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	Version 3 (integrated amendment 1, update 1, Switzerland local amendment 1, integrated amendment 2)
Date of last version of protocol	04 September 2015
IMPACT study number	16560
Study type	☒ PASS ☐ non-PASS
EU PAS register number	ENCEPP/SDPP/4564
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, 67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

Marketing authorization holder

Marketing authorization holder(s)	Bayer Healthcare AG, Leverkusen, Germany
MAH contact person	Keiko Nakajima, 67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, 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
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
mRECIST	modified Response Evaluation Criteria in Solid Tumor
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

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

Function:	Study medical expert
Name:	Keiko Nakajima
Title:	Global Medical Affairs Physician
Address:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

Function:	Study conduct responsible
Name:	Matthew Willis
Title:	Global Project Manager Non-Interventional Studies
Address:	Bayer AG, Bldg. S102, Müllerstrasse 178, 13353 Berlin, Germany

Function:	Study safety lead
Name:	Aruna Mehra
Title:	Global Safety Leader, Global Pharmacovigilance
Address:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

Function:	Study statistician
Name:	Yoriko de Sanctis
Title:	Global Integrated Analysis Statistician
Address:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

Function:	Study data manager
Name:	Daniel Wolf
Title:	Global Data Manager Non-Interventional Studies
Address:	Bayer HealthCare, Bldg. K9, 51368 Leverkusen, Germany

Function:	Study epidemiologist
Name:	Jihong Zhong
Title:	Global Epidemiologist
Address:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

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	Version 3 (integrated amendment 1, update 1, Switzerland local amendment 1, integrated amendment 2)
Date of last version of protocol	04 September 2015
IMPACT study number	16560
Study type	☒ PASS ☐ non-PASS
Author	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, 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 the first interim analysis after 500 patients observed for at least 6 months. Based on results of the 1st interim analysis, the second interim analysis is planned after approximately 1000 patients have been observed for at least 6 months, in order to evaluate patient sample size and feasibility for conducting the propensity score analysis. 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: Q4 2015 Last patient last visit: Q2 2017 End of data collection (clean database) Q3 2017 Final report of study results: Q1 2018

5. Amendments and updates

5.1. Amendment 1

This protocol has been amended once on May 15, 2013 due to comments received from steering committee members in a meeting on April 28, 2013.

Tabular Summary of Changes

Amendments and Updates		
Protocol section	**Amendment or update**	**Reason**
9.2.2. Inclusion criterion/criteria	One inclusion criterion added	Patients with a BCLC A stage or lower have better prognosis than more advanced BCLC stage patients and are likely to be treated a longer time until reaching the point of TACE non-eligibility, which is the critical decision point for the primary objective in this study. In addition, the survival time may exceed the planned observation time in a majority of such patients. Thus, it has been decided to include only patients with BCLC stage B or higher.
9.2.3. Exclusion criterion/criteria	One exclusion criterion added	To avoid inclusion of a too widespread patient population that would dilute the population for analysis of the primary objective, it has been decided to exclude patients with a systemic anti-cancer therapy prior to the first TACE.
9.2.5. Visits	Information added for the time of initial visit in case that the first TACE is documented retrospectively	As baseline data is needed at the time of first TACE, the whole initial visit has to be documented retrospectively.
9.3. Table 2	References to the CLIP score deleted	CLIP score will not be documented. All data needed to calculate this score can be taken out of the CRF.
9.3.3. Demographic data and other baseline characteristics	One variable added and one category changed	Sex was missing as variable and the category “caucasian” within the variable “race” was changed to “white” according to the Bayer standard database specifications.
9.3.4. Laboratory data	Two values added	Platelets and baseline C reactive protein have been added.

Amendments and Updates		
Protocol section	**Amendment or update**	**Reason**
9.3.8. Disease status summary	Wording for two criteria changed. One criterion deleted. Three criteria excluded for initial visit.	"More than two" was incorrect. This had to be changed to "Two or more". Jaundice has been deleted, because total bilirubin level is documented in the laboratory data, which is more precise. Criteria referring to prior TACE have been excluded for the initial visit, because the observation starts with the first TACE.
9.3.9. Tumor assessment	Other criteria for response evaluation have been added	Response evaluation should preferably be done according to mRECIST. However, the physician can use alternative criteria in case that an evaluation according to mRECIST is not done in his regular clinical practice.
17. Annex 4	CLIP deleted, numbering of sections changed, one section amended	CLIP score will not be documented (see above). For some section headers the numbering was missing. In section 17.5. mRECIST has been added.

