Non-interventional study information

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non-PASS
EU PAS register number	To be added at time of registration
Active substance	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Medicinal product	Nexavar®
Product reference	BAY43-9006
Procedure number	Not applicable
Marketing authorization holder(s)	Bayer Healthcare AG
Joint PASS	No
Research question and objectives	This study will collect data of patients who are treated with TACE followed by sorafenib for hepatocellular carcinoma (HCC) or without sorafenib after TACE. In contrast to a prior observational study on sorafenib (GIDEON study, Marrero et al., ASCO 2011), where pre-treatment with TACE was documented retrospectively, this study will collect more detailed information concerning TACE treatments in a prospective manner. This will enable us to evaluate the time to meet criteria for TACE non-eligibility. Outcome of patients will be analyzed in relation to the timing of initiation of sorafenib. It is planned to compare outcome of patients with early start of Sorafenib treatment to those without early start of sorafenib treatment after TACE. In addition, practice patterns of the physicians

	involved in the care of patients with HCC under real-life conditions will be evaluated. The primary objective of this study is the comparison of two cohorts of hepatocellular carcinoma patients regarding overall survival (OS) from time of TACE non-eligibility. The two cohorts of special interest are defined based on the investigators' treatment decisions (i.e. patients with early start of Sorafenib treatment vs. patients without early start of Sorafenib treatment). Secondary objectives are: • To evaluate progression-free survival (PFS), time to progression (TTP), tumor response and AE from time of TACE non-eligibility overall and in the cohorts of special interest • To evaluate overall survival (OS), progression-free survival (PFS), time to progression (TTP), tumor response and AE from start of sorafenib treatment. • To determine duration of treatment (DOT) of sorafenib after TACE with respect to the start of sorafenib treatment (early vs. not early). • To determine time to meet TACE non-eligibility criteria from initial TACE according to the guidelines • To determine the proportions of patients who receive sorafenib after TACE and those who do not receive sorafenib after TACE, respectively, regionally and globally • To evaluate response to TACE by number of TACEs • To evaluate deterioration of liver dysfunction in the course of TACE treatment and thereafter. • To evaluate OS from initial TACE for all patients in the study irrespective of their treatment after TACE • To evaluate deviations from recommendations for TACE use in the treatment guidelines for TACE use, regionally and globally • In addition, practice patterns of the physicians involved in the care of patients with HCC under real-life conditions will be evaluated.
Country(-ies) of study	About 30 countries in the region Europe/Canada, Asia

	Pacific and Latin America.
Author	Keiko Nakajima, Bayer HealthCare Pharmaceuticals, Montville, New Jersey, USA

Marketing authorization holder

Marketing authorization holder(s)	Bayer Healthcare AG, Leverkusen, Germany
MAH contact person	Keiko Nakajima, Bayer HealthCare Pharmaceuticals, Montville, New Jersey, USA

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse Event
ADR	Adverse Drug Reaction
AFP	Alpha fetoprotein
APASL	Asian Pacific Association for the Study of the Liver
ATC	Anatomical Therapeutic Chemical
BCLC	Barcelona clinic liver cancer staging
BHC	Bayer HealthCare
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CLIP	Cancer of the Liver Italian Program
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTHA	CT hepatic arteriography
CTAP	CT arterial portography
DC Bead®	Embolic Drug-Eluting Bead
DMP	Data Management Plan
DOT	Duration of Treatment
EASL	European Association for the Study of the Liver
EC	European Commission
ECOG	Eastern Co-operative Oncology Group
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration

FPFV	First Patient First Visit
GCP	Good Clinical Practice
GCL	Global Clinical Leader
GPM	Global Project Manager
GPP	Good Publication Practice
GPV	Global Pharmacovigilance
GSL	Global Safety Lead
GVP	Good Pharmacovigilance Practice
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HEOR	Health Economics and Outcomes Research
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
IT	Information Technology
JSH	The Japanese Society of Hepatology
KM	Kaplan-Meier
LD	Longest Diameter
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
LPM	Local Project Manager
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NIS	Non-Interventional Study
OS	Overall Survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PD	Progressive Disease

PFS	Progression-Free Survival
PR	Partial Response
PS	Performance Status
PSUR	Periodic Safety Update Report
PVCH	Pharmacovigilance Country Head
QPPV	Qualified Person responsible for PharmacoVigilance
QRP	Quality Review Plan
RECIST	Response Evaluation Criteria in Solid Tumor
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SPC	Summary of Product Characteristics
Study team	It consists of representatives from Bayer and CRO
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TAE	Transarterial embolization
TACE	Transarterial chemoembolization
TEAE	Treatment-Emergent Adverse Event
TNM	TNM classification used to describe the stage of cancer: the status of the Tumor, Nodes (lymph nodes) and Metastases are described
TTP	Time to Progression
US	Ultrasoundgraph
WHO DD	World Health Organization – Drug Dictionary

3. Responsible parties

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Information including contact details on investigators and other site personnel for each country in which the study is performed as well as for the Steering Committee Members is available upon request and listed in Annex 1.

4. Abstract

Title	OPTIMIS - Outcomes of HCC patients treated with TACE followed or not followed by sorafenib and the influence of timing to initiate sorafenib
Protocol version identifier	Final version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non-PASS
Author	Keiko Nakajima, Bayer HealthCare Pharmaceuticals, Montville, New Jersey, USA
Rationale and background	This study will collect data of patients who are treated with TACE followed by sorafenib for hepatocellular carcinoma (HCC) or patients without Sorafenib after TACE. In contrast to a prior observational study on sorafenib (GIDEON study, Marrero et al., ASCO 2011), where pre-treatment with TACE was documented retrospectively, this study will collect more detailed information concerning TACE treatments in a prospective manner. This will enable us to evaluate the time to meet criteria for TACE non-eligibility and outcomes of patients depending on the timing when they initiate sorafenib.
Research question and objectives	The primary objective of this study is the comparison of two cohorts of hepatocellular carcinoma patients regarding overall survival (OS) from time of TACE non-eligibility. The two cohorts of special interest are defined based on the investigators' treatment decisions (i.e. patients with early start of Sorafenib treatment vs. patients without early start of Sorafenib treatment). Secondary objectives are: • To evaluate progression-free survival (PFS), time to progression (TTP), tumor response and AE from time of TACE non-eligibility overall and in the cohorts of special interest • To evaluate overall survival (OS), progression-free survival (PFS), time to progression (TTP), tumor response and AE from start of sorafenib treatment. • To determine duration of treatment (DOT) of sorafenib

