Post Authorization Safety Study (PASS) Report - Study Information

Acronym/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
Report version and date	v1.0, 29 MAY 2018
Study type / Study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4564
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
Study Initiator and Funder	Bayer AG
Research question and objectives	This study collected data of patients who were treated with transarterial chemoembolization (TACE) followed by sorafenib for hepatocellular carcinoma (HCC) or without sorafenib after TACE. Outcomes of patients were analyzed in relation to the timing of initiation of sorafenib. It was planned to compare outcomes of patients with early start of sorafenib treatment to those without early start of sorafenib treatment after TACE. In addition, practice patterns of the investigators involved in the care of patients with HCC under real-life conditions were evaluated. The primary objective of this study was the comparison of two cohorts of HCC a patients regarding overall survival (OS) from time of TACE non-eligibility. The two cohorts of special interest were defined based on the investigators'

	treatment decisions (i.e. patients with early start of sorafenib treatment vs. patients without early start of sorafenib treatment).
Country(-ies) of study	25 countries in the region Europe/Canada, Asia Pacific and Latin America.
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, Leverkusen, Germany
Marketing authorization holder contact person	[redacted]

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1. Abstract

Acronym/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
Report version and date **Author**	v1.0, 29 MAY 2018, [redacted]
Keywords	Hepatocellular carcinoma, sorafenib, TACE, TACE non-eligibility, BCLC
Rationale and background	Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. Transarterial chemoembolization (TACE) is currently the recommended treatment option for patients with intermediate HCC (Barcelona Clinic Liver Cancer [BCLC] stage B) with multinodular tumors without vascular invasion or extrahepatic spread. 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.
Research question and objectives	This study collected data of patients who were treated with TACE followed by sorafenib for HCC or without sorafenib after TACE. Outcomes of patients were analyzed in relation to the timing of initiation of sorafenib. In addition, practice patterns of the investigators involved in the care of patients with HCC under real-life conditions were evaluated. The primary objective of this study was the comparison of two cohorts of HCC patients regarding overall survival (OS) from time of TACE non-eligibility. The two cohorts of special interest were defined based on the investigators' treatment decisions (i.e. patients with early start of sorafenib treatment vs. patients without early start of sorafenib treatment).
Study design	Non-interventional, international, prospective, open-label, multi-center study.

Setting	25 countries in the region Europe/Canada, Asia Pacific and Latin America. The enrollment period was planned to be 18 months with a minimum follow-up period of 18 months resulting in total study duration of 36 months.
Subjects and study size, including dropouts	Overall, 1676 patients were enrolled and 1650 patients received TACE (overall TACE population). In the overall TACE population, 42.1% of patients died and 25.5% of patients prematurely discontinued the study. The population of TACE administered patients who became TACE non-eligible after initial TACE based the criteria specified in the protocol included 507 patients. A total of 515 patients received sorafenib.
Variables and data sources	Data were collected from medical records including historic data and data documented during visits that took place in routine practice.
Results	In patients who became TACE non-eligible during the study based on the criteria specified in the protocol, the median OS was 590 days (95% confidence interval [CI]: 474;695 days). As allocation bias was not corrected for, no comparison between the cohorts (patients with early start of sorafenib treatment vs. patients without early start of sorafenib treatment, each based on the investigators' treatment decisions) can be made. The study indicated multiple TACE treatments prior to sorafenib therapy in a substantial number of patients. A total of 400 sorafenib-treated patients (77.7%) experienced treatment-emergent adverse events (TEAEs). In 52.6% of patients, the TEAEs were related to sorafenib treatment. Overall, the most frequently reported TEAEs were diarrhea (18.4%), palmar-plantar erythrodysesthesia syndrome (17.7%), and neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (12.8%).
Discussion	Overall, it could be shown that TACE treatment varies greatly between patients and does not necessarily adhere to treatment guidelines with respect to TACE non-eligibility. The overall safety profile of sorafenib observed in this study is in line with the known profile.
Marketing Authorization Holder(s)	Bayer AG, Leverkusen, Germany

Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators for each country and site participating in the study are listed in a stand-alone document (see Annex 1) which is available upon request.

2. List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse Event
AG	Aktiengesellschaft
ALBI	Albumin-bilirubin
APASL	Asian Pacific Association for the Study of the Liver
ATC	Anatomical Therapeutic Chemical (Classification System)
BCLC	Barcelona Clinic Liver Cancer
CHIP	Chiba Hepatocellular Carcinoma in intermediate-stage prognostic
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EASL	European Association for the Study of the Liver
ECOG	Eastern Co-operative Oncology Group
EDC	Electronic Data Capture
EORTC	European Organization of Research and Treatment of Cancer
EU	European Union
HAP	Hepatoma Arterial-Embolization Prognostic (Score)
HCC	Hepatocellular Carcinoma
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
JSH	Japan Society of Hepatology
MedDRA	Medical Dictionary for Regulatory Activities
RECICL	Response Evaluation Criteria in Cancer of the Liver
(m)RECIST	(modified) Response Evaluation Criteria In Solid Tumors
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PFS	Progression-Free Survival
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SAP	Statistical Analysis Plan

SOAP	Sorafenib Analysis Population
SOC	System Organ Class
STATE	Selection for Transarterial Chemoembolization Treatment
TACE	Transarterial Chemoembolization
TCE	Overall Transarterial Chemoembolization Population
TEAE	Treatment-Emergent Adverse Event
TEB	Transarterial Chemoembolization Eligible until End of Study
TESAE	Treatment-Emergent Serious Adverse Event
TNE	Transarterial Chemoembolization Non-Eligible Population
TNEB	Transarterial Chemoembolization Non-Eligible at Inclusion Visit
TNM	Tumor, Nodes (lymph nodes) and Metastases (Classification)
TTP	Time To Progression
US(A)	United States (of America)

3. Investigators

Contact details and the list of all investigators are provided in a stand-alone document in Annex 1 and can be provided upon request.

4. Other responsible parties

4.1 Sponsor contact names

Function: [redacted]
Name: [redacted]

Function: [redacted]
Name: [redacted]

Function: [redacted]
Name: [redacted]

Function: [redacted]
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Function: [redacted]
Name: [redacted]

Function: [redacted]
Name: [redacted]

Function: [redacted]
Name: [redacted]

Contact details of the responsible parties at Bayer AG are available upon request.

4.2 Contract research organization

Contract Research Organization (CRO) contact details:

[redacted]

4.3 Steering committee

Information on the Steering Committee Members and also the respective Charters are kept as a stand-alone document (see Annex 1) and is available upon request.

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection (actual FPFV)	Q3 2013	28 OCT 2013	None
End of data collection (database clean)	Q3 2017	10 NOV 2017	None
Registration in the EU PAS register	Q3 2013	22 AUG 2013	None
IEC or IRB approval - Study protocol version 1.0	Q2 2013	First approval: NA Last approval: NA	First protocol version was amended 2 months after becoming effective
IEC or IRB approval -Study protocol version 2.0	Q3 2013	First approval: 21 AUG 2013 Last approval: 12 AUG 2015	None
IEC or IRB approval -Study protocol version 3.0	Q4 2015	First approval: 31 MAY 2016 Last approval: 12 AUG 2016	None
First Interim analysis	500 patients observed for at least 6 months	31 MAR 2015	None

Milestone	Planned date	Actual date	Comments
Second Interim Analysis	1000 patients observed for at least 6 months	23 DEC 2015	None
Final report of study results	Q1 2018	29 MAY 2018	None

*A complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1) which is available upon request.
EU PAS: European Union Post-Authorization Study, FPFV: first patient first visit, IEC: Independent Ethics Committee, IRB: Institutional Review Board, NA: not applicable

6. Rationale and background

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the sixth most common cancer in the world, the second most common cause of cancer-related death (1), and the leading cause of death in patients with cirrhosis (2, 3, 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 (6). Thus, 80% of HCC develops in patients with liver cirrhosis and this preneoplastic condition is the strongest predisposing factor (2, 7). 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 (8, 9). In HCC patients, prediction of prognosis is complex due to heterogenic conditions 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). Barcelona Clinic Liver Cancer (BCLC) staging system is one of the commonly applied staging systems. The 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 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). At the time of study start, sorafenib was 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 [SHARP], 26). For patients who have failed TACE, a subanalysis for the SHARP study also indicated a trend of survival benefit under sorafenib treatment. A non-interventional study in patients treated with sorafenib (GIDEON) indicated multiple TACE treatments prior to sorafenib therapy in a substantial number of patients. In this study, shorter duration of treatment of sorafenib in the real practice than the treatment duration of sorafenib according to SHARP also has been observed (27, 28).

This study was an international, prospective, open-label, multi-center, non-interventional study to evaluate outcomes of all patients who were 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 collected more detailed information concerning TACE treatments in a prospective manner, for enabling evaluation of the time to meet non-eligibility criteria according to the protocol (see section 9.1.1 of the study protocol version 3.0; provided as a stand-alone document to be found in Annex 1 and available upon request).

