ACTION Statistical Analysis Plan

A phase II triAl of Cabozantinib for hepaTocellular carcInoma patients intOlerant to sorafenib treatment or first line treatment different to sorafeNib. (ACTION trial)

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Statistical Analysis Plan

Medical Statistics Core Facility
IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer)
183, Mallorca Street. Floor 0, office 86. 08036 Barcelona. Spain
Phone: +34 93 227 54 00 Ext 4383
email: bioestadistica@idibaps.org

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Institution	Medical Statistics Core Facility IDIBAPS - Hospital Clínic de Barcelona
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SIGNATURES

Created by

Medical Statistics Core Facility
IDIBAPS - Hospital Clínic Barcelona
Ms. Gema Domenech, MSc
Project Statistician

Gema Domenech — Date: 05/11/2021

Revised by:

Medical Statistics Core Facility
IDIBAPS - Hospital Clínic Barcelona
Mr. José Rios, MsC
Responsible for Statistical Analysis

José Ríos — Date: 05/11/2021

Approved by:

BCLC group. Liver Unit. ICMDM. CIBEREHD. IDIBAPS. Hospital Clínic
Dra. Maria Reig, MD, PhD
Principal investigator

Maria Reig — Date: 05/11/2021

BCLC group. Liver Unit. ICMDM. CIBEREHD. IDIBAPS. Hospital Clínic
Dr. Jordi Bruix, MD, PhD
Medical Coordinator

Jordi Bruix — Date: 05/11/2021

1 TABLE OF CONTENTS

2 STUDY PERSONNEL

2.1 SPONSOR

Sponsor: Fundació Clínic per a la Recerca Biomèdica *

* Fundació Clínic per a la Recerca Biomèdica (FCRB)
C/Roselló149-153

2.2 PRINCIPAL INVESTIGATOR AND MEDICAL COORDINATOR

Principal Investigator: Dr. Maria Reig, MD, PhD **
mreig1@clinic.cat

Medical Coordinator: Dr. Jordi Bruix, MD, PhD **
jbruix@clinic.cat

** BCLC group. Liver Unit. ICMDM. CIBEREHD.
IDIBAPS - Hospital Clinic Barcelona
Hospital Clínic de Barcelona
C/Villarroel 170, Esc. 11, 4ª planta
08036 Barcelona, Spain
Phone: +34 93 227 98 03

2.3 STATISTICIANS

Project Statistician Ms. Gema Domenech, MSc ***
gdomene1@clinic.ub.es

Responsible of Statistical Analysis Mr. José Ríos, MSc ***
jose.rios@idibaps.org

*** Medical Statistics Core Facility
IDIBAPS - Hospital Clinic Barcelona
C/ Mallorca 183, Floor 0, office 86
08036 Barcelona, Spain
Phone: +3493 227 54 00 ext (4383)

3 LIST OF ABBREVIATIONS

ADO	Available Data Only
AE	Adverse Events
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence Interval
CIBEREHD	Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FACT-HEP	Functional Assessment of Cancer Therapy – Hepatobiliary cancer
HCC	Hepatocelluar Carcinoma
ICH	International Conference on Harmonization
ICMDM	Institut Clínic de Malalties Digestives i Metabòliques
IDIBAPS	Institut d'investigacions Biomèdiques August Pi iSunyer
LSM	Leas Square Means
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Models for Repeated Measurements
ORR	Objective Response Rate
OS	Overall Survival
PEP	Primary endpoint
PP	Per protocol
PPS	Post-progression survival
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Standard Error
SD	Standard Deviation
SCReN	Spanish Clinical Research Network
TTP	Time to progression
VAS	Visual Analogical Scale

4 SCOPE OF ANALYSIS PLAN

The statistical analysis will be carried out in accordance with the principles specified in the International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/363/96)[1]. This SAP will follow the general regulatory recommendations given in the ICHE9[1] guidance, as well as other specific guidance on methodological and statistical issues[2]. Also, it will stick to the recommendations given by the consensus documents of the scientific journals[3,4,5] to improve reliability and value of medical research literature by promoting transparent and accurate reporting of clinical research studies.

5 SOFTWARE METHODS

All tables and listings will be produced using SAS System[6] (Release 9.4 or an upgraded version) and will be presented in WinWord documents.

6 STUDY OBJECTIVES

6.1 PRIMARY OBJECTIVES

The aim of this study will be to test the safety of cabozantinib in patients sorafenib intolerant according to the RESORE trial[7] definition and in patients treated with first-line treatments other than sorafenib. Indeed, although a phase III trial (CELESTIAL)[¡Error! No se encuentra el origen de la referencia.] showed improved OS with acceptable toxicity in sorafenib intolerant patients or in those who progressed on sorafenib, no clear definition was applied to identify those patients. The **primary endpoints** are the rate and type of AEs leading to treatment discontinuation, the rate and type of AEs, serious AEs (SAEs), rate of related-AE and rate of death.