	after TACE with respect to the start of sorafenib treatment (early vs. not early). • To determine time to meet TACE non-eligibility criteria from initial TACE according to the guidelines • To determine the proportions of patients who receive sorafenib after TACE and those who do not receive sorafenib after TACE, respectively, regionally and globally • To evaluate response to TACE by number of TACEs • To evaluate deterioration of liver dysfunction in the course of TACE treatment and thereafter. • To evaluate OS from initial TACE for all patients in the study irrespective of their treatment after TACE • To evaluate deviations from recommendations for TACE use in the treatment guidelines for TACE use, regionally and globally • In addition, practice patterns of the physicians involved in the care of patients with HCC under real-life conditions will be evaluated.
Study design	Company-sponsored international, prospective, open-label, multi-center, non-interventional, post-authorization safety study.
Population	Female and male patients with a diagnosis of hepatocellular carcinoma (HCC) will be enrolled in the participating study countries and sites during the enrollment period. All treatment decisions prior inclusion of a patient as well as during the observation must be made by the investigator based on his regular medical practice. Patients must give written informed consent prior to documentation. During the course of the study, patients will be assigned to one of the following cohorts of special interest: 1. Patients with early start of sorafenib treatment 2. Patients without early start of sorafenib treatment A detailed definition of these cohorts can be found in the section 9.7.4. of the protocol.
Variables	Eligibility for the study, visit dates, demography, diagnosis, medical history/comorbidities, prior medication/treatment, exposure/treatment, concomitant medication/treatment, tumor assessment, response assessment to treatment, performance

	status, reason for ending the observation, adverse events (AE)
Data sources	Medical records, routine measurements (e.g. tumor assessment), patients, other physicians
Study size	In order to achieve 1,500 completely documented patients, approximately 1670 patients will be enrolled assuming a 10% loss to follow-up rate.
Data analysis	STATISTICAL CONSIDERATIONS: In general, statistical analyses will be of explorative and descriptive nature. Analyses will be performed for the total study population (overall analysis) and separately for the two patient cohorts of special interest, as appropriate. The primary efficacy endpoint is Overall Survival (OS). It is defined in this study as the time period from documented TACE non-eligibility to death due to any cause. For the two cohorts of special interest, Kaplan-Meier (KM) estimates for OS will be displayed. Furthermore, these two cohorts will be compared regarding overall survival using a Cox proportional hazards model. In order to cope with confounding typically present in non-randomized studies a stratified propensity score approach will be applied. The propensity score model will be determined in an outcome-blinded manner including variables potentially affecting the treatment decision at time of TACE non-eligibility as well as known confounders. Based on the resulting propensity scores, equally sized strata will be determined and within each stratum the stratum-specific hazard ratio will be estimated. Subsequently, an overall hazard ratio estimate as well as the corresponding 95% confidence interval will be determined based on the stratum-specific estimates. Where applicable, the same propensity score approach will be applied in order to compare the two cohorts regarding secondary endpoints. It is planned to have 1 interim analysis after 500 patients observed for at least 6 months. This analysis will not include the formal comparison of the two cohorts of special interest. The final analysis will be performed after end of the study, which is the date after which the last enrolled subject will have been in the study for 18 months, or is lost to follow-up or has died.
Milestones	First patient first visit: Q3 2013 Last patient first visit: Q1 2015

	Last patient last visit:	Q3 2016
	End of data collection (clean database)	Q4 2016
	Final report of study results:	Q2 2017

5. Amendments and updates

None

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol.

Table 1: Milestones

Milestone	**Planned date**
Start of data collection	Q3 2013
Last patient first visit	Q1 2015
Interim analysis	500 patients observed for at least 6 months
Last patient last visit	Q3 2016
End of data collection (clean database)	Q4 2016
Final report of study results	Q2 2017

7. Rationale and background

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the fifth most common cancer in the world, the third most common cause of cancer-related death(1), and the leading cause of death in patients with cirrhosis (2-4). Over the next two decades, an increasing number of patients with HCC are expected (5). HCC develops commonly but not exclusively in a setting of chronic liver injury, which leads to inflammation, hepatocyte regeneration, liver matrix remodeling, fibrosis, and ultimately cirrhosis, which is the most important risk factor in the development of HCC regardless of cause (8). Thus, 80% of HCC develops in patients with liver cirrhosis and this preneoplastic condition is the strongest predisposing factor (2, 9). Major etiologies of liver cirrhosis include chronic hepatitis B and C, alcohol consumption, steatosis, diabetes, certain medications or exposures to toxic agents and genetic and metabolic diseases (6, 7). In HCC patients, prediction of prognosis is complex due to heterogenic condition because of underlying liver dysfunction (10). Guidelines recommend that HCC staging systems should consider tumor stage, liver function and health status (11). Currently, however, there is no worldwide consensus on the use of any one staging system in HCC (12). BCLC staging system is one of the commonly applied staging systems. BCLC system links staging with treatment modalities and estimates life expectancy based on published response rates to various treatments (13, 14).

Transarterial chemoembolization (TACE) is currently the recommended treatment option for patients with intermediate HCC (BCLC B) with multinodular tumors without vascular invasion or extrahepatic spread (15). The efficacy of TACE was established in two positive trials in selected populations (16, 17) and one meta-analysis (18). However, as intermediate stage HCC comprises a heterogeneous

group of patients who vary considerably in terms of disease extent and liver function, TACE may not address the needs of all the patients (19, 20). TACE refractory/failure is acknowledged in some treatment guidelines, including those of AASLD the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APASL) and the Japan Society of Hepatology (JSH) (12, 21, 22). The guideline of the European Organization of Research and Treatment of Cancer (EORTC) also recommends that patients for whom the standard of care is not applicable are offered the next most suitable treatment option within the same stage (15). Some data suggest that BCLC B patients can be identified for whom TACE is contraindicated, or who, despite receiving at least one session of TACE, may not benefit from further TACE treatments (19, 20, 21). For example, a patient with HCC who does not respond to at least two cycles of TACE, or who has disease recurrence after TACE, may be considered candidates for treatment with sorafenib (12, 18).

Sorafenib is a multikinase inhibitor with reported activity against Raf-1, B-Raf, VEGFR2, PDGFR, c-Kit receptors, among others receptor tyrosine kinases and serine threonine kinases (23, 24). Sorafenib is the only approved systemic treatment in advanced HCC globally as of 2012. Sorafenib prolonged overall survival (OS) of patients with advanced HCC, with acceptable safety profile, as shown in two randomized, placebo-controlled, double-blinded Phase III studies (25, 26). For patients who have failed TACE, a subanalysis in SHARP also indicated a trend of survival benefit. A non-interventional study in patients treated with sorafenib, Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) indicated multiple TACE treatments prior to sorafenib therapy in a substantial number of patients prior to sorafenib. In this study, shorter duration of treatment (DOT) of sorafenib in the real practice than the treatment duration of sorafenib in SHARP also has been observed (27, 28).