Please note that this study was designed to evaluate outcomes of all patients with early start of sorafenib treatment after TACE (cohort 1) and patients without early start of sorafenib treatment after TACE (cohort 2), each based on the investigators' treatment decisions. However, after the second interim analysis, it was found that cohort allocation was imbalanced (cohort 1: cohort 2 = 1: 9). With the low patient numbers in cohort 1, as well as multiple covariates, a comparison based on a propensity score matched population was not appropriate. In addition, there were significant differences in patient management among regions (China, Japan, Korea, Europe, and other countries). Based on the results of the second interim analysis and discussion with the Steering Committee members, it was decided not to compare both cohorts, but to summarize all results by regions of interest (study region), as well as for the overall population.

7. Research question and objectives

7.1 Primary objective(s)

The primary objective of this study was changed to describe OS from time of TACE non-eligibility in two cohorts of special interest not only overall but also by study region. The two cohorts were defined based on the investigators' treatment decisions (i.e. patients with early start of sorafenib treatment vs. patients without early start of sorafenib treatment including no sorafenib treatment)[1].

[1] The primary objective was adapted in the statistical analysis plan (SAP). The original wording from the study protocol was "The primary objective is to evaluate TACE treatment and outcomes (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, each based on the investigators' treatment decisions."

7.2 Secondary objective(s)

Secondary objectives were[2]:

- To evaluate progression-free survival (PFS), time to progression (TTP), tumor response and adverse events (AEs) from time of TACE non-eligibility[3].
- To evaluate OS, PFS, TTP, tumor response and AEs from start of sorafenib treatment.
- To determine duration of treatment 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 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[4].
- In addition, practice patterns of the investigators involved in the care of patients with HCC under real-life conditions were evaluated.

8. Amendments and updates

Amendments and changes to the study protocol are summarized in Table 2. For a complete list of changes, see section 5 of the study protocol version 3.0 (provided as a stand-alone document to be found in Annex 1 and available upon request).

[2] The secondary objective "To determine the proportions of patients who receive sorafenib after TACE and those who do not receive sorafenib after TACE, respectively, regionally and globally" was deleted in the SAP.
[3] The specification "overall and in the cohorts of special interest" was deleted in the SAP.
[4] The specification „regionally and globally" was deleted in the SAP.

Table 2: Amendments

No.	Date	Section of study protocol	Amendment / Update	Reason
1	15 May 2013	Several	Section 9.2.2: One inclusion criterion added Section 9.2.3: One exclusion criterion added Section 9.2.5: Information added for the time of initial visit in case that the first TACE was documented retrospectively Sections 9.3, 9.3.3, 9.3.4,9.3.8, 9.3.9, and 17: adaption of variables	To include only patients with BCLC stage B or higher and to exclude patients with a systemic anti-cancer therapy prior to the first TACE. As baseline data was needed at the time of first TACE, the whole initial visit had to be documented retrospectively. Documentation of Cancer of the Liver Italian Program (CLIP) score deleted. Sex was missing as variable and the category "Caucasian" within the variable "race" was changed to "white". Platelets and baseline C reactive protein were added. "More than two" was incorrect. This was changed to "Two or more". Jaundice was deleted. Criteria referring to prior TACE were excluded for the initial visit, because the observation starts with the first TACE. Response evaluation was preferably to be done according to modified Response Evaluation Criteria In Solid Tumors (mRECIST).
	04 Jul 2013 (Version 2.1)		The standard definition of AEs 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 was changed.

No.	Date	Section of study protocol	Amendment / Update	Reason
	30 Oct 2013	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 6 of the study protocol V3.0 (provided as stand-alone document in Annex 1)	
2	04 Sep 2015 (Version 3.0)	Several	Section 6: Milestones updated Section 9.1.1: Definition of non-eligible for TACE was modified. Section 9.3.4: Lab values updated Section 9.7: Statistical section updated	To increase enrollment period. Child Pugh class B or C was excluded from the definition. Gamma-Glutamyl-Transferase and Cholinesterase added. Following the decision to conduct a second interim analysis, this section was revised. Assessment of outcome by procedures of TACE was added.

9. Research methods

9.1 Study design

This study was a non-interventional, international, prospective, open-label, multi-center study. The treating investigator decided on the treatment of the patient based on medical assessments in close relation to the patient's physical and psychological status. All treatment decisions followed the real-life treatment behavior of the investigator.

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' OS. At the time of the study start there was no homogeneous approach in the treatment of patients with HCC. In most countries TACE was a preferred treatment, but the range of patients it was used for, was wide. Though, in most countries it was one of the first therapeutic options for unresectable HCC, the number of TACEs as well as subsequent therapies were very flexible.

9.1.1 Primary endpoint

The primary endpoint was OS from time of TACE non-eligibility.

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

A patient was classified non-eligible for TACE, if at least one of the criteria in section 9.4.8 except 'advanced liver disease (Child Pugh class B or C) was met.

Time of TACE non-eligibility was the first point in time in the study when TACE non-eligibility was met according to the documentation in the case report form (CRF). In case of a pre-existing TACE non-eligibility, time of TACE non-eligibility was 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 were:

- OS from initial TACE was 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 were censored at the last date known to be alive.
- PFS from initial TACE was defined as the time interval measured from the day of the first TACE to documented (radiological or clinical) progression or death, whichever came first.
- TTP from initial TACE was 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 were censored at their last date of tumor evaluation.
- Tumor response to TACE by modified Response Evaluation Criteria In Solid Tumors (mRECIST) were evaluated according to the categories "Complete Response", "Partial Response", "Stable Disease", and "Not evaluable" by mRECIST for each TACE.
- Duration of TACE treatment was 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 was no longer applicable regardless of the reason for discontinuation including death).
- TACE unsuitability was determined according to the selected guidelines including AASLD, APASL, JSH, European Association for the Study of the Liver (EASL)-EORTC guidelines, etc.[5]
- Time to TACE non-eligibility was determined according to the selected guidelines including AASLD, APASL, JSH, EASL-EORTC guidelines, etc.

[5] TACE unsuitability was not analyzed individually for the APASL and EASL-EORTC guidelines. However, these guidelines were used to define TACE non-eligibility based on the criteria presented in section 9.9.2.1.

- Deterioration of liver dysfunction was evaluated throughout the study. Deteriorations of liver dysfunction were defined as below
    - Deterioration of Child Pugh score (A5, A6, B7, B8, B9)[6]
    - Liver dysfunction reported as AE or deterioration of aspartate aminotransferase, alanine aminotransferase or bilirubin (from Grade 1 to Grade 2-5, from Grade 2 to 3-5, Grade 3 to Grade 4 or 5)[6]
    - Any liver related adverse events or deterioration of liver related events according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03[6]
    - Change of liver related lab data (aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, prothrombin international normalized ratio [INR])

Specific secondary endpoints for patients treated with sorafenib were:

- OS from initiation of sorafenib was 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 were censored at the last date known to be alive.
- PFS from initiation of sorafenib was defined as the time interval measured from the start date of sorafenib treatment to documented (radiological or clinical) progression or death, whichever came first.
- TTP from initiation of sorafenib was 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 were censored at their last date of tumor evaluation.
- Duration of sorafenib treatment was 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 was 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 was analyzed providing absolute and relative frequencies of the tumor status categories.
- Incidence of treatment-emergent adverse events (TEAEs) – patients were 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 of the study protocol V3.0 (provided as stand-alone document in Annex 1).

[6] Please note that this endpoint was not analyzed.

The following additional endpoints were needed for analysis of the defined objectives:

- PFS from TACE non-eligibility was defined as the time interval from TACE non-eligibility to documented (radiological or clinical) progression or death, whichever came first.
- TTP from TACE non-eligibility was defined as the time interval from TACE non-eligibility to the date of documented progression. Patients without tumor progression at the end of the study were censored at their last date of tumor evaluation.
- Tumor response from time of TACE non-eligibility by mRECIST were planned to be evaluated according to the categories "Complete Response", "Partial Response", "Stable Disease", and "Not evaluable" by mRECIST for each TACE. However, it was decided to exclude this from the analysis (see section 10.4.2.1).
- Switch to sorafenib or other systemic and non-systemic cancer therapy was evaluated according to the categories "Before initial TACE", "After one TACE", "After two TACEs", and "After more than two TACEs"
- Duration of treatment of sorafenib after TACE is provided for patients who became TACE non-eligible after initial TACE by cohort and was defined as days from the first sorafenib dose to the date of permanent discontinuation of sorafenib plus one.
- Deviations from recommendations for TACE use in the treatment guidelines for TACE use based on the number of patients for whom the treatment decision for a new TACE was made by the investigator after TACE non-eligibility.

9.2 Setting

The study was performed in 25 countries in the region Europe/Canada, Asia Pacific and Latin America[7]. A total of 1,670 patients were planned to be enrolled. The enrollment period was planned to be 18 months with a minimum follow-up period of 18 months resulting in total study duration of 36 months.

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

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

In the case that the first TACE was documented retrospectively under the pre-requisites detailed in section 9.3.2. the baseline data asked for in the initial visit also had to be documented retrospectively.

