INTRA-ARTERIAL TREATMENT WITH IRINOTECAN (DEBIRI) LOADED MICROBEADS CONCOMITANTLY WITH FOLFOX SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH COLORECTAL CANCER WITH NON-RESECTABLE LIVER METASTASES

Phase II non-randomized - multicenter

FFCD 1201 - DEBIRI

Statistical Analysis Plan

Final analysis

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2 Abbreviations and definitions

ACE	embryonic carcino antigen
EI	Adverse event
ISG	Serious adverse event
5FU	5-fluorouracil
FFCD	French-speaking Federation of Digestive Oncology
FOLFIRI	FOLinic acid - Fluorouracil - IRInotecan
HR	Hazard ratio
ITT	Intent to treat
KM	Kaplan Meier
LSN	Upper limit of normal
N	Normal
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
WHO	World Health Organization
Q1-Q3	Quartiles
RECIST	Response Evaluation Criteria In Solid Tumors
RC	Full Answer
RP	Partial response
RO	Objective answer
SG	Overall survival
SSP	Progression-free survival
SD	Stable disease
TAP	Thoracic-Abdomino-Pelvic
CT	CT scan

3 Introduction

3.1 Objectives of the study

3.1.1 Main objective

The primary objective of this study is to evaluate the progression-free survival rate (proportion of patients alive without progression) at 9 months after the start of treatment according to the RECIST 1.1 criteria, assessed by the investigator. The events to be considered will be progression or death.

3.1.2 Secondary objectives

The secondary objectives of the study are to evaluate:

- Tolerance to the treatment
- Best response according to RECIST v1.1 criteria (as determined by the investigator)
- Best response according to EASL criteria (evaluated in centralized review)
- Progression-free survival according to RECIST v1.1 criteria
- Progression-free survival
- Overall survival
- The rate of secondary resections
- Changes in tumor marker levels
- The maximum depth of response
- Early response rate (1ère assessment at 8 weeks)

3.1.3 Exploratory studies

The objective is to search for predictive factors of progression-free survival and/or overall survival.

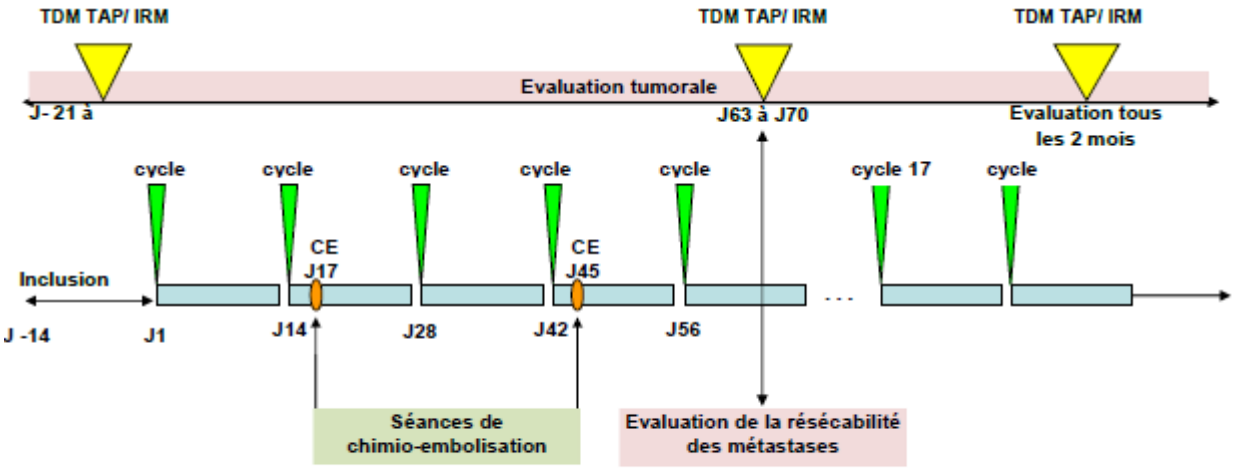
4 Experimental design

4.1 Scheme of the study

This is an open-label, non-randomized, multi-center Phase II trial.

