FFCD 1104 - EVACEL

EVEROLIMUS AS A TREATMENT AFTER EMBOLISHMENT OR CHEMIOEMBOLIZATION OF HEPATIC METASTASIS OF DIGESTIVE ENDOCRINE TUMOR

PHASE II - MONOBRAS- MULTICENTER

Eudract number: 2012-002224-32

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FFCD 1104 - EVACEL

EVEROLIMUS AS A TREATMENT AFTER EMBOLISHMENT OR CHEMIOEMBOLIZATION OF HEPATIC METASTASIS OF DIGESTIVE ENDOCRINE TUMOR

PHASE II - MONOBRAS- MULTICENTER

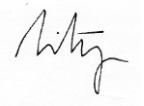
EudraCT N°: 2012-002224.32

Version 1.1 of 15.04.2013 amendment 2-3

This version of the protocol is approved by :

The Promoter : Ms. Cecile GIRAULT Date: 15.04.2013Signature :

The Coordinator : Dr Thomas WALTER Date: 04/15/2013Signature :



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 provides 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 specified in the research protocol
- 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 subject to the patient's signature of the specific consent and to send the samples according to the recommendations,
- complete all the items in the observation book, ensure the quality of the data collection and the proper management of the products
- retain research data and documents until notified by the sponsor that they are no longer required
- 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 from the sponsor's representatives, and make available to them all source documents and materials relating to the research in order to ensure quality control of the data recorded in the case report form. The investigator accepts 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 observation book,
- Allow time for the ARC FFCD to sign the forms, answer any questions and take action

Date: Signature:

CENTER STAMP:

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

LIST OF ABBREVIATIONS USED IN THE TEXT

AFSSAPS : French agency for the sanitary safety of health products
ALAT : alanine amino transferase
ANSM : National Agency for the Safety of Medicines and Health Products
ASAT : aspartate amino transferase
CPP : Committee for the Protection of Persons
CRGA: Centre for Randomization, Data Management and Analysis
ECG : electrocardiogram
INR : International Normalized Ratio
IV : intravenous
LNS : upper limit of normal
PNN : neutrophilic polynuclear cells
RCP : multidisciplinary consultation meeting
TAP : thoracoabdomino-pelvic
APTT : activated partial thromboplastin time
CT : CT scan
NET : neuroendocrine tumor
PT : prothrombin rate
5HIAA : 5-hydroxyindoleacetic acid

SYNOPSIS

Essay title:	**EVEROLIMUS AS A TREATMENT AFTER EMBOLISHMENT OR CHEMIOEMBOLIZATION OF HEPATIC METASTASIS OF DIGESTIVE ENDOCRINE TUMOR PHASE II - MONOBRAS- MULTICENTER**
Trial number	FFCD 1104 - EVACEL
Developer	French-speaking Federation of Digestive Oncology (FFCD)
Coordinator(s)	Dr Thomas WALTER
Objectives	**Principal:** The primary objective of the study is to determine whether treatment with everolimus for 24 months prolongs progression-free survival according to RECIST 1.1 criteria. The primary endpoint will be progression-free survival at 24 months in patients receiving hepatic embolization or chemoembolization followed by everolimus therapy. **Secondary:** - Progression-free survival at 24 months (hepatic and non-hepatic) - Overall survival at 24 months - Tolerance of the treatment during the 24 months of treatment
Inclusion criteria	- Histologically proven metastatic endocrine tumor of the gastrointestinal tract (TENPATH review mandatory), well differentiated (grade 1 and 2 according to the WHO 2010 classification, appendix 2) - Predominantly hepatic involvement compared to other metastatic locations requiring embolization or chemoembolization - Hepatic metastasis(es) measurable according to RECIST V1.1 criteria, unresectable or not accessible to local radiofrequency treatment - Indication, validated in RCP, for hepatic arterial embolization or chemoembolization for antitumor purposes due to the progressive nature of liver metastases (morphological progression over the last 12 months according to RECIST V1.1 criteria) - Age ≥ 18 years - General condition WHO ≤ 2 - Adequate biological workup: o Neutrophils ≥ 1,500/mm^3 , platelets ≥ 100,000/mm, Hb > 10 g/dL o Serum bilirubin ≤ 1.5 x upper normal limit (UL), INR < 1.3 (or < 3 on anticoagulants), ALT and AST ≤ 5 x UL o PAL ≤ 5 N o Creatinine ≤ 1.5 x LNS o 24-hour proteinuria (for patients who will receive streptozotocin for chemoembolization) < 1.5 N o Fasting serum cholesterol ≤ 300 mg/dL or 7.75 mmol/L and triglycerides ≤ 2.5 x LNS (in the event that one or both of these thresholds are exceeded, the patient can be included in the study only after initiation of appropriate lipid-lowering therapy) - Complete resolution or persistence with a maximum grade of 1 (except for transaminases or INR if anticoagulant) of toxicities from any previous treatments (NCI CTC version 4.0) - Minimum time to previous treatment: 28 days - Information to the patient and signature of an informed consent, after verification of the eligibility criteria - Affiliation to a social security system
Non-inclusion **criteria**	- Duodeno-pancreatic endocrine tumor - Poorly differentiated and/or grade 3 endocrine tumor

	- Indication for embolization or chemoembolization for symptomatic purposes only - Previous treatment with hepatic arterial embolization or chemoembolization - Previous treatment with an mTOR inhibitor (somatostatin analogues for anti-secretory purposes are allowed) - Symptomatic bone metastasis(es) - Any progressive unbalanced condition: hepatic insufficiency, renal insufficiency, respiratory insufficiency, congestive heart failure NYHA III-IV, unstable angina, myocardial infarction, significant arrhythmias - Interstitial lung disease - Patients with uncontrolled diabetes defined as HBa1C > 8 - Patients receiving chronic corticosteroids or immunosuppressants - Hypersensitivity to everolimus, other rapamycin derivatives or any of the excipients - Major surgery, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment. Incompletely healed wound or anticipated need for major surgery during the course of the study - Patient with contraindication to vascular occlusion procedures o Portal thrombosis o Bilio-digestive anastomosis - HIV patients on antiretroviral therapy - Malignant pathology within the last 5 years except for basal cell skin carcinoma or cervical cancer *in situ* treated curatively - Pregnant or breastfeeding woman - Lack of effective contraception (for men or women of childbearing age) - Predictable non-compliance - Medical, geographical, sociological, psychological or legal situation that would prohibit the patient from completing the study or signing an informed consent - Concurrent patient participation in other experimental research that could influence the primary endpoint of the study
Study design and treatment **plan**	Hepatic arterial embolization or chemoembolization followed by 24 months of everolimus treatment. Possibility of performing hepatic arterial embolization alone or in combination with doxorubicin or streptozotocin chemotherapy. The modalities and the treatment plan (number of sessions planned to obtain a complete hepatic treatment, maximum 2 sessions authorized) must be defined before the patient's inclusion in the trial and specified in the report of the PCR. Everolimus (10 mg/d) will be started 7 days after embolization or chemoembolization or after improvement of liver toxicity to a grade ≤1. Treatment should not be initiated beyond 30 days after embolization or chemoembolization. Duration of everolimus treatment: 24 months after the first embolization or chemoembolization in the absence of unacceptable toxicity. In the situation where several embolization or chemoembolization sessions are planned, everolimus will be stopped for the time of the embolization or chemoembolization (stopped the day before the embolization or chemoembolization and restarted as described above) Morphological evaluation every 3 months by triphasic thoraco-abdomino-pelvic CT scan
Statistical methods	According to the literature, the median progression-free survival after embolization or chemoembolization ranges from 15 to 19 months with a progression-free survival rate of approximately 35%. As there is no information