On July 4, 2013 the standard definition of Adverse events was updated according to the new European Pharmacovigilance Legislation Module VI.

In parallel to finalization of the protocol amendment 1, the sign-off process for PASS protocols has been changed. Prior to the change a stand-alone amendment was written and signed. The new process requires signature of the integrated protocol version. Thus, together with the above mentioned update, this integrated protocol version 2.1 again was circulated for sign-off.

5.2. Switzerland local amendment 1

The protocol text for the study was amended for Switzerland according to Swissmedic. A full summary of the changes is presented in Annex

5.3. Amendment 2

Tabular Summary of Changes

Amendments and Updates		
Protocol section	**Amendment or update**	**Reason**

Amendments and Updates		
Protocol section	**Amendment or update**	**Reason**
Section 6. Milestones	Milestones updated	Following decision to increase enrollment period, milestones have been updated.
Section 9.1.1. Primary endpoint	Definition of non-eligible for TACE was modified.	Child-Pugh class B or C was excluded from the definition.
Section 9.3.4. Laboratory data	Lab values updated as were missing from previous version	Gamma-Glutamyl-Transferase (GGT) and Cholinesterase (ChE) added.
Section 9.7. Data analysis	Statistical section updated	Following the decision to conduct a second interim analysis, this section was revised. Assessment of outcome by procedures of TACE has been added as analysis of other data (Section 9.7.7).

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	Q4 2015
First Interim analysis	500 patients observed for at least 6 months
Second Interim Analysis	1000 patients observed for at least 6 months
Last patient last visit	Q2 2017
End of data collection (clean database)	Q3 2017
Final report of study results	Q1 2018

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. 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 except 'advanced liver disease (Child-Pugh class B or C) 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 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 with BCLC stage B or higher.
- 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 criteria

- Patients who have received TACE in the past but the data about TACE required in this protocol are not available
- Patients who received any systemic anti-cancer therapy prior to the first TACE
- 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.

In the case that the first TACE is documented retrospectively under the pre-requisites detailed in section 9.2.2. the baseline data asked in the initial visit also has to be documented retrospectively.

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)	**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)	**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)
- sex
- race (asian, white, black, other). Note: race will not be recorded in countries where legally not permitted.
- weight (kg / pound)
- height (cm / inch)
- alcohol use
- status of cigarettes smoking
- medical history of HCC
- history of liver disease
- general medical history

9.3.4. Laboratory data

- platelets
- INR
- Total bilirubin
- ALT
- AST
- Alkaline phosphatase
- Creatinine
- Creatinine clearance
- Albumin
- Sodium
- LDH
- Alpha fetoprotein
- C reactive protein (baseline only)
- Gamma-Glutamyl-Transferase (GGT)

- Cholinesterase (ChE)

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.
- Two or more 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. (excluded from initial visit)
- Two or more consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT at the 4 weeks after adequately performed TACE. (excluded from initial visit)
- TACE failure by investigator's assessment (excluded from initial visit)
- 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 preferably by mRECIST. In case that an assessment by mRECIST is not possible, because this is not routinely done at the site of the treating physician, also other evaluation criteria can be used. In any case the criteria used have to be documented along with the tumor evaluation and the physician should use the same criteria throughout all tumor evaluations of one patient.

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 the first interim analysis after 500 patients observed for at least 6 months. This first interim analysis was conducted on 26th February 2015. This analysis did not include the formal comparison of the two cohorts of special interest, as planned. Based on results of the 1st interim analysis, the second interim analysis is planned after approximately 1000 patients have been observed for at least 6 months, in order to evaluate patient sample size and feasibility for conducting the propensity score analysis. 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 subjects will have been in the study for 18 months, or have been lost to follow-up or have 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. Analysis of other data

The following outcomes will be summarized by procedures of TACE Overall cohort (Section 9.7.5 for definition of Overall cohort) by region:

- OS
- Response to each TACE
- Deterioration of liver dysfunction (Section 9.1.2 for definition)

9.7.8. 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,
- Medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- Drug exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)

- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

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 forwarded 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.

