Everolimus as treatment after embolization or chemoembolization of liver metastases of digestive endocrine tumor. Phase II single arm multicenter EVACEL - FFCD 1104

Statistical Analysis Plan

Final analysis

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2 Abbreviations and definitions

CHE	Chemoembolization
CP	Main criterion
SEE	Serious Adverse Event
	5HIA5-hydroxyindoleacetic acid
INR	International Normalized Ratio
ITTIntention to treat	
NCI-CTCNational	Cancer Institute Common Toxicity Criteria
	RCMultidisciplinary consultation meeting
RECIST	Response evaluation criteria in solid tumors
SPPopulation of tolerance	
	NeuroEndocrine tumor

3 Introduction

3.1 Rationale for the study

Neuroendocrine tumors (NETs) are a heterogeneous group of rare tumors (estimated prevalence between 0.4 and 1 per 100,000 population per year).

Treatment of digestive endocrine tumors

There are numerous therapeutic options and the choice of treatment depends essentially on the location of the primary tumor, the stage of extension and the tumor's evolution. In all cases, the decision must be taken after multidisciplinary discussion. Symptomatic management of hormonal hypersecretion is imperative. Surgical removal of the primary tumor is usually recommended. In the case of well-differentiated NETs with little progression, initial surveillance may be proposed with an evaluation of the tumor's evolution. If the tumor is slowly progressive (tumor stability without new localization), surveillance, 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 intra-arterial hepatic chemotherapy with embolization. As metastases are mainly vascularized by the arterial route, this approach allows to induce a targeted anoxia. Chemoembolization is effective in controlling clinical manifestations related to hormonal hypersecretion. The ENETS-01 trial, the only prospective randomized trial comparing embolization and chemoembolization (26 patients included), showed no difference in progression-free survival at 24 months between the chemoembolization (38%) and embolization (44%) groups. In the MD Anderson study (81 patients), the 24-month progression-free survival rate was 35%. In a French study (67 patients), the 24-month progression-free survival rate was about 35%.

Rationale for antiangiogenic therapy after (chemo)embolization

Digestive NETs are characterized by their hypervasculature. Tumor endocrine cells secrete excess VEGF which is likely to play an important role in the angiogenic process associated with endocrine tumorogenesis. Embolization stimulates angiogenesis with an increase in circulating VEGF levels and the main mechanism associated with a progressive recovery after (chemo)embolization is tumor revascularization from collateral vessels. Therefore, treatment with antiangiogenic action after (chemo)embolization could improve tumor control.

Everolimus

Inhibitors of the mTOR pathway have antiangiogenic activity, which explains in part their antitumor effect. In the phase II study by Yao *et al.*, the everolimus dose of 10 mg was retained for further development. Only the phase III RADIANT II study concerned NET of the digestive tract. This study randomized 430 patients between everolimus (10 mg/d) and placebo, combined in both arms with octreotide LP30mg/28d. Progression-free survival was 16.4 months in the everolimus arm versus 11.3 months in the placebo arm (HR = 0.77; 95% CI = 0.59-1.00; *p* NS) on centralized review. The center-read analysis (12.0 months *versus*

8.6 months, HR = 0.78; 95% CI = 0.62-0.98; *p* S) supported the superiority of everolimus with a very acceptable safety profile.

3.2 Objectives of the trial

3.2.1 Objective main

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.

3.2.2 Secondary objectives

The secondary objectives of the study are to evaluate:

- 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

3.2.3 Exploratory analyses

An exploratory analysis is planned to:

- Search for factors predictive of progression-free survival and/or overall survival
- To compare liver progression-free survival between embolization alone and chemoembolization.

4 Study population

The study includes patients with well-differentiated metastatic NET of the gastrointestinal tract.

4.1 Inclusion criteria

- Histologically proven metastatic endocrine tumor of the gastrointestinal tract (TENPATH review mandatory), well differentiated (grade 1 and 2 according to WHO 2010 classification)
- 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 ≥ 1.5 x 10^9 /L, platelets ≥ 100 x 10^9 /L, 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) < 1.5 N
    - 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

4.2 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

5 Experimental design

5.1 Scheme of the study

This is a single-arm, multi-center Phase II trial.

