponsor using an SAE reporting form (checking the Follow-up No. X box to specify that it is a follow-up report and not an initial report) within 24 hours of obtaining it. It also forwards the latest follow-up to the resolution or stabilization of the SAE.

He keeps the documents concerning the suspected adverse reaction in order to allow, if necessary, to complete the information previously transmitted.

XI. ANCILLARY STUDIES

- **Associated 'lipid' study**

Recent publications show that the plasma lipoprotein profile influences the risk of colorectal cancer; a high level of HDL cholesterol is a good prognosis.

One of the objectives of this study will be to evaluate the relationship between the different parameters of the lipid profile and lipoprotein metabolism on the response to treatment.

A lipid profile (including cholesterol, triglycerides, LDL and HDL profiles, activity of plasma lipid transfer proteins, etc.) will be performed before and after the protocol treatment.

If your center is participating in this study, you will have a specific information note to offer to your patients (Appendix 2).

Two **fasting** samples **(16 hours fasting)**, on 7 mL EDTA tube will be taken; the first one before any administration and the other one at the time of the first evaluation (after the chemoembolization sessions, between D63 and D70).

These samples will be centrifuged on site at 1500 g, for 15 min, at 4°C and this maximum 4 hours after sampling. The supernatant will be aliquoted in 1 mL tubes; they will be stored at -80°C until the end of the inclusions. The sponsor will organize a grouped shipment on dry ice.

- **Associated anatomopathological study**

At the end of the study, if a sufficient number of patients have undergone secondary resections of liver metastases, a collection of surgical parts will be organized. The objective will be to evaluate the histological response according to the TRG grade. Will be analyzed:

- healthy peri-tumor liver parenchyma
- liver metastases

The surgical specimens will be analyzed macroscopically and microscopically by standard techniques of morphological cytological and architectural studies, standard staining (Hematoxylin Eosin (HES), and Periodic Acid Shiff (PAS)), and immunohistochemistry, to determine: the limits of excision, tumor response and tumor necrosis to treatment on histological criteria, but also the impact on the healthy parenchyma of the chemoembolization procedure, by assessing hepatic fibrosis, hepatic necrosis, steatosis and steatohepatitis, and vascular lesions of the healthy parenchyma.

XII. STATISTICAL ANALYSIS

XII.1 Provisional timetable for the study

Expected start date of inclusion: April 2013

Expected completion date of inclusion: April 2015

Expected completion of study: July 2017

XII.2 Judging criteria

XII.2.1 Main criterion

The primary endpoint will be the proportion of patients alive without progression (death will be considered as progression) at 9 months after the start of treatment according to RECIST V1.1 criteria, as assessed by the investigator.

Progression-free survival time will be defined as the time interval between the date of inclusion and the date of progression or death (regardless of cause). For patients alive without progression, the time interval between the date of inclusion and the date of last morphological evaluation will be taken.

XII.2.2 Secondary Criteria

The secondary endpoints will be:

- Tolerance to the treatment
- Response rate according to RECIST v1.1 criteria at 9 months (according to the investigator)
- Response rate according to EASL criteria (assessed by centralized review) at 9 months
- Hepatic progression-free survival according to RECIST v1.1 criteria at 9 months
- Overall survival
- Progression-free survival
- The rate of secondary resections
- Changes in tumor marker levels

Liver progression-free survival will be defined as the time interval between the date of inclusion and the date of liver progression as assessed by the investigator's RECIST V1.1 criteria or death (regardless of cause) or the date of the last morphological assessment for patients alive without progression.

Overall survival will be defined as the time interval between the date of inclusion and the date of death regardless of the cause of death or the date of last news for living patients.

Tolerance to treatment will be assessed by:

- duration of treatment, doses received, dose reductions and deferrals
- Toxicities collected at each monthly visit, and described according to NCI-CTC version 4.0 criteria; Grade 3, Grade 4 and Grade 5 toxicities will be reviewed
- the number and description of SAEs

Changes in tumor marker levels (CEA and CA 19-9) will be assessed throughout the study.

XII.3 Calculation of the number of subjects needed

A 1-step Fleming design will be used, with a one-sided α risk of 5% and a power (1-β) of 90%.