	on progression-free survival in the literature, the hypotheses were built on the progression-free survival data. The assumptions used to calculate the number of subjects are as follows: H0: a 24-month progression-free survival rate of less than 35% is not acceptable H1: A 24-month progression-free survival rate of more than 35% would demonstrate the utility of adjuvant everolimus therapy with an expected 24-month progression-free survival rate of 50%. To obtain a power of 80% with a first-species risk of 5% (one-sided), it is required to include 68 patients according to the assumptions established above (using the exact binomial distribution). Taking into account a rate of lost to follow-up or patients not evaluable for any reason except death, 72 patients will be included. The data will be described according to the usual methods detailed in the statistical analysis plan. The analysis will be performed on an intention-to-treat basis.
Number of subjects needed	72 patients
Planned study period	Expected start date of inclusion: November 2012 Expected completion date of inclusion: April 2016 Primary endpoint analysis: April 2018 End of study: January 2019

EXAMINATION AND FOLLOW-UP SCHEDULE

	BEFORE TREATMENT	DURING EMBOLIZATION OR CHEMOEMBOLIZATION		DURING TREATMENT WITH EVEROLIMUS (24 months maximum)	AFTER STOPPING TREATMENT WITH EVEROLIMUS (after 24 months)
	Within 4 weeks prior to inclusion	Within 7 days prior to each embolization or chemoembolization	After embolization or chemoembolization	Every 3 months +/- 1 week	Every 3 months +/- 1 week
Informed consent	X				
CLINICAL EXAMINATION					
Weight, general condition WHO	X	X		X	X
Functional symptoms related to hormonal hypersecretion	X				
Medical and surgical history and treatments related to the endocrine tumor	X				
MORPHOLOGICAL EXAMINATION					
Triphasic thoracoabdomino-pelvic CT (to be performed in the investigating center, without injection, arterial time, portal time) ***with measurement of liver metastases according to RECIST v1.1 criteria**	**X***		**X****	**X***	**X*****
ECG ± cardiological opinion if necessary	X				
BIOLOGICAL ASSESSMENT					
CBC/platelets, total and conjugated bilirubin, AST, ALT, PAL, creatinine, 24-hour proteinuria if treated with streptozotocin	X	X		X	
INR, TCA	X	X		X	
albumin, urea, blood ionogram, GGT	X			X	
Serum cholesterol and triglycerides, fasting blood glucose and HbA1c	X			X	
Chromogranin A, urinary 5HIAA	X			X	
B viral serology (HBV-DNA, HBsAg, anti-HBsAb, anti-HBcAb) and C****	X			X****	
Pregnancy test for women of childbearing age	X (within 7 days of starting treatment)				

*With target measurement according to RECIST v1.1 criteria
**To be performed for technical reasons only. Measurements should not be used for evaluation of tumor response
*** If everolimus is discontinued for reasons other than hepatic progression, continue morphological monitoring until hepatic progression occurs
**** In case of B and C viral serology, follow up the DNA and RNA load respectively every 3 to 6 weeks (see table 2-2 and 2-3)

I. OBJECTIVES OF THE TRIAL

1. Main objective

The primary objective of the study is to determine whether treatment with everolimus for 24 months prolongs progression-free survival according to RECIST 1.1 criteria. The primary endpoint will be progression-free survival at 24 months in patients receiving hepatic embolization or chemoembolization followed by everolimus therapy.

2. Secondary objectives

Secondary objectives will be the 24-month assessment of:

- Progression-free survival (hepatic and non-hepatic)
- Overall survival
- Tolerance of the treatment during the 24 months of treatment

II. PATIENT SELECTION

1. Inclusion criteria

- Histologically proven metastatic endocrine tumor of the gastrointestinal tract (TENPATH review mandatory), well differentiated (grade 1 and 2 according to the WHO 2010 classification, appendix 2)
- Predominantly hepatic involvement compared to other metastatic locations requiring embolization or chemoembolization
- Hepatic metastasis(es) measurable according to RECIST V1.1 criteria, unresectable or not accessible to local radiofrequency treatment
- Indication, validated in RCP, for hepatic arterial embolization or chemoembolization for antitumor purposes due to the progressive nature of liver metastases (morphological progression over the last 12 months according to RECIST V1.1 criteria)
- Age ≥ 18 years
- General condition WHO ≤ 2
- No contraindication to embolization or chemoembolization
- No contraindication to everolimus treatment
- Adequate biological workup:
    - Neutrophils ≥ 1,500/mm^3 , platelets ≥ 100,000/mm^3 , Hb > 10 g/dL
    - Serum bilirubin ≤ 1.5 x upper normal limit (UL), INR < 1.3 (or < 3 on anticoagulants), ALT and AST ≤ 5 x UL
    - Creatinine ≤ 1.5 x LNS
    - 24-hour proteinuria (for patients who will receive streptozotocin for chemoembolization) < 1.5N
    - Fasting serum cholesterol ≤ 300 mg/dL or 7.75 mmol/L and triglycerides ≤ 2.5 x LNS (in the event that one or both of these thresholds are exceeded, the patient can be included in the study only after initiation of appropriate lipid-lowering therapy)
- Complete resolution or persistence with a maximum grade of 1 (except for transaminases or INR if anticoagulant) of toxicities from any previous treatments (NCI CTC version 4.0)
- Minimum time to previous treatment: 28 days
- Information to the patient and signature of an informed consent, after verification of the eligibility criteria

- Affiliation to a social security system

2. Non-inclusion criteria

- Duodeno-pancreatic endocrine tumor
- Poorly differentiated and/or grade 3 endocrine tumor
- Indication for embolization or chemoembolization for symptomatic purposes only
- Previous treatment with hepatic arterial embolization or chemoembolization
- Previous treatment with an mTOR inhibitor (somatostatin analogues for anti-secretory purposes are allowed)
- Symptomatic bone metastasis(es)
- Any progressive unbalanced condition: hepatic insufficiency, renal insufficiency, respiratory insufficiency, congestive heart failure NYHA III-IV, unstable angina, myocardial infarction, significant arrhythmias
- Interstitial lung disease
- Patients with uncontrolled diabetes defined as HbA1c > 8
- Patients receiving chronic corticosteroids or immunosuppressants
- Hypersensitivity to everolimus, other rapamycin derivatives or any of the excipients
- Major surgery, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment. Incompletely healed wound or anticipated need for major surgery during the course of the study
- Patient with contraindication to vascular occlusion procedures
    - Portal thrombosis
    - Bilio-digestive anastomosis
- HIV patients on antiretroviral therapy
- Malignant pathology within the last 5 years except for basal cell skin carcinoma or cervical cancer *in situ* treated curatively
- Pregnant or breastfeeding woman
- Lack of effective contraception (for men or women of childbearing age)
- Predictable non-compliance
- Medical, geographical, sociological, psychological or legal situation that would prohibit the patient from completing the study or signing an informed consent
- Concurrent patient participation in other experimental research that could influence the primary endpoint of the study

III. INCLUSION ASSESSMENT

- **<u>Within 4 weeks prior to the first embolization or chemoembolization and before inclusion</u>**