5.2 Treatment arm

There is a single study treatment arm consisting of:

- 1 to 2 embolization or chemoembolization sessions (sessions spaced 4 to 8 weeks apart).
- 10 mg/day everolimus (started 7 days after embolization or chemoembolization)

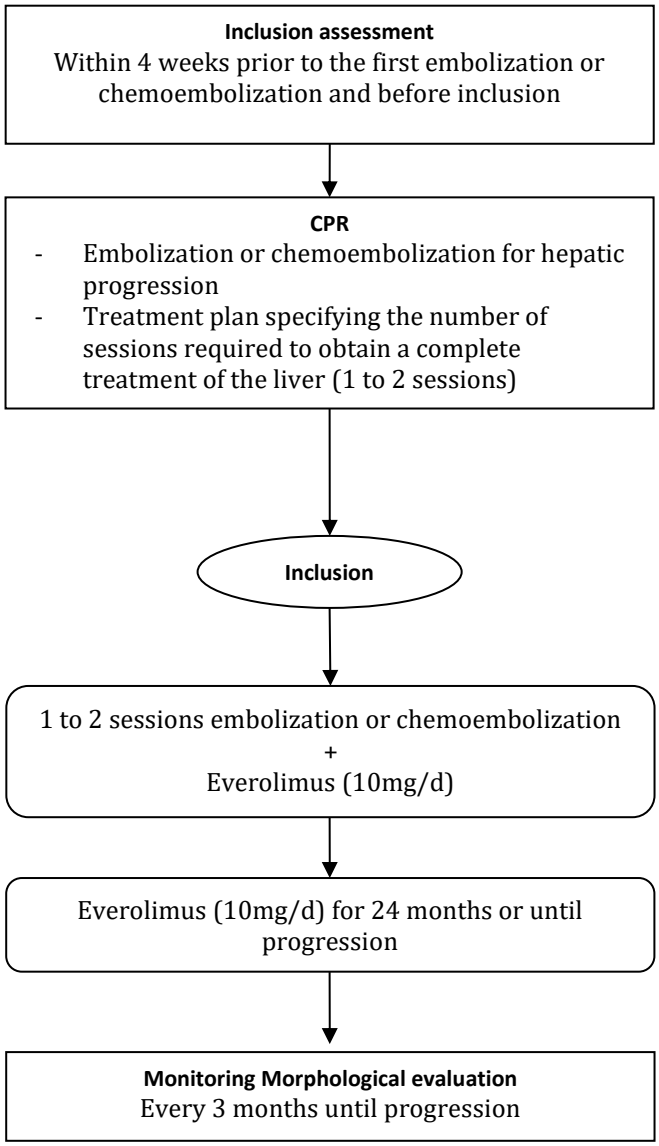
The maximum treatment period is 24 months.

5.3 Randomization and blinding

The trial is an open-label trial. There is no randomization in this trial.

5.4 Chronological sequence

Each patient will follow the chronological sequence described below:



5.5 Justification 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% at 24 months. As there is no information on hepatic 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 of more than 35% would demonstrate the utility of adjuvant 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 5% rate of lost to follow-up or patients who cannot be evaluated for any reason except death, **72 patients** will be included.

5.6 Steps of the test

5.6.1 Analysis Final

The final analysis will be performed 24 months after the inclusion of the 72ème patient. The point date for the analysis is therefore: 01/09/2017

Out of 68 evaluable patients, if 31 or more patients are alive without liver progression at 24 months, the treatment will be declared worthwhile.

5.6.1 Late analysis

Not applicable.

5.7 Judging criteria

5.7.1 Main criterion

The primary endpoint is the rate of living patients without liver progression 24 months after inclusion. Hepatic progression is defined according to RECIST V1.1 criteria and is based on centralized review (or on the investigator's opinion in case of impossible review).