The assumptions are:

- H0: A proportion of patients living without progression of 55% during the first 9 months is uninteresting;
- H1: A proportion of patients living without progression of more than 55% during the first 9 months would show the interest of the treatment; a proportion of 75% is hoped for.

Total number: **48 evaluable patients**

Taking into account a rate of 20% of patients lost to follow-up or not evaluable, **58 patients should be included**.

At the end of recruitment:

During analysis:

- if 32 or fewer patients are alive without progression, then the treatment is considered ineffective
- if 33 or more patients are alive without progression, then the treatment is considered effective

The decision rule will be adjusted based on the actual number of evaluable patients.

XII.4 Statistical analysis plan

Analysis Populations:

Patients included in the study will be described on an intention-to-treat (ITT) basis as well as patients not evaluable for the primary endpoint.
A patient is considered evaluable if he or she has had chemoembolization and received at least one cycle of chemotherapy and for whom we have at least one evaluation during the 9 months of follow-up.
All efficacy analyses will be performed on a modified intention-to-treat basis (evaluable patients) included in the study regardless of eligibility criteria and treatment received.
Tolerability population: the ITT population that received at least one dose of the treatments.
In all cases of discontinuation, the patient remains in the intention-to-treat analysis. There is no exclusion period for a subsequent therapeutic trial.

Key analyses:
A statistical analysis plan will be written prior to freezing the database.
The description of clinical and medical variables will be done using percentages (95% confidence interval) for qualitative variables and mean (standard deviation) and median (Min-Max) as well as inter-quartile range (Q1-Q3) for quantitative analysis.
Survivals and times will be estimated by the Kaplan Meier (KM) method. They will be described by medians and rates at different time points with their 95% confidence intervals.
Median follow-up time will be calculated using the reverse Kaplan Meir method.
The time to onset of grade 3/4/5 toxicity will be estimated using the Kaplan Meier method.

Exploratory Analyses:

- research into factors predictive of progression-free survival and/or overall survival

XII.5 Independent Committee Supervisory Committee

An independent committee composed of 1 clinician / 1 methodologist / 1 pharmacovigilant expert will be formed before the start of the trial.
It will have to decide on the continuation of the study in light of the safety data. The sponsor may refer to it at any time in the event of significant events concerning the safety of the treatment. An analysis of SAEs is planned after the inclusion and intra-arterial treatment of the first 10 patients.

XII.6 Imaging Review Committee/Radiologist Panel

The anonymized copies of the evaluation reports will be centralized at the CRGA on the 'FFCD Images' platform using a secure transmission via the company ETIAM.

The RECIST version 1.1 and EASL responses will be reviewed by this panel of independent radiologists at a later date, who will confirm the responses and dates of tumor progression or recurrence once all study examinations have been retrieved.

XII.7 Steering Committee

A Steering Committee will be set up. It will be chaired by the study coordinator, Prof. Julien TAIEB. This committee will also include the president of the FFCD, the statistician of the FFCD and the president of the Biological Research Committee (if applicable). Its mission will be, among others, to take decisions related to the management of the research (amendment, premature closure if necessary, ...).

XII.8 14.2 Biological Research Committee

If it is decided to set up the collection of surgical parts relating to secondary hepatic resections, a Biological Research Committee will be established. Its mission will be to deal with problems related to the collection and banking of specimens and the organization of their analysis. The committee shall meet regularly and report its proposals to the Board of Directors. This committee will include the study coordinator and a biologist; the chairperson of this committee will be designated afterwards.

XIII. JUSTIFICATION OF THE TEST

The treatment of metastatic colorectal cancer has become more diverse in recent years. Several chemotherapy regimens and targeted therapies are available as first-line treatment. The majority of liver metastases are not immediately resectable (in about 85% of patients) and studies with different combinations indicate that aggressive first-line chemotherapy in initially inoperable patients can achieve complete resection of metastatic disease (1). It is therefore important to develop new therapeutic strategies in metastatic colorectal cancer.