The final data collection (last visit) was at patient's death or at end of study (including premature discontinuation; whichever was earlier). If the documentation was stopped prematurely, the reasons for the end of observation had to be given. If a patient joined an interventional clinical study during

[7] Please note that this does not correspond to the regions as defined in the SAP.

the course of observation, at least the information on survival was still collected up to the end of this study.

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

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

Table 3: 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 [a]	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 [b]		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 [b]	X	X	
AE		X	X
Concomitant medication (including non-systemic therapy for HCC)	X	X	X
Reasons for end of observation			X
Investigator's signature			X [c]

[a] The time interval between two documented tumor assessments was assumed to be 6 - 12 weeks, although this was at the treating investigator's discretion.
[b] Had to be documented at each follow-up visit.
[c] One signature at the end of documentation.
BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Co-operative Oncology Group , HCC: hepatocellular carcinoma, TACE: transarterial chemoembolization, TNM: tumor, nodes (lymph nodes) and metastases (classification).

9.3 Subjects

9.3.1 Eligibility

Patients enrolled in this study had a diagnosis of unresectable HCC in whom a decision to treat with TACE was made at time of study enrollment. Patients were to be enrolled consecutively in order to avoid any selection bias and thus to increase the likelihood of representativeness.

9.3.2 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 computed tomography (CT), CT hepatic arteriography / CT arterial portography or magnetic resonance imaging (MRI).
- Patients with BCLC stage B or higher.
- Patients for whom a decision to treat with TACE was made at time of study enrollment. Patients who had received one TACE in the past also could be enrolled, if the TACE was done at the same site and all required data about such previous TACEs were available. TACE included both conventional TACE with lipidiol (or similar agents) and chemotherapeutic agent(s) and TACE with DC Beads® excluding transarterial embolization without chemotherapeutic agent.
- Patients with unresectable HCC (incurable with curative treatments including resection or ablation or not eligible for resection or local ablation).
- Patients had to have signed an informed consent form.
- Patients had to have a life expectancy of at least 8 weeks.

9.3.3 Exclusion criteria

- Patients who had received TACE in the past but the data about TACE required by the protocol were not available.
- Patients who had received any systemic anti-cancer therapy prior to the first TACE.
- Patients who were 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 were to be considered.

9.4 Variables

9.4.1 Primary outcome variable(s)

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

9.4.2 Secondary outcome variable(s)

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

9.4.3 Demographic data and other baseline characteristics

The following data were recorded:

- Birthdate (at least year)
- Sex
- Race (Asian, White, Black, Other)[8]
- Weight (kg / pound)
- Height (cm / inch)
- Alcohol use
- Status of smoking (cigarettes)
- Medical history of HCC
- History of liver disease
- General medical history

9.4.4 Laboratory data

- Platelets
- Prothrombin INR
- Total bilirubin
- Alanine aminotransferase

[8] Note: race was not recorded in countries where legally not permitted.

- Aspartate aminotransferase
- Alkaline phosphatase
- Creatinine
- Creatinine clearance
- Albumin
- Sodium
- Lactate dehydrogenase
- Alpha fetoprotein
- C reactive protein (baseline only)
- Gamma-Glutamyl-Transferase
- Cholinesterase

9.4.5 Pretreatment of HCC

For patients who were not newly diagnosed, any systemic or non-systemic pretreatments were documented.

9.4.6 Concomitant medication

Information on concomitant medication to be collected included:

- Trade name or International Nonproprietary Name (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"

9.4.7 Visit date(s)

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

- Date (day, month, year)

9.4.8 Disease status summary

The following criteria were 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)
- Eastern Co-operative Oncology Group (ECOG) performance status ≥1
- BCLC C or D
- Vascular invasion.
- Two or more consecutive incomplete necrosis (depositions (50%) of lipiodol) were 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) were 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 creatinine clearance rate <30 mL/min)
- Other (to be specified)

9.4.9 Tumor assessment

Patients were assessed for response to TACE and tumor assessment preferably by mRECIST. In case that an assessment by mRECIST was not possible, because this was not routinely done at the site of the treating investigator, also other evaluation criteria could be used. In any case the criteria used were to be documented along with the tumor evaluation and the investigator was to use the same criteria throughout all tumor evaluations for one patient.

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

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

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

9.4.10 Physical examination

The following criteria were assessed at initial visit and every follow-up visit:[9]

- Weight
- Blood pressure

9.4.11 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

9.4.12 Adverse events

Information on AEs to be documented:[10]

- Diagnosis or symptoms
- Start and stop dates
- NCI-CTCAE grading
- Sorafenib treatment before the start of the AE
- Seriousness
- Relationship

[9] Physical examinations are routine assessments in clinical practice and were therefore included in the CRF.
[10] Adverse events are routinely collected in clinical practice and were therefore included in the CRF.

- Actions taken
- Outcome
- Other specific treatment(s)

9.4.13 Reasons for choice of treatment

The treating investigator decided 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 followed the real-life treatment behavior of the investigator. As there could be expected a wide range of factors influencing treatment decisions over the entire observation period, this was not captured in the CRF in detail. In any case reasons for stop of sorafenib were documented.

9.5 Data sources and measurement

The investigator collected historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collected treatment-related data, results of tumor assessments and other disease status information, which were also documented in the medical record, during visits that took place in routine practice. For any AEs that occurred, information was directly obtained from the patient. In case a patient was seen by more than one physician for his/her disease (e.g. the patient was monitored by a physician other than the initial investigator), the initial investigator was to make every effort to collect information on any visits (including results) that took 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.

9.6 Bias

As a non-interventional study, limitations inherent to observational studies might have generated potentially biased results. Originally, the study aimed to compare two non-randomized cohorts of patients as defined in section 9.9.2.2. In order to control for the imbalance according to non-randomized cohort allocation, propensity score matching was planned (see section 9.7.4 and 9.7.8 of the study protocol version 3.0; provided as a stand-alone document to be found in Annex 1 and available upon request). However, due to the low numbers of patients in cohort 1 and multiple covariates, a comparison based on a propensity score matched population was not appropriate. All analyses were done in a descriptive manner.

Therefore, as this is an observational study in a heterogeneous population and no propensity score matching was done, careful attention should be paid to when describing the patient population, and caution should be applied to the interpretation of results. Comparisons to previous studies, and/or across analysis sets and cohorts will be biased.

Patients were to be enrolled consecutively to reduce selection bias.

9.7 Study size

The primary objective of the study was 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, each based on the investigators' treatment decisions) regarding OS as defined in section 9.9.2.4. The enrollment period was 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 1500 patients who have

a complete documentation, it was envisaged to enroll 1670 patients accounting for an expected loss to follow up rate of approximately 10%.

It was expected that out of the 1500 completely documented patients at least 250 would become part of cohort 1 (patients with early start of sorafenib treatment based on the investigators' treatment decisions) while at least the same number of patients would become part of cohort 2 (patients without early start of sorafenib treatment based on the investigators' treatment decisions). Further assuming a prolongation of median survival time from 9 to 12 months in patients with early start of sorafenib treatment, exponential distribution of OS, 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%.

Please note that after the second interim analysis, it was found that cohort allocation was imbalanced (cohort 1: cohort 2 = 1: 9). With the low patient numbers in cohort 1, as well as multiple covariates, a comparison based on a propensity score matched population was not appropriate.

9.8 Data transformation

Not applicable.

9.9 Statistical methods

9.9.1 Main summary measures

The statistical analysis is described in detail in the Statistical Analysis Plan (SAP, version 1.1, dated 07 NOV 2017) and can be found in Annex 1 as a stand-alone document.

The statistical evaluation were performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, North Carolina, USA).

Statistical analyses were of explorative and descriptive nature. All variables were 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 [SD], minimum [Min], median, quartiles and maximum [Max]). Continuous variables were described by absolute value and as change from baseline per analysis time point, if applicable. Selected continuous variables were categorized in a clinically meaningful way. Time to event data were described by Kaplan-Meier estimates (including number failed, number censored, 25^{th} and 75^{th} percentiles with respective 95% confidence interval [CI] and median with 95% CI).

This study was designed to evaluate outcomes of all patients with early start of sorafenib treatment after TACE (cohort 1) and patients without early start of sorafenib treatment after TACE (cohort 2), each based on the investigators' treatment decisions. However, after the second interim analysis, it was found that cohort allocation was imbalanced (cohort 1: cohort 2 = 1: 9). With the low patient numbers in cohort 1, as well as multiple covariates, a comparison based on a propensity score matched population was not appropriate. In addition, there were significant differences in patient management among regions (China, Japan, Korea, Europe, and other countries). Based on the results of the second interim analysis and discussion with the Steering Committee members, it was decided not to compare both cohorts, but to summarize all results by regions of interest (study region), as well as for the overall population.

9.9.2 Main statistical methods

9.9.2.1 General Statistical Considerations

If not otherwise specified, the analyses were presented for the overall population as well as by cohort.

The 4 different sets of criteria applied to evaluate TACE non-eligibility are shown in Table 4.