6.2 SECONDARY OBJECTIVES

Secondary endpoints are time to progression, pattern of progression, overall survival, post-progression survival, rate of patients who develop new extra-hepatic spread and ORR. Radiologic tumor response will be defined according to the RECIST 1.1[9] and then will be evaluated by BCLC-RECIST[10].

6.3 EXPLORATORY OBJECTIVES

Exploratory objectives are:

- To evaluate the role of tissue biomarkers (see section 7.7 for timing-points) in determining the antitumoral activity of cabozantinib.
- To describe the quality of life.
- The gut microbiota composition at different time points.

This study will collect blood and biopsy samples but the exploratory objectives will be done in a second study only if the study meets the safety end-point.

7 TRIAL CHARACERISTICS

7.1 STUDY DESIGN

The study is a prospective, multicenter, open-label, non-controlled phase IIa study evaluating cabozantinib for the treatment of patients with unresectable hepatocellular carcinoma sorafenib intolerant according to the RESORCE trial definition or who received other first-line treatments than sorafenib. Treated patients will be followed until death, withdrawal of consent or until the end of the duration of the study.

7.2 STUDY TREATMENTS

In this protocol investigational products is cabozantinib.
See protocol section 6.1 for more information about dose modification rules for the study treatment.

7.2.1 Cabozantinib

Cabozantinib will be initiated at full dose (60 mg/day) and the dose will be modified upon development of adverse events according to the manufacturer's recommendations and continued until symptomatic tumor progression, unacceptable adverse events, patient decision or death.

7.3 DISCONTINUATION OF THE STUDY

7.3.1 End of study

After discontinuation from study therapy, there is 1 follow-up visit required within seven days of discontinuation (on site visit), and additional survival follow-up (on-site or phone visits). The study will end when survival follow-up collection has concluded. The last visit will be defined as the latest follow-up Visit. Additional survival follow-up may continue beyond the time of this analysis.

7.3.2 Discontinuation of cabozantinib

Subjects MUST discontinue study medication:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, abnormal laboratory test results or any illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Clinical deterioration (see protocol section 6.1.7 for more details)
- Pregnancy
- Termination of the study by the promoter
- Specific criteria for discontinuation of outlined in (see protocol section 6.1.6 for more details)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Protocol defined disease progression unless subject is eligible for treatment beyond progression (see protocol section 6.1.7.1 for more details).
- In the case of pregnancy, the investigator must immediately notify the Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Principal Investigator must occur.
- All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in section. The only exception to this requirement is when a subject withdraws

consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate CRF page.

7.3.3 Post study drug study follow-up

In this study, overall survival is a secondary endpoint. Subjects who discontinue study drug must continue to be followed for collection of survival follow-up data until death or the conclusion of the study. Survival follow-up visits should be planned every 3 months from Follow-Up Visit-1 and may be performed by phone contact or office visit.

7.3.4 Withdrawal of consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the Investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The Investigator should explain the withdrawal of consent in detail in the medical records, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.

7.3.5 Lost to follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails or whatsapp messages as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

7.4 JUSTIFICATION OF SAMPLE SIZE

The sample size calculation will be triggered by the primary outcome, i.e, the rate of adverse events (AE) with CTCAE≥3 excluding palmar-plantar erythordysthesia (critical AEs). The expected rate for this outcome was 56% in this population[¡Error! No se encuentra el origen de la referencia.]. The Simon's two-stage optimal design[11] will be used to test the alternative hypothesis that with cabozantinib the rate of critical AEs will be reduced at least to 32.5% against the null hypothesis of 56% as previously observed. In the first stage, 14 patients will be accrued. If there are 8 or more critical AES in these 14 patients, the study will be stopped because of futility. Otherwise, 26 additional patients will be accrued for a total of 40. The null hypothesis will be rejected if 23 or fewer critical AEs are observed in 40 patients. This design yields a type I error rate of 2.5% one-sided and power of 80% when the true response rate is 67.5%.

All patients exposed to the study treatment (regardless of protocol adherence) will count be safety, and thus no need to sample size increases as per potential withdrawals are foreseen.

