Idarubicin-loaded bead chemoembolization of hepatocellular carcinoma not amenable to curative treatment

Phase II single-arm multicenter

IDASPHERE II - FFCD 1307

Statistical Analysis Plan

Final analysis

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1 Table of contents

2 Abbreviations and definitions

CHCCarcinoma	Hepatocellular carcinoma
CHE	Chemoembolization
CP	Main criterion
SEE	Serious adverse event
HCC18	Hepatocellular Carcinoma (Quality of Life module)
MRI	Magnetic resonance imaging
ITT	Intention to treat
NCI-CTC	National Cancer Institute Common Toxicity Criteria
TAP	Thoraco-abdomino-pelvic
CT scan	Tododensitometry
TP	Prothrombin rate
RECISTResponse evaluation criteria in solid tumors	

3 Introduction

3.1 Objectives of the trial

3.1.1 Objective main

The primary objective of the study is to evaluate the objective response rate (complete and partial response) at 6 months, assessed according to mRECIST criteria in centralized review.

3.1.2 Secondary objectives

The secondary objectives of this study are to evaluate:

- The 6-month objective response rate (mRECIST) assessed by the investigator
- 6-month objective response rate (EASL)
- Time to treatment failure
- The best response according to mRECIST
- Progression-free survival
- Overall survival
- Treatment tolerance
- Quality of life (QLQ-C30 questionnaires and its HCC18 module specific to HCC)

3.1.3 Translational study

A translational study is planned as part of this trial:

- biological with blood samples for the determination of circulating VEGF and progastrin
- imaging (cone-beam CT) to correlate chemoembolized tumor and non-tumor volume measurements with VEGF assays

4 Experimental design

4.1 Study diagram

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

4.2 Treatment arms

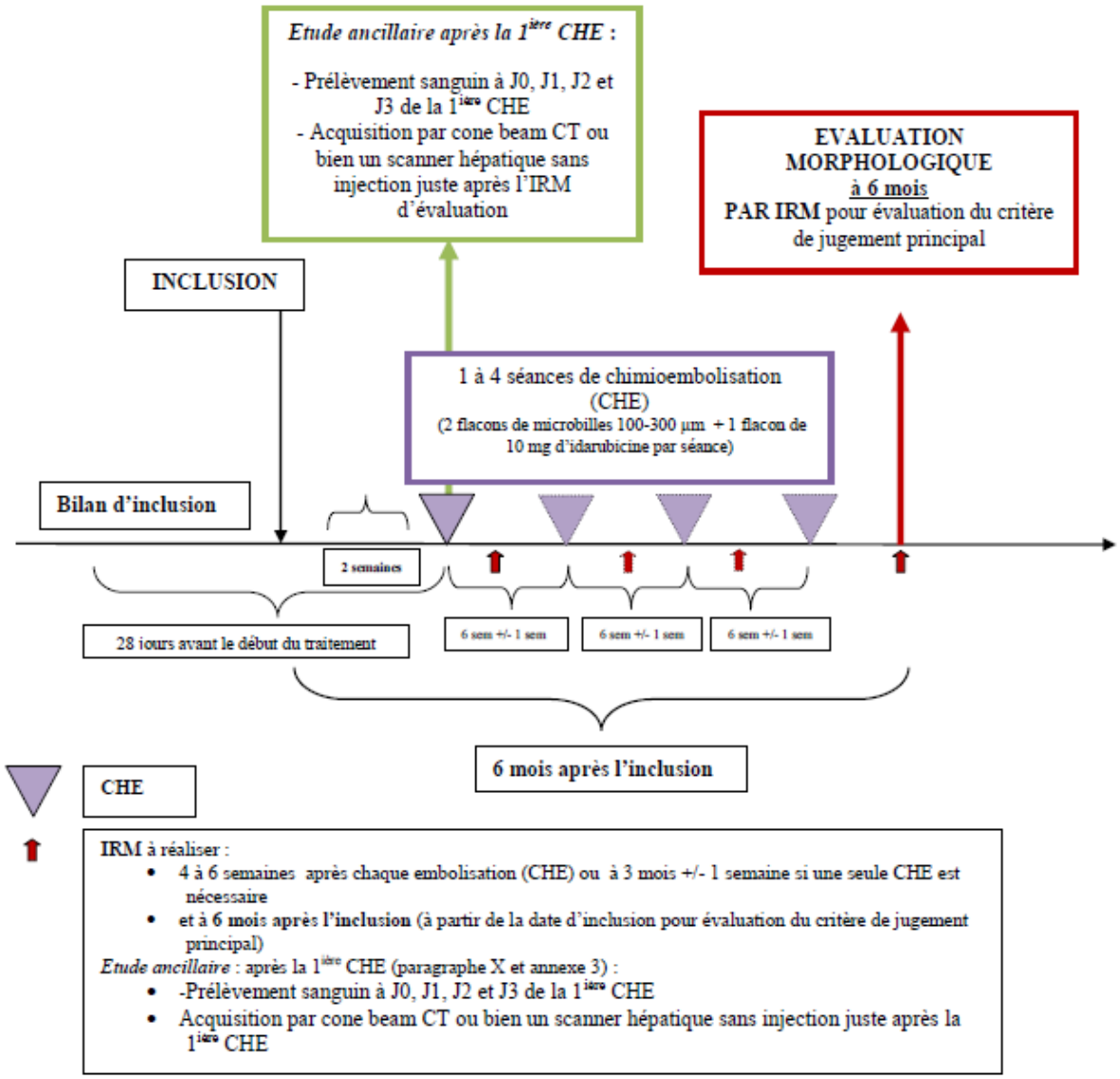
There is a single study treatment arm consisting of 1 to 4 sessions of chemoembolization (sessions spaced 6 weeks +/- 1) with idarubicin-loaded microbeads (100-300 µm) (10 mg).