Table 4: TACE non-eligibility criteria

	Criteria Set 1: Protocol specified criteria	Criteria Set 2: AASLD based criteria	Criteria Set 3: Child Pugh based criteria	Criteria Set 4: JSH based criteria
Extrahepatic spread (N1, M1)	X	X	X	X
ECOG performance status ≥1	X			
BCLC C or D	X	X	X	
Advanced liver disease (Child–Pugh class C)[1,2]	X		X	
Vascular invasion	X	X	X	X
Hepatic vein invasion	X	X	X	X
Portal vein thrombosis	X	X	X	X
Lack of portal blood flow	X	X	X	X
Clinical symptoms of end-stage cancer	X	X	X	X
Clinical encephalopathy	X	X	X	X
Refractory ascites	X	X	X	X
Extensive tumor with massive replacement of both entire lobes	X	X	X	X
Technical contraindications to hepatic intra-arterial treatment	X	X	X	X
TACE failure by investigator's assessment	X	X	X	
Two or more consecutive incomplete necrosis (depositions (50%) of lipiodol) are seen by response evaluation CT within the treated tumors ≥4 weeks after adequately performed TACE	X		X	X
Two or more consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT ≥4 weeks after adequately performed TACE.	X		X	X
Renal insufficiency (creatinine ≥2 mg/dL or creatinine clearance rate <30 mL/min)	X	X	X	X
Untreated varices at high risk of bleeding	X	X	X	X
Active lung disease	X	X	X	X
Active cardiovascular disease	X	X	X	X
Increased risk of liver failure and death	X	X	X	X
Continuous elevation of tumor markers even though right after TACE[3]	X		X	X
Comorbidities involving compromised organ function	X	X	X	X
Bile duct occlusion or incompetent papilla due to stent or surgery	X	X	X	X
Other (as specified on the CRF)	X		X	X

[1] Child Pugh class B is considered as TACE eligible (as of protocol version 3.0)
[2] Child Pugh class is derived by CRF section "Child Pugh Classification"
[3] This criterion was added in the Statistical analysis plan version 1.1
AASLD: American Association for the Study of Liver Diseases, CRF: case report form, CT: computed tomography, JSH: Japan Society of Hepatology, TACE: transarterial chemoembolization

All therapies documented were coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. In addition, AEs were coded according to the NCI-CTCAE Version 4.03.

Definition of derived variables and subgroups can be found in section 4.6 of the SAP.

9.9.2.2 Analysis sets

The overall TACE population (TCE)

All enrolled patients were included into TCE, except the following patients:

- he/she has not undertaken initial TACE treatment
- he/she has not signed or insufficiently dated his/her informed consent. Patients with withdrawn consent might have been excluded, according to local requirements.
- his/her documented date of informed consent was before the start of the study in the corresponding site (this was an indication of a retrospective enrollment).

TACE non-eligible population (TNEx; x: Criteria number)

All patients valid for TCE who were eligible for TACE based on criteria x (x is a criteria number; see section 9.9.2.1) at the inclusion visit and changed to TACE non-eligibility based on criteria x with the exception of patients treated with sorafenib or any other systemic anti-cancer treatment prior to time of TACE non-eligibility were included.

Programmatic assignment of patients to the following cohorts was implemented as follows:

- Cohort 1: Patients with early start of sorafenib treatment.

  This cohort comprises all patients for whom the investigator decided at the time of TACE non-eligibility to choose sorafenib as the next treatment option (regardless of whether TACE treatment was continued or not).

- Cohort 2: Patients without early start of sorafenib treatment.

  This cohort comprises all patients for whom the investigator decided 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 was made at a later point in time, patients who were never treated with sorafenib as well as patients for whom another systemic cancer treatment was chosen by the investigator either at time of TACE non-eligibility or at a later point in time.

In the remainder of the document, this set is termed “population of (TACE administered) patients who became TACE non-eligible after initial TACE”.

TACE non-eligible at inclusion visit (TNEBx; x: Criteria number)

All patients valid for TCE who were not eligible for TACE prior to the first TACE based on criteria x (x is a criteria number; see section 9.9.2.1) were included.

In the remainder of the document, this set is termed “population of (TACE administered) patients non-eligible for TACE prior to the first TACE”.

Sorafenib analysis population (SOAP):

All patients included if they took at least one unit (i.e. dose/administration) of sorafenib, except patients who have not signed or insufficiently dated their informed consent. Patients with withdrawn consent might have been excluded, according to local requirements.

In the remainder of the document, this set is termed "population of sorafenib treated patients".

For a definition of the **population of patients TACE eligible until end of study**, see SAP section 5.1 (provided as a stand-alone document to be found in Annex 1 and available upon request).

9.9.2.3 Population Characteristics

Patient disposition was analyzed descriptively.

All background data such as patient demographics, diagnosis and prior treatment of HCC, past medical history, concomitant diseases, and concomitant medications were described by presenting frequency distributions and/or basic summary statistics. Tables on concomitant medications show absolute and relative frequencies by the first two Anatomical Therapeutic Chemical (ATC) levels anatomical main group and therapeutic subgroup.

Background data were summarized for the five populations described in section 9.9.2.2.

In addition, the background data of age, sex, and BCLC stage (at first diagnosis and at inclusion visit) were summarized separately for the subgroup of patients with first TACE documented retrospectively versus the subgroup with first TACE collected during the study. Retrospective TACE was defined as TACE that had been administered before date of informed consent.

The following prognostic scores were presented descriptively for the overall TACE population (the variables to derive these scores and derivation rules are provided in section 4.6.2 of the SAP):

- Chiba HCC in intermediate-stage prognostic (CHIP) score: for the categories of 0-2, 3, 4, 5 and 6-7. Since the CHIP score was developed for patients with Child Pugh Score ≤9, patients whose Child Pugh Score was >9 were excluded from this summary.
- Selection for Transarterial Chemoembolization Treatment (STATE) score: for the categories of <18 and ≥18 [11].
- Hepatoma arterial-embolization prognostic (HAP) score: for the categories of 0 (HAP A), 1 (HAP B), 2 (HAP C), >2 (HAP D).

For TACE administered patients non-eligible for TACE prior to the first TACE , treatment decisions (i.e. monitoring only, new TACE, new initiation of sorafenib treatment) at the first follow-up visit were tabulated. Each combination of treatment decisions, i.e. new TACE and other local treatment, were presented with the percentages adding to 100%.

For TACE administered patients who became TACE non-eligible after initial TACE, treatment decisions at the first follow-up visit after TACE non-eligibility were presented by visit number where TACE non-eligibility was detected. In addition, for patients whose treatment decision at the time of TACE non-eligibility was "new TACE", the subsequent treatment decisions were tabulated.

[11] Please note that the SAP stated ≤18 and >18 (see section 9.9.5).

Duration of exposure to sorafenib was summarized for sorafenib treated patients, using the time from the first sorafenib dose to the date of permanent discontinuation of sorafenib.

Imputations for missing dates are described in section 4.3.2 and section 6.3.4 in the SAP.

Use of systemic anti-cancer treatments and use of non-systemic anti-cancer treatments are tabulated by type of treatment.

9.9.2.4 Analysis of Primary Outcome Variable(s)

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

The analysis population for this primary endpoint was the population of TACE administered patients who became TACE non-eligible after initial TACE.

Kaplan-Meier estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% CI and median with 95% CI) and Kaplan-Meier plots for OS are displayed for the overall population as well as by the two patient cohorts of special interest (see section 9.9.2.2 for a definition of these cohorts).

In addition, the primary endpoint was summarized by subgroups of interest: number of previous TACEs (prior to non-eligibility; 1, 2, 3, 4-5, or ≥6) and response to the first TACE (complete response, partial response, or no response) based on radiological progression (best response regardless of type of assessment), Response Evaluation Criteria In Solid Tumors (RECIST), mRECIST. In case multiple TACEs were performed on the same day they were counted as one TACE.

Imputations for incomplete death dates are described in section 4.3.1 of the SAP.

9.9.2.5 Analysis of Secondary Outcome Variable(s)

Overall survival (OS) from initial TACE / from start of sorafenib

OS was defined as the time (days) from initial TACE (for overall TACE population) or time from start of sorafenib (for sorafenib treated patients) to the date of death due to any cause. Patients lost to follow-up or alive at the end of the study were censored at the last date they were known to be alive.

Kaplan-Meier estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% CI and median with 95% CI) as well as Kaplan-Meier curves were provided for OS from the first TACE (for overall TACE population) and OS from the start of sorafenib treatment (sorafenib treated patients).

Imputations for incomplete death dates are described in section 4.3.1 of the SAP.

Progression-free survival (PFS)

PFS was defined as the time (days) from initial TACE (for overall TACE population), time of TACE non-eligibility (for population of TACE administered patients who became TACE non-eligible after initial TACE), or start of sorafenib (for sorafenib treated patients) to the date of first observed disease progression (any radiological or clinical) or death due to any cause, whichever was earlier. Patients without disease progression or death up to end of study were censored at the date of last tumor evaluation. Patients without any tumor evaluation after inclusion were censored at day 1. PFS was calculated considering all assessment types. These progression assessments considered clinical progression in addition to each radiological assessment.

Kaplan-Meier estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% CI and median with 95% CI) as well as Kaplan-Meier curves are provided for PFS from initial TACE (for overall TACE population), PFS from time of TACE non-eligibility (for population of TACE administered patients who became TACE non-eligible after initial TACE), and PFS from the start of sorafenib treatment (for sorafenib treated patients).