7.5 INTERIM ANALYSES

We plan to conduct 1 fixed pre-scheduled interim analyses for futility as per the Simon's design as described in section 7.4. The interim analysis will be conducted after follow-up data from the first 14 patients will be available after at least 30 days from study inclusion, or otherwise presenting an occurrence of the primary outcomes. The DSMB will consist of 3 members (2 hepatologists and 1 nurse) and an agreed charter by all members will come into operation before the initiation of the study recruitment. To note, this interim futility analysis will have no impact on the type I error at the end of the trial, and thus alpha adjustment is not needed.

The interim analyses will be performed by a statistician of the Medical Statistics core facility independent to the trial design, conduct of the trial and final analysis.

A previous Data Review will be performed before lock of database for the interim analysis. Data Review Meeting with the sponsor in order to carry out the valid population to the interim analysis (according with section 7.4 and 7.5 specifications).

The interim analysis report will be included the conclusions for the observed data according to the stopping roles in section 7.4 and complete list of adverse events characteristics by subject.

7.6 STATISTICAL INTERIM AND MULTIPLICITY ADJUSTMENT

The analysis will follow the principles specified in the ICHE9[1] and the CPMP/EWP/908/99[12] Points to Consider on Multiplicity issues in Clinical Trials guidelines.

The Simon's two-stage optimal design will be conducted in order to futility evaluation for this reason no multiplicity adjustments are needed. All statistical tests will be applied with 0.05 two-sided significant level.

7.7 FLOW CHART OF TRIAL PROCEDURES

Each cycle has 28 days.	Screening[1]	Cycles (+/- 72 hours) (Day 15 only for Cycle 1 and 2)		First radiologic progression	EOT (after last dose +7 days)	Follow-up[2]
		Day 1	Day 15			
Demographics	x					
General Informed Consent	x					
Inclusion/Exclusion criteria and Eligibility	x					
		Tumor and disease assessments				
Disease assessment by RECIST v1.1 Every 8 weeks from Day 1 Cycle 2 (+/- 7 days)	X					
Fresh tumor biopsy *(See section 7.4)*	x			x[3]		
		Study procedures and examinations				
Physical examination	x	x	x	x	X	
ECOG performance status	x	x	x	x	X	
12-lead ECG[4]	x				X	
Vital signs[5]	x	x	x	x	X	
Assessment of AEs/SAEs	x	x	x	x	X	
Concomitant medications	x	x	x	x	x	
Diet and gut microbiota	x					
		Laboratory tests				
Serum chemistry[6]	x	x	x	x	x	
Hematology[7]	x	x	x	x	x	
Coagulation (PT, INR, PTT)	x	x	x	x	x	
HBsAg and HBsAb, HBcAb and HCV Ab; HBeAg and HBeAb, HBV DNA and HDV RNA and HDV Ab(HBV+ subjects only); HCV RNA (HCV+ subjects only)	x				x	
Thyroid function tests (TSH, free T3, free T4)	x					
Urinalysis	x	x	x		x	
Urine or serum pregnancy test (WOCBP)	x					
		Other procedures[8]				
Other laboratory blood tests and assays[9]		X	X Only in C1	x		
Other liver tissue analysis[10]	x			x		
Patient-reported Quality of Life (EQ-5D, EORTC-QLQ C30, EORTC-HCC18 and FACT-Hep)[11]		x		x	x	
Other stool tests and assays[12] Day 1 Cycle 4 and in case of OR or PD		x			x	

EOT: End of Treatment; **OR**: Objective Response; **PD:** Progressive Disease

[1] The time period between study entry and the commencement of protocol treatment is not to exceed 28 days.

[2] Follow-up visits could be on-site or phone visits after the last visit and will include survival data and liver cirrhosis complications evaluation every 3 months. If the patient does not start any other treatment after end of treatment, radiologic follow-up with the same scheduled will be preferred. Laboratory tests will be performed at the discretion of the treating investigator until death or the end of the study.

[3] A biopsy will be performed at the time of progression whenever possible.
[4] Note: The ECG should be performed within the 7 days prior the randomization. If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.
[5] Including height (only at screening visit) weight, body temperature, respiratory rate, seated blood pressure, heart rate and oxygen saturation (at rest and after mild exercise)

[6]AST, ALT, GGT, Alkaline Phosphatase alkaline phosphatase, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Albumin, Creatinine, Alpha alpha fetoprotein, Calcium, Sodium, Potassium, Glucose, Uric Acid, triglycerides, Total Protein, Lipase, Amylase, Magnesium, Phosphate, lactic dehydrogenase LDH, Chloride, Glomerular filtration rate.

[7]Complete blood count with differential

[8] All the samples included in this section, will be centrally analyzed in a second-study

[9]Other laboratory blood tests will include peripheral Blood Mononuclear Cells (PBMCs) immunophenotyping, serum biomarker analysis, polymorphism detection associated with treatment response/resistance, circulating-free DNA analysis, circulating mRNA/miRNA. In case of any cabozantinib dose reduction a blood sample for PBMCs and serum biomarker analysis is recommended but no mandatory. Serum biomarker will be analyzed at each cabozantinib dose reduction. For details see the laboratory manual.