4.3 Randomization and blinding

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

4.4 Chronological sequence

Each patient will follow the chronological sequence described below:



4.5 Justification of the number of subjects required

The assumptions used to calculate the number of subjects required are :

- H0: A proportion of patients with an objective response at 6 months of 25% or less is not acceptable.
- H1: A proportion of patients with an objective response at 6 months of more than 25% would demonstrate the efficacy of the treatment. A rate of 40% is hoped for.

Using a 2-stage Fleming design (Fleming, 1982) with a one-sided alpha risk of 5% and power of 90%, it is necessary to include **86 evaluable patients**.

Taking into account a 5% rate of patients lost to follow-up or not evaluable, **91 patients** will be included.

4.6 Test steps

4.6.1 First stage: interim analysis

An interim analysis was performed in January 2017 after inclusion of 46 patients (44 evaluable for the primary endpoint). At this stage, out of 44 evaluable patients, according to the decision rules, 19 or more patients needed an objective response at 6M to judge the treatment effective.
22 patients met this criterion and the treatment was therefore deemed effective. The trial was therefore stopped for efficacy (rejection of H0).

4.6.2 Second stage: final analysis

In view of the results of the interim analysis and the discontinuation of the study for efficacy, the final analysis will be performed with a last news date for each patient after 01/01/2017.

4.6.3 Transition between the two stages

Not applicable

5 Study population for analysis

5.1 Definition of analysis populations

5.1.1 Intention-to-treat (ITT) population

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

5.1.2 Population of analysis for primary endpoint (CP)

The analysis population for the primary endpoint is defined as all evaluable patients included in the study, regardless of eligibility criteria. A patient is considered evaluable if he or she has undergone at least one chemoembolization and one post-treatment evaluation.
A patient without any imaging will be considered non-evaluable.
A patient who dies within the first 6 months (whatever the cause) is evaluable and considered a failure for the primary endpoint.
Patients without a 6-month assessment will be reviewed according to the following rules:

- If the patient has a later evaluation (6 months or more) and is not in objective response at that date, he/she will be considered as not having an objective response at 6 months.
- If the patient has a documented objective response at more than 6 months without imaging at 6 months, this patient should be reviewed.