Anti-tumor therapy

Intravenous triple therapy combining 5FU, oxaliplatin, and irinotecan has been evaluated in randomized trials (Falcone et al, (2); Souglakos et al, (3)). They showed good response rates (43-60% according to RECIST criteria), progression-free survival (about 62% at 9 months), secondary resection rates of liver metastases and overall survival. Tolerability was acceptable if the WHO performance status at inclusion was <2, bilirubinemia <1.5 times LNS, and primary neutropenia prophylaxis (G-CSF) was administered. These trials suggest that the combined use of 5FU, oxaliplatin, and irinotecan is an option in the treatment of first-line metastatic colorectal cancer.

Intra-arterial chemotherapy

It has been shown in numerous trials over the past 20 years that intra-arterial chemotherapy can improve response rates and overall survival, particularly in patients with liver-limited metastatic disease. In patients with liver-limited metastases, locoregional chemotherapy exposes liver tumor cells to high concentrations with minimal systemic toxicity. However, FUDR and, more recently, oxaliplatin have been the most extensively tested drugs by this route, with high response and secondary resection rates of liver metastases (4-7), but no large phase III is currently available to validate their use in daily practice. In addition, there is a clear lack of standardization of the therapeutic protocol for IA injection and the use of intra-arterial devices is still limited to very specialized centers.

Advantages of the DEBIRI

An intra-arterial hepatic chemotherapy protocol with irinotecan-loaded microbeads (DEBIRI) has recently been developed. Preliminary results are promising. A phase II study of 82 patients with unresectable liver metastases, after failure of two lines of chemotherapy, treated with DEBIRI achieved a 78% response rate and improved quality of life in 90% of patients (8). Acute toxicity is common (post-embolism syndrome in 80% of cases) but easily manageable.

This treatment was also tested in another second- or higher-line study in 55 patients with colorectal cancer with unresectable liver metastases (9). Results showed a 75% response rate at 1 year and a median overall survival of 19 months. This treatment also appeared to be well tolerated, with 28% grade 1-3 toxicities. It did not appear to be more toxic in combination with systemic chemotherapy (continuous IV or oral 5FU, n = 16) than alone.

More recently, a randomized phase III study in the same population (colorectal cancer with liver metastases after at least 2 lines of treatment) compared FOLFIRI to DEBIRI (10). Results were encouraging with response rates of 68.6% in the experimental arm versus 20% in the control arm. Quality of life, median overall survival and progression-free survival were also improved in the experimental arm. Tolerance showed more acute toxicities (grade 2-3) in the experimental arm and more late toxicities (grade 2-3) in the control arm. Finally, healthcare costs were reduced in the experimental arm.

Finally, DEBIRI was combined with FOLFOX in a 1ère metastatic line of treatment for patients with metastatic colon cancer in a phase I study of 10 patients. Response rates at 9 and 12 months were 100%, with 40% secondary resection or removal of metastases. The combination was well tolerated with only one grade 3 event (hypertension).

Objectives

The objective of this study is to evaluate the feasibility, safety, and efficacy of chemotherapy combining conventional systemic FOLFOX with DEBIRI intra-arterially in the liver as first-line therapy in patients with CRC with predominantly hepatic metastases in a multicenter, single-arm phase II trial.

XIV. REFERENCES

1 **Pozzo C**, Basso M, Cassano A, et al: Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 15:933-939, 2004

2 **Falcone** A, Ricci S, Brunetti I, et al: Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007 May 1;25(13):1670-6

3 **Souglakos** J, Androulakis N, Syrigos K, et al: FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial

from the Hellenic Oncology Research Group (HORG). Br J Cancer. 2006 Mar 27;94(6):798-805

4 **Boige** V, Malka D, Elias D, et al: Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. Ann Surg Oncol. 2008 Jan;15(1):219-26

5 **Kemeny** NE, Melendez FD, Capanu M, et al: Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma J Clin Oncol. 2009 Jul 20;27(21):3465-71

6 **Carnaghi** C, Santoro A, Rimassa L, et al: The efficacy of hybrid chemotherapy with intravenous oxaliplatin and folinic acid and intra-hepatic infusion of 5-fluorouracil in patients with colorectal liver metastases: a phase II study. Invest New Drugs. 2007 Oct;25(5):479-85

7 **Malka** D., Bourredjem A., Caramella C. et al: Intra-arterial hepatic oxaliplatin (IAH), 5-fluorouracil (FU), leucovorin (LV), and intravenous (IV) cetuximab in 1st-line unresectable colorectal liver metastases (UCM): final results from the CHOICE multicenter phase II trial. JFHOD 2012**.** CO.58

8 **Martin RC**, Joshi J, Robbins K, et al: Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study.