[10]Other liver tissue analysis will include tumor and non-tumor infiltrated immune cell population characterization (fresh tissue from biopsy analyzed in situ in each recruiting center) and tumor and non-tumor cell transcriptome analysis (samples can be frozen and stored until analysis). Note that these samples will be obtained accordingly to the time point of "fresh tumor biopsy" but all the analysis will be performed in a second-study.

[11] Patient-reported Quality of Life (EQ-5D, EORTC-QLQ C30, EORTC-HCC18 and FACT-Hep) will be administered at Day 1 of Cycle 1 and Cycle 3, then at Day 1 every 3 cycle and at end of treatment s.

[12]Other stool tests and assays will include gut microbiota composition and/or metabolomic analysis.

8 STATISTICAL ANALYSIS

8.1 ANALYSIS POPULATIONS

There are only one population for this study:

- Safety Set: All eligible patients who have received at least one dose of Cabozantinib will be included in the Safety population.

The population will be fully defined and documented during the Data Review and before the database lock. The objective will be to carry out the population selection and definition of the final study population.

The Safety population will be used for all analysis including the efficacy secondary endpoints.

8.2 FLOW CHART

A flow diagram will be performed according to ICHE3 and the consort statement in order to summarize the number of patients at study losses by time at each stage. Patients screened, eligible, consented, randomized, receiving their allocated treatment, withdrawing/lost to follow up, and included in the population set defined in the section 8.1.

8.3 ENDPOINTS DEFINITION

8.3.1 Primary outcomes

The primary outcomes are related to safety assessment as follow:

- Rate of adverse events (AE) with Common Terminology Criteria for Adverse Events (CTCAE)≥3 excluding palmar-plantar erythordysthesia, rate of AEs, rate of related-AEs and rate of death. Rate of AEs leading to treatment discontinuation.
- Adverse events will be graded following version 5.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose.

8.3.2 Secondary outcomes

ORR will be the first relevant ranked secondary outcome:

- Defined as a partial or complete response at any time, i.e. the best response from inclusion along all follow-up.

The rest of secondary end points are:

1. Time to progression (TTP): time to the first progression, defined as the time from the inclusion date to progression (i.e. date of progression event or censoring – date of inclusion + 1).
2. Pattern of progression:
   - Intrahepatic growth (IHG): increased size of intrahepatic target lesions or progression of intrahepatic "non-target" lesions at baseline.
   - New intrahepatic lesion (NIH): emergence of new intrahepatic lesions
   - Extrahepatic growth (EHG): increased size of extrahepatic target lesions, progression of extrahepatic "non-target" lesions at baseline or progression of the existing vascular invasion.
3. Rate of patients who develop new extra-hepatic spread

4. Overall survival (OS): defined as the time from the inclusion date to death from any cause (i.e. date of death event or censoring – date of inclusion + 1).
5. Post-progression survival (PPS), for those patients who progressed, the time from the progression date to death from any cause (i.e. date of death event or censoring – date of 1st progression + 1).

Please see description of the censoring rules for time to event variables in section 8.5.1.

8.4 VARIABLES

8.4.1 Demographic characteristics, screening and baseline

The following pre-treatment characteristics (only recruited pre-treatment) will be analysed:

- Informed consent
- Demographic data and vital signs
- Clinical characteristics at HCC diagnosis
- Clinical characteristics at study entry
- Comorbidities
- First line treatment
- Selection criteria

8.4.2 Safety variables and other evolution variables

The safety variables and other evolution variables (recruited at different times) will be the follow:

- Adverse Events evaluations for the primary outcomes:
  - Rate of AEs
  - Rate of SAEs
  - Rate of AEs (CTCAE)≥3 excluding palmar-plantar erythordysthesia
  - Rate of related-AEs
  - Rate of AEs leading to treatment discontinuation
  - Rate of death
- Variables related to the secondary outcomes:
  - Objective Response Rate (ORR)
  - Rate of patients who develop new extrahepatic spread
  - Overall survival (OS)
  - Time to progression (TTP)
  - Pattern of progression.
    - Intrahepatic growth (IHG).
    - New intrahepatic lesion (NIH)
    - Extrahepatic growth (EHG)
    - New extrahepatic lesion (NEH): emergence of new extrahepatic lesions or emergence of vascular invasion
  - Post-progression survival (PPS)
- BCLC staging system and CHILD-PUGH scale
- Tumor disease assessment
- Central test and stool test
- Tumor biopsy
- Physical examination
- General examinations: vital signs, ECOG and oxygen saturation