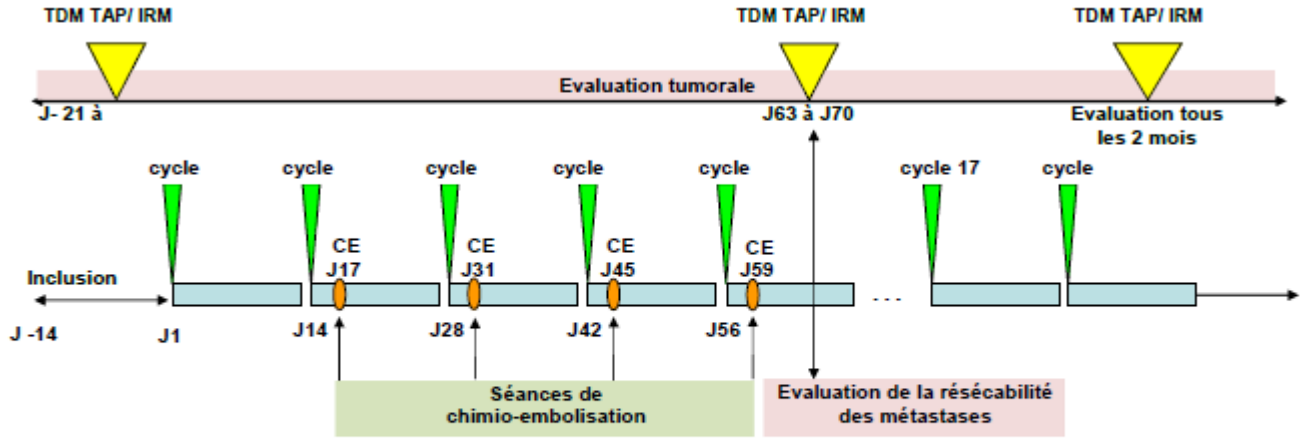
4.2 Chronological sequence

- **Bilobar treatment in 2 sessions**



Après ce plan de traitement initial, tous les patients recevront une chimiothérapie par FOLFOX toutes les 2 semaines, selon le schéma habituel jusqu'à progression ou toxicité inacceptable.

- **Sequential unilobar treatment in 4 sessions**



Le traitement par chimio-embolisation, pourra, au choix de l'investigateur, être administré de manière unilobaire et séquentielle, en 4 séances. Ainsi, le foie droit et le foie gauche seront traités en alternance. Les administrations de DEBIRI seront alors réalisées à J17, J31, J45, J59 (+/- 2j), ou en cas de décalage de cure de chimiothérapie, 3j (+/- 2j) après C2, C3, C4 et C5 de FOLFOX.Après ce plan de traitement initial, tous les patients recevront une chimiothérapie par FOLFOX toutes les 2 semaines, selon le schéma habituel jusqu'à progression ou toxicité inacceptable.

4.3 Justification of the number of subjects needed

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

The clinical assumptions made were:

H_0 : A 55% progression-free live proportion during the first 9 months is unattractive;

H_1 : A proportion of patients alive without progression of more than 55% during the first 9 months would show the interest of the treatment; a proportion of 75% is hoped for.

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

The decision rules are as follows: of the 48 evaluable patients

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

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

4.4 Planning of the trial analyses

Only a final analysis is planned.

4.5 Adjustments

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.

5 Study populations for analysis

5.1 Definition of analysis populations

5.1.1 Intent-to-treat (ITT) population

The intention-to-treat population is defined as all patients included in the study, regardless of eligibility criteria.

5.1.2 Modified intention-to-treat (mITT) population - evaluable patients

The modified intention-to-treat population is defined as all ***evaluable*** included patients, regardless of their eligibility criteria and treatment received.
A patient is considered evaluable if:

- he had a chemoembolization and
- received at least one cycle of chemotherapy and
- at least one assessment during the 9 months of follow-up was done

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

5.1.3 Tolerance population (TP)

The tolerance population is defined as all patients included in the study who received at least one dose of FOLFOX treatments.

5.1.4 Per-protocol (PP) population

The per-protocol population was defined as all patients who received the 2 or 4 planned DEBIRI sessions and met the inclusion/exclusion criteria of the study.

6 General information about statistical methods

Statistical analyses will be performed by the CRGA.

6.1 Software

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

6.2 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 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 the date of the last examination performed or the last treatment or the last medical consultation/visit.
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.

6.3 Missing Data Conventions

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

6.4 Definition of the baseline

Baseline measurements will be the last measurement taken prior to inclusion or the last measurement taken prior to the first administration of treatment.

6.5 Statistics

The confidence intervals provided will be two-sided 95% confidence intervals except for the primary endpoint where the calculated confidence interval will be a one-sided 95% confidence interval.