5.7.2 Secondary endpoints of effectiveness

5.7.2.1 Rate of living patients without liver progression in mRECIST at 24 months

The rate of living patients without liver progression 24 months after inclusion will also be described according to mRECIST criteria and based on centralized review.

5.7.2.2 Survival without liver progression

It is defined as the time from the date of inclusion to the date of first hepatic progression (based on centralized review or on the investigator's opinion in case of impossible review) or the date of death (regardless of cause). Living patients without hepatic progression will be censored at the point date or the date of last morphological evaluation.

Live patients for whom no morphological evaluation is available will be censored at inclusion date + 1 day.

5.7.2.3 Progression-free survival

It is defined as the time between the date of inclusion and the date of first hepatic or extrahepatic progression (based on centralized review or on the investigator's opinion in case of unavailable review) or

the date of death (regardless of cause). Patients alive without progression will be censored at the point date or the date of last morphological evaluation.
Live patients for whom no morphological evaluation is available will be censored at inclusion date + 1 day.

5.7.2.4 Overall survival

It is defined as the time between the date of inclusion and the date of death (regardless of cause). Patients lost to follow-up or alive at the time of analysis will be censored at the date of last news.

5.7.3 Secondary tolerability criteria

The following secondary safety endpoints will also be analyzed:

Regarding Embolization/Chimioembolization:

- The number of embolizations and chemoembolizations actually performed per patient;
- The number of embolizations or chemoembolizations planned in PCR;
- The territories of (chemo) embolisations
- Complications during the procedure;
- Post-session complications.

Regarding Everolimus treatment:

- Duration of treatment;
- The time between the end of 1ère (chemo)embolization and the resumption of everolimus therapy;
- The time between the end of 2ème (chemo)embolization and the resumption of everolimus treatment;
- Treatment compliance;
- The number of patients who had at least one dosage change;
- The number of patients who had at least one temporary stop or deferral;
- Toxicities (graded according to NCI-CTC v 4.0).

5.7.1 Other criteria

- The evolution of the WHO performance index
- Best response under treatment (based on centralized review)
- The administration of G-CSF

5.7.2 Exploratory analyses

- An analysis of the predictive factors for overall survival and progression-free survival will be performed;
- In an exploratory manner, the progression-free survival between embolization alone and chemoembolization will be compared (if the number of patients in each group is sufficient).

6 Study population for analysis

6.1 Definition of Analysis Populations

6.1.1 Intent-to-treat (ITT) population

The intention-to-treat population is defined as all patients included in the study, regardless of eligibility criteria and treatment received. All analyses will be performed on an intention-to-treat basis, unless specifically mentioned for certain criteria.

6.1.2 Population of analysis for primary endpoint (PC)

The analysis population for the primary endpoint is defined as the ITT population of evaluable patients. A patient is considered evaluable if he or she has received at least one dose of everolimus and at least one treatment-related imaging.

A patient who dies (from any cause after treatment) or progresses in liver function before 24 months is evaluable and considered a failure for the primary endpoint.

Patients without a 24-month evaluation will be reviewed according to the following rules:

- If the patient has a later assessment (27 months or more) and is not progressing at that time, then they will be considered progression-free at 24 months
- The other patients will be reviewed at a medical review to decide, in view of the patient's entire file, whether they can be considered as failed or as truly non-evaluable (a rate of 5% of additional patients has been planned for these situations).

A listing of patients excluded from the CP population will be provided with the reasons for their exclusion.

6.1.1 Population per protocol (PP)

The per-protocol population is defined as all patients included in the study without major protocol deviation (i.e. meeting the criterion "Endocrine tumor of the gastrointestinal tract"), having at least one (chemo)embolization and at least 1 month of everolimus treatment (started within 30 days post-HEC).

A listing of patients excluded from the PP population will be provided with the reasons for exclusion.

6.1.2 Population for tolerance analysis (SP)

It is defined as the ITT population that received at least one dose of everolimus. The safety criteria will be evaluated in this population.

A listing of patients excluded from the PP population will be provided with the reasons for exclusion.

6.2 Definition of analysis subgroups

Not applicable

7 Statistical methods

Statistical analyses will be performed by the CRGA.