    - Complete clinical examination: weight, general condition WHO (Appendix 5), functional symptoms related to hormonal hypersecretion
    - Medical and surgical history and treatments related to the endocrine tumor
    - Biological workup (***the biological workup for the first two points should be performed before inclusion and repeated 7 days before the 1^{ière} embolization or chemoembolization if inclusion beyond 7 days***):
        - CBC/platelets, urea and creatinine + calculated creatinine clearance (Cockcroft formula appendix 5), blood ionogram
        - INR, aPTT, albumin, alkaline phosphatases, AST, ALT, bilirubin (total and conjugated), gamma-GT, 24-hour proteinuria (for patients who will receive streptozotocin for chemoembolization)

- Serum cholesterol and triglycerides
- Fasting blood glucose and HbA1c
- B viral serology (test for HBsAg, if positive test for HBV-DNA, anti-HBsAb, anti-HBcAb) and C
- Chromogranin A, urinary 5HIAA
- Pregnancy test for women of childbearing age (to be performed within 7 days before the first day of treatment)

- Triphasic thoracoabdomino-pelvic CT (without injection, arterial time, portal time) with measurement of liver metastases according to RECIST V1.1 criteria (Appendix 3). The examination must be performed in an expert center (ideally the investigating center).
- ECG +/- cardiological consultation if necessary

IV. INCLUSION

Inclusion will be performed after the assessment to define eligibility and after signing the patient's informed consent.

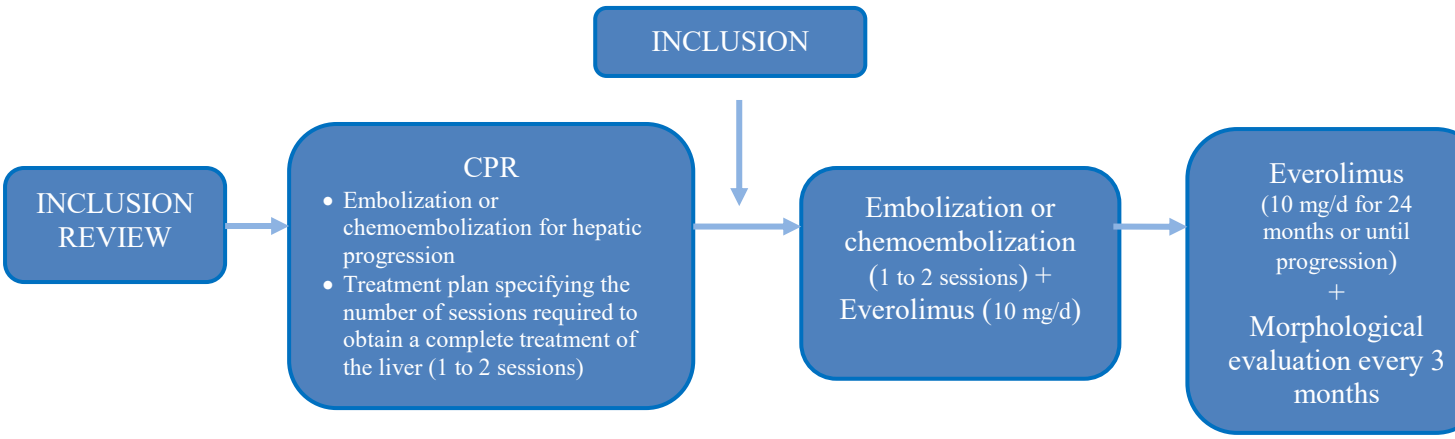
The inclusion number will be assigned by faxing the inclusion form in the observation booklet to the FFCD's Randomization - Management - Analysis Center (CRGA) in Dijon: FAX number: **03 80 38 18 41**. The CRGA is open from Monday to Friday from 9:00 am to 6:00 pm.

At the same time, confirmation of inclusion will be sent to LC2, the company responsible for the distribution of everolimus, within 48 hours from Monday to Thursday.

An advance observation booklet will be sent out at the opening of the center. An observation booklet will be sent after each inclusion.

After inclusion, treatment should be started within 30 days after 1^{ière} embolization or 1^{ière} chemoembolization.

V. THERAPEUTICAL SCHEME



VI. TREATMENT

1- Embolization or Chemoembolization

Possibility of performing hepatic arterial embolization alone or associated with chemotherapy with doxorubicin or streptozotocin.
The two embolization or chemoembolization sessions should be spaced 4 to 8 weeks apart.
The modalities and the treatment plan (number of sessions planned to obtain a complete hepatic treatment, maximum 2 sessions authorized) must have been defined before the inclusion of the patient in the trial and specified on the report of the PCR.
When 2 embolization or chemoembolization sessions are planned, a CT scan may be performed before the 2ème session if necessary for technical reasons. **This CT scan should not be used to evaluate the tumor response.**

DESCRIPTION OF THE TECHNIQUE

Pre-therapeutic angiography should always be performed to confirm portal system patency and tumor hypervascularity and to rule out a significant arteriovenous shunt.
Identification and protection of the cystic and gastric arteries is recommended.

We will always try to favor chemoembolization versus simple embolization. If the choice is simple embolization, it should be performed with particles of 500 microns maximum and until complete stagnation in the targeted arteries.

Desirable doses for chemoembolization injections

- **100 mg doxorubicin** (reconstituted in 5 mL or the smallest possible volume of fluid). Doxorubicin may be reconstituted in X-ray contrast medium to increase density and promote emulsion stability or 1500 mg of streptozotocin
- **10 ml of lipiodol ideally**
- **Spherical embolization particles: from 100 to 700** microns depending on the operator's preference and should always be performed until complete stasis.

PREPARATION AND INJECTION TECHNIQUE

Chemoembolization

The use of loaded microspheres is not allowed chemoembolization must involve the use of an emulsion of doxorubicin or streptozotocin and Lipiodol

- Preparation of the emulsion with two 20CC uher lock syringes connected by a three-way valve. The mixing process should be initiated by pushing the doxorubicin or streptozotocin towards the Lipiodol (the aim is to promote a water-in-oil emulsion) and by making about 20 back and forth syringes. The mixture obtained must be injected before embolization under scopic control and with a flow rate avoiding arterial reflux.
- The use of a microcatheter is recommended in case of localized disease in order to obtain an ultra-selective positioning.
- It is imperative to try to perform the embolization in addition to the chemopiodol and therefore to stop the injection of the drug/Lipiodol emulsion before complete stagnation, or failing that to wait at least 10 minutes after injection of the chemopiodol to obtain a flow capable of allowing the embolization.
- Subsequent particle embolization should result in complete stasis in the targeted arteries at least to the second-order arteries in case of lobar involvement.

Embolization

The use of spherical embolization particles of 100 to 500 microns according to the

operators' choice. The injection is done in a slow way with spheres suspended in the saline/contracts mixture in order to avoid aggregation of particles responsible for proximal occlusions. Embolization is complete to the second and third order branches. Stasis should be observed for 10 minutes before deciding to terminate the procedure. There is no limitation in the volume of embolization that can be used.

- **For patients with bilobar involvement, each lobe must be treated separately. A catheter is placed in a lobar hepatic artery for total embolization. The second session should be performed on the other lobe.**
- The use of a microcatheter is recommended in case of localized disease in order to obtain an ultra-selective positioning

Patients with localized lesion(s) should be treated with an even distribution of the dose of doxorubicin or streptozotocin within the lesion(s). If possible, chemoembolization should be repeated in the same manner. The two sessions should be separated by 4 to 8 weeks.
For patients with bilobar involvement, each lobe should be treated separately. A catheter is placed in a lobar hepatic artery and the full dose of doxorubicin/lipiodol or streptozotocin/lipiodol is administered. The second session should be performed in the other lobe.