13. List of references

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94(2):153-6.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362(9399):1907-17.
3. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340(10):745-50.
4. Bruix J, Hessheimer AJ, Forner A, Boix L, Vilana R, Llovet JM. New aspects of diagnosis and therapy of hepatocellular carcinoma. Oncogene 2006;25(27):3848-56.
5. Alsowmely AM, Hodgson HJ. Non-surgical treatment of hepatocellular carcinoma. Aliment Pharmacol Ther 2002;16(1):1-15.
6. Thomas MB, Abbruzzese JL. Opportunities for targeted therapies in hepatocellular carcinoma. J Clin Oncol 2005;23(31):8093-108.
7. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126(2):460-8.
8. Huang MA, Marrero JA. Hepatocellular carcinoma. Curr Opin Gastroenterol 2002;18(3):345-50.
9. Ganne-Carrie N, Trinchet JC. Systemic treatment of hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2004;16(3):275-81.
10. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol. 2005;40:225-35.
11. Marrero JA, et al. Prognosis of hepatocellular carcinoma: comparison. Hepatology. 2005;41:707-16.
12. Bruix et al. Hepatology 2011;53:1020-2.
13. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol 2005;40(3):225-35.
14. Forner et al. Hepatocellular carcinoma. Lancet 2012;379:1245-55.
15. EASL-EORTC. Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
16. Llovet et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma : a randomised controlled trial. Lancet 2002;359:1734-9.
17. Lo et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma . Hepatology 2002;35:1164-71.
18. Llovet et al. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoemboliza- tion improves survival. Hepatology 2003;37:429-42.

19. Raoul et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212-20.

20. Piscaglia et al. The intermediate hepatocellular carcinoma stage: should treatment be expanded? Dig Liver Dis 2010;42 Suppl 3:S258-S263.

21. Kudo et al. Management of Hepatocellular Carcinoma in Japan : Consensus Based Clinical Practice Guidelines Proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version. Dig Dis 2011;29:339-64.

22. Omata et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010;4:439–74

23. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 2006;5:835–844.

24. Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24:4293–4300.

25. Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.

26. Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo controlled trial. Lancet Oncol. 2009 Jan;10(1):25-34

27. Geschwind JH, Lencioni R, Marrero J, Venook A, Ye SL, Nakajima K, Cihon F, Kudo M. Worldwide trends in locoregional therapy for hepatocellular carcinoma (HCC): Second interim analysis of the Global Investigation of Therapeutic Decisions in HCC and of Its Treatment with Sorafenib (GIDEON) study. J Clin Oncol 30, 2012 (suppl 4; abstr 317)

28. Kudo M, Ye SL, Venook A, Marrero J, Nakajima K, Cihon F, Lencioni R. Second interim analysis of GIDEON multiregional variation in patient characteristics, previous treatment history, and sorafenib use. AASLD 2011

29. Code of Federal Regulations. Title 21, Volume 1. 21CFR 11: Electronic records; electronic signatures. 62 FR 13464, Mar. 20, 1997. Revised 01.04.2012.

30. Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. Official Journal of the European Junion. 20.06.2012.

31. EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals, EFPIA, October 2007.

32. ENCePP guide on methodological standards in pharmacoepidemiology. European Medicines Agency. EMA/95098/2010. 05.11.2010.

33. Eudralex - Volume 9A of the Rules Governing Medicinal Products in the European Union: the Guidelines on Pharmacovigilance for Medicinal Products for Human Use. 2008.Available online: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm.

34. ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2D), November 2003.

35. Graf C, Battisti WP, Bridges D, Bruce-Winkler V, Conaty JM, Ellison JM, Field EA, Gurr JA, Marx ME, Patel M, Sanes-Miller C, Yarker YE; International Society for Medical Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. BMJ. 2009; 339: b4330..

36. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2008; 61(4): 344-9.

37. Marrero JA, Lencioni R, Kudo M, Ye S, Nakajima K, Cihon F, Venook AP. Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON) second interim analysis in more than 1,500 patients: Clinical findings in patients with liver dysfunction. J Clin Oncol 29: 2011 (suppl; abstr 4001)

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	28 April 2013	List of Steering committee members
2	NX1301_active physician list_final	Will be available at end of recruitment	List of all active physicians
3	OPTIMIS_FINAL CRF_Version 6.0	28 November 2014	CRF final content for EDC development
4	NX1301_EDC_tutorial Version 1.0	02 September 2013	EDC System description
5	NX1301_EDC_validation Version 1.6	31 August 2011	EDC System Validation
6	NX1301_DAT_DMP Version 1.0	19 September 2013	Data Management Plan
7	NX1301_DAT_SAP Version 1.6	1 July 2015	Statistical Analysis Plan