Imputations for incomplete death or progression dates are described in section 4.3.1 of the SAP.

Time to progression (TTP)

TTP was defined as the time in days from initial TACE (for overall TACE population), time of TACE non-eligibility (for population of TACE administered patients who became TACE non-eligible after initial TACE), or start of sorafenib (for sorafenib treated patients) to the date of first documented disease progression. Only radiologically documented progression of tumor was considered as disease progression. Clinical progression as judged by the investigators was not considered as progressive disease, unless accompanied by radiological progression. Patients without radiological progression up to the end of study were censored at the date of last radiological tumor evaluation. Patients without any radiological tumor evaluation after inclusion were censored at day one.

Kaplan-Meier estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% CI and median with 95% CI) as well as Kaplan-Meier curves are provided for TTP from initial TACE (for overall TACE population), TTP from time of TACE non-eligibility (for population of TACE administered patients who became TACE non-eligible after initial TACE), and TTP from start of sorafenib treatment (for sorafenib treated patients).

Imputations for incomplete progression dates are described in section 4.3.1 of the SAP.

Duration of treatment of sorafenib

Duration of treatment of sorafenib after TACE is provided for TACE administered patients who became TACE non-eligible after initial TACE by cohort and was defined as days from the first sorafenib dose to the date of permanent discontinuation of sorafenib plus one. If the date of permanent discontinuation was missing, the date was imputed based on the last known alive date as described in section 4.3.2 of the SAP. For patients who did not take any sorafenib, the duration of sorafenib was considered missing.

TACE practice pattern of the investigators

- **Duration of exposure to TACE treatment** was provided for the overall TACE population, the population of TACE administered patients non-eligible for TACE prior to the first TACE, the population of TACE administered patients who became TACE non-eligible after initial TACE and was defined as the time interval from the first TACE to the date of the last TACE plus one. For the population of TACE administered patients eligible for TACE until end of study, duration of exposure to TACE treatment was defined as the time interval from the first TACE to the end of observation plus one.
- **Number of TACEs** (number of patients by number of TACEs: 1, 2, 3, 4-5, or ≥6) for the overall TACE population, the population of TACE administered patients non-eligible for TACE prior to the first TACE, the population of TACE administered patients who became TACE non-eligible after initial TACE, the population of TACE administered patients eligible for TACE until end of study , and sorafenib treated patients. In case multiple TACEs were performed on the same day they were counted as one TACE

- **Intervals between TACEs** (for patients who took more than one TACE) for the overall TACE population, the population of TACE administered patients non-eligible for TACE prior to the first TACE, the population of TACE administered patients who became TACE non-eligible after initial TACE, and the population of TACE administered patients eligible for TACE until end of study
- **Area of TACE procedures** (whole liver, right side, left side, single segment, sub-sub segment only as defined in section 4.6.4 of the SAP) by number of TACEs for the overall TACE population, the population of TACE administered patients non-eligible for TACE prior to the first TACE, the population of TACE administered patients who became TACE non-eligible after initial TACE, and the population of TACE administered patients eligible for TACE until end of study
- **Time to meet TACE non-eligibility criteria from the first TACE** for the population of TACE administered patients who became TACE non-eligible after initial TACE
- **Number of patients who had radiofrequency ablation in combination with TACE** (if radiofrequency ablation was done between the first TACE until 30 days after the last TACE) for the overall TACE population, the population of TACE administered patients non-eligible for TACE prior to the first TACE, the population of TACE administered patients who became TACE non-eligible after initial TACE, the population of TACE administered patients eligible for TACE until end of study , and sorafenib treated patients

Tumor response for each TACE over time

Tumor response to each TACE was summarized overall (irrespective of their type of assessment) and by type of assessment (EASL, Response Evaluation Criteria in Cancer of the Liver [RECICL], RECIST 1.1, mRECIST, or other) for the overall TACE population, the population of TACE administered patients who became TACE non-eligible after initial TACE, the population of TACE administered patients non-eligible for TACE prior to the first TACE, and the population of TACE administered patients eligible for TACE until end of study. For each TACE, the first response evaluation after the respective TACE was considered.

Tumor response was also summarized by area of TACE procedures (whole liver, right side, left side, single segment, sub-sub segment only as defined in section 4.6.4 of the SAP). In addition, the latest tumor response compared to the inclusion visit and to the start of sorafenib was provided by type of assessment.

No imputations were performed for missing or unevaluable tumor responses and for tumor assessment dates that were not reported.

Practice pattern of the investigators

The number of patients with the following treatment flows was provided for the overall TACE population: sorafenib before initial TACE, switch to sorafenib after 1, 2, or >2 TACEs, other systemic anti-cancer treatment before initial TACE, switch to other systemic treatment after 1, 2, or >2 TACEs, other non-systemic anti-cancer treatment before initial TACE, switch to other non-systemic anti-cancer treatment after 1, 2, or >2 TACEs.

Deterioration in liver function (based on laboratory parameters)

Liver dysfunction (based on laboratory parameters) was summarized descriptively for the overall TACE population.

The following summaries were provided for each of the liver-related laboratory parameters, i.e., aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, and prothrombin INR:

- Box plots for pre-TACE value (defined as latest value during the pre-TACE period for the following TACEs.), and acute value (defined as worst value during acute period) and chronic value (defined as worst value during chronic period) of the subsequent TACE
- Change from pre-TACE value to acute and chronic values in subsequent TACE
- Change from pre-TACE value of the first TACE to the value in the chronic period of the last TACE
- Frequency tables of laboratory values by grade (as defined in Table 4-5 of the SAP) for the pre-TACE, acute and chronic period of each TACE
- Number of patients who had a deterioration of liver dysfunction during the acute or chronic period of each TACE by area of TACE procedure (whole liver, right side, left side, single segment, sub-sub segment only as defined in section 4.6.4 of the SAP). Deterioration of liver dysfunction was defined as a change of aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, or prothrombin INR from normal to Grade 1-4, Grade 1 to Grade 2-4, Grade 2 to Grade 3 or 4, or Grade 3 to Grade 4
- Change from pre-TACE value to acute value and chronic value of the first TACE summarized by BCLC stage at study entry, lesion size (longest diameter at inclusion visit: missing, <30 mm, 30 to 70 mm, >70 mm), number of lesions at inclusion visit (missing, 0, 1, 2, 3, ≥4), TACE eligible status at baseline, grade of baseline total bilirubin, and by up to seven criteria at the inclusion visit (i.e., if the sum of longest diameter of liver lesion and total number of lesions is ≤7 or >7)

Summaries for the acute period include all patients who had a pre-TACE value and acute value of each TACE. Summaries for the chronic period include all patients who had a pre-TACE value and a chronic value of each TACE. In addition, all summaries are provided for patients who had a pre-TACE, acute and chronic value. If patients received the following TACE within 90 days from the previous TACE, the subsequent TACE was not considered for analyses.

Figure 1 shows a definition of the time periods for the subsequent TACE.

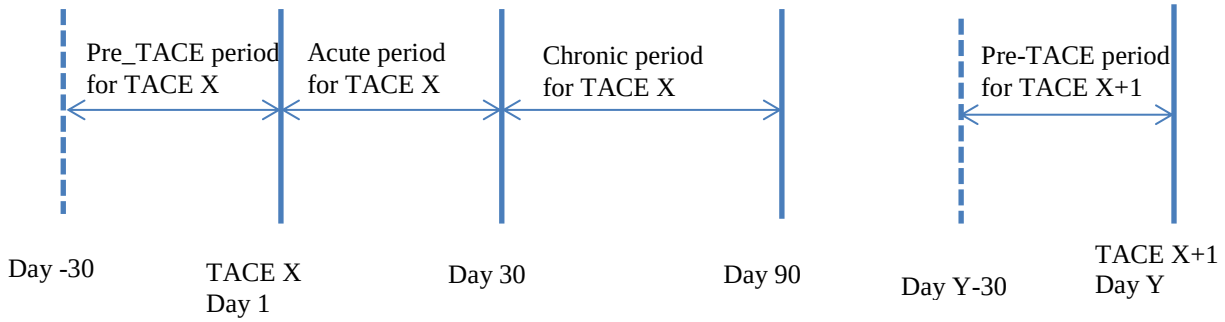

Figure 1: Definition of pre-TACE, acute and chronic periods
TACE: transarterial chemoembolization, x: number of TACE

9.9.2.6 Safety Analysis

Deaths

Cause of death was summarized for sorafenib treated patients, for the overall TACE population, and for the population of TACE administered patients who became TACE non-eligible after initial TACE (by cohort).

Adverse events

AEs were summarized for sorafenib treated patients, for the overall TACE population, and for the population of TACE administered patients who became TACE non-eligible after initial TACE (by cohort), using the NCI-CTCAE (version 4.0) and the MedDRA coding system (version 20.1).

For each event and overall, the incidence proportions were summarized for the classifications (and populations) presented in Table 6-1 of the SAP.