Embolization or chemoembolization must always be associated with appropriate analgesic treatment, prophylactic antibiotic therapy and/or premedication with corticosteroids, the modalities of which are left to the discretion of the investigator.

Repeat chemoembolization sessions:
Three sessions are planned with intervals of 6 to 8 weeks.
The second and third session will be performed depending on the initial tumor response. An additional session is not recommended in case of complete lipiodolated fixation of all tumor targets.
In case of bleeding and/or severe liver failure secondary to an embolization or chemoembolization session, the following session(s) will be cancelled. For any other toxicity secondary to a TACE session, the performance of one (or two) additional sessions will be left to the discretion of the investigator.

Lipiodol and doxorubicin or streptozotocin are reported to health authorities as non-investigational drugs.
However, the tolerance of 2 embolization or chemembolization sessions will be collected in the observation booklet.

2- Everolimus treatment

Everolimus, an investigational treatment, is being provided as part of the study. It will be supplied in boxes of 30 tablets. The tablets will be either 10 mg or 5 mg. The boxes will be labeled "clinical trial" as recommended.

The dosage is 10 mg/day, i.e. 1 tablet of 10 mg or 2 tablets of 5 mg. In case of toxicity, refer to paragraph VII for dose adjustments.

Everolimus treatment will be continued for a maximum of 24 months after the first embolization or chemoembolization.

Everolimus will be started 7 days after embolization or chemoembolization or when liver toxicities have returned to a grade ≤1 according to the NCI CTIC version 4.0 toxicity scale. Treatment should not be initiated beyond 30 days after embolization or chemoembolization.

If embolization or chemoembolization cannot be performed after patient inclusion, everolimus MUST NOT be started.
If embolization or chemoembolization is postponed, wait for embolization or chemoembolization to start everolimus as described above. If embolization or chemoembolization is definitely cancelled, DO NOT ADMINISTER everolimus and follow the patient according to the recommendations (see paragraph VIII-2: monitoring after cessation of treatment).

For the second session, everolimus will be stopped the day before the session and restarted in the same manner as initially, i.e., 7 days after embolization or chemoembolization or when liver toxicities have returned to a grade ≤1 according to the NCI CTIC toxicity scale version 4.0 and within a maximum of 30 days after embolization or chemoembolization.

Method of administration
Everolimus should be taken orally once a day at the same time each day, with or without food. The tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.
If a dose is missed, the patient should not take an additional dose, but should take the next prescribed dose.

3- Concomitant treatments to be avoided

Everolimus is a substrate of CYP3A4 and a moderate inhibitor of P-glycoprotein (PgP). Therefore, the absorption and subsequent elimination of everolimus may be influenced by drugs that act on CYP3A4 and/or PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.
Known and theoretical interactions with selective inhibitors and inducers of CYP3A4 and PgP are described in the Table below.

CYP3A4 and PgP inhibitors that may increase everolimus concentrations: CYP3A4 or PgP inhibitors may increase blood levels of everolimus by decreasing the metabolism or efflux of everolimus from intestinal cells.
CYP3A4 and PgP inducers that may decrease everolimus concentrations: Substances that are CYP3A4 and PgP inducers may decrease blood levels by increasing everolimus metabolism or efflux of everolimus from intestinal cells.

Effect of other active substances on everolimus

Active substances by interaction	**Recommendations for Concomitant Administration**
***Potent* CYP3/PgPA INHIBITORS**	
Ketoconazole	Concomitant administration of everolimus not recommended
Itraconazole, posaconazole, voriconazole	
Telithromycin, clarithromycin	
Nefazodone	
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir	
***Moderate* CYP3A4/PgP INHIBITORS**	

Erythromycin	Use with caution when concomitant administration with moderate CYP3A4 or PgP inhibitors cannot be avoided. If co-administration with a moderate CYP3A4 or PgP inhibitor is required, a dose reduction to 5 mg daily and 5 mg every other day may be considered. However, there is insufficient clinical data on dose adjustment. Due to inter-subject variability, the recommended dose adjustments may not be optimal for all individuals, so close monitoring for adverse effects is recommended.
Verapamil	
Ciclosporin oral	
Fluconazole	
Diltiazem	
Amprenavir, fosamprenavir	
Grapefruit juice or other foods that affect CYP3A4/PgP	The combination should be avoided

***Potent* CYP3/PgPA INDUCTORS**	
Rifampicin	Avoid concomitant use with strong CYP3A4 inducers. If co-administration with a strong CYP3A4 inhibitor is required, an everolimus dose increase of 10 mg daily up to 20 mg daily, using a 5 mg step increase, is applied on day 4^{ième} and day 8^{ième} after initiation of inducer therapy. This dose of everolimus is established to adjust the AUC to the range of values observed without inducer. However, there are no clinical data available with this dose adjustment. When treatment with the potent inducer is stopped, the dose of everolimus should be returned to the dose used prior to initiation of concomitant administration.
Corticosteroids (e.g. dexamethasone, prednisone, prednisolone)	
Carbamazepine, Phenobarbital, Phenytoin	
Efavirenz, Nevirapine	
St. John's wort (*Hypericum Perforatum*) with an effect on CYP3A4/PgP	Preparations containing St. John's wort should not be used during everolimus treatment

The use of live vaccines should be avoided during everolimus treatment (examples of live vaccines: intranasal influenza vaccine, measles vaccine, mumps vaccine, rubella vaccine, oral polio vaccine, BCG (Bacillus Calmette-Guérin), varicella vaccine, and Typhoid Ty21a vaccine)

4- Treatment with somatostatin analogues

In patients who were receiving somatostatin analogue therapy for symptomatic purposes prior to embolization or chemoembolization, this therapy should be continued after embolization or chemoembolization unless determined by the investigator. In the absence of carcinoid

syndrome, somatostatin analogue therapy is not permitted after embolization or chemoembolization.

VII. EXPECTED TOXICITIES AND DOSE ADJUSTMENT

1. Dose adjustment after the first embolization or chemoembolization

No dose adjustment of doxorubicin or streptozotocin is planned for chemoembolization sessions. There are no plans to adjust the dose of lipiodol for embolization sessions.

Embolization or chemoembolization will only be performed if hematological, renal and hepatic functions are satisfactory i.e. if:

- PNN $\geq$ 1.5 10^9 /L,
- Platelets $\geq$ 75 x 10^9 /L
- Hemoglobin $\geq$ 10 g/dL
- INR < 1.3N or < 3 on anticoagulants or PT $\geq$ 50
- Creatinine level $\leq$ 1.5N
- Total bilirubin < 1.5N
- ASAT, ALAT $\leq$ 5N
- PAL < 5N

In case of grade 3 or 4 non-hematological toxicity attributable to the first embolization or chemoembolization session, no further embolization or chemoembolization is performed. Only everolimus will be continued for a maximum of 24 months.

2. Everolimus dose adjustment

All toxicity will be assessed according to the NCI-CT v4.0 scale (Appendix 4).

The rules for everolimus dose adjustment in case of observed hematological and non-hematological toxicities are defined in Tables 1.1, 1.2.

All interruptions or changes to the study drug must be recorded

Monitoring of suspected everolimus toxicity

Patients whose treatment is temporarily or permanently discontinued due to an adverse event or laboratory abnormality suspected to be related to everolimus should be monitored at least weekly until the adverse event resolves or returns to grade 1. If the patient's treatment is to be delayed for more than 21 days from the day of the next scheduled dose, the patient should be excluded from the study.