This study is an international, prospective, open-label, multi-center, non-interventional study to evaluate outcomes of all patients who are treated with TACE followed by sorafenib and patients who did not receive sorafenib after TACE. In contrast to the GIDEON study, where pre-treatment with TACE was documented retrospectively, this study will collect more detailed information concerning TACE treatments in a prospective manner. This will enable us to evaluate the time to meet non-eligibility criteria according to this protocol (see 9.1.1.).

8. Research questions and objectives

8.1. Primary objective(s)

The primary objective is to evaluate TACE treatment and outcomes (overall survival (OS) from time of TACE non-eligibility) of hepatocellular carcinoma patients with early start of Sorafenib treatment and those without early start of sorafenib treatment after TACE.

8.2. Secondary objective(s)

Secondary objectives are:

- To evaluate progression-free survival (PFS), time to progression (TTP), tumor response and AE from time of TACE non-eligibility overall and in the cohorts of special interest
- To evaluate overall survival (OS), progression-free survival (PFS), time to progression (TTP), tumor response and AE from start of sorafenib treatment.
- To determine duration of treatment (DOT) of sorafenib after TACE with respect to the start of sorafenib treatment (early vs. not early).
- To determine time to meet TACE non-eligibility criteria from initial TACE according to the guidelines
- To determine the proportions of patients who receive sorafenib after TACE and those who do not receive sorafenib after TACE, respectively, regionally and globally
- To evaluate response to TACE by number of TACEs
- To evaluate deterioration of liver dysfunction in the course of TACE treatment and thereafter.
- To evaluate OS from initial TACE for all patients in the study irrespective of their treatment after TACE
- To evaluate deviations from recommendations for TACE use in the treatment guidelines for TACE use, regionally and globally
- In addition, practice patterns of the physicians involved in the care of patients with HCC under real-life conditions will be evaluated.

9. Research methods

9.1. Study design

This study is an international, prospective, open-label, multi-center, non-interventional study.

A prospective, non-interventional design was chosen, because the collection of data on real-life treatment can help to get a clearer picture of the clinical practice in HCC and on the influence this might have on patients' overall survival. Currently there is no homogeneous approach in the treatment of patients with HCC. In most countries TACE is a preferred treatment, but the range of patients it is used for, is wide. Though, in most countries it is one of the first therapeutic options for unresectable HCC, the number of TACEs as well as subsequent therapies are very flexible.

9.1.1. Primary endpoint(s)

The primary endpoint is overall survival (OS) from time of TACE non-eligibility.

OS is defined as the time interval from TACE non-eligibility to death due to any cause. Patients alive at the end of study will be censored at the last date known to be alive.

A patient is classified non-eligible for TACE, if at least one of the criteria in 9.3.8 is met.

Time of TACE non-eligibility is the first point in time in the study when TACE non-eligibility is met according to the documentation in the CRF. In case of a pre-existing TACE non-eligibility, time of TACE non-eligibility will be defined as the time of enrollment.

9.1.2. Secondary endpoint(s)

The secondary endpoints for all patients and the two cohorts of special interest are:

- Overall Survival (OS) from initial TACE is defined as the time interval from the day of the first TACE to death due to any cause. Patients alive at the end of the study will be censored at the last date known to be alive.
- Progression-free survival (PFS) from initial TACE is defined as the time interval measured from the day of the first TACE to documented (radiological or clinical) progression or death, whichever comes first.
- Time to progression (TTP) from initial TACE is defined as the time interval from the day of first TACE to the date of documented progression. Patients without tumor progression at the end of the study will be censored at their last date of tumor evaluation.
- Tumor response to TACE by mRECIST will be evaluated according to the categories "Complete Response", "Partial Response", "Stable Disease", and "Not evaluable" by mRECIST for each TACE.
- Duration of TACE treatment is defined as the time interval from of the day of first TACE to the date of permanent discontinuation of TACE (when an investigator decides TACE is no longer applicable regardless of the reason for discontinuation including death).
- TACE unsuitability will be determined according to the selected guidelines including AASLD, APASL, JSH, EASL-EORTC guidelines …etc.
- Time to TACE non-eligibility will be determined according to the selected guidelines including AASLD, APASL, JSH, EASL-EORTC guidelines …etc.
- Deteriorations of liver dysfunction will be evaluated throughout the study. Deteriorations of liver dysfunction are defined as below
    - Deterioration of Child-Pugh score (A5, A6, B7, B8, B9)
    - Liver dysfunction reported as AE or deterioration of AST, ALT or Bilirubin (from Grade1 to Grade 2-5, from Grade 2 to 3-5, Grade 3 to Grade 4 or 5.)
    - Any liver related adverse events or deterioration of liver related events according to CTCAE Version 4.03
    - Change of liver related lab data (AST, ALT, Bilirubin, Alb, INR)

Specific secondary endpoints for patients treated with sorafenib are:

- Overall survival (OS) from initiation of sorafenib is defined as the time interval measured from start date of sorafenib treatment to death due to any cause. Patients alive at the end of study will be censored at the last date known to be alive.
- Progression-free survival (PFS) from initiation of sorafenib is defined as the time interval measured from the start date of sorafenib treatment to documented (radiological or clinical) progression or death, whichever comes first.
- Time to progression (TTP) from initiation of sorafenib is defined as the time interval from start date of sorafenib treatment to the date of documented progression. Patients without tumor progression at the end of the study will be censored at their last date of tumor evaluation.
- Duration of sorafenib treatment is defined as the time interval from start date of sorafenib treatment to the date of permanent discontinuation of sorafenib treatment (regardless of the reason for discontinuation including death).
- The tumor status at different visits response according to mRECIST will be evaluated according to the categories “Complete Response”, “Partial Response”, “Stable Disease”, “Clinical Progression”, “Radiological Progression”, and “Not evaluable at this visit”. The best overall response will be analyzed providing absolute and relative frequencies of the tumor status categories.
- Incidence of Treatment-emergent Adverse Events (TEAEs) – patients will be monitored for TEAEs using the NCI-CTCAE Version 4.03. Details on the collection, management and reporting of TEAEs can be found in section 11.

9.1.3. Strengths of study design

The strength of the non-interventional study design is that is allows to observe diverse populations in a broad range of settings (natural environment) reflecting reality. All decisions in terms of diagnostic procedures, treatments, management of the disease and resource utilization are fully dependent on mutual agreement between the patient and the attending physician, without interference by a sponsor or study protocol.

9.2. Setting

9.2.1. Eligibility

Patients enrolled in this study have a diagnosis of unresectable HCC in whom a decision to treat with TACE has been made at time of study enrollment.