For sorafenib treated patients, 'treatment emergent' was defined as any event arising or worsening after the start of sorafenib treatment until 30 days after the last sorafenib treatment. For the overall TACE population, a similar definition for treatment emergent events was applied, using the start and stop dates of the TACE +30 days.

For the population of TACE administered patients who became TACE non-eligible after initial TACE, summaries of AEs are presented by cohort for the AEs starting on or after the date of non-eligibility to the end of the study.

Change in Albumin-bilirubin grade

Frequency tables are provided for pre-TACE Albumin-bilirubin (ALBI) grade (Grade 1, Grade 2, Grade 3 as defined in section 4.6.5 of the SAP) and the worst ALBI grade of chronic period. Tables are provided for each TACE.

Other safety parameters

Laboratory parameters were summarized for the overall TACE population for the period starting with the first TACE administration through the last TACE administration plus 30 days. Laboratory

parameters for sorafenib treated patients were summarized similarly, for the first to last sorafenib administration plus 30 days.

In addition, frequency tables were provided for alpha-fetoprotein (<200, 200-400, or >400 ng/mL) and platelets (≥75.0, <75.0-50.0, <50.0-25.0, <25.0 x giga/L).

Blood pressure was summarized descriptively.

9.9.3 Missing values

Imputation of incomplete dates was performed for birth dates, time to event data, sorafenib administration, concomitant local anti-cancer therapy, and adverse events. Details can be found in section 4.3 of the SAP (version 1.1, dated 07 NOV 2017; provided as a stand-alone document to be found in Annex 1 and available upon request).

Missing or unevaluable tumor assessments (including assessments not done and incomplete assessment that did not result in an unambiguous tumor response according to Response Evaluation Criteria in Solid Tumor (RECIST), modified RECIST (mRECIST), EASL or RECICL were not used in the calculation of derived efficacy variables, and no imputation was performed for missing / unevaluable tumor response. It should be noted that partial dates for tumor assessments were not permitted by the electronic data capture (EDC) system. Tumor assessment dates that were not reported were not imputed.

Other missing values were not imputed. Frequency tables for categorical data included the number of missing values as additional categories. Percentages were calculated as proportion of each category including the category of missing values.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

The original SAP, version 1.0, dated 16 Oct 2017, was amended (Version 1.1 dated 07 NOV 2017; provided as stand-alone document in Annex 1 and available upon request) to add the missing criteria "Continuous elevation of tumor markers even though right after TACE" (see section 9.9.2.1).

In addition, the following changes were made in the SAP compared to the study protocol Version 3.0:

- Primary and secondary objectives were changed (see section 7).
- Originally, the study was planned to use propensity score based methods to control for the imbalance according to non-randomized cohort allocation. However, due to the low number of patients in cohort 1 and multiple covariates it was decided that all analyses were done in a descriptive manner.
- The protocol foresaw analysis of the data for all patients who were treated with at least one TACE, all patients who were treated with sorafenib, as well as for the two cohorts of special interest, as applicable. As not all patients qualified for calculation of the primary endpoint, further analysis populations were defined (see section 9.9.2.2).The definition of duration of exposure to TACE treatment was adapted to present data more precisely. This became necessary due to the nature of the documented data also leading to the specification of additional analysis sets.
- ART score was added as a separate standalone analysis.

- AEs occurring during treatment for HCC were not summarized for each treatment for HCC, but for sorafenib treated patients, for the population of TACE administered patients who became TACE non-eligible after initial TACE and for the overall TACE population.

The following adaptions were made after finalization of the SAP:

- The analysis for the latest radiological tumor response compared to inclusion visit was performed only for the overall TACE population and the latest radiological tumor response compared to start of sorafenib was performed for sorafenib treated patients overall and by type of assessment as intended.
- For consistency with the other analyses sets, all analysis for the populations of TACE administered patients who became TACE non-eligible after initial TACE were provided for the overall populations (not only by cohort) as well.
- Cut-offs for the STATE score categories were adapted to reflect current scientific standards in line with published literature.

9.10 Quality control

Before study start at the sites, all investigators were sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations.

A global CRO was 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 were recorded in a standardized CRF. After data entry, missing or implausible data were queried and the data were validated. A check for multiple documented patients was done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (provided as stand-alone document in Annex 1 and available upon request). The same plan specifies measures for handling of missing data and permissible clarifications.

In a subset of patients (at least 10% of all patients) quality reviews were conducted, including telephone interviews and on-site visits. The purpose was to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors accessed medical records on site for data verification. Detailed measures for quality reviews were described in the Quality Review Plan (provided as stand-alone document in Annex 1 and available upon request). The overall outcome of the quality review was summarized in the final Quality Review Report (as a stand-alone document to be found in Annex 1 and available upon request).

Medical Review of the data was performed according to the Medical Review Plan (provided as stand-alone document in Annex 1 and available upon request) to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of safety-related information or the progress of the study. The outcomes of the Medical Review were summarized in the Medical Review report (provided as stand-alone document in Annex 1 and available upon request).

National and international data protection laws as well as regulations on observational non-interventional studies were to be followed. Electronic records used for patient documentation were to

be validated according to 21 Code of Federal Regulations (CFR) Part 11 (United States Food and Drug Administration [FDA]) (29).

10. Results

The study aimed to evaluate the time to meet criteria for TACE non-eligibility and the outcome of patients in relation to the timing of initiation of sorafenib. These data can be found in section 10.4.1, section 10.4.2.1, section 10.4.2.2, section 10.4.2.3, and section 10.4.2.4. Additionally, details on TACE treatments (section 10.4.2.5, section 10.4.2.6, and section 10.4.2.7) and practice patterns of the investigators (section 10.4.2.8 and section 10.4.2.9) were collected.

10.1 Participants

A total of 1793 patients were screened for this study (Table 5). Of these, 1676 patients were enrolled and 1650 patients received TACE (Table 6).

An overview on the eligibility criteria of the screened patients is presented in Table 5.

Table 5: Eligibility criteria - SCR

	Total N=1793 n (%)
Inclusion criteria	
Patients with histologically/cytologically documented or radiographically diagnosed HCC	
Missing	2 (0.1%)
No	8 (0.4%)
Yes	1783 (99.4%)
Patients for whom a decision to treat with TACE had been made at time of study enrollment	
Missing	2 (0.1%)
No	61 (3.4%)
Yes	1730 (96.5%)
Patients with unresectable HCC	
Missing	2 (0.1%)
No	6 (0.3%)
Yes	1785 (99.6%)
Patients with a life expectancy of at least 8 weeks	
Missing	2 (0.1%)
No	4 (0.2%)
Yes	1787 (99.7%)
Patients with a BCLC stage B or higher	
Missing	2 (0.1%)
No	30 (1.7%)
Yes	1761 (98.2%)
Informed consent form signed	
Missing	3 (0.2%)
No	7 (0.4%)
Yes	1783 (99.4%)

	Total N=1793 n (%)
Exclusion criteria	
Patients for whom the data about a prior TACE required in this protocol were not completely available	
Missing	1 (<0.1%)
No	1784 (99.5%)
Yes	8 (0.4%)
Patients who were treated according to a trial protocol for intervention including a locoregional therapy or systemic therapy	
Missing	1 (<0.1%)
No	1788 (99.7%)
Yes	4 (0.2%)
Hospice patients	
Missing	1 (<0.1%)
No	1788 (99.7%)
Yes	4 (0.2%)
Patients who received any systemic anti-cancer therapy prior to the first TACE	
Missing	1 (<0.1%)
No	1773 (98.9%)
Yes	19 (1.1%)

BCLC: Barcelona Clinic Liver Cancer Staging, HCC: hepatocellular carcinoma, n: number of patients, N: number of patients in analysis set, SCR: screening set, TACE: transarterial chemoembolization.
Source: Table 14.1.1 / 1, Table 14.1.1 / 2

The most frequent violation of inclusion criteria was that no decision to treat with TACE was made at time of study enrollment (3.4%), followed by no BCLC stage B or higher (1.7%). The most common exclusion criterion present was that the patients received any systemic anti-cancer therapy prior to the first TACE (1.1%). For all other inclusion and exclusion criteria, violations were reported in less than 1% of patients.

This study evaluated outcomes of all patients with early start of sorafenib treatment after TACE (cohort 1) and patients without early start of sorafenib treatment after TACE (cohort 2), each based on the investigators' treatment decisions. To evaluate TACE non-eligibility the following 4 different sets of criteria were applied:

- Criteria 1: Protocol specified
- Criteria 2: AASLD based
- Criteria 3: Child Pugh based
- Criteria 4: JSH based

These criteria are reflected in the analysis sets for TACE administered patients who became TACE non-eligible after initial TACE, as well as for TACE administered patients non-eligible for TACE prior to the first TACE and TACE administered patients eligible for TACE until end of study.

Additionally, patients who became TACE non-eligible after initial TACE were stratified according to their sorafenib treatment:

- Cohort 1: treated with sorafenib early (based on the investigators' treatment decisions)
- Cohort 2: not treated with sorafenib early (based on the investigators' treatment decisions)

For more detail, see section 9.9.2.1 and 9.9.2.2.

An overview of the analysis sets is given in Table 6 and Figure 2.