Table 1.0 Guidelines for Everolimus Dose Level Changes

Dose level	Dose and frequency of administration
0 (initial dose)	**10 mg per day**
-1	**5 mg per day**
-2	**5 mg every 2 days**

a. Dose adjustment for non-hematologic and hematologic toxicities

Table 1-1 Dose adjustment criteria for everolimus toxicity and reinstatement of everolimus therapy

NON-HEMATOLOGICAL AND NON-HEPATIC Toxicity (NCI-CTC V4.0)	Actions
Grade 2 (except pneumonia - see Table 1-4)	If toxicity is tolerable to the patient, maintain the same dose. In case of intolerable toxicity for the patient, discontinue everolimus until recovery to grade≤ 1. Then reintroduce everolimus at the same dose. If an event returns to grade 2, discontinue everolimus until recovery to grade≤ 1. Then reintroduce everolimus at the lower dose level.
Grade 3 (except hyperlipidemia*) (except pneumonia - see Table 1-4)	Interrupt everolimus until recovery to grade≤ 1. Then reintroduce everolimus at the lower dose level. For pneumonia, consider short-term steroid therapy.
Grade 4	Stopping everolimus
Any non-hematologic toxicity requiring interruption for a period ≥ 3 weeks	Stopping everolimus

*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed with medical treatments.

Table 1-2

HEMATOLOGICAL Toxicity (NCI-CTC V4.0)	Grade	Actions
Thrombocytopenia	Grade 2 (platelets < 75, ≥ 50 x 10^9 /l)	Interrupt everolimus until recovery to grade≤ 1 (≥ 75 x 10^9 /l). Then reintroduce everolimus at the initial dose. If thrombocytopenia returns to grade 2, discontinue everolimus until recovery to grade≤ 1. Then reintroduce everolimus at the lower dose level.
	Grade 3 (platelets < 50, ≥ 25 x 10^9 /l)	Interrupt everolimus until recovery to grade ≤ 1 (platelets ≥ 75 x 10^9 /L). Then resume everolimus at a lower dose level.

		If thrombocytopenia recurs at grade 2, discontinue everolimus.
	Grade 4 (platelets < 25 x 10^9 /L)	Stopping everolimus
Neutropenia	Grade 3 (neutrophils < 1, ≥ 0.5 x 10^9 /L)	Interrupt everolimus until recovery to grade≤ 1 (neutrophils ≥ 1.5 x 10^9 /l). Then resume everolimus at the initial dose. If PNN returns to grade 3, withhold everolimus until PNN is ≥ 1.5 x 10^9 /l. Then resume everolimus at the lower dose level. Discontinue study treatment if a third episode of Grade 3 neutropenia occurs
	Grade 4 (neutrophils < 0.5 x 10^9 /L)	Interrupt everolimus until recovery to grade≤ 1 (neutrophils ≥ 1.5 x 10^9 /l). Then resume everolimus at the lower dose level. If Grade 3 or 4 neutropenia occurs despite this dose reduction, discontinue everolimus
Febrile neutropenia	Grade 3	Discontinue everolimus until fever resolves and grade ≤ 1 neutropenia returns. Continue everolimus interruption until PNN is ≥ 1,500/mm^3 and fever disappears. Then resume everolimus at the lower dose level. If febrile neutropenia recurs, discontinue everolimus.
	Grade 4 (life-threatening)	Stopping everolimus
Any hematological toxicity	Requiring an interruption for a period ≥ 3 weeks	Stopping everolimus

Table1-3:

Toxicity ANEMIA (Hemoglobin decrease) NCI-CTC v4.0	**Grade**	**Dose adjustment**
Anemia	**Grade 1 or 2**	No change in dose
	Grade 3	Interrupt everolimus until recovery to grade **≤ 2,** then resume everolimus at the same dose. If return to grade 3, withhold everolimus until grade ≤ 2, then resume at lower dose level. Discontinue everolimus in case of 3^{ième} grade 3 episode.
	Grade 4	Permanent discontinuation of everolimus

b. Known adverse reactions to everolimus

-The most common grade -34 adverse events -(frequency ≥ 2% in at least one pivotal study) were anemia, fatigue, diarrhea, infections, stomatitis, hyperglycemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphatemia, hypercholesterolemia, diabetes mellitus, and pneumonitis. Grades follow the CTCAE version 4.0 classification.

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections, including cases of hepatitis B reactivation, have been described in patients treated with everolimus. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure), sometimes with fatal outcome.

Physicians and patients should be aware of the increased risk of infection with everolimus. Pre-existing infections should be treated before starting everolimus therapy. During treatment with everolimus, vigilance for signs and symptoms of infection should be exercised; if an infection is diagnosed, appropriate treatment should be initiated as soon as possible and temporary or permanent discontinuation of everolimus should be considered. If a diagnosis of invasive systemic fungal infection is made, everolimus must be discontinued and appropriate antifungal therapy initiated.

Hypersensitivity reactions with symptoms including anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling (edema) of the airways or tongue, with or without respiratory failure) have been observed with everolimus.

Hyperglycemia has been reported in clinical trials. It is recommended that fasting blood glucose be monitored prior to initiation of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved prior to initiating everolimus therapy in a patient. Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with everolimus. In these cases, topical treatments are recommended, but alcohol or hydrogen peroxide mouthwashes should be avoided.

Elevations in serum creatinine, usually mild, have been reported in clinical trials. It is recommended that renal function be monitored before starting everolimus therapy and periodically thereafter.

Decreases in hemoglobin, lymphocytes, platelets and neutrophils have been reported in clinical

trials. It is recommended that complete blood counts be monitored prior to the initiation of everolimus therapy and periodically thereafter.

The use of live vaccines and close contact with individuals who have received live vaccines should be avoided during treatment with everolimus.
Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported.

c. Management of stomatitis/oral mucositis/aphthae

Oral stomatitis/mucositis/ mouth ulcers due to everolimus should be treated with local symptomatic therapy. It should be noted that investigators in previous trials have described oral toxicities associated with everolimus in terms of mouth ulcers rather than mucositis or stomatitis. If your examination reveals canker sores rather than more general inflammation of the mouth, please classify the adverse event as such. Please follow the template below for treatment of oral stomatitis/mucitis/aphthas:

1. For mild toxicity (Grade 1), use conservative measures such as **alcohol-free mouthwash or salt water mouthwash (0.9%)** several times a day until resolved.
2. For more severe toxicity (grade 2, in which case patients are able, despite pain, to maintain adequate oral nutrition, or grade 3 in which case patients cannot maintain adequate oral nutrition), the proposed treatments are **analgesic topical oral treatments (i.e., local anesthetics such as benzocaine, butylaminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without **topical corticosteroids,** such as triamcinolone acetonide 0.1% gingival paste (Orabase Kenalog®).
3. Agents containing hydrogen peroxide, iodine and thyme derivatives may tend to exacerbate mouth ulcers. It is best to avoid these agents.
4. Antifungal agents should be avoided unless a fungal infection has been diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients as they are potent inhibitors of everolimus metabolism, resulting in higher everolimus exposures. Therefore, topical antifungal agents are preferable if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

d. Management of hyperlipidemia and hyperglycemia

Hyperlipidemia and hypertriglyceridemia should be treated according to local best clinical practice.

e. Management of non-infectious lung disease

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Non-infectious lung disease (including interstitial lung disease) has also been described in patients treated with everolimus. A diagnosis of non-infectious lung disease should be considered in patients presenting with non-specific respiratory signs and symptoms such as cough or dyspnoea, hypoxia, pleural effusion, and when infectious, neoplastic or other non-drug causes have been excluded by appropriate investigations. Patients should be asked to report promptly any new or worsening respiratory symptoms.