- Laboratory test:
  - Urinalysis
  - Hematology
  - Biochemistry and electrolyte
  - Thyroid function
  - Specific laboratory test
- EQ-5D
- FACT-Hep
- EORTC-QLQ-C30
- EORTC QLQ-HCC18
- Exitus information
- Survival status by follow-up
- Cabozantinib treatment information
- Visit control (conducted yes/no)
- Screen failure information
- End of treatment
- End of study
- Concomitant medication
- The rest of Adverse Events evaluations
- Protocol deviations

8.5 STUDY ESTIMAND, HANDLING OF MISSING DATA AND CENSORING RULES

The handling of missing data will follow the principles specified in the ICH-E9 and the CPMP/EWP/1776/99 Rev1[13]. Guideline on Missing Data in confirmatory trials Guidelines. As per the ICH E9(R1) (Addendum on estimands and sensitivity analysis in clinical trials EMA/CHMP/ICH/436221/2017)[14], the plan for the assessment of the Primary endpoint (PEP) (in this study includes the main secondary outcome) is described here after using the 4 attributes of the estimand:

1. Population: as described in protocol and section 8.1 of this SAP, all analyses will be carried out using Safety population.
2. Endpoints: (please see details on the endpoints definitions in section 8.3)
   a. Non confirmatory primary endpoints (PEPs): the rate and type of:
      - Any AEs
      - Related-AEs
      - Rate of death
      - AEs leading to treatment discontinuation
      - Serious AEs (SAEs)
      - Rate of AEs (CTCAE)≥3 excluding palmar-plantar erythordysthesia
   b. Secondary endpoints (SEP):
      - ORR (main secondary outcome)
      - Overall survival (OS)
      - Time to progression (TTP)

- Pattern of progression
- Post-progression survival (PPS)
- Rate of patients who develop new extra-hepatic spread

3. Intercurrent events (ICEs): the relevant intercurrent events expected to occur in this study includes the following situations and the method for handling will be the same for all of them due to the safety characteristics of the primary objective. The "Treatment Policy" strategy will be used, i.e., all observed data will be used regardless of the intercurrent event.
    a. No treatment initiation: exclusion from the analysis.
    b. Main estimand: any other situation regardless of the ICE (use of rescue medication, prohibited concomitant medication, treatment discontinuation, or any reason leading to study discontinuation): "Treatment Policy" strategy (i.e. all observed data will be considered regardless of any previous ICE).
    c. Supplementary estimand: for some relevant efficacy secondary endpoints, data after ICEs will be censored (see table below) and will be based on the while on treatment strategy.
4. Population-level summary:
    a. Estimation of rates and 95%CI for the PEPs by means of Clopper-Pearson exact method will be used as the population-level summary (see sections 8.6.5.1 and 8.6.5.2.1).
    b. Time to event variables will be described using the Kaplan-Meier method (see section 8.6.5.2.2).

	Primary Estimand	Supplementary Estimand
Primary endpoints		
Any AEs Related-AEs Rate of death AEs leading to treatment discontinuation Serious AEs (SAEs) Rate of AEs (CTCAE)≥3 excluding palmar-plantar erythordysthesia	Treatment policy	None
Secondary endpoints		
ORR (main secondary outcome)	Treatment policy	While on treatment*
Overall survival (OS)		
Time to progression (TTP)		
Pattern of progression	Treatment policy	None
Rate of patients who develop new extra-hepatic spread		
Post-progression survival (PPS)		

*(censored after treatment ICEs)

The ORR rate will be handled using the Treatment Policy strategy. In the unexpected case of missing due to no radiologic assessment was conducted, the composite strategy will be applied by imputing to ORR to failure.

No formal imputations will be performed for any other variable. For the categorical variables the analyses will be based on the Available Data Only (ADO) approach. With regards to the continuous variables, mixed models[15,16,17]are robust to the presence of missing at random (MAR) and conducts the analysis with all participants despite the presence of missingness. Of note, this method calculates the estimations based on the variance-covariance structure but without any formal imputations.

No formal imputation will be used for dates due to all post-inclusion dates are complete date.