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)	☒	☐	☐	19
1.1.2 The objectives of the study?	☒	☐	☐	20
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)	☒	☐	☐	20
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?	☒	☐	☐	22
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	22
2.2.2 Age and sex?	☐	☐	☒	
2.2.3 Country of origin?	☐	☐	☒	
2.2.4 Disease/indication?	☒	☐	☐	22
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)	☒	☐	☐	22/23

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?	☒	☐	☐	21
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	20
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)	☒	☐	☐	25
3.4 Is sample size considered?	☒	☐	☐	27
3.5 Is statistical power calculated?	☒	☐	☐	28

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.)	☒	☐	☐	22/27
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.)	☒	☐	☐	21
4.1.3 Covariates?	☒	☐	☐	30
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)	☒	☐	☐	22/27
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	21
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	30
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)	☒	☐	☐	28
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	22
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	28
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	28

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)	☒	☐	☐	27
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)	☒	☐	☐	27
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	26/27
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?	☒	☐	☐	26/27

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?	☒	☐	☐	21
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)	☒	☐	☐	29/30

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?	☒	☐	☐	23
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)	☒	☐	☐	30
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	30/31
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	30/31
7.4 Does the protocol address other limitations?	☒	☐	☐	31

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	29
8.2 Is the choice of statistical techniques described?	☒	☐	☐	28-30
8.3 Are descriptive analyses included?	☒	☐	☐	28

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.4 Are stratified analyses included?	☒	☐	☐	29
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	30/31
8.5.2 Effect modifiers?	☒	☐	☐	30/31
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	30/31
8.6.2 Effect modification?	☒	☐	☐	30/31

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)	☒	☐	☐	31/32
9.2 Are methods of quality assurance described?	☒	☐	☐	31
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	31
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?	☒	☐	☐	18
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	18
	☒	☐	☐	18
9.5.3 Study completion?	☒	☐	☐	18
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?	☒	☐	☐	36
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?	☒	☐	☐	32
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	32/33

Comments:

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

Date: 04/07/2013

Signature: _____

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

15. 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	Version 3
Date of last version of protocol	04 September 2015
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: _____, _____

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	Version 3
Date of last version of protocol	04 September 2015
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:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

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

Date, Signature: _____, _____

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	Version 3
Date of last version of protocol	04 September 2015
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:	Matthew Willis
Title:	Global Project Manager Non-Interventional Studies
Address:	Bayer AG, Bldg. S102, Müllerstrasse 178, 13353 Berlin, Germany

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

Date, Signature: _____, _____

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	Version 3
Date of last version of protocol	04 September 2015
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:	Yoriko de Sanctis
Title:	Global Integrated Analysis Statistician
Address:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

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

Date, Signature: _____, _____

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	Version 3
Date of last version of protocol	04 September 2015
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:	Daniel Wolf
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: _____, _____

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	Version 3
Date of last version of protocol	04 September 2015
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:	Global Epidemiology
Name:	Jihong Zong
Title:	Director
Address:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

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

Date, Signature: _____, _____

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	Version 3
Date of last version of protocol	04 September 2015
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:	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

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

Date, Signature: _____, _____

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	Version 3
Date of last version of protocol	04 September 2015
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	67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