Patients with radiological changes suggestive of non-infectious lung disease with few or no symptoms may continue everolimus therapy without a change in dosage. In the presence of moderate symptoms (Grade 2), discontinuation of treatment should be considered until symptoms improve. Administration of corticosteroids may be indicated. Everolimus may be reintroduced at a reduced dose until recovery to Grade 1 or higher.

When symptoms of non-infectious lung disease are severe (Grade 3), everolimus treatment should be discontinued and corticosteroids may be indicated until clinical symptoms resolve. Everolimus treatment may be reintroduced at a reduced dose depending on individual clinical circumstances.

Table 1-4Management of non-infectious lung disease

PNEUMOPATHY (NCI-CT V 4.0)	INVESTIGATION REQUIRED	CARE	EVEROLIMUS DOSE ADJUSTMENT
Grade 1	Chest CT in the lung window and respiratory function tests, including spirometry, DLCO, and room air O_2 saturation at rest. Repeat chest x-ray/computed tomography every 2 cycles until normal.	No specific treatment is required	Administer 100% of the everolimus dose.
Grade 2	Chest CT in lung windows and pulmonary function tests, including spirometry, DLCO, and room air O_2 saturation at rest. Repeat with each subsequent cycle until normalcy is achieved. Bronchoscopy is recommended *	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Reduce everolimus dose until recovery to a grade≤ 1. Everolimus may also be discontinued if troublesome symptoms occur. Patients will discontinue treatment if they fail to recover to a grade ≤ 1 within 3 weeks
Grade 3		Prescribe corticosteroids if an infectious origin is excluded. Gradually reduce the dose according to medical indication.	Withhold treatment until recovery to a grade ≤ 1. The treatment protocol may be restarted within 2 weeks at a reduced dose (by one level) if there is evidence of clinical benefit. Patients will discontinue treatment if they fail to recover to a grade ≤1 within 2 weeks.
Grade 4		Prescribe corticosteroids if an infectious origin is excluded. Gradually reduce the dose according to medical indication.	Stop the treatment.

*Bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.

f. Management of reactivation /flare-up of hepatitis

In cancer patients with hepatitis B virus, either carrier or chronic, the administration of antivirals during cancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated morbidity and mortality (Loomba et al. 2008).

- **Monitoring and prophylaxis for hepatitis B reactivation**

Table 2-1 provides detailed information on monitoring and prophylactic treatment based on initial viral load and serologic marker test results.

Table 2-1: Actions to be Taken for Initial Positive Hepatitis B Results

Test	Result	Result	Result	Result	Result
HBV DNA	+	+ or -.	-	-	-
HBsAg	+ or -.	+	-	-	-
HBsAb	+ or -.	+ or -.	+ and without prior HBV vaccination	+ or -.	- or + with previous HBV vaccination
HBsAb	+ or -.	+ or -.	+ or -.	+	-
Recommendation	Prophylaxis should be initiated 1-2 weeks prior to the first dose of study drug Monitor HBV DNA approximately every 6 weeks		No prophylaxis Monitor HBV DNA approximately every 3 weeks		No specific action

Antiviral prophylaxis should be continued for at least 4 weeks after the last dose of study drug.

For the definition of hepatitis B reactivation and guidelines for its management, refer to Table 2-2.

Table 2-2: Hepatitis B Management Guidelines

HBV reactivation (with or without clinical signs and symptoms)*.	
For patients with initial findings: HBV DNA positive OR HBsAg positive --- Reactivation is defined as: [1-log increase in HBV DNA from baseline HBV	Treat: Start a second antiviral AND Discontinue study drug until resolution: ≤ baseline levels of HBV DNA In case of resolution within ≤ 28 days the study drug should be restarted at a lower dose, if available. If the patient is already receiving the lowest dose of study drug per protocol, the patient should restart the study drug at the same dose after resolution. Both antiviral therapies should be continued for at least 4 weeks after the last dose of study drug is administered.

DNA OR new onset of measurable HBV DNA]	If resolution occurs within >28 days patients should discontinue study drug but continue both antiviral treatments for at least 4 weeks after the last dose of study drug.
For patients with initial results: HBV DNA and HBsAg negative AND [HBsAb positive (with no prior history of HBV vaccination), OR HBcAb positive] ---------- reactivation is defined as follows: New appearance of measurable HBV DNA	Treat: Start antiviral medication AND Discontinue study drug until resolution: ≤ baseline levels of HBV DNA In case of resolution within ≤ 28 days the study drug should be restarted at a lower dose, if available. If the patient is already receiving the lowest dose of study drug per protocol, the patient should restart the study drug at the same dose after resolution. Antiviral therapy should be continued for at least 4 weeks after the last dose of study drug is administered. In case of resolution within > 28 days patients should discontinue study drug, but continue antiviral therapy for at least 4 weeks after the last dose of study drug.

* All hepatitis B reactivations should be recorded as a Grade 3 adverse event (CTCAE v 4.0 Other Adverse Events Associated with Metabolic or Biological Abnormalities: Viral Reactivation), unless the investigator considers them life-threatening in which case they should be recorded as a Grade 4 adverse event (CTCAE v 4.0 Other Adverse Events Associated with Metabolic or Biological Abnormalities: Viral Reactivation). The date of viral reactivation is the date on which **both** the DNA and ALAT criteria are met (e.g., for a patient with HBV DNA positive on 01-01-10 and an ALAT level ≥ 5 x ULN on 01-04-10, the date of viral reactivation is 01-04-10).

- **Hepatitis C Outbreak Surveillance**

The following two categories of patients should be monitored every 6 weeks for HCV reactivation:

- Patients with detectable HCV RNA by PCR analysis in basal state.
- Patients with a known history of hepatitis C virus (HCV) infection, despite a negative baseline viral load test (including those who have been treated and considered "cured")

For the definition of hepatitis C reactivation and guidelines for its management, see Table 2-3 Guidelines for the Management of Hepatitis C.

Table 2-3: Guidelines for the Management of Hepatitis C

HCV outbreak	
For patients with baseline results: detectable HCV RNA, an HCV outbreak is defined as follows:	Discontinue study drug but continue monitoring as part of the study.

Increase in HCV RNA by 2 log10 IU/ml AND ALT elevation: 5 x ULN or 3 x baseline, whichever is higher	
For patients with baseline results: Known history of hepatitis C without detectable HCV RNA, an HCV outbreak is defined as: New appearance of detectable HCV RNA AND ALT elevation: 5 x ULN or 3 x baseline, whichever is higher	Discontinue study drug but continue monitoring as part of the study. .

* All hepatitis C outbreaks should be recorded as a Grade 3 event (CTCAE v 4.0 Other Adverse Events Associated with Metabolic or Biological Abnormalities: Viral Outbreak), unless the investigator considers them life-threatening, in which case they should be recorded as a Grade 4 event (CTCAE v 4.0 Other Adverse Events Associated with Metabolic or Biological Abnormalities: Viral Outbreak)

VIII. PATIENT MONITORING DURING TREATMENT AND AFTER WITHDRAWAL OF TREATMENT

1. Monitoring during treatment

Within 7 days prior to each embolization or chemoembolization session

- Clinical assessment: weight, general condition (WHO)
- Evaluation of the tolerance of the previous embolization or chemoembolization
- Biological check-up:
  - CBC-platelets
  - INR, aPTT, creatinine, bilirubin (total, conjugated), AST, ALT, PAL

NB: An abdominal CT scan may be performed if necessary for technical reasons before the 2nd embolization or chemoembolization session. Caution: this imaging should not be used to evaluate the response to treatment of metastases.