9.2.2. Inclusion criterion/criteria

- Patients with histologically/cytologically documented or radiographically diagnosed HCC. Radiographic diagnosis needs typical findings of HCC by radiographic method i.e. on multi-dimensional dynamic CT, CT hepatic arteriography (CTHA)/CT arterial portography (CTAP) or MRI.
- Patients in whom a decision to treat with TACE has been made at time of study enrollment. Patients that have received one TACE in the past also can be enrolled, if the TACE was done at the same site and all required data about such previous TACEs are available. TACE includes both conventional TACE with lipidiol (or similar agents) and chemotherapeutic agent(s) and TACE with DC Beads® excluding TAE without chemotherapeutic agent.

- Patients with unresectable HCC (incurable with curative treatments including resection or ablation or not eligible for resection or local ablation)
- Patients must have signed an informed consent form
- Patients must have a life expectancy of at least 8 weeks

9.2.3. Exclusion criterion/criteria

- Patients who have received TACE in the past but the data about TACE required in this protocol are not available
- Patients who are treated according to a trial protocol for intervention including a locoregional therapy or systemic therapy
- Hospice patients

All contra-indications according to the local marketing authorization should be considered.

9.2.4. Representativeness

No further selection than outlined in Section 9.2.1-9.2.3 should be made and patients should be enrolled consecutively in order to avoid any selection bias and thus to increase the likelihood of representativeness.

9.2.5. Visits

The start of the study is the date from which information on the first study subject can be first recorded in the study dataset. The end of the study is date after which the last enrolled subject will have been in the study for 18 months, or is lost to follow-up or has died.

The investigator documents an initial, follow-up visits and a final visit for each patient in the case report form (CRF). After the initial visit at least one follow-up visit should be documented. A certain number or frequency of visits is not requested by this protocol. Documentation follows the actual clinical practice. A visit is defined as any status assessment or new treatment decision the treating physician takes with the presence of the patient. The time interval between two documented status assessments is assumed to be 6 - 12 weeks, although this will be at the treating physician's discretion.

The final data collection (last visit) is at patient's death or at end of study (whatever is earlier). If the documentation is stopped prematurely, the reasons for the end of observation have to be given. If a patient will join an interventional clinical study during the course of observation, at least the information on survival will still be collected up to the end of this study.

The observation period for each patient is estimated to be about 18 months and covers the period from first TACE to death. If a patient will still be alive at time of study closure, this will be documented in the final visit.

The CRF is available upon request. The respective document is listed in Annex 1.

9.3. Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during initial visit and follow-up visits.

Table 2: Tabulated overview on variables collected during the study

	Study Entry/ Initial visit	Follow-up visit	Last visit / End of observation
patient information and consent	**X**		
specialty of the investigator and previous physician(s)	**X**		
demographic data	**X**		
Current alcohol consumption	**X**		
etiology of underlying disease/findings	**X**		
past medical history and concomitant diseases	**X**		
date of initial HCC diagnosis	**X**		
Disease status at initial diagnosis (BCLC stage, TNM classification, CLIP score)	**X**		
previous treatments for HCC	**X**		
height	**X**		
smoking	**X**		
alcohol use	**X**		
visit date	**X**	**X**	**X**
blood pressure	**X**	**X**	
body weight	**X**	**X**	
Disease status (BCLC stage, TNM classification, CLIP score)	**X**	**X**	
Child-Pugh score	**X**	**X**	
performance status (ECOG)	**X**	**X**	
Tumor assessment *	**X**	**X**	
response evaluation compared to initial TACE		**X**	
response evaluation compared to most recent TACE		**X**	
response evaluation compared to initiation of sorafenib		**X**	
laboratory data	**X**	**X**	
Decision on further treatment**		**X**	
Details on TACE treatment (date, embolization agent, drug name)		**X**	
Details on sorafenib therapy (dates, daily dose, interruptions)		**X**	
Details on other systemic therapy for HCC		**X**	
Disease status summary**	**X**	**X**	
AE		**X**	**X**
concomitant medication (including non-systemic therapy for HCC)	**X**	**X**	**X**
Reasons for end of observation			**X**
physician's signature			**X (one signature at the end of documentation)**

* The time interval between two documented tumor assessments is assumed to be 6 - 12 weeks, although this will be at the treating physician's discretion

** Must be documented at each follow-up visit

9.3.1. Primary outcome variable(s)

- Date of death
- Time of TACE non-eligibility
- Time of decision to treat with Sorafenib

9.3.2. Secondary outcome variable(s)

- Documented disease progression
- Response assessment to treatment
- Start and stop date of sorafenib treatment
- Assessments for liver function
- Documented Adverse Event

9.3.3. Demographic data and other baseline characteristics

The following data will be recorded:

- birthdate (at least year)
- race (asian, caucasian, black, other). Note: race will not be recorded in countries where legally not permitted.
- weight (kg)
- height (cm)
- alcohol use
- status of cigarettes smoking
- medical history of HCC
- history of liver disease
- general medical history

9.3.4. Laboratory data

- INR
- Total bilirubin
- ALT
- AST
- Alkaline phosphatase
- Creatinine
- Creatinine clearance
- Albumin
- Sodium
- LDH
- Alpha fetoprotein

9.3.5. Pretreatment of HCC

For patients that are not newly diagnosed, any systemic or non-systemic pretreatments will be documented.

9.3.6. Concomitant medication

Information on concomitant medication (as defined in Section 6.2) to be collected includes:

- Trade name or INN
- Start date (at least year)
- Stop date or "continued"
- Daily dose, if applicable
- Indication: "treatment of HCC", "treatment of concomitant disease", "treatment of AE"

9.3.7. Visit date(s)

Information on visit date(s) at initial visit and each documented follow-up visit includes:

- Date (day, month, year)

9.3.8. Disease status summary

The following criteria will be assessed at initial visit and every follow-up visit:

- lack of portal blood flow (because of portal vein thrombosis, portosystemic anastomoses or hepatofugal flow)
- Patients with lobar or segmental portal vein thrombosis.
- Patients with advanced liver disease (Child–Pugh class B or C)
- Clinical symptoms of end-stage cancer
- Extrahepatic spread (N1, M1)
- ECOG PS >=1
- BCLC C or D
- Vascular invasion.
- More than two consecutive incomplete necrosis (depositions (50%) of lipiodol) are seen by response evaluation CT within the treated tumors at the 4 weeks after adequately performed TACE.
- More than two consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT at the 4 weeks after adequately performed TACE
- TACE failure by investigator's assessment
- Jaundice
- Clinical encephalopathy
- Refractory ascites
- Hepatorenal syndrome
- Extensive tumor with massive replacement of both entire lobes
- Technical contraindications to hepatic intra-arterial treatment
- Renal insufficiency (creatinine ≥2 mg/dL or CrCl <30 mL/min
- Other (to be specified)

9.3.9. Tumor assessment

Patients will be assessed for response to TACE and tumor assessment by mRECIST.