Quantitative data will be described using the following descriptive statistics: number, mean, standard deviation, median, first and third quartile, and minimum and maximum. These statistics will be considered the usual statistics for the analysis of quantitative variables. Quantitative variables can be categorized using their median or a cut-off known from the medical literature.

Categorical variables will be summarized, using the following descriptive statistics: the number, frequencies and percentages for each level of the variable. These statistics will be considered as the usual statistics for the analysis of categorical variables.
When necessary, the 95% confidence intervals for the proportions can be calculated from the exact binomial distribution.

Survival data will be estimated and plotted using the Kaplan Meier method (Kaplan and Meier., 1958). They will be described by the median and rates calculated at different time points with their two-sided 95% confidence intervals. The 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 estimated by the reverse Kaplan-Meier method (Shemper, 1996).

As an exploratory measure, for the uni and multivariate analyses, the hazard ratios will be estimated using a Cox model (Cox, 1984). The hypothesis of proportionality of the rates will be tested using the graphical representation and the test based on Schöenfeld's residuals (Grambsch, 1994); the linearity of the effect of the continuous variables on the risk will be evaluated 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 Statistical analysis

	Population ITT	Population ITTm	Tolerance population	Population Per protocol
Description of Baseline				
Eligibility criteria for inclusion	X	X		X
Demographic characteristics	X	X		X
Clinical characteristics at inclusion	X	X		X
Biological characteristics at inclusion	X	X		X
Characteristics related to the disease	X	X		X
Median follow-up time	X	X		X
Main criterion				
Progression-free survival rate at 9 months	X	X		X
Secondary criteria				
Overall survival, progression-free survival	X	X		X
Progression-free survival at 9 months	X	X		X
Response rate (RECIST) at 9 months	X	X		X
Response rate (EASL) at 9 months (centralized review)	X	X		X
Secondary resection rate	X	X		X
Evolution of tumor marker levels	X	X		X
Tolerance				
Administration of the treatment (duration, dose received ...)			X	
Toxicities			X	
Exploratory analysis	X	X		X

7.1 Patient characteristics at inclusion

7.1.1 Inclusion Characteristics - Eligibility

Population: ITT

Patient eligibility at inclusion will be 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 inclusion and non-inclusion criteria

7.1.2 Demographic characteristics

Population: ITT

The following characteristics at inclusion will be described:

- Age (years);
- Inclusion center (number of patients included per center);

- Gender (Male *vs* Female).

7.1.3 Clinical characteristics

Population: ITT

The following characteristics at inclusion will be described:

- Weight (kg);
- General WHO status (0 *vs* 1 *vs* 2);
- Score by Köhne.

  Definition:

  Bottom:

  - WHO 0-1 and a single metastatic tumor site

  Intermediate:

  - WHO 0-1 and more than one metastatic tumor site and PAL ≤ 300 U/L
  - WHO >1 and white blood cells ≤ 10 x 10^9 /L and a single metastatic tumor site

  High :

  - WHO 0-1 and more than one metastatic tumor site and PAL > 300 U/L
  - WHO >1 and white blood cells > 10 x 10^9 /L
  - WHO >1 and white blood cells ≤ 10 x 10^9 /L and more than one tumor site

7.1.4 Biological characteristics

- Leukocytes (/mm^3) ;
- Albumin (µmol/L);
- PAL (Ul/L);
- ACE (µg/L);
- CA19-9 (Ul/mL).

7.1.5 Characteristics related to the disease

Population: ITT

The following characteristics at inclusion will be described:

- Time from cancer diagnosis to inclusion date (months)
- Location of the primary tumor
- Metastatic location (for liver metastases, right lobe/left lobe and number of liver metastases, presence of lung metastases)
- History (diabetes, hypertriglyceridemia, hypercholesterolemia, hypertension, other (a list will be provided))
- Concomitant treatments (statin, fibrate, anti-coagulant, anti-hypertensive, aspirin, other (a list will be provided))
- KRAS status
- Performance of a PET scan (presence of pulmonary metastases, locoregional lymph nodes, other ...)
- Previous treatment and description of the type of treatment (RCT, CT, surgery, radiofrequency ...)

7.2 Monitoring characteristics

7.2.1 Definition of median follow-up time

Population: ITT

Median follow-up time is defined as the time interval between the date of inclusion and the date of last news (patients alive or lost to follow-up) or for deceased patients, the date of death (regardless of cause).

7.2.2 Evaluation of the median follow-up time

The median follow-up time (for living patients) and its 95% confidence interval will be calculated in months. It will be estimated by the inverse Kaplan Meier method.