Every 3 months (+/- 1 week) from the date of the first embolization or chemoembolization (except DNA and ARC monitoring for positive serology)

- Clinical assessment: WHO, weight, evaluation of side effects
- Bioassay:
  - CBC/platelets, urea and creatinine + calculated creatinine clearance (Cockcroft formula), blood ionogram
  - INR, aPTT, albumin, alkaline phosphatase, AST, ALT, bilirubin (total and conjugated), gamma-GT
  - Serum cholesterol and triglycerides
  - Fasting blood glucose and HbA1c
  - Chromogranin A, urinary 5HIAA
- If HBV positive, monitor DNA approximately every 3 weeks or 6 weeks depending on the result (see Table 2-2)

- If HCV positive, monitor RNA every 6 weeks (see Table 2.3)
- Morphological assessment**:** triphasic thoracic-abdominal-pelvic CT scan with target measurement according to RECIST V1.1 criteria (Appendix 3). Evaluation CT scans should be performed in the same center as the initial examination

NOTE: Patients whose treatment is temporarily or permanently discontinued due to an adverse event or laboratory abnormality suspected to be related to everolimus should be monitored at least weekly until the adverse event resolves or returns to Grade 1

2. Post-treatment monitoring protocol

- **After discontinuation of treatment for hepatic progression**
  - After hepatic progression, the clinical, biological and morphological monitoring of the patient will be left to the investigator's discretion

- **After discontinuation of treatment for a reason other than hepatic progression** (e.g. toxicity, extra-hepatic progression, patient's wish, :
  - Morphological surveillance: CT every 3 months until liver progression occurs, according to the same modalities as the initial morphological evaluation (triphasic thoraco-abdomino-pelvic CT with target measurement according to RECIST V1.1 annex 3)

IX. 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
- Disease progression (hepatic, extra-hepatic, clinical)
- Patient refusal
- Death of the patient

X. CENTRALIZED PROOFREADING OF TDM

To address the primary endpoint of efficacy of everolimus treatment after embolization or chemoembolization, a centralized review of morphological examinations of the inclusion workup and follow-ups will be performed by an independent review committee.

To do this, make a copy of the imaging to be kept in the patient's file. The FFCD CRA in charge of your center will make an anonymized copy of the CD ROM and send the imaging to the FFCD imaging platform.

XI. MANAGEMENT OF SERIOUS ADVERSE EVENTS (SIA)

Security assessment parameters

Safety will be assessed by evaluating the general and clinical condition of the patients and by collecting events occurring between visits during consultations, by regular blood tests. Toxicities will be assessed using the NCI-CTC-AE version 4.0 toxicity scale (see Appendix 4).

Definitions

a. 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.

b. Serious Adverse Event (SAE)

A serious adverse event is any event that

- 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

The terms disability and incapacity correspond to any temporary or permanent physical or psychological handicap, clinically significant and affecting the physical activity and/or quality of life of the patient.

Any clinical event or laboratory result considered serious by the investigator and not corresponding to the severity criteria defined above is considered medically significant. They may put the patient at risk and require medical intervention to prevent an outcome corresponding to one of the above mentioned severity criteria (e.g. overdose, second cancers, pregnancies and new events may be considered as 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 without delay 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.

c. 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).

d. Unexpected Serious Adverse Effect

An unexpected serious adverse reaction is an event that is not mentioned, or that differs in nature, intensity, or evolution from the product's reference document (Investigator's Brochure or RCPs).

In this essay the reference documents will be:

- For everolimus, the Summary of Product Characteristics for Afinitor® (Appendix 6)

The versions of the Investigator's Brochure and PCR (used for the definition of expected or unexpected everolimus) will be the latest available on the anniversary date of the start of the trial.

What to do

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 7), 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 last 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.

XII. STATISTICAL ANALYSIS

1. Provisional timetable for the study

The end of the trial will be 4 years after the inclusion of the last patient included. For the purposes of the study, the follow-up time for patients will be 24 months after inclusion.

The rate of inclusion is estimated at 3 patients per month, so the duration of inclusion is 24 months.

The study duration to meet the primary and secondary endpoint is 24 months. Six months will be required to clean the base and perform the analysis + final report (March 2015).

Expected start date of inclusions: November 2012
Expected completion date of inclusion: April 2016
Primary endpoint analysis: April 2018
Theoretical end of study: January 2019

2. Analysis

Main criterion

The primary endpoint will be to assess liver progression (death will be considered as progression) during the 24 months of everolimus treatment according to RECIST V1.1 criteria (Appendix 3).

The time to progression-free survival (based on review or on the opinion of the investigator if review is not possible) will be defined as the time interval between the date of inclusion and the date of liver progression or death (regardless of cause). For living patients without hepatic progression, the time interval between the date of inclusion and the date of last morphological evaluation will be taken.

Secondary criteria

The secondary endpoints will be:

- Progression-free survival (hepatic or non-hepatic) at 24 months
- Overall survival at 24 months
- Tolerance of the treatment during the 24 months of treatment

Progression-free survival will be defined as the time interval between the date of inclusion and the date of progression (hepatic or non-hepatic) as assessed by 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
- the evolution of the WHO performance index.

Calculation of the number of subjects needed

According to the literature, the median progression-free survival after embolization or chemoembolization ranges from 15 to 19 months with a progression-free survival rate of approximately 35%. As there is no information on progression-free survival in the literature, the hypotheses were built on the progression-free survival data.

The assumptions used to calculate the number of subjects are as follows:

H0: a 24-month progression-free survival rate of less than 35% is not acceptable

H1: A 24-month liver progression-free survival rate greater than 35% would demonstrate the utility of everolimus therapy with an expected 24-month liver progression-free survival rate of 50%,

To obtain a power of 80% with a first-species risk of 5% (one-sided), it is required to include 68 patients according to the assumptions established above (using the exact binomial distribution).

Taking into account a rate of lost to follow-up or patients not evaluable for any reason except death, 72 patients will be included.

3. Statistical analysis plan

Populations of analysis

Patients included in the study will be described (ITT) as well as patients not evaluable for the primary endpoint.

A patient is considered evaluable if he or she has received at least one dose of everolimus and one evaluation.

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.

Main 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) and mean (standard deviation) and median (Min-Max) as well as the inter-quartile range (Q1-Q3).

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 results for the primary endpoint will also be described by a Water Fall plot representing for each patient the percentage change at 24 months in liver metastasis size since the measurement at inclusion according to the response according to the RECIST V1.1 criteria.

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
- comparison of progression-free survival between embolization alone and chemoembolization

4. Independent committees

An independent committee will be formed and will include at least: two physicians (onco-gastroenterologists), a statistician, a pharmacovigilance expert. The independent committee may meet at any time during the protocol when deemed necessary by the Sponsor.

XIII. JUSTIFICATION OF THE TEST

Neuroendocrine tumors (NETs) are a heterogeneous group of rare tumors. The prevalence of these tumors is estimated to be between 0.4 and 1 per 100,000 inhabitants per year. In the gastrointestinal tract, the most frequent locations are the appendix (19%), the small intestine (15%) and the rectum (11%). Neuroendocrine tumors of the small intestine mainly affect young adults between 30 and 35 years of age, while those of the colon tend to occur around 60 years of age [[1].