7.1 General information on statistical analysis methods

7.1.1 Software

Statistical analyses will be performed with SAS software version 9.4 or later. Some graphs can be made with R software version 2.11 or later.

7.1.2 Adjustments to SSP

Adjustments may be made to this analysis plan in case of amendments to the protocol, or if phenomena not initially foreseen require statistical adaptations. In all cases, these modifications must be made before the database is frozen.

7.1.3 Agreements concerning dates and durations

Time since inclusion will be defined as the time since the day of inclusion, with the day of inclusion considered as day 1.

The time since the start of treatment will be defined as the time since the day of the first treatment, the day of the first treatment being considered as day 1.

Therefore, the durations will be calculated according to the following rule, for example for the duration between death and inclusion: day of death - day of inclusion **+ 1**.

The day before the day of inclusion (*resp.* the day before the day of treatment) will be considered as day -1 (day 0 does not exist).

The last date of news will be by default the date of the last examination/monitoring performed.

The following conversion rules will be used to convert the number of days into months or years: 1 month = 30.4375 days; 1 year = 365.25 days.

7.1.4 Outlier Conventions

Outliers will be subject to a confirmation request to the investigating center. In case of confirmation, their value will not be modified and will be taken into account as it is during the analysis.

7.1.5 Missing Data Conventions

Except in the cases specified, missing data will not be replaced.

In case of partially missing data concerning dates, the following rule will be applied: when the day is missing, the day will be considered as the 15th of the month.

7.1.6 Definition of the baseline

Baseline measurements will be the last measurements taken at inclusion. In case of missing data, the last measurement performed before the first administration of the treatment will be used.

7.1.7 Statistics

Quantitative variables will be described using the number, median, mean, standard deviation of the mean, minimum, maximum, and interquartile range (Q1-Q3). Quantitative variables may be categorized using their median or a cut-off known from the medical literature.

Categorical variables will be described using percentages, and if necessary their two-sided 95% confidence intervals (calculated using the exact method).
Missing values will not be included in the calculation of frequencies and percentages.

The **confidence intervals** provided will be two-sided 95% confidence intervals, except for the primary criterion where a one-sided 95% confidence interval will be given.

Survival data will be estimated and plotted using the Kaplan-Meier method (Kaplan and Meier, 1958).
This will be described by the median and rates calculated at different times. Two-sided 95% confidence intervals will be provided. Confidence intervals for the rates will be constructed from the Greenwood variance calculated using the log-log transformation.
The median follow-up time will be calculated using the reverse Kaplan-Meier method (Shemper, 1996).

For uni and multivariate analyses, hazard ratios will be estimated using a Cox model (Cox, 1984). The proportionality of the rates will be tested using the graphical representation and the test based on Schöenfeld residuals (Grambsch, 1994); the linearity of the effect of the continuous variables on the risk will be assessed from the graphical representation of the martingale residuals. Confidence intervals for the coefficient estimates of the Cox models will be calculated using the Wald method.

7.2 Patient characteristics at inclusion

7.2.1 Eligibility

Population ITT

Patient eligibility at inclusion will be verified and described by:

- Number and percentage of patients who met all inclusion criteria
- Number and percentage of patients who met all non-inclusion criteria
- Number and percentage of patients who met all criteria (inclusion and non-inclusion)

7.2.2 Demographic characteristics

Population ITT and CP

The following characteristics at inclusion will be described:

- Inclusion center (number of patients included per center)
- Age (year)
- Gender (Male *vs* Female)

7.2.3 Clinical characteristics

Population ITT and CP

The following characteristics at inclusion will be described:

- WHO general status (0 *vs* 1 *vs* 2)
- BMI (kg/m^2)

- Presence of carcinoid heart disease (Yes *vs.* No)

7.2.4 Biological characteristics

Population ITT and CP

The following characteristics at inclusion will be described:

- Presence of anti-coagulant (Yes *vs* No)
- Chromogranin A (ng/mL)
- Urinary 5HIAA (mg/24h)
- Albumin (g/L)
- Total bilirubin (µmol/L)
- Conjugated bilirubin (µmol/L)
- PAL (Number of x the normal)
- ALT (Number of x normal)
- ASAT (Number of x normal)
- Hemoglobin (g/dL),
- PNN (/mm^3)
- Wafers (x10^3 /mm^3)
- Creatinine clearance (ml/min)
- B Viral serology: HBsAg (Negative *vs.* Positive); and if Positive :
  - HBV-DNA (Negative *vs* Positive)
  - Anti-HBs Ac (Negative *vs* Positive)
  - Anti-HBc Ac (Negative *vs* Positive);
- Viral C serology: HCV antibody (Negative *vs.* Positive)

7.2.5 Characteristics related to the disease

Population ITT and CP

The following characteristics at inclusion will be described:

- The grade of the tumor (G1 *vs* G2)
- The site of the primary tumor (Esophagus *vs* Jejunum-Ileon *vs* Appendix *vs* Stomach *vs* Colon *vs* Rectum *vs* Other); A listing of other locations will be provided.
- The presence of bilateral liver metastases (Yes *vs.* No)
- Percentage of liver invasion;
- The presence of extrahepatic metastases (Yes *vs.* No), and if yes, the location;
- Presence of previous treatments:
  - Surgery of the primary (Yes *vs.* No),
  - Locoregional treatment of liver metastases (Yes *vs.* No) and if yes,
    Type of treatment (Surgery and/or Radiofrequency and/or Other)
  - History of somatostatin analogue treatment (Yes *vs.* No) and if yes,
    Treatment in progress (Yes *vs.* No)
    The aim of the treatment (anti-tumor *vs* functional)
  - Other previous treatment (Yes *vs.* No)

7.3 Monitoring characteristics

Population ITT

The median follow-up time and its 95% confidence interval will be calculated in months.

7.4 Evaluation of the primary endpoint

Population CP

The rate of patients alive without progression at 24 months will be calculated and presented using its one-sided 95% confidence interval (exact confidence interval, binomial distribution).

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.

7.5 Evaluation of effectiveness

7.5.1 Rate of living patients without liver progression in mRECIST at 24 months

Population CP

The 24-month live progression-free rate in mRECIST will be calculated and presented using its one-sided 95% confidence interval (exact confidence interval, binomial distribution).

7.5.2 Survival without liver progression

CP, ITT and PP population (if the number of patients allows it)

The time scale considered will be the month.

Progression-free survival will be plotted using the Kaplan Meier estimator. Median survival and rates at different time points will be calculated along with their 95% confidence intervals.

7.5.3 Progression-free survival

CP, ITT and PP population (if the number of patients allows it)

The time scale considered will be the month.

Progression-free survival (hepatic or not) will be plotted using the Kaplan Meier estimator. Median survival and survival rates at 4, 8, 12, 18, 24 months will be calculated along with their 95% confidence intervals.

7.5.4 Overall survival

CP, ITT and PP population (if the number of patients allows it)

The time scale considered will be the month.

Overall survival will be plotted using the Kaplan Meier estimator. Median survival and survival rates at 4, 8, 12, 18, 24 months will be calculated along with their 95% confidence intervals.

7.5.5 Best response

Population CP, ITT and PP

The best response under treatment (CR, PR, S, P) will be calculated and described according to the usual descriptive statistics. The objective response rate (OR = CR and PR) will also be described.

7.6 Assessment of tolerance

7.6.1 Embolization or chemoembolization

Population ITT

Treatment by (chemo)embolization will be described by:

- The number of embolizations (1 vs 2) per patient and the total number of embolizations performed
- The number of chemoembolizations performed and the type: by doxorubicin or streptozotocin
- The number and percentage of patients who had (of the population of patients who had at least one embolization/chemoembolization):
  - 1 single embolization session
  - 1 single chemoembolization session
  - 2 embolization sessions
  - 2 sessions of chemoembolization
- Cross-tabulation of the number of embolizations or chemoembolizations planned in the PCR (at inclusion) and the number of embolizations or chemoembolizations actually performed.