Table 6: Sample sizes and analysis sets

	Total n (%)
Enrolled patients	1676 (100.0%)
Number of TACE administered patients (overall TACE population) [1]	1650 (98.4%)
Number of TACE administered patients non-eligible for TACE prior to the first TACE [2]	
TACE non-eligibility protocol specified	636 (37.9%)
TACE non-eligibility AASLD based	631 (37.6%)
TACE non-eligibility Child Pugh based	635 (37.9%)
TACE non-eligibility JSH based	369 (22.0%)
Number of TACE administered patients eligible for TACE until end of study [3]	
TACE non-eligibility protocol specified	438 (26.1%)
TACE non-eligibility AASLD based	610 (36.4%)
TACE non-eligibility Child Pugh based	540 (32.2%)
TACE non-eligibility JSH based	831 (49.6%)
Number of TACE administered patients treated with systemic anti-cancer therapy (including sorafenib) started prior to time of TACE non-eligibility [4]	
TACE non-eligibility protocol specified	69 (4.1%)
TACE non-eligibility AASLD based	71 (4.2%)
TACE non-eligibility Child Pugh based	59 (3.5%)
TACE non-eligibility JSH based	59 (3.5%)
Number of TACE administered patients who became non-eligible for TACE after initial TACE and before end of the study [5]	
TACE non-eligibility protocol specified	507 (30.3%)
Cohort 1	47 (2.8%)
Cohort 2	460 (27.4%)
TACE non-eligibility AASLD based	338 (20.2%)
Cohort 1	46 (2.7%)
Cohort	292 (17.4%)
TACE non-eligibility Child Pugh based	416 (24.8%)
Cohort 1	46 (2.7%)
Cohort 2	370 (22.1%)
TACE non-eligibility JSH based	391 (23.3%)
Cohort 1	45 (2.7%)
Cohort 2 (	346 (20.6%)
Number of patients treated with sorafenib [6]	515 (30.7%)

[1] The population was denoted “TCE” in the statistical output.
[2] The population was denoted “TNEBx” in the statistical output.
[3] The population was denoted “TEBx” in the statistical output.
[4] Please note that these patients were not considered a separate analysis set, but were excluded from the population of patients who became TACE non-eligible after initial TACE.
[5] The population was denoted “TNEx” in the statistical output.
[6] The population was denoted “SOAP” in the statistical output.
Note 1: Cohort 1 includes patients with early start of sorafenib treatment based on the investigators’ treatment decisions.
Note 2: Cohort 2 includes patients without early start of sorafenib treatment based on the investigators’ treatment decisions.
AASLD: American Association for the Study of Liver Diseases, JSH: Japan Society of Hepatology, n: number of patients, TACE: transarterial chemoembolization, x: TACE non-eligibility criterion number.
Source: Table 14.1.1 / 3

Of the 1676 enrolled patients, 1650 (98.4%) were included in the overall TACE population.

Between 22% and 38% (based on the 4 TACE non-eligibility criteria presented above) of the enrolled patients received TACE but were already non-eligible for TACE prior to the first TACE. Between 26% and 50% of patients received TACE and remained eligible for TACE until end of study.

Additionally, about 4% of patients who became TACE non-eligible after initial TACE were treated with systemic anti-cancer therapy that was started prior to time of TACE non-eligibility and were excluded from the population of TACE administered patients who became TACE non-eligible after initial TACE.

Therefore, the population of patients who became TACE non-eligible after initial TACE included 507 patients (30.3%) based on the TACE non-eligibility criteria specified in the protocol, 338 patients (20.2%) based on AASLD, 416 patients (24.8%) based on Child Pugh, and 391 patients (23.3%) based on JSH. In all of these 4 populations, cohort 1 (treated with sorafenib early based on the investigators' treatment decisions) included less than 50 patients, while the remaining patients were in cohort 2 (not treated with sorafenib early based on the investigators' treatment decisions).

A total of 515 patients (30.7% of enrolled patients) received sorafenib.

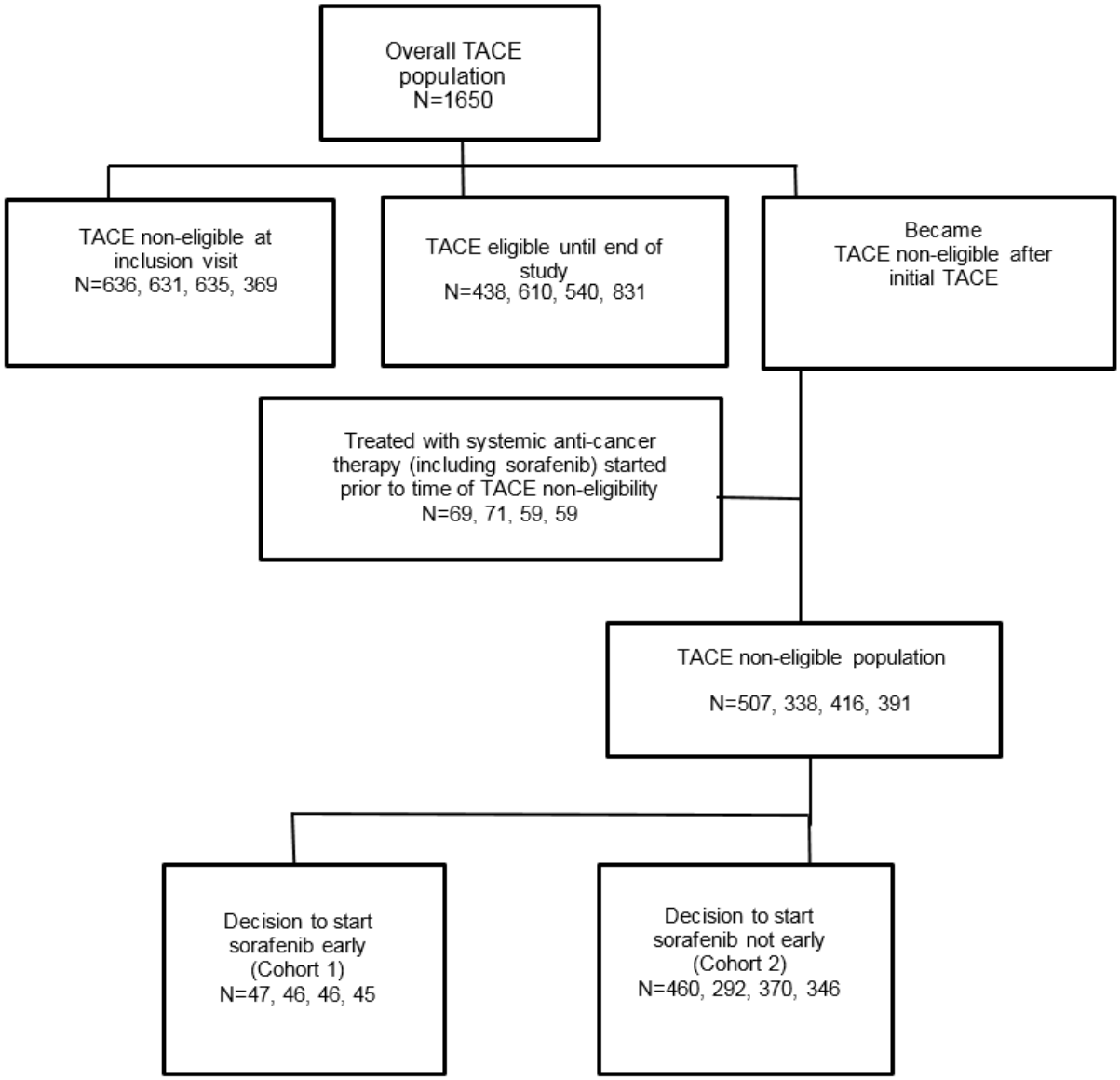

Figure 2: Patient enrollment and analysis sets

Note 1: denotes the number of patients in the analysis set based on the 4 TACE non-eligibility criteria: Protocol specified, AASLD based, Child Pugh based, JSH based.
AASLD: American Association for the Study of Liver Diseases, JSH: Japan Society of Hepatology, TACE: transarterial chemoembolization
Source table: 14.1.1 / 3

The remainder of the text focuses on the population of TACE administered patients who became non-eligible for TACE after initial TACE according to the TACE non-eligibility criteria 1 (protocol specified), as well as the overall TACE population. Results for the TACE non-eligibility criteria 2 (AASLD based), 3 (Child Pugh based), and 4 (JSH based) can be found in the statistical output. Additionally, results for the population of TACE administered patients non-eligible for TACE prior to the first TACE, and results for the population of TACE administered patients eligible for TACE until end of study are provided in the statistical output (provided as stand-alone document in Annex 1 and available upon request).

Results regarding sorafenib treatment and AEs are provided based on sorafenib treated patients.

The reason for end of observation is summarized in Table 7.