8.5.1 Censoring rules

TTP:

- Death without progression will be censored at the time of the last adequate radiological tumor assessment.
- Progression documented between scheduled assessments: Event at date of adequate radiological tumor assessment
- If a patient has not progressed at the time of database cutoff, the TTP of this patient will be censored at the last adequate tumor assessment before the database cutoff.
- Documented progression or death after missing ≥2 consecutive post-baseline tumor assessments: date of last adequate tumor assessment before missed assessments or date of inclusion, whichever is later.
- Patient lost to follow-up (or withdrew consent from study participation) before documented progression: date of last adequate tumor assessment.
- Please see comment below on the "treatment policy" and "while on treatment" estimands

Overall survival (OS):

- If a patient is alive at the time of last contact before the database cutoff, the OS of this patient will be censored at the date of last contact.
- Patient lost to follow-up (or withdrew consent from study participation) before death: date of last documented alive information
- Please see comment below on the "treatment policy" and "while on treatment" estimands

Post-progression survival (PPS)

- Same rules as OS

Handling of "treatment policy" and "while on treatment" estimands: If a patient discontinues study treatment or any other ICE is recorded before any event is documented, data from this patient will not be censored for the primary estimand (treatment policy). However, data will be censored for the supplementary estimand (while on treatment) at the last tumor assessment before the discontinuation of study treatment.

8.6 STATISTICAL METHODS

Non-inferential analysis will be performed due to the safety nature of the study. The following sections refer to descriptive statistics for the different variables of section 8.4.
All analyses will be performed using Safety set.

8.6.1 General Descriptive Analysis

The results will be presented of standard methods[18]:

- Continuous variables: Mean, 95%CI of Mean (95% mean confidence interval), SD (standard deviation), minimum, P25 (percentile 25), Median, P75 (percentile 75), maximum and N.
- Categorical variables: total frequency and percentages and for each category.
- Ordinal variables with few categories (less than 10) will be described using two tables: one including continuous variables descriptive parameters (as long as the interpretation is reasonable) and the other including categorical variables descriptive parameters. For ordinal variables with >10 categories, the same approximation used for continuous variables will be applied.

Where applicable, these summaries will be provided by time-point (scheduled time-point) including the absolute differences from baseline. The data of unscheduled time-points will be only listed.
Additionally, only for the size of tumor the relative difference from baseline will be also described.

8.6.2 Specific Descriptive Analysis

For the binary variables related to the primary and secondary outcomes, the estimation of rates and 95% CI will be performed by means of Clopper-Pearson exact method.

The Kaplan-Meier method will be used to describe the time to event endpoints, the median and their 95% CI. Analysis will follow censoring rules as described in section 8.5.1.

The continuous efficacy variable recruited by time-point will be analysed as a descriptively by means of the MMRM approach, fitting time-point as a fixed effect, and the subject and error terms as random. The dependent variable will be the absolute values (or absolute change from baseline when applicable). The within-patient variance-covariance matrix will be assumed to be unstructured. If this analysis fails to converge, the following structures will be tested in the following order until convergence: AR(1) (Auto-Regressive first order), Toeplitz and CS (Compound Symmetry). Time-point effects have been estimated by means of Least Square Means (LSM) and their standard error (SE) and 95% CI. Time-course evolutions have been estimated by LSM and their SE and 95%CI. The same analysis with a previous rank transformation applies to ordinal variables.

8.6.3 Definitions and derivation of data

The following definitions and derivations will be used for this study:

- The analyses will be performed by visits and the baseline values for the calculation of the differences (absolute or relative) with respect to the baseline using the following strategy:
    - Baseline values will be defined as the last measurement taken before the first administration.

- The value of the baseline visit in case of measurement existing in that visit.
- The value of the screening visit if there is no measurement in the baseline visit.

- Start of the treatment period will be defined as the date of inclusion
- Absolute differences from baseline for each visit:
  - Absolute differences = observed value - baseline value
- Relative differences from baseline (only for the size or tumour):
  - Relative difference = [observed value-baseline value] / baseline value

8.6.4 Demographic characteristics, screening and baseline

Descriptive statistics and listings for each variable per visit (Screening Visit or Baseline Visit) will be performed.
This analysis will be performed using Safety set on ADO approach.
Results are presented by means of individual tables and listings for each of the variables described in section 8.6.1.
The comorbidities will be tabulated and listed by type of comorbidity. The number of patients with at least one comorbidity globally and by type of comorbidity will be described. The following type of comorbidities will be considered: myocardial infarction, deep venous thrombosis, pulmonary embolism, transient ischemic attack, ischemic stroke, cerebral hemorrhage, lower GI bleeding, diabetes mellitus type I, diabetes mellitus type II, hypertension, heart failure, phlebitis, gastrointestinal ulcer, angina pectoris, esophageal varices, upper GI bleeding and others (the description of others will be only listed).