7.3 Evaluation of the primary efficacy endpoint

Population: ITTm

7.3.1 Definition of the primary endpoint

The primary endpoint is to evaluate the rate of patients alive without progression at 9 months after the start of treatment. Progression is defined as radiological progression according to RECIST V1.1 criteria, as assessed by the investigator.

Patients who progressed or died (from any cause) within 9 months of initiation of therapy (Day 1 of Cure 1) will be considered to have failed the primary endpoint at 9 months.

The scans selected for analysis will be the scans before and up to 9 months with a +/- 1 month window.

Patients without a 9-month evaluation will be reviewed according to the following rules:

- If the patient has a late assessment (10 months or more) and is not progressing at that time, then they will be considered progression-free at 9 months.
- If the patient has documented progression at more than 9 months without imaging at 9 months, then that patient will be considered to be in progression at 9 months. If progression is documented at more than 11 months, the patient will not be considered to be in progression at 9 months.
- If progression is documented before the 9-month assessment, the patient is considered to be in progression at 9 months.

7.3.2 Evaluation of the primary endpoint

The primary endpoint will be assessed on the ITTm population. This criterion will be described according to the usual descriptive statistics. A one-sided 95% confidence interval will be calculated using the exact method.

The decision rules to be applied on 48 patients evaluable in the analysis (ITTm population) are:

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

These may be adjusted based on the actual number of evaluable patients included.

7.4 Evaluation of secondary efficacy criteria

7.4.1 Best response according to RECIST v1.1 criteria (as determined by investigator)

Population:

7.4.1.1 Definition

The best response is described by the rates of complete, partial, stable, progression, or non-evaluable response over the course of treatment. Response is assessed by the investigator according to RECIST V1.1 criteria.

7.4.1.2 Evaluation

Rates will be described using standard statistics.

7.4.2 Best response according to EASL criteria (according to centralized review)

Population:

7.4.2.1 Definition

The best response is described by the rates of complete response, partial response, stability, and progression over the course of treatment. Response is assessed at the centralized review according to EASL criteria.

7.4.2.2 Evaluation

Rates will be described using standard statistics.

7.4.3 Depth of response (DpR)

Population:

7.4.3.1 Definition

It is defined as the relative difference between the sum of the largest diameters of RECIST target lesions at NADIR in the absence of new lesions or progression of non-target lesions and the sum of the largest diameters of RECIST target lesions at inclusion. It will be given according to the investigator and according to the centralized review of the images.

7.4.3.2 Evaluation

It will be described using standard statistics.

7.4.4 Early response rate (ETS: early tumor shrinkage)

Population:

7.4.4.1 Definition

Early (8-week) tumor shrinkage rate is defined as the relative difference between the sum of the largest diameters of the RECIST target lesions at 8 weeks and this sum at inclusion. Tumor shrinkage will be observed when the relative

difference is > 20% and > 30% (2 thresholds). It will be given according to the investigator and according to the centralized review of the images.

7.4.4.2 Evaluation

Rates will be described using standard statistics.

7.4.5 Hepatic progression-free survival according to RECIST v1.1 criteria

Population:

7.4.5.1 Definition

It is defined as the time interval between the date of inclusion and the date of 1ère hepatic (radiological) progression or the date of death (from any cause). Patients alive and without progression will be censored at the date of last news.

7.4.5.2 Evaluation

The time scale considered will be the month.
Survival rates will be calculated at different time points using the Kaplan Meier estimator and its 95% confidence interval.

7.4.6 Progression-free survival

Population: ITT

7.4.6.1 Definition of progression-free survival

It is defined as the time interval between the date of inclusion and the date of 1ère radiological progression or the date of death (from any cause). Patients alive and without progression will be censored at the date of last news.

7.4.6.2 Assessment of progression-free survival

The time scale considered will be the month.
Progression-free survival will be plotted using the Kaplan Meier estimator and survival rates at different time points (6, 9, 12 and 18 months) will be calculated along with their 95% confidence intervals.

7.4.7 Overall survival

Population: ITT

7.4.7.1 Definition of overall survival

It is defined as the time interval 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 report.

7.4.7.2 Evaluation of overall survival

The time scale considered will be the month.
Overall survival will be plotted using the Kaplan Meier estimator and survival rates at different time points (6, 9, 12 and 18 months) will be calculated along with their 95% confidence intervals.