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

5.1.3 Tolerance population (SP)

The tolerance population is defined as the intention-to-treat population having received at least one chemoembolization.

Tolerance criteria will be assessed for this population.

A list of patients excluded from the SP population will be provided, together with the reasons for their exclusion.

5.2 Definition of analysis subgroups

Not applicable.

6 General information on statistical methods

Statistical analyses will be carried out by CRGA.

6.1 Software

Statistical analyses will be carried out using SAS software version 9.4 or later. Some graphs may be produced using R software version 2.11 or later.

data.

6.2 Agreements concerning dates and durations

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

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

As a result, durations are calculated using the following rule, for example for the time elapsed between death and inclusion: day of death - day of inclusion **+ 1**.

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

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

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

6.3 Outlier conventions

Outliers will be confirmed by the investigating center. In the event of confirmation, their value will not be modified, and will be taken into account as it is during the analysis.

6.4 Missing data conventions

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

6.5 Baseline definition

Baseline measurements are the last measurements taken at inclusion. In the event of missing data, the last measurement taken before the first treatment is used.

6.6 Statistics

Quantitative variables will be described using headcount, median, mean, standard deviation of the mean, minimum, maximum and inter-quartile range (Q1-Q3). Quantitative variables can 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 bilateral 95% confidence intervals (calculated using the exact method).
Missing values are not taken into account when calculating frequencies and percentages.

The **confidence intervals** provided will be two-sided 95% confidence intervals, except for the main 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. 95% confidence intervals will be provided. Confidence intervals for rates will be constructed from the Greenwood variance calculated using the log-log transformation.
The median follow-up time is calculated using the reverse Kaplan-Meier method (Shemper, 1996).

The treatment hazard ratio will be estimated using a univariate Cox model (Cox, 1984). The hypothesis of proportionality of rates will be tested using the graphical representation and test based on Schöenfeld residuals (Grambsch, 1994); the linearity of the effect of continuous variables on risk will be assessed using the graphical representation of martingale residuals. Confidence intervals for Cox model coefficient estimates will be calculated using Wald's method.

7 Statistical analysis

7.1 Patient characteristics at inclusion

7.1.1 Patient eligibility

Population ITT

Patients' eligibility for 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)

7.1.2 Demographic characteristics

Population ITT

The following characteristics at inclusion will be described:

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

7.1.3 Clinical features

Population ITT

The following characteristics at inclusion will be described:

- WHO general status (0 *vs* 1)
- BMI (kg/m)^2
- BCLC (A *vs* B *vs* C)
- Child-Pugh (A *vs* B7 *vs* B8 *vs* B9 *vs* no cirrhosis)
- Pain assessment
- Medical history :
  - Etiology of hepatopathy (hepatitis B, hepatitis C, alcohol, hemochromatosis, metabolic disease, other)
  - Presence of associated cirrhosis (Yes vs. No)
  - Presence of metabolic syndrome (Yes vs. No)

7.1.4 Biological characteristics

Population ITT

The following characteristics at inclusion will be described:

- Wafers (x10 /mm)^{33}
- PNN (/mm^3),
- Creatinine (µmol/L)
- Albumin (g/L)
- P rate (%)
- Hemoglobin (g/dL),
- Total bilirubin (Number of x normal)
- Conjugated bilirubin (number of x normal)
- AST (Number of x normal)
- ALAT (Number of x normal)
- PAL (Number of x normal)
- GGT (Number of x normal)
- AFP (Number of x normal)
- Blood glucose (g/L)
- V factor (%)
- Sodium (g/L)

7.1.5 Disease-related characteristics

Population ITT

The following characteristics at inclusion will be described:

- Tumor volume as % of liver volume (> 50% *vs* ≤ 50%)
- Tumor extension (unilobar *vs.* bilobar)
- Number of nodules (1 *vs* 2-3 *vs* > 3 *vs* infiltrating)
- Size of largest nodule in right and left livers (in mm)
- Presence of tumor portal thrombosis (No *vs.* Yes), and if so, type (Sectoral *vs.* Segmental *vs.* Sub-segmental)

7.2 Follow-up features

Population ITT

7.2.1 Definition of median follow-up time

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 (whatever the cause).