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

Date, Signature: _____, _____

16. Annex 4. Additional information.

16.1. BCLC Staging System

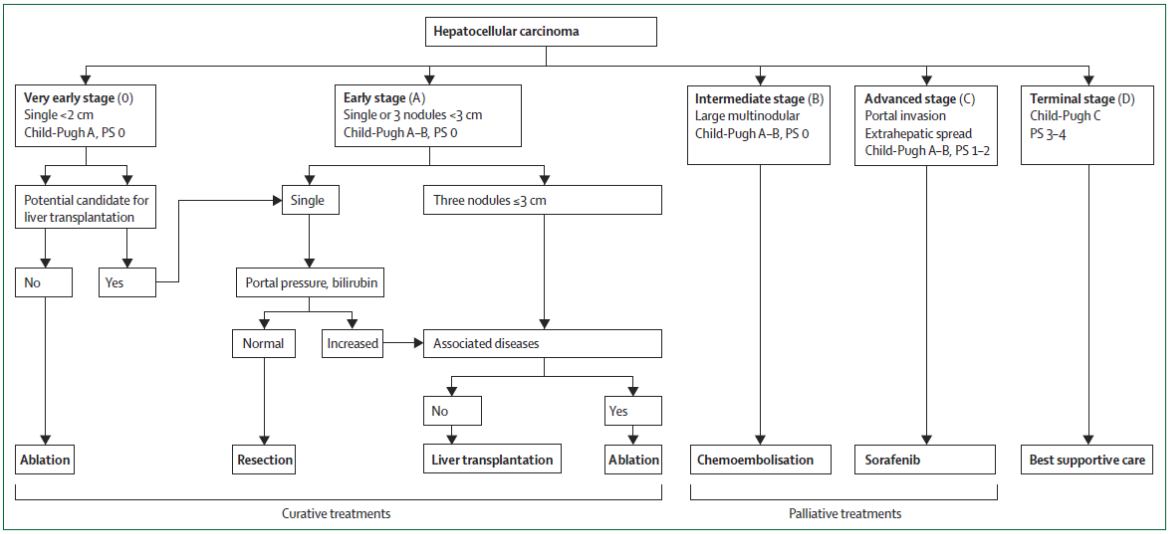

Figure 2: BCLC staging and treatment strategy

16.2. 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)

16.3. 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, N0, M0
- Stage IVA Any T, N1, M0
- Stage IVB Any T, Any N, M1

16.4. 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).

16.5. RECIST Criteria

Modified RECIST (mRECIST)

Response and progression should preferably be evaluated in this study using a modified version of RECIST version 1.1, which combines quantitative assessment of a set of lesions using unidimensional measurements with qualitative assessment of all other lesions (Eisenhauer EA et al.; New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). EJC 2009 45:228-247).

The modifications introduced for the assessment of intrahepatic lesions are based on the modified RECIST criteria published in 2010 for the assessment of hepatocellular carcinoma (Lencioni R and Llovet JM; Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Sem Liver Dis 2010 30;1:52-60).

Results from a number of previous clinical studies in HCC have demonstrated that RECIST does not adequately capture the extent of tumor necrosis induced by interventional therapies or new molecular targeting drugs. Only viable tumor, assessed by properly designed CT or MRI studies, should be included in the tumor burden, and viable tumor should be defined as uptake of contrast agent in the arterial phase of dynamic imaging studies. Consequently, a modification of RECIST was first proposed by a panel of experts, and further expanded. This proposal is based on the fact that the diameter of the target lesions with viable tumor tissue should be the basis of measurements for intrahepatic lesions. In addition, there are specific modifications of the original criteria regarding the assessment of vascular invasion, lymph nodes, ascites, pleural effusion, and new lesions. (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)

The expert panel has adopted the concept of viable tumor endorsed by European Association for the Study of the Liver (EASL) and proposed amendments (Llovet JM, et al. 2008) to RECIST in the determination of tumor response for HCC, which have been incorporated into the criteria in this trial as described herein.

Definitions

Intrahepatic lesions: Malignant findings within the liver parenchyma, the portal vein, and the porta hepatis region. The rules for the assessment of intrahepatic lesions (including when a new lesion is considered to have appeared) incorporate the referenced modifications for HCC.

Extrahepatic lesions: All malignant lesions, other than those defined as intrahepatic as above. These lesions will be assessed using the standard RECIST 1.1 approach.

Measurable lesions: Lesions that, at baseline, meet the requirements for being reproducibly quantifiable. The requirements are different for intrahepatic and extrahepatic lesions, and are described below. Lesions that meet the requirements are considered eligible for quantitative assessment during the study.

Non-measurable lesions: Lesions that, at baseline, do not meet the below-described requirements, cannot be chosen for quantitative assessment, and must be assessed qualitatively.

Target lesions: Lesions that are chosen at baseline (from the set of measurable lesions) for quantitative assessment throughout the trial, using rules outlined below. A lesion that has been selected as a target lesion remains a target lesion for the rest of the trial.

Non-target lesions: Lesions that are not chosen at baseline for quantitative assessment, and must be assessed qualitatively throughout the trial. A lesion that has been selected as a non-target lesion remains a non-target lesion for the rest of the trial.

Typical HCC enhancement: A lesion is considered to have typical HCC enhancement if it shows enhancement during the arterial phase of contrast administration, with washout in the portal venous or late venous phase.

Methods of Measurement

All measurements must be recorded in millimeters (or decimal fractions of centimeters).