9 **Aliberti C** et al. Transarterial chemoembolization (TACE) of liver metastases (LM) from colorectal carcinoma (CRC) adopting drug eluting beads preloaded with irinotecan (DEBIRI): Results of a phase II study on 82 patients. J Clin Oncol 27:15s, 2009 (suppl; abstr 4092)

10 **Fiorentini G** et al. ESMO 2010 Abstract 588

11 **Martin RC** et al: Toxicity of irinotecan-eluting beads in the treatment of hepatic malignancies: results of a multi-institutional registry. Cardiovasc Intervent Radiol. 2010 Oct;33(5):960-6

12 **Martin RC**, Scoggins CR, Tomalty D, et al: Irinotecan Drug-Eluting Beads in the Treatment of Chemo-Naive Unresectable Colorectal Liver Metastasis with Concomitant Systemic Fluorouracil and Oxaliplatin: Results of Pharmacokinetics and Phase I Trial.
Journal of Gastrointestinal Surgery, Online First™, 24 April 2012

XV. LEGAL AND ETHICAL ASPECTS ADMINISTRATIVE CONSIDERATIONS

XV.1 STUDY SPONSOR

The sponsor of the study is the Fédération Francophone de Cancérologie Digestive (FFCD). The study was registered under the number EudraCT 2012-004166-18.

XV.2 REMINDER OF THE TEXTS IN FORCE

This trial will be conducted according to French law.

XV.3 PUBLIC LIABILITY INSURANCE

Insurance was taken out by the sponsor on 11/01/2012 under the number (137.681) with SHAM, in accordance with Article L 1121-10 of the Public Health Code (Appendix 10).

XV.4 APPLICATION FOR AUTHORIZATION TO THE CPP AND AFSSAPS

This protocol has been authorized by the CPP (Comité de Protection des Personnes) Ile-de-France 8, on 14/01/2013 (appendix 11).

This protocol received a favorable opinion from the ANSM, Agence Nationale de Sécurité du Médicament et des Produits de Santé (formerly AFSSAPS) on 8/01/2013 (Appendix 12).

XV.5 COLLECTION OF THE PATIENT'S CONSENT

The investigator undertakes to collect, after information, the clinical and biological consent (if applicable) of the patient in writing; the information sheets and consent forms are in appendix 1 and 2. A copy of these consents must be kept by the investigator for 15 years. The original must be given to the patient.

XV.6 INFORMATION TO HOSPITAL MANAGEMENT AND RESEARCH AGREEMENT

Prior to the implementation of the study, the hospital management will be informed by the sponsor of the investigator's interest in participating in this trial.

A no-cost research agreement will be established between the investigating center administrator and the sponsor.

XV.7 DATA ARCHIVING

The files will remain confidential and can only be consulted under the responsibility of the doctors in charge of the patients. The sponsor and the health authorities in case of inspection will have direct access to these documents.

At the end of the trial, the observation book will be kept for 15 years by the investigator.

XV.8 IT SUPPORT

In accordance with the text of the law n° 78-17 of January 6, 1978 modified by the law of August 9, 2004, relating to data processing, files and freedoms, the data of the trial will be recorded in a data bank of the Center of Randomization and Management Analysis of the FFCD, with the exception of the elements relating to the identity of the patients.

XV.9 DATA PROCESSING

The FFCD's Center for Randomization Management and Analysis (CRGA) will be responsible for data management and analysis.

XV.10 MONITORING, QUALITY ASSURANCE AND INSPECTIONS BY AUTHORITIES

The investigator agrees in advance that the records of the patients included in the trial may be consulted by a person mandated by the FFCD and/or by the health authorities to carry out an audit. On-site monitoring of records, scheduled after agreement with the investigator, may take place during and after the trial inclusion period.

This protocol will be monitored by the FFCD's mobile ARCs.

The investigator agrees to sign the observation books at the end of each visit.

XVI. PUBLICATION

The current FFCD publication rules will be applied (Appendix 9)