Treatment of digestive endocrine tumors

There are many therapeutic options, and the choice of treatment depends primarily on the location of the primary tumor, the stage of extension, and the tumor's progression [[2]. Given the great variability of cases, it is difficult to establish a precise decision tree for the treatment of digestive NETs. In all cases, the decision should be made after multidisciplinary discussion. Symptomatic management of hormonal hypersecretion is imperative and should be initiated without waiting for the extension workup. Surgery, the only curative treatment, should always be discussed initially, and secondarily, after obtaining a therapeutic response. Surgical removal of the primary tumor is usually recommended, even in cases of advanced NET. In the metastatic situation, the therapeutic indications must be discussed taking into account the location of the primary tumor and the metastases, the cellular differentiation, the evolution with evaluation of the speed of growth of the metastases. In the case of well-differentiated NETs with little progression, an initial surveillance can be proposed with a first evaluation at a few weeks to assess the tumor evolution.
If the tumor is slowly progressive (tumor stability without new localization), monitoring, possibly associated with treatment with somatostatin analogues, may be proposed. If the tumor is progressive (morphological progression or new metastatic sites), antitumor treatment should be considered. In the case of NET of the digestive tract, which is not very chemosensitive, (chemo)-embolization in case of isolated or predominant liver metastases is often the preferred option.

Place of (chemo)embolization

The principle of intra-arterial chemoembolization is to combine chemotherapy administered via the hepatic intra-arterial route with embolization [[3]. As metastases are, contrary to normal liver, mainly vascularized by the arterial route, this approach allows to induce a targeted anoxia, potentiated by the administration of a cytotoxic agent.
Chemoembolization is effective in controlling clinical manifestations related to hormonal hypersecretion, especially during carcinoid syndrome, in 70 to 100% of patients depending on the series.
The ENETS-01 trial, the only prospective randomized trial that compared embolization and chemoembolization, included only 26 patients. There was no difference in progression-free survival at 24 months (the primary endpoint) between the chemoembolization (38%) and embolization (44%, p=0.9) groups[4]. In the larger retrospective non-randomized series, progression-free survival rates are not always specified [5, 6, 7]. In the MD Anderson study (81 patients), the 24-month progression-free survival rate was 35% with a median progression-free survival of 17 months. [6]. In a French study, the median progression-free survival was 14.5 months with a 24-month progression-free survival rate of about 35% in 67 patients [7].
A post-embolization syndrome (fever, abdominal pain, nausea, vomiting, hepatic cytolysis) is frequent and requires appropriate symptomatic treatment. The possibility of an acute carcinoid crisis justifies the prescription of a treatment with somatostatin analogues. These techniques are contraindicated in case of biliary-digestive anastomosis or biliary prosthesis because of a major risk of infectious complication with hepatic abscess. Portal vein thrombosis and hepatocellular insufficiency are also contraindications.

Rationale for antiangiogenic therapy after (chemo)embolization

Digestive NETs are characterized by their hypervascularization. Endocrine tumor cells secrete excess VEGF which is likely to play an important role in the angiogenic process associated with endocrine tumorigenesis [8, 9]]. However, the mechanisms that regulate the angiogenic process associated with endocrine tumorigenesis in digestive NETs remain poorly understood.

Embolization stimulates angiogenesis with an increase in circulating VEGF levels [10] levels, and the main mechanism associated with a progressive recovery after (chemo)embolization is tumor revascularization from collateral vessels. In this context, a treatment with antiangiogenic action administered after (chemo)embolization could improve tumor control. A recent phase II study evaluated sunitinib therapy in this setting with encouraging results [10].

Everolimus

Inhibitors of the mTOR pathway have antiangiogenic activity, which partly explains their antitumor effect *in vitro* and *in vivo* [11]. Regarding everolimus, promising initial results have led to a development program in digestive NETs. In a phase II study, Yao *et al.* reported the use of everolimus combined with delayed octreotide in 60 patients with well differentiated NET [12]. The objective response was 30% in the 30 patients treated with the 10-mg dose versus 13% for patients treated with 5 mg. Among patients with "carcinoid" tumors, the objective response rate was 17%, with stabilization achieved in 80% of patients, at the cost of moderate side effects. This study led to the selection of the 10 mg everolimus dose for further development of the product in the RADIANT I, II and III studies [12, 13, 14]. Only the RADIANT II study involved NET of the gastrointestinal tract [13]. This international multicenter phase III study randomized everolimus (10 mg/d) to placebo, combined in both arms with octreotide LP30 mg/28 d. Four hundred and thirty patients with documented progression within 12 months prior to inclusion were included. One-third of the patients had been previously treated with chemotherapy and nearly 80% with a delayed somatostatin analogue. Progression-free survival was 16.4 months in the everolimus plus delayed octreotide arm versus 11.3 months in the placebo plus delayed octreotide arm (HR = 0.77; 95% CI = 0.59-1.00; p = 0.026) in centralized readout (primary objective of the trial), not statistically significant according to the study analysis design since the expected predefined p was 0.0246. The center-read analysis (12.0 months *versus* 8.6 months, HR = 0.78; 95% CI = 0.62-0.98; p = 0.018) and after predefined statistical adjustments (HR = 0.60; 95% CI = 0.44-0.84; p = 0.0014), which were secondary objectives of the trial, supported the superiority of everolimus. The interim analysis of overall survival showed no difference between the two groups (HR = 1.22; 95% CI = 0.91-1.62; p = 0.908). The safety profile of this molecule is quite acceptable, with mainly grade 1-2 toxicities and less than 7% grade 3-4 toxicities.

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XIV. LEGAL AND ETHICAL ASPECTS ADMINISTRATIVE CONSIDERATIONS

STUDY SPONSOR

The sponsor of the study is the Fédération Francophone de Cancérologie Digestive (FFCD). The study was registered under the number EudraCT 2012-002224-32.

REMINDER OF THE TEXTS IN FORCE

This test will be carried out according to the new European Directive 2001/20/EC.

LIABILITY INSURANCE

Insurance was taken out by the sponsor on 14/05/2012 with SCHAM insurance (Société Hospitalière d'Assurance Mutuelle) under the number 137.681, in accordance with Article L 1121-10 of the Public Health Code (Appendix 9).

APPLICATION FOR AUTHORIZATION TO THE CPP AND AFSSAPS

This protocol has been authorized by the CPP (Committee for the Protection of Individuals) XI of St Germain en Laye, 5/07/2012 (Appendix 10)
This protocol received a favorable opinion from the ANSM (Agence Nationale de Sécurité du médicament et des produits de santé, formerly AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé)) on 29/06/2012 (Appendix 11).

COLLECTION OF THE PATIENT'S CONSENT

The investigator undertakes to collect, after information, the clinical consents of the patient in writing (information sheets and consent forms in Appendix 1). A copy of this consent must be kept by the investigator for 15 years, to be presented to the supervisory authorities in case of inspection. The original should be given to the patient.

HOSPITAL MANAGEMENT INFORMATION 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.

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.

COMPUTER 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.

DATA PROCESSING

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

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 conduct an audit. On-site visits to the files, scheduled after agreement by the investigator, may take place during or after the period of inclusion in the trial
This protocol will be monitored by the FFCD's mobile ARCs.

XV. PUBLICATION RULES

They shall be in accordance with those established by the FFCD (Appendix 8).

XVI. APPENDICES