TACE response to most recent TACE will be assessed within 12 weeks after TACE and recorded for each TACE.

Response evaluation will also be done compared to initial TACE. For patients treated with sorafenib, response evaluation compared to initiation of sorafenib will be added.

Tumor assessment will be made at physicians' discretion using CT scan or MRI or equivalent imaging exam, starting from initial TACE.

9.3.10. Exposure/treatment

Information on TACE to be documented:

- Date of administration
- Embolization agent
- Drug name

Information on sorafenib to be documented:

- Start date of treatment
- Prescribed dose
- Frequency of daily intake
- Date and details on dose adaptions
- Dates and details on treatment interruptions
- Date of permanent stop of treatment
- Reason(s) for interruptions or stop of treatment

Information on other systemic treatments to be documented:

- Start date of treatment
- Drug name or tick for "investigational drug"
- Stop date of treatment

9.3.11. Reasons for choice of treatment

The treating physician will decide on the treatment of the patient based on his medical assessments in close relation to the patient's physical and psychological status. All treatment decisions will follow the real-life treatment behavior of the physician. As there can be expected a wide range of factors influencing treatment decisions over the entire observation period, this will not be captured on the CRF in detail. In any case reasons for stop of sorafenib will be documented.

9.4. Data sources

The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data, results of tumor assessments and other disease status information, also documented in the medical record, during visits that take place in routine practice. For any adverse events that occur, information is directly obtained from the patient. In case a patient is seen by more than one physician for his/her disease (e.g. the patient is monitored by a physician other than the initial investigator), the initial investigator should make every effort to collect information on any visits (including results) that have taken place outside the investigator's site due to the patient's disease, for example by interviewing the respective physician or patient or by obtaining an accompanying letter with detailed information and results.

9.5. Study size

The primary objective of the study is the comparison of two cohorts (i.e. cohort 1: patients with early start of Sorafenib treatment vs. cohort 2: patients without early start of Sorafenib treatment) regarding overall survival as defined in Section 9.7.4. The enrollment period is planned to be 18 months with a minimum follow-up period of 18 months resulting in total study duration of 36 months. In order achieve approximately 1,500 patients who have a complete documentation, it is envisaged to enroll 1,670 patients accounting for an expected loss to follow up rate of approximately 10%.

It is expected that out of the 1,500 completely documented patients at least 250 will become part of cohort 1 (patients with early start of Sorafenib treatment) while at least the same number of patients

will become part of cohort 2 (patients without early start of Sorafenib treatment). Further assuming a prolongation of median survival time from 9 to 12 months in patients with early start of Sorafenib treatment, exponential distribution of overall survival, equal cohort sizes of 250 patients, no loss of patients for evaluation due to poor overlap of the cohorts' propensity score distributions, 18 months of enrollment, and a total study duration of 36 months, a power of 83% can be achieved in a one-sided log-rank test with type I error rate alpha of 2.5%. SAS© PROC POWER, version 9.2, has been used for power calculation.

9.6. Data management

The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice.

A global Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request. The respective document is listed in Annex 1.

Each patient is identified by a unique central patient identification code. This code is only used for study purposes. The patient code consists of a combination of a country code, site number and patient number. For the duration of the study and afterwards, only the patient's investigator is able to identify the patient based on the patient identification code.

For information on quality control, refer to section 9.8

9.7. Data analysis

9.7.1. Statistical considerations

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

All analyses will be performed for the total study population (overall analysis) and separately for each study region. In addition, country-specific analyses might be performed, if patient numbers are sufficient and analyses are required for local reasons. Patients receiving at least one TACE will be included in the analysis. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender, baseline characteristics).

Sample size and disposition information by analysis time point will be displayed in a frequency table.

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. In addition Adverse Events will be coded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP is available upon request. The respective document is listed in Annex 1.

It is planned to have 1 interim analysis after 500 patients observed for at least 6 months. This analysis will not include the formal comparison of the two cohorts of special interest. The final analysis will be

performed after end of the study, which is the date after which the last enrolled subject will have been in the study for 18 months, or is lost to follow-up or has died.

9.7.2. Analysis of demography, disease details, prior and concomitant medication and other baseline data

All background data such as patient demographics, diagnosis and prior treatment of HCC, past medical history, concomitant diseases, and concomitant medication will be described by presenting frequency distributions and/or basic summary statistics.

9.7.3. Analysis of treatment data

Statistical summaries will be provided by cohort summarizing for duration of exposure to TACE treatment. Duration of TACE treatment is defined as the time interval from of the first TACE to the date of permanent discontinuation of TACE (when an investigator decides no longer TACE is applicable regardless of the reason for discontinuation including death).

In addition, for patients treated with sorafenib, duration of exposure to Sorafenib will also be provided.

Duration of exposure will be calculated in person time.

9.7.4. Analysis of primary outcome(s)

The primary efficacy endpoint is Overall Survival (OS). It is defined in this study as the time (days) from time of TACE non-eligibility to death due to any cause. Patients lost to follow-up or alive at the end of the study will be censored at the last date known to be alive.

For statistical evaluation, two patient cohorts of special interest will be compared regarding the primary endpoint. These two cohorts are defined as:

- Cohort 1: Patients with early start of Sorafenib treatment. This cohort comprises all patients where the physician decides at the time of TACE non-eligibility to choose Sorafenib as the next treatment option (regardless of whether TACE treatment is continued or not).
- Cohort 2: Patients without early start of Sorafenib treatment. This cohort comprises all patients where the physician decides at the time of TACE non-eligibility not to choose Sorafenib as the next treatment option.
  This cohort also includes patients with TACE non-eligibility for whom the decision to treat with Sorafenib is made at a later points in time, patients who are never treated with Sorafenib as well as patients for whom another systemic cancer treatment has been chosen be the physician either at time of TACE non-eligibility or at a later point in time.

According to the definition of the two cohorts, patients where no TACE non-eligibility occurred during the study do not qualify for this analysis. In addition, patients treated with Sorafenib or any other systemic anti-cancer treatment prior to time of TACE non-eligibility are excluded from this analysis. These groups will be described separately.

As part of the descriptive analysis, Kaplan-Meier (KM) estimates for OS will be displayed for the two patient cohorts of special interest.