7.4.8 Secondary resection rate

Population:

7.4.8.1 Definition

The secondary resection rate is defined as the percentage of patients who had surgery for liver metastases.
The calculated secondary resection rate is defined as the percentage of R0 resection, R1 resection and R2 resection.

7.4.8.2 Evaluation

Rates will be described using standard descriptive statistics.

7.4.9 Evolution of tumor marker levels

7.4.9.1 Definition

The evolution of tumor markers (CEA and CA19-9) will be evaluated throughout the study, from inclusion to progression. It will be described at each evaluation.

7.4.9.2 Evaluation

The delta for CEA and CA19-9 (value at assessment - value at baseline/value at baseline) *100 will be described at each assessment and plotted as a boxplot.

7.5 Assessment of tolerance

Population:

Tolerance to treatment will be assessed by:

- Duration of treatment, doses received, dose decreases, and deferrals;
- Toxicities described according to NCI-CTC version 4.0 criteria;
- Number and description of SAEs

7.5.1 Chemoembolization

Chemoembolization therapy (CHE) will be described by:

- The number of HEC performed per patient and the total number of HEC performed by type of treatment. Causes will be described for patients who did not have the total number of HECs as per the protocol.
- The number and percentage of patients who had 1 HEC, 2 HEC, 3 HEC or 4 HEC according to the type of treatment (uni-lobar or bi-lobar)

- The type of treatment, the lobe involved, the dose of irinotecan administered. Causes will be described when the dose of irinotecan was not administered completely.
- The number of HEC deferrals and the causes of deferrals
- The number and percentage of patients treated with G-CSF

The consequences of treatment will also be described:

- The length of hospitalization
- The number and percentage of patients who experienced side effects during the procedure. A listing of other side effects during the procedure will be reported.
- Number and percentage of patients with pain >3 (VAS)
- The pain assessment (VAS) before HEC and within 24 hours after HEC will be described by grade (frequency of VAS for all HEC).

7.5.2 Administration of FOLFOX

7.5.2.1 Duration of treatment

The duration of the treatment will be described by:

- The number of treatments per patient;
- The duration of treatment (converted to months) will be calculated by the formula:

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

  Therapeutic breaks and any deferral days during this period will not be subtracted from this duration.

It will be described according to the usual descriptive statistics.

7.5.2.2 Doses administered

- The average number of treatments will be carried over.
- Compliance will be calculated according to the formula :

  (Cumulative dose received (in mg) / theoretical protocol dose (in mg)) x 100

The protocol doses of treatment are :

Oxaliplatin = 85 mg/m^2.

5FU bolus = 400 mg/m2

Continuous 5FU = 2400 mg/m^2.

Folinic acid = 400mg/m^2.

Compliance will be described by molecule according to the usual descriptive statistics.

7.5.2.3 Postponement of cures, modification of administration and reason for modification

- The number and percentage of patients with at least one deferred treatment and the reasons for these deferrals

- The number of patients with at least one dose change will be described by treatment type. Causes of dose changes will be presented. A listing of others will be provided.
- The number and percentage of patients who permanently discontinued protocol treatment and the causes of discontinuation will be described.

All parameters will be described according to the usual descriptive statistics.

7.5.2.4 Subsequent line

- The number of patients who received a subsequent line and subsequent patterns will be described.
- The number of patients who received a new HEC and the number of subsequent HECs will be described. A listing of the products used to load the beads will be provided.

All parameters will be described according to the usual descriptive statistics.

7.5.3 Toxicities

Toxicities during treatment will be described according to NCI-CTC version 4.0 criteria by:

- The number of patients and toxicities by maximum grade and type;
- The number and percentage of patients with at least one toxicity across all courses by grade;
- The number and percentage of patients with at least one maximum grade 3-4-5 toxicity over all courses or at least one maximum grade 1-2 toxicity;

7.5.4 E.I.G

A summary of the SAEs will be provided by pharmacovigilance.

7.6 Exploratory Analyses

7.6.1 Definition

The exploratory analysis focuses on the search for factors predictive of progression-free survival and/or overall survival.

Progression-free survival is defined as the time interval from the date of inclusion to the date of 1ère radiological progression or the date of death (from any cause). Patients alive and progression-free will be censored at the date of last report.

Overall survival is defined as the time interval 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 report.

The variables for which the p-value is lower than 0.10 in univariate analysis or judged clinically relevant among the list to be defined will be retained for the multivariate analysis.

7.6.2 Evaluation

For univariate 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's 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.