Will also be described (percentage on the total number of embolisations and/or chemoembolisations performed):

- The territory of (chemo)embolisations
- The presence of a complication during the procedure (No *vs.* Yes), and if so:
  - presence of hepatic arterial occlusion by dissection or spasm (No *vs.* Yes)
  - presence of bleeding at the puncture site (No *vs.* Yes)
  - presence of another complication (No *vs.* Yes)
- The presence of a post-session complication (No *vs.* Yes), and if yes, a listing of these complications.

7.6.2 Administration of oral everolimus treatment

7.6.2.1 Duration of treatment

Population SP

The duration of treatment (converted into months) will be calculated by the formula :

Start date of last intake - start date of first intake + 1 day

Temporary stoppages and any deferral days during this period will not be subtracted from this duration. It will be described according to the usual descriptive statistics.

7.6.2.2 Doses administered

Population SP

Compliance will be calculated according to the formula: cumulative dose received (in mg) / protocol dose (in mg)

The theoretical protocol dose being equal to 10 mg x treatment duration (in days).
It will be described according to the usual descriptive statistics.

7.6.2.1 Modified dosage and temporary discontinuation

Population SP

The number of patients who had at least one dosage change and the number of patients who had at least one temporary stop or deferral will be described according to standard descriptive statistics.

7.6.2.2 Permanent cessation of treatment

Population SP

The number and percentage of patients permanently discontinuing protocol treatment and the reasons for discontinuing protocol treatment (% of the number of patients discontinuing treatment) will be described according to standard descriptive statistics. .

7.6.2.1 Other criteria

Population SP

The time from the end of 1ère (chemo)embolization to the resumption of everolimus treatment will be calculated in days and described according to standard descriptive statistics.
Similarly, the time between the end of the 2ème (chemo)embolization and the resumption of everolimus treatment will be calculated and presented.

7.6.3 ISG

The summary of the SAEs will be provided by pharmacovigilance.

7.6.4 Toxicities

Population SP

Toxicities (graded according to NCI-CTC v 4.0) will be described by:

- The total number of patients by maximum grade of toxicity (grade 1-2-3-4-5);
- The number of patients and the maximum toxicity grade achieved (grade 1-2-3-4-5) by SOC and type of toxicity;
- Total number of patients by maximum grade of toxicity by grouping grades (grade 1-2 and grade 3-4-5);
- The number of patients and the maximum grade of toxicities achieved by grouping the grades (grade 1-2 and grade 3-4-5) by SOC and type of toxicities.

7.6.5 WHO

Population SP

The evolution of the WHO performance index during treatment will be described by cross-tabulating the WHO index at inclusion with the WHO index of the last available on-treatment assessment.

7.7 Evaluations of exploratory analyses

- An analysis of predictive factors for overall survival and progression-free survival will be performed using univariate and multivariate Cox models. The predictive factors studied will be the parameters identified at inclusion:
  - Previous treatment (yes *vs.* no)
  - WHO (0 *vs* 1-2)
  - Age (< *vs.* ≥ median)
  - Gender (Male *vs* Female)
  - Presence of carcinoid heart disease (yes *vs.* no)
  - Tumor grade (G1 *vs* G2)
  - Tumor site (appendix *vs.* jejunum/ileum *vs.* colon/rectum *vs.* other)
  - Bilateral liver metastases (yes *vs.* no)
  - Extrahepatic metastases (yes *vs* no)
  - BMI (< 25 *vs* ≥ 25)
  - Chromogranin A (>2N *vs* < 2N with N=200 ng/mL)
  - Decrease from Chromogranin A inclusion at M3 (2 thresholds will be tested: > 50% *vs* ≤ 50% and > 30% *vs* ≤ 30%)
  - Decrease from baseline in urinary 5HIAA at M3 (2 thresholds will be tested: > 50% *vs* ≤ 50% and > 30% *vs* ≤ 30%)

- As an exploratory measure, progression-free survival between embolization alone and chemoembolization will be compared by a logrank test (if the number of patients in each group is sufficient).