In an effort to deal with confounding typically present in non-randomized studies, a stratified propensity score approach will be applied for further evaluation. This approach is undertaken with the intention to create strata containing patients in both treatment cohorts for which background variables (covariates) are balanced. The propensity score model will be determined based on variables

potentially affecting the treatment decision at time of TACE non-eligibility as well as other variables potentially related to the outcome. Balance of covariates (including important interactions) within each stratum will be investigated, and the propensity score will be re-estimated, as necessary, until adequate balance is demonstrated. All of this will be done in an outcome-blinded manner. Assuming that adequate balance is achieved, equally sized strata will be determined based on the resulting final propensity scores. Within each stratum, the stratum-specific hazard ratio will be estimated based on the applied Cox-model. Subsequently, an overall hazard ratio estimate as well as the corresponding 95%-confidence interval will be calculated based on the stratum-specific estimates applying inverse variance-weighting. Further details will be given in the SAP.

9.7.5. Analysis of secondary outcome(s)

The secondary efficacy endpoints will be analyzed for the two cohorts described below

- Overall: Includes all patients who were treated with at least one TACE
- Sorafenib: Includes all patients who were treated with sorafenib

or for the two cohorts of special interest, as applicable.

9.7.6. Analysis of safety data

Adverse events will be summarized for the overall safety population and by cohort using the National Cancer Institute (NCI) Common Terminology Criteria Adverse Event CTCAE and the MedDRA coding system. Event rates for each adverse event, as well as drug related AEs and serious AEs, will also be summarized by NCI CTCAE grade for the overall safety population and by cohort.

Other safety parameters, including blood pressure, will be summarized descriptively.

AEs occurred during treatment for HCC also will be summarized for each treatment for HCC.

Subgroup analyses stratified with prognostic/predictive factors collected at baseline may be explored.

9.7.7. Bias, confounding and effect-modifying factors

As the study aims to compare two non-randomized cohorts of patients as defined in 9.7.4, all factors probably influencing treatment assignment as well as the outcome have to be taken into account to avoid false positive or false negative interpretation of data. It will be tried to control for the effect of confounders using propensity score based methods (see 9.7.4). Possible confounders are:

- Demography (age, gender)
- Etiology (Hepatitis C, Hepatitis B, alcoholic)
- Previous treatment (hepatectomy, number of previous TACE)
- Response to the last TACE
- Barcelona-Clinic Liver Cancer (BCLC) Stage at the time of TACE non-eligibility
- Liver dysfunction: Child-Pugh status at the time of TACE non-eligibility
- Tumor size at the time of TACE non-eligibility
- Vascular invasion at the time of TACE non-eligibility
- Extrahepatic spread at the time of TACE non-eligibility

- Number of lesions at study entry: at the time of TACE non-eligibility
- Physicians' speciality
- Region

A complete list of expected confounders will be added to the SAP.

It is important to note that the propensity score method can only account for confounders that have been measured in the study, but of course not for any unknown or unmeasured confounders. As a consequence, it cannot be ensured that the resulting hazard ratio estimation is completely free of bias and thus the results have to be interpreted with care.

9.8. Quality control

9.8.1. Data quality

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

A global CRO will be selected and assigned for EDC system development, quality assurance, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request. The respective document is listed in Annex 1.

National and international data protection laws as well as regulations on observational non-interventional studies will be followed. Electronic records used for patient documentation will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA)[29]. The documentation is available upon request. The respective document is listed in Annex 1.

9.8.2. Quality review

In a subset of patients (at least 10% of all patients) source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request. The respective document is listed in Annex 1.

9.8.3. Storage of records and archiving

The sponsor will make sure that all relevant documents of this PASS including CRFs and other patient records will be stored after end or discontinuation of the study at least for 15 years. Other instructions for storage of medical records will remain unaffected.

The investigators participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to also store documents for a retention period of at least 15 years.

Statistical programming performed to generate results will be stored in the productive area of the programming system (TOSCA) for at least 15 years at the sponsor's site.

9.8.4. Limitations of the research methods

Since the number of relevant covariates is presumably very high, a pure descriptive statistical approach may not be sufficient to fully interpret the results. Results from this study are prone to selection bias and confounding. It is acknowledged that biases of channeling and confounding by indication are present in observational studies despite more advanced study designs and analytical methods such as propensity score matching or adjustment for multiple covariates associated with drug use and the clinical outcome.

Some limitations of the study are inherent and result from the non-interventional character and the fact of voluntary participation of investigators and patients.

10. Protection of human subjects

10.1. Ethical conduct of the study

This study is a non-interventional study where sorafenib is prescribed in the usual manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2. Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012[30]). Recommendations given by other organizations will be followed as well (e.g. EFPIA[31], ENCePP[32]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (GVP) will be followed; the relevant competent authorities of the EU member states will be notified according to Volume 9A[33].

10.3. Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC/IRB is required, documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The IEC/IRB must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to applicable laws and regulations.

10.4. Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing. In countries where required by law or regulation, the investigator must have the IECs/IRB written

approval/favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

10.5. Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6. Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data. Study findings stored on a computer will be stored in accordance with local data protection laws.

All records identifying the patient will be kept confidential and will not be made publicly available. Patient names will not be supplied to the sponsor. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

11. Management and reporting of adverse events/adverse reactions

11.1. Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.[34]

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

The AE may be:

- A new illness

- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator drug
- An effect related to study procedure
- Any combination of one or more of these factors
- An effect related to lack of drug effect,
- An effect related to medication errors,
- An effect related to overdose, drug abuse or drug misuse, drug dependency
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Drug exposure during pregnancy

As mentioned above no causal relationship with a study medication is implied by the use of the term "adverse event".

An Adverse Drug Reaction (ADR) is any AE suspected as having a reasonable causal relationship to the studied drug. It is defined as a response to a drug, which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

An AE is serious if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be automatically considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours, OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), OR
- The admission is not associated with an adverse event (i.e. social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms. Medically important events may jeopardize the patient and may require intervention to prevent another serious condition.

11.2. Collection

Starting with the first TACE, all non-serious Adverse Events (AE) must be documented on the AE Report Form of to the electronic CRF within 5 days of awareness. All serious AEs (SAE) must be documented immediately (within 24 hours of awareness).

For each AE/SAE, the investigator must assess and document the seriousness, duration, causal relationship to study drug (TACE/sorafenib/other systemic anti-cancer drug), action taken and outcome of the event.

If a pregnancy occurs during the study, although it is not a serious adverse event, it should be reported within the same time limits as a serious adverse event. The result of a pregnancy should be followed carefully and any abnormal result of the mother or baby should be reported.

The documentation of any AE/SAE ends with the completion of the "End of observation" section of the electronic CRF. However, any AE/SAE occurring up to 30 days after the last intake of Sorafenib has to be documented, even if this period goes beyond the end of observation.