For measurements of tumors other than lymph nodes, the longest unbroken diameter seen on an axial slice is recorded. Lymph nodes must always be measured in the short axis (the longest measurement on an axial slice perpendicular to the longest diameter of the lymph node). Lymph nodes less than 10 mm in short axis diameter are defined as normal.

The cytological confirmation of the neoplastic origin of ascites or pleural effusion that appears or worsens during treatment when the subject 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.

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.

Clinical Lesions - Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes) and ≥ 10mm diameter as assessed using calipers. 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, chest CT is preferable.

CT / MRI - CT is the best currently available and reproducible methods to measure target lesions selected for response assessment. CT scans should be performed with cuts of 5 mm or less in slice thickness. For assessment of the liver, a three phase enhancement protocol is required, which includes scans prior to contrast administration, during the arterial phase of contrast, and during the portal venous or delayed (systemic venous) phase. MRI is also acceptable. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy / Laparoscopy - The use of these techniques for objective tumor evaluation is not advised.

Cytology / Histology - These techniques can be used to differentiate between PR and CR in rare cases.

Baseline Assessment

Identifying measurable disease:

Non-nodal tumor lesions: Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thickness greater than 5mm are used, the minimum size should be twice the slice thickness.
- 20 mm by chest x-ray
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- For lesions within the liver parenchyma, only the portion of the lesion that shows typical HCC enhancement should be included in the measurement.

Malignant lymph nodes: To be considered pathologically enlarged, a lymph node must be ≥ 10 mm in short axis when assessed by CT scan (except nodes in the porta hepatis – see below). To be considered measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Identifying non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with short axis 10-14 mm) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/ abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.

Intrahepatic lesions: For lesions in the liver parenchyma, those that show typical HCC enhancement with longest diameter <10 mm, as well as those that show typical enhancement in a complex pattern that does not lend itself to reproducible measurement are considered non-measurable.

Porta hepatis lymph nodes: Lymph nodes detected at the porta hepatis can be considered malignant, but not measurable, if the lymph node short axis is at least 2 cm. Nodes in the porta hepatis are never considered measurable.

Portal vein thrombosis: Malignant portal vein thrombosis should be considered a non-measurable lesion.

Selection of target and non-target lesions:

At baseline, lesions are divided into those that will be followed quantitatively (target lesions) and those that will be followed qualitatively (non-target lesions).

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesion with the longest diameter), be representative of all involved organs and should be suitable for reproducible repeated measurements. For the purposes of this selection, paired organs (such as the lungs) should be regarded as a single organ, and all lymph nodes should be regarded as a single organ.

If measurable lesions are present in the liver parenchyma, they should always be selected as target lesions before any other lesions are chosen. Up to 2 liver lesions can be selected, just as with any other organ.

The sum of the diameters (longest diameter for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference measurement when looking for evidence of objective response at later visits.

If there are more than five measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions.

Non-target lesions include all non-measurable lesions, plus any measurable lesions over and above the 5 listed as target lesions. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g.; ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Post-baseline assessment

At every visit after baseline, the investigator will assess the target lesions selected at baseline quantitatively (as described below), assess the non-target lesions selected at baseline qualitatively, and search for new lesions. The lesion assessments are then combined into an assessment of the entire subject at that visit (called the visit response or the overall response).

<u>Target lesion assessment</u>

The investigator will measure each target lesion in the same manner as at baseline. Extrahepatic non-nodal lesions will be measured using their longest diameter. Malignant lymph nodes (excluding those in the porta hepatis, which can never be target lesions) will be measured in short axis diameter. Intrahepatic target lesions will be measured in the longest diameter that shows typical HCC enhancement (excluding areas of necrosis).

If a lesion decreases in size to the point where it is still present, but cannot be measured accurately, a default value of 5 mm should be recorded for its diameter. If a lesion has disappeared, a value of 0 mm should be recorded for its diameter. If a lesion has split into distinct fragments, the longest diameter of each fragment should be measured, and the diameters added together. If two lesions have merged, the longest diameter of the entire resulting lesion should be measured.