8.6.5 Safety variables and other efficacy variables

8.6.5.1 Variables related to the primary outcomes

The binary variables related to primary outcomes (rate of AEs (CTCAE)≥3 excluding palmar-plantar erythordysthesia, rate of AEs, rate if related AEs, rate of SAEs, and rate of AEs leading to treatment discontinuation) will be described by means of rate and 95% CI calculated using the Clopper-Pearson exact method.

These analyses will be performed Safety set on ADO approach.

8.6.5.2 Variables related to the secondary outcomes

The analyses performed for the variables related to the secondary endpoints are described in the following sections.

8.6.5.2.1 Binary variables

The binary variables related to the secondary outcomes (see section 8.4.2 for more details) will be described by means of rate and 95% CI calculated using the Clopper-Pearson exact method.
These binary variables are the following:

- ORR defined as the best response.
- Rate of patients who develop new extrahepatic spread.
- Progression rate in general and by Pattern of progression (see section 8.3.2 for more details).

These analyses will be performed using Safety set on ADO approach. For the ORR (as a best response) the missing data will be imputed as a failure.

The timing of response will be plotted using a Swimmer plot.

8.6.5.2.2 Time to event endpoint

The Kaplan-Meier method will be used to describe the survival functions the median and their 95% CI for time to event variables. These analyses will follow censoring rules as described in section 8.5.1.

These variables are the follow:

- Overall survival
- Time to the first progression
- Post-progression survival (in general and split by pattern progression)

These analyses will be performed using Safety set on ADO approach.

8.6.5.3 Other variables

A descriptive analysis will be performed for all variables of section 8.4.2 with the appropriate descriptive statistics (see section 8.6.1).

The continuous variables (laboratory parameters, vital signs and other continuous variables included in section 8.4.2) recruited by time (absolute values and absolute differences when applicable) will be analyzed by means of MMRM model specified in section 8.6.2. The same model with previous rank transformation will be applied to ordinal variables.

These analyses will be performed using Safety set on ADO approach.

The following sections describe the specific statistical analysis.

8.6.5.3.1 Tumor size

The tumor size of target lesions (absolute values, absolute difference and relative differences) will be described by time-point.

Also the absolute values and absolute differences will be analysed by means of MMRM model specified in section 8.6.2.

The relative change in tumor size will be plotted by means of Spider plot and the best change in the tumor size using a waterfall plot.

8.6.5.3.2 Duration of response

Additionally, the duration of response will be described with the appropriate descriptive statistics (see section 8.6.1).

The timing of response will be plotted using a Swimmer plot.

8.6.5.3.3 EQ-5D

The items of EuroQoL-5D questionnaire (mobility, self care, usual activities, pain discomfort and anxiety depression) will be analysed according to the EQ-5D-3L user guide[19]. All item responses will be transformed in responses of three levels and two levels, as follows:

- Three levels: no problems, some problems and extreme problems
- Two levels: no problems and problems.

Descriptive statistical analyses by time-point will be performed for three levels response and for two levels response (as a continuous and as a categorical variable). Also, analyses by means of MMRM model with a previous rank transformation will be applied using three and two levels.

VAS EQ-5D will be analysed by the same MMRM.

8.6.5.3.4 FACT-Hep

Questionnaire FACT-Hep (version 4)[20] on clinical status included 45 items, 27 of which will be used for the determination of the following scale scores:

- Subscales:
  - Physical Well-Being subscale, PWB
  - Social/Family Well-Being subscale, SWB
  - Emotional Well-Being subscale, EWB
  - Functional Well-Being subscale, FWB
  - Hepatobilliary Cancer subscale, HCS
- FACT-G Total Score, FACTG
- FACT-Hep Trial Outcome Index (TOI)
- FACT-Hep total score

The individual items will be described as a continuous and as a categorical variable (see section 8.6.1) by time-point.
The subscales and the different total scores will be also described as a continuous variable and the MMRM will be applied.

8.6.5.3.5 EORTC-QLQ-C30

Questionnaire EORTC-QLQ-C30 (version 3)[21] included 30 items and all of them will be used for the determination of the following scale scores:

- Global health status/QoL, QL2
- Functional scales:
  - Physical functioning, PF2
  - Role functioning, RF2
  - Emotional Functioning, EF
  - Cognitive functioning, CF
  - Social functioning, SF
- Symptom scales
  - Fatigue, FA
  - Nausea and vomiting, NV
  - Pain, PA
  - Dyspnoea, DY
  - Insomnia, SL
  - Appetite loss, AP
  - Constipation, CO
  - Diarrhoea, DI
  - Financial difficulties, FI

The individual items will be described as a continuous and as a categorical variable (see section 8.6.1) by time-point.
The scales scores will be also described as a continuous variable and the MMRM will be applied.