As long as the patient has not received any TACE or any other studied treatment, AEs/SAEs do not need to be documented as such in this non-interventional study. However, they are part of the patient's medical history.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3. Management and submission to regulatory authorities

Non-serious AEs

The outcome of all reported AEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ADRs

All non-serious ADRs occurring under treatment with Sorafenib will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI) and according to national regulations by the sponsor; however, all investigators must obey local legal requirements.

For non-serious ADRs occurring under treatment with TACE, other systemic anti-cancer drugs or other non-systemic anti-cancer drugs the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the electronic CRF will be forewarded immediately (within 24 hours of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the sponsor for SAEs occurring under Sorafenib treatment; however, all investigators must obey local legal requirements.

For SAEs that occurred while administering TACE treatment, other systemic anti-cancer drugs or other non-systemic anti-cancer drugs the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

11.4. Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis. If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

12. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov". Results will be disclosed in a publicly available database within the standard timelines.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the sponsor. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines[35], STROBE[36]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the sponsor.

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14. Annex 1. List of stand-alone documents

Table 3: List of stand-alone documents

Number	Document reference number	Date	Title
1	NX1301_SC members	Will be available after first Steering Committee Meeting	List of Steering committee members
2	NX1301_active physician list_final	Will be available at end of recruitment	List of all active physicians
3	NX1301_INV_CRF_Draft9	28 Feb 2013	CRF draft
4	NX1301_EDC_summary	Will be available at time of first country ready to enroll	EDC System description
5	NX1301_EDC_validation	Will be available at time of first country ready to enroll	EDC System Validation
6	NX1301_DAT_DMP	Will be available at time of first country ready to enroll	Data Management Plan
7	NX1301_DAT_SAP	Will be available before study database lock	Statistical Analysis Plan
8	NX1301_DAT_QRP	Will be available at time of first country ready to enroll	Quality Review Plan

15. Annex 2. ENCePP checklist for study protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	17
1.1.2 The objectives of the study?	☒	☐	☐	18
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	18
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is not a hypothesis-testing study.

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	20
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	20
2.2.2 Age and sex?	☐	☐	☒	
2.2.3 Country of origin?	☐	☐	☒	
2.2.4 Disease/indication?	☒	☐	☐	20
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	20/21

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	19
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	23
3.4 Is sample size considered?	☒	☐	☐	25
3.5 Is statistical power calculated?	☒	☐	☐	26

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	20/25
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	19
4.1.3 Covariates?	☒	☐	☐	28
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	20/25
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	28
4.3 Is the coding system described for:				

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	26
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	20
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	26
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	26

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☒	☐	☐	25
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	25
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	23/24 + 25
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	24/25

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	27/28

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	21
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	28
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	28/29
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	28/29
7.4 Does the protocol address other limitations?	☒	☐	☐	29

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	27
8.2 Is the choice of statistical techniques described?	☒	☐	☐	26-28
8.3 Are descriptive analyses included?	☒	☐	☐	26

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.4 Are stratified analyses included?	☒	☐	☐	27
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	28/29
8.5.2 Effect modifiers?	☒	☐	☐	28/29
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	28/29
8.6.2 Effect modification?	☒	☐	☐	28/29

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29/30
9.2 Are methods of quality assurance described?	☒	☐	☐	29
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	29
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	16
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	16
	☒	☐	☐	16
9.5.3 Study completion?	☒	☐	☐	16
9.5.4 Reporting? (i.e. interim reports, final study report)				
9.6 Does the protocol include a section to document future amendments and deviations?	☐	☒	☐	
9.7 Are communication methods to disseminate results described?	☒	☐	☐	34
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	Steering Committee

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	30
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	30/31

Comments:

Name of the coordinating study entity[1]: Bayer HealthCare, Global Non-Interventional Studies

Date: 04/03/2013

Signature: _____

[1]*A legal person, institution or organization which takes responsibility for the design and/or the management of a study.*

16. Annex 3. Signature pages

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final Version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Qualified person responsible for pharmacovigilance (QPPV)
Name	Michael Kayser
Title	European Qualified Person for Pharmacovigilance
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: 14/3/2013, M Kayser

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final Version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Marketing authorization holder(s)	Bayer Healthcare AG
Function:	Study medical expert
Name:	Keiko Nakajima
Title:	Global Medical Affairs Physician
Address:	Bayer HealthCare Pharmaceutical Inc, P.O. Box 1000 Montville, NJ, USA

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: March 10, 2013 Keiko Nakajima

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final Version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Marketing authorization holder(s)	Bayer Healthcare AG
Function:	Study conduct responsible
Name:	Kathrin Stauch
Title:	Global Project Manager Non-Interventional Studies
Address:	Bayer HealthCare, Bldg. K56, 51366 Leverkusen, Germany

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: March 13, 2013, K. Stauch

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate sorafenib
Protocol version identifier	Final Version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Marketing authorization holder(s)	Bayer Healthcare AG
Function:	Study statistician
Name:	Alice Benson
Title:	Global Integrated Analysis Statistician
Address:	Bayer HealthCare Pharmaceutical Inc, P.O. Box 1000 Montville, NJ, USA

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: March 14, 2013 Alice Benson

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final Version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Marketing authorization holder(s)	Bayer Healthcare AG
Function:	Study data manager
Name:	Anja Laske
Title:	Global Data Manager Non-Interventional Studies
Address:	Bayer HealthCare, Bldg. K9, 51368 Leverkusen, Germany >

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: 14.03.13 , Anja Laske

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final Version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib
Marketing authorization holder(s)	Bayer Healthcare AG
Function:	Study epidemiologist
Name:	Alexander Michel
Title:	Global Epidemiologist
Address:	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: 6 March 2013, Dr A Michel

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final Version
Date of last version of protocol	05 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Marketing authorization holder(s)	Bayer Healthcare AG
Function:	Study safety lead
Name:	Aruna Mehra
Title:	Global Safety Leader, Global Pharmacovigilance
Address:	Bayer HealthCare Pharmaceutical Inc, P.O. Box 1000 Montville, NJ, USA

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: 14 Mar 2013, Aruna

Signature Page

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate **s**orafenib
Protocol version identifier	Final Version
Date of last version of protocol	01 March 2013
IMPACT study number	16560
Study type	☒ PASS ☐ non PASS
EU PAS register number	To be added at time of registration
Active substance (medicinal product)	ATC L01XE - Protein kinase inhibitors, Sorafenib L01DB - Anthracyclines and related substances, Doxorubicin, Epirubicin L01XA - Platinum compounds, Cisplatin
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Head of initiating Function
Name	Svetlana Kobina
Title	Head Global medical Affairs Oncology
Address	Bayer HealthCare Pharmaceutical Inc, P.O. Box 1000 Montville, NJ, USA

The undersigned confirms his agreement that the study will be conducted under the conditions described in this protocol.