The sum of diameters will be calculated by adding all target lesion diameters. The sum of diameters is always compared to two reference points: the baseline sum of diameters, and the smallest sum of diameters seen during the trial (also called the nadir). The baseline may actually be the nadir, if there has been no reduction in the sum of diameters during the trial. The target lesion response is then classified as follows:

Target lesion response	
Complete response (CR)	Complete disappearance of target lesions outside the liver Complete disappearance of typical HCC enhancement from all target liver lesions All target lymph nodes <10 mm
Partial response (PR)	At least a 30% decrease in the sum of diameters from baseline
Progressive disease (PD)	At least a 20% increase in the sum of diameters from the smallest value seen during the trial (including baseline), with at least a 5 mm absolute increase in the sum
Stable disease (SD)	Neither enough shrinkage to qualify as PR, nor enough growth to qualify as PD
Non-evaluable (NE)	One or more target lesions not evaluated because of imaging issues, coverage, or change in imaging technique
Please note that when lymph nodes are included as target lesions, a CR may occur even when the sum of diameters is not zero, since a normal lymph node will have a diameter greater than zero but less than 10 mm.	

Non-target lesion assessment

Non-target lesions are assessed as a whole. After examining each non-target lesion, the investigator will classify the non-target lesion response as follows:

Non-target lesion response	
Complete response (CR)	Complete disappearance of non-target lesions outside the liver Complete disappearance of typical HCC enhancement from all non-target liver lesions All non-target lymph nodes <10 mm Resolution of malignant portal vein thrombosis (if present)
Progressive disease (PD)	Unequivocal progression of non-target lesions as a whole
Non-CR/Non-PD	Non-target lesions still present, without unequivocal progression
Not all evaluated	One or more non-target lesions not evaluated because of imaging issues, coverage, or change in imaging technique

To achieve unequivocal progression in patients with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.

New lesions

Outside the liver, any new lesion that is considered unequivocally malignant is evidence of progression, with no minimum size requirement.

For lesions within the liver, a new lesion can be classified as HCC (and therefore evidence of progression) if its longest diameter is at least 1 cm and it shows typical HCC enhancement. A new lesion that is at least 1 cm without typical HCC enhancement can be diagnosed as HCC if it shows at least 1 cm growth in subsequent scans. A lesion that is smaller than 1cm in longest diameter is not considered a new lesion according to the rules of this protocol.

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. This means that if a new lesion is not unequivocal at the time of initial detection, but later becomes unequivocal, the date of progression will be the date it was first detected.

Visit response

The response of the target lesions, the response of the non-target lesions, and the presence or absence of new lesions are combined into the visit response for the entire subject at this visit, using the tables below.

Response for patients with target and non-target lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	documented at least 6 wk. from randomization
Not all evaluated	Non-PD	no	NE	
PD	Any	Yes or No	PD	
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 for patients with non-target lesions only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* Non-CR/non-PD is preferred over “stable disease” for non-target disease.		

The following text descriptions of the visit response are logically equivalent to the tables above.

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Stable Disease (SD): Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions from the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions also constitute progressive disease. Ascites or pleural effusion will be recorded as disease progression only if proven malignant.

In the absence of measurable disease, the same general concepts apply as noted above.

Progression is assessed on the basis of intrahepatic and extrahepatic disease together. Either the growth of intrahepatic lesions with typical arterial enhancement, or the growth of

extrahepatic tumors, can indicate progression, if the sum of diameters (for target lesions) or the qualitatively assessed total tumor burden (for non-target lesions) indicates progression.

Best Response

The best overall response is the best visit response recorded from the start of the study treatment until the end of treatment. If SD is the best response seen during the study, it must be maintained for at least 42 days after the start of treatment.

Response duration

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable disease duration

Stable disease is measured from the start of the treatment until the criteria for progression are met.

17. Annex 5. Prior signature pages

This annex contains the signature pages of the first final protocol version as well as the signature pages of the stand-alone Protocol Amendment 1. The page numbers are referring to the original documents and not to this protocol version.

18. Annex 6. Switzerland Local Amendment Summary:

All changes in bold face italics, deletions with strike-through.

New local text:

9.8.2. Quality Review

In a subset of patients (at least 10% of key data (as needed to assure good data quality) at all sites) source data verification will be conducted. 100% Source data verification will be done for all informed consent forms at all sites.

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.

New local text:

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].

In Switzerland, the study will be performed as a Phase IV study, as there are no special regulations available for non interventional studies. This means that the study has to be submitted to and approved by the local ethics committee (Most probably a study in risk category "A" according to the new law on human research and its ordinances from 01 January 2014).

New local text:

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. ***Switzerland: the sponsor must also have an authorization of the informed consent form by the local ethics committee.***

New local text:

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.

In Switzerland all patients participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.