7.2.2 Evaluation of 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 using the inverse Kaplan Meier method.

7.3 Evaluation of primary endpoint efficacy

Population CP

7.3.1 Definition of primary efficacy endpoint

The primary endpoint is the objective response rate 6 months after inclusion. Objective response (complete and partial response) is defined according to mRECIST criteria and based on centralized review (or on the investigator's opinion if review is not possible).

7.3.2 Evaluation of primary efficacy endpoint

The objective response rate at 6 months will be calculated and presented with its one-sided 95% confidence interval (exact confidence interval, binomial distribution).

7.4 Evaluation of secondary efficacy endpoints

7.4.1 OR patient rate by investigator and mRECIST

7.4.1.1 Definition

The rate of patients in objective response (complete and partial response) 6 months after inclusion according to mRECIST criteria will also be evaluated according to the investigator.

7.4.1.2 Evaluation

The objective response rate at 6 months will be calculated and presented with its 95% confidence interval.

7.4.2 OR patient rate according to EASL

7.4.2.1 Definition

The rate of objective response (complete and partial response) 6 months after inclusion will also be evaluated according to EASL criteria in centralized review and according to the investigator.

7.4.2.2 Evaluation

The objective response rate at 6 months will be calculated and presented with its 95% confidence interval.

7.4.3 Time to treatment failure

7.4.3.1 Definition

It is defined as the time between the date of inclusion and the date of definitive cessation of treatment or death (whatever the cause). Patients without definitive treatment discontinuation and not deceased will be censored at the date of their last HEC.

7.4.3.2 Evaluation

The time scale considered is the month.

Time to treatment failure will be plotted using the Kaplan Meier estimator. Median times and rates at different temporalities will be calculated, along with their 95% confidence intervals.

7.4.1 Better response to treatment

7.4.1.1 Definition

The best response to treatment will be assessed according to mRECIST criteria.

7.4.1.2 Evaluation

The best response to treatment (CR, PR, S, P) will be calculated and described using standard descriptive statistics. It will be described according to the investigator.

7.4.2 Progression-free survival

7.4.2.1 Definition

It is defined as the time between the date of inclusion and the date of first progression assessed by centralized review, or the date of death (whatever the cause). Patients alive without progression will be censored at the date of last evaluation.

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

7.4.2.2 Evaluation

The time scale considered will be the month.

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

7.4.3 Overall survival

7.4.3.1 Definition

It is defined as the time interval between the date of inclusion and the date of death (all causes). Living patients will be censored at the date of last news.

7.4.3.2 Evaluation

The time scale considered will be the month.

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

7.5 Tolerance assessment

Population SP

7.5.1 Chemoembolization

Chemoembolization will be described by :

- The number of chemoembolizations performed per patient
- Chemoembolization territories
- HEC postponements (number of postponements, number of days postponed, cause)
- Complications during the procedure
- Post-treatment complications.

7.5.2 Toxicities

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

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

7.5.3 Serious adverse events

A **summary of all SAEs** will be provided by pharmacovigilance.

7.6 Quality of life assessment

Quality of life is assessed using the EORTC QLQ-C30 and HCC18 questionnaires.

The scores of these questionnaires at inclusion will be described using standard statistics.

8 Quality assurance

8.1 Input

Data entry and consistency checks will be described in the data management plan.

8.2 Base monitoring

8.2.1 Test analysis

During the study, one or more test analyses will be carried out. All statistical analyses will be performed on the database extracted at that time. The purpose of these analyses is to :

- anticipate the drafting of statistical analysis programs;
- highlight inconsistencies in patient records not identified by data management rules;
- identify problems not considered when drafting the protocol and statistical analysis plan.

Identified problems requiring modification or clarification of the protocol or analysis plan will be discussed with the coordinator.

8.2.2 Dual programming

Double programming of the primary and secondary efficacy criteria will be carried out by two different statisticians. Results will be compared, and errors discussed and corrected.