8.6.5.3.6 EORTC QLQ-HCC18

Questionnaire EORTC-QLQ-HCC18[22] is a supplementary questionnaire module to be employed in conjunction of QLQ-C30 (is a Hepatocellular Carcinoma Module), included 18 items and all of them will be used for the determination of the following scale scores:

- Symptom scales

  - Fatigue, FATI
  - Body image BI
  - Jaundice, JAUN
  - Nutrition, NUTR
  - Pain, PA
  - Fever, FEV
- Single items
  - Abdominal swelling, AB
  - Sex life, SX

The individual items will be described as a continuous and as a categorical variable (see section 8.6.1) by time-point.
The scale scores will be also described as a continuous variable and the MMRM will be applied.

8.6.5.3.7 Adverse events

A summary of treatment-emergent adverse events (AEs), including the number of events reported, the number and percentage of patients reporting at least one event of each of the following:

- Any AE
- Any severe AE (grade greater or equal to 3 in the NCI CTCAE v5.0)
- Any AEs (CTCAE)≥3 excluding palmar-plantar erythordysthesia
- Any treatment-related AE (with cabozantinib)
- Any severe treatment-related AE
- Any AE with outcome of death
- Any serious AE
- Any treatment-related serious AE
- Any AE leading to discontinuation of the treatment permanently (cabozantinib)
- Any treatment-related AE leading to discontinuation of the treatment permanently (regorafenib, nivolumab or both)

The number and percentage of patients who experience one or more treatment-emergent AEs as well as the number of AE episodes will be tabulated by body system, preferred term (according to MedDRA v21.1), seriousness, intensity, action taken, outcome, relationship to the study drug and NCI CTCAE v5.0.

8.6.5.3.8 Concomitant medication

The concomitant medication after randomization will be described by time-point and study product. Concomitant medication and its characteristics will be listed. The number of patients with at least concomitant medication globally and by ATC code (according to ATC classification index with the last version of WHO-DD at the end of last patient follow-up) will be described.

8.7 POST-HOC STATISTICAL ANALYSIS

No subgroup analyses are planned in the protocol.

Due to clinical relevance in this study of the first-line treatment a subgroup analysis is required by sponsor for the following groups:

- Sorafenib as first-line treatment
- Other than sorafenib as first-line treatment

The analyses related to the non confirmatory primary endpoints (PEPs) and secondary endpoints will be also performed by subgroup.

9 TABLES

For the table of safety variable and other efficacy variables (where applicable according to section 8.7) the results will be present fall all subjects and by subgroup classification (within the same table).

9.1 Demographic characteristics, screening and baseline.

Table 1. Study population.
Table 2. Informed consent.
Table 3. Demographic data and vital signs.
Table 4. Clinical characteristics at HCC diagnosis.
Table 5. Clinical characteristics at study entry.
Table 6. Comorbidities. Number (%) of subjects reporting one or more Comorbidity (globally and by type of comorbidity).
Table 7. First line treatment.
Table 8. Selection criteria.

9.2 Safety variables and other efficacy variables.

Table 9. **Primary outcomes**. Rate of AEs, SAEs, related-AEs, AEs leading to discontinuation, deaths and AEs (CTCAE)≥3 excluding palmar-plantar erythordysthesia.
Table 10. **Secondary outcomes**. ORR and time to ORR.
Table 11. **Secondary outcomes**. Overall survival.
Table 12. **Secondary outcomes**. Time to progression (TTP)
Table 13. **Secondary outcomes**. Pattern of progression.
Table 14. **Secondary outcomes**. Post-progression survival.
Table 15. **Secondary outcomes**. Rate of patient who develop new extrahepatic spread.
Table 16. **Duration of response**.
Table 17. BCLC staging system and CHILD-PUGH scale.
Table 18. Tumor disease assessment (including tumor size).
Table 19. Central test and stool test. Samples Yes/No.
Table 20. Tumor biopsy.
Table 21. Physical examination.
Table 22. General examinations: vital signs, ECOG and oxygen saturation.
Table 23. Laboratory test. Urinalysis.
Table 24. Laboratory test. Hematology.
Table 25. Laboratory test. Biochemistry and alectrolyte.
Table 26. Laboratory test. Thyroid functions.
Table 27. Laboratory test. Specific laboratory test.
Table 28. EQ-5D. Individual items.
Table 29. EQ-5D. Three level items.
Table 30. EQ-5D. Two level items.
Table 31. EQ-5D. EQ VAS.
Table 32. FACT-Hep. Directly items.
Table 33. FACT-Hep. Subscales.
Table 34. FACT-Hep. Total scores.
Table 35. EORTC-QLQ-C30. Directly items.

10 LISTINGS

11 FIGURES

12 REFERENCES

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