Date, Signature: March 13, 2013 S Kobina

17. Annex 4. Additional information.

BCLC Staging System

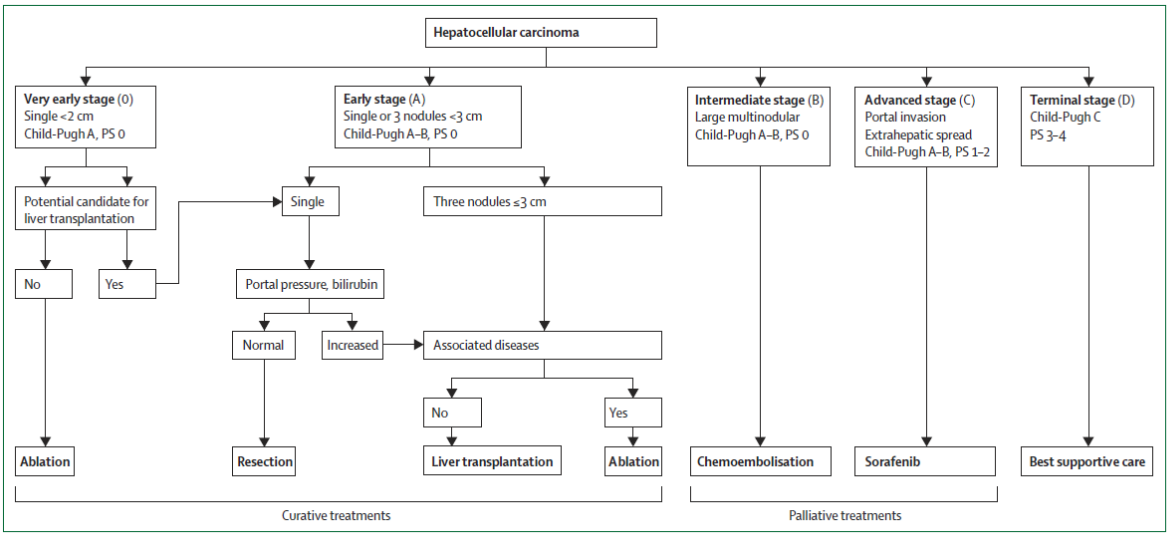

Figure 2: BCLC staging and treatment strategy

17.1. Performance Status (PS) (Eastern Cooperative Oncology Group [ECOG])

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

TNM Classification

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Solitary tumor without vascular invasion
- T2: Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- T3a: Multiple tumors >5cm
- T3b: Single tumor or multiple tumors of any size involving a major branch of the PV or HV
- T4: Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

[Note: The regional lymph nodes are the hilar (i.e., those in the hepatoduodenal ligament, hepatic, and periportal nodes). Regional lymph nodes also include those along the inferior vena cava, hepatic artery, and portal vein. Any lymph node involvement beyond these nodes is considered distant metastasis and should be coded as M1. Involvement of the inferior phrenic lymph nodes should also be considered M1.]

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC Stage Groupings

- Stage I T1, N0, M0
- Stage II T2, N0, M0
- Stage IIIA T3a, N0, M0
- Stage IIIB T3b, N0, M0
- Stage IIIC T4, N1, M0
- Stage IVA Any T, N1, M0
- Stage IVB Any T, Any N, M1

17.2. Cancer of the Liver Italian Program (CLIP) Scoring System

Points	0	1	2
Chile-Pugh stage	A	B	C
Tumor morphology	Uninodular and extension ≦ 50%	Multinodular and extension ≦ 50%	Massive or extension > 50%
AFP (ng/mL)	< 400	≧400	
Portal vein thrombosis	No	Yes	

17.3. Liver Status – Child-Pugh Classification

Points Scored for Observed Findings

	Points Scored for Observed Findings		
	1	2	3
Encephalopathy grade [a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, mg/dL	< 2	2 to 3	> 3.0
Serum albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time, sec (prolonged)	< 4	4-6	> 6

a *Encephalopathy grades:

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Assessment as good operative risk (A) if 5 or 6 points; moderate risk (B) if 7 to 9 points, and poor operative risk (C) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics).

17.4. RECIST Criteria

Response and progression will be evaluated in this study using the international criteria proposed by RECIST (Response Evaluation Criteria in Solid Tumors) committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PE, CT, XR, MRI) or as ≥ 10 mm with spiral CT scan.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI) and cystic lesions are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of 10 lesions representative of all involved organs should be identified as **target lesions** and be recorded and measured at baseline. These 10 lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for **all target lesions** will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. If there are > 10 measurable lesions, those not selected as **target lesions** will be considered together with non-measurable disease as **non-target lesions**.

Non-target Lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 10 listed as **target lesions**. Measurements are not required, but these lesions should be noted at baseline and should be followed as “present” or “absent”. All lesions that arise during the study and lesions that change from non-measurable to measurable during the study should be entered as non-target lesions.

Best Response:

All subjects will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): disappearance of all clinical and radiological evidence of tumor (both **target** and **non-target**).

Partial Response (PR): at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.

Stable Disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD): at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Appearance of new lesions will also constitute progressive disease. In exceptional circumstances unequivocal progression of a non-measured lesion may be accepted as evidence of disease progression.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	>4 wk. Confirmation
CR	Non-CR/Non-PD	No	PR	>4 wk. Confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once > 6 wk. from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	
*Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of treatment.				

Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

Stable Disease Duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Duplicate copies of all imaging studies used for tumor response evaluation will be made available for review by an independent radiologist or by the sponsor upon request.

Clinical Lesions - Clinical lesions will only be considered measurable when they are superficial (egg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray - Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT / MRI - CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound - When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy / Laparoscopy - The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment

and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

Cytology / Histology - These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

RECIST amendments

Complete response - disappearance of any intratumoral arterial enhancement in all target lesions.

Partial response - at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.

Progressive disease - an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started.

Progressive disease will also be declared on the appearance of one or more new lesions. A newly detected hepatic nodule will be classified as HCC - and therefore will be declared as evidence of progression - when its longest diameter is at least 10 mm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is hypervascularization in the arterial phase with washout in the portal venous or late venous phase. Lesions larger than 10 mm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm interval growth in subsequent scans. An individual radiological event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiological testing.

Stable disease - any cases that do not qualify for either partial response or progressive disease.

For nonenhancing atypical lesions, the conventional RECIST criteria will be applied.
As per RECIST, cytopathological confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease.

Llovet JM, et al.; Panel of Experts in HCC-Design Clinical Trials: Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma. J Natl Cancer Inst. 2008 May 21;100(10):698-711