Table 7: Reason for end of observation – overall TACE population

	Total N=1650 n (%)
Number of completed patients	537 (32.5%)
Number of patients who died	694 (42.1%)
Primary reason for premature discontinuation from study	421 (25.5%)
Screening failure	7 (0.4%)
Lost to follow-up	372 (22.5%)
Participation in another study	2 (0.1%)
Transfer to other physician	33 (2.0%)
Other	5 (0.3%)
Missing	2 (0.1%)

Note 1: the population was denoted "TCE" in the statistical output.
Note 2: Table may include patients who died during the study and primary reason for discontinuation is other than "death"
n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization.
Source: Table 14.1.1 / 4

Of the 1650 patients in the overall TACE population, 32.5% completed the study (i.e., end of study was documented as reason for end of observation) and 42.1% of patients died. For the remaining patients (25.5%), the most frequent primary reason for premature discontinuation from study was "lost to follow-up" (22.5%).

A total of 36.3% of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) completed the study and 45.0% of patients died. For the remaining patients (18.7%), the most frequent primary reason for premature discontinuation from study was "lost to follow-up" (15.4%) (Table 14.1.1 / 5). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.1 / 6, Table 14.1.1 / 7, and Table 14.1.1 / 8, respectively.

Of the sorafenib treated patients, 23.3% of patients completed the study and 51.8% of patients died. For the remaining patients (25.2%), the most frequent primary reason for premature discontinuation from study was "lost to follow-up" (22.7%) (Table 14.1.1 / 17).

10.2 Descriptive data

10.2.1 Descriptive data for patients who became TACE non-eligible after initial TACE

This section summarizes the demographic and baseline disease characteristics as well as the descriptive data of the population of TACE administered patients who became TACE non-eligible after initial TACE based on the criteria specified in the protocol (denoted as TNE1 in the statistical output). This population is used to analyze the primary and secondary objectives regarding time to meet criteria for TACE non-eligibility and outcome of patients.

Additionally, deviations from recommendations for TACE were evaluated for this population, as well as for the populations of TACE administered patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh, and based on JSH.

10.2.1.1 Demographics and baseline disease characteristics

10.2.1.1.1 Demographic characteristics

Demographic characteristics of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) are presented in Table 8.

Table 8: Demography – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507	Cohort 1 N=47	Cohort 2 N=460
Region n (%)			
China	19 (3.7%)	3 (6.4%)	16 (3.5%)
Japan	94 (18.5%)	20 (42.6%)	74 (16.1%)
Korea	109 (21.5%)	6 (12.8%)	103 (22.4%)
Other Asia	100 (19.7%)	3 (6.4%)	97 (21.1%)
Europe / North America	175 (34.5%)	14 (29.8%)	161 (35.0%)
Central / South America	10 (2.0%)	1 (2.1%)	9 (2.0%)
Sex n (%)			
Male	420 (82.8%)	39 (83.0%)	381 (82.8%)
Female	87 (17.2%)	8 (17.0%)	79 (17.2%)
Age calculated at date of informed consent (years)			
n	507	47	460
Mean	64.9	67.9	64.6
SD	10.9	10.9	10.8
Median	65.0	71.0	64.0
Min, Max	29, 90	31, 85	29, 90
Race n (%)			
Missing	1 (0.2%)	0 (0.0%)	1 (0.2%)
White	117 (23.1%)	9 (19.1%)	108 (23.5%)
Asian	296 (58.4%)	30 (63.8%)	266 (57.8%)
Not reported	92 (18.1%)	8 (17.0%)	84 (18.3%)
Multiple	1 (0.2%)	0 (0.0%)	1 (0.2%)

	Total N=507	Cohort 1 N=47	Cohort 2 N=460
BMI at inclusion visit (kg/m^2)			
n	467	46	421
Missing	40	1	39
Mean	25.206	24.841	25.245
SD	4.595	4.283	4.631
Median	24.580	23.875	24.610
Min, Max	15.99, 46.88	18.71, 37.25	15.99, 46.88
Systolic blood pressure at inclusion visit (mmHg)			
n	443	43	400
Missing	64	4	60
Mean	128.2	126.9	128.3
SD	17.6	17.1	17.6
Median	127.0	128.0	127.0
Min, Max	84, 216	91, 162	84, 216
Diastolic blood pressure at inclusion visit (mmHg)			
n	443	43	400
Missing	64	4	60
Mean	74.7	73.7	74.8
SD	10.9	10.5	11.0
Median	74.0	74.0	74.0
Min, Max	38, 115	50, 98	38, 115
Alcohol use n (%)			
Missing	2 (0.4%)	0 (0.0%)	2 (0.4%)
Abstinent	297 (58.6%)	29 (61.7%)	268 (58.3%)
Light	95 (18.7%)	7 (14.9%)	88 (19.1%)
Moderate	64 (12.6%)	5 (10.6%)	59 (12.8%)
Heavy	49 (9.7%)	6 (12.8%)	43 (9.3%)
Smoking history n (%)			
Missing	3 (0.6%)	0 (0.0%)	3 (0.7%)
Never	215 (42.4%)	28 (59.6%)	187 (40.7%)
Former	180 (35.5%)	12 (25.5%)	168 (36.5%)
Current	109 (21.5%)	7 (14.9%)	102 (22.2%)

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: Cohort 1 includes patients with early start of sorafenib treatment based on the investigators’ treatment decisions.
Note 3: Cohort 2 includes patients without early start of sorafenib treatment based on the investigators’ treatment decisions.
BMI: body mass index, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization
Source: Table 14.1.2 / 2

Most of the patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) were male (82.8%) and the majority of patients was Asian (58.4%). The mean age was 64.9 years. The majority of patients were abstinent from alcohol (58.6%). Most frequently, patients never (42.4%) or formerly smoked (35.5%).

Patients most frequently were enrolled from the region Europe / North America (34.5%), Korea (21.5%), and other Asia (19.7%).

Regarding countries, patients most frequently were from Korea (21.5%), Japan (18.5%), and France (16.6%) (Table 14.1.2 / 2).

Differences between the cohorts were mainly seen regarding region, age and smoking behavior. However, due to the low number of patients in cohort 1 and heterogeneity in the study cohorts, these results have to be interpreted with caution. Also allocation bias was not corrected for.

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 3,Table 14.1.2 / 4, and Table 14.1.2 / 5, respectively.

A summary of the demographic data by prospective and retrospective documentation for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) is presented in Table 9.

Table 9: Demography by prospective and retrospective documentation – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Prospective documentation N=292	Retrospective documentation N=215
Sex n (%)		
Male	240 (82.2%)	180 (83.7%)
Female	52 (17.8%)	35 (16.3%)
Age calculated at date of informed consent (years)		
n	292	215
Mean	64.6	65.3
SD	11.2	10.4
Median	64.0	66.0
Min, Max	29, 90	35, 89
BCLC stage at inclusion n (%)		
Missing	12 (4.1%)	19 (8.8%)
Stage B	280 (95.9%)	195 (90.7%)
Stage C	0 (0.0%)	1 (0.5%)

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: “Prospective documentation” was denoted as “no” and “retrospective documentation” was denoted as “yes” in the statistical output.
BCLC: Barcelona Clinic Liver Cancer Staging, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 16

Of the 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), 215 were enrolled retrospectively and 292 patients were enrolled prospectively. There were no major differences between these patients regarding sex, age and BCLC stage at inclusion.

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 17, Table 14.1.2 / 18, and Table 14.1.2 / 19, respectively.

The last measured laboratory values prior to or at inclusion visit for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) are presented in Table 10. Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 171, Table 14.1.2 / 172, and Table 14.1.2 / 173, respectively.

Table 10: Last measured laboratory values prior to or at inclusion visit - Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507 n (%)
Platelets	
Missing	50 (9.9%)
≥140 Giga/L	180 (35.5%)
<140-75 Giga/L	182 (35.9%)
<75-50 Giga/L	52 (10.3%)
<50-25 Giga/L	31 (6.1%)
<25 Giga/L	12 (2.4%)
Prothrombin INR	
Missing	68 (13.4%)
≤1.0 x ULN (1.22)	339 (66.9%)
>1.0-1.5 x ULN (1.22)	92 (18.1%)
>1.5-2.5 x ULN (1.22)	7 (1.4%)
>2.5 x ULN (1.22)	1 (0.2%)
Bilirubin	
Missing	38 (7.5%)
<2 mg/dL	414 (81.7%)
2-3 mg/dL	44 (8.7%)
>3 mg/dL	11 (2.2%)
Alanine Aminotransferase	
Missing	38 (7.5%)
≤1.0 x ULN (53 U/L)	308 (60.7%)
>1.0-3.0 x ULN (53 U/L)	146 (28.8%)
>3.0-5.0 x ULN (53 U/L)	11 (2.2%)
>5.0-20.0 x ULN (53 U/L)	4 (0.8%)
>20.0 x ULN (53 U/L)	0 (0.0%)
Aspartate Aminotransferase	
Missing	60 (11.8%)
≤1.0 x ULN (47 U/L)	200 (39.4%)
>1.0-3.0 x ULN (47 U/L)	219 (43.2%)
>3.0-5.0 x ULN (47 U/L)	22 (4.3%)
>5.0-20.0 x ULN (47 U/L)	6 (1.2%)
>20.0 x ULN (47 U/L)	0 (0.0%)
Creatinine	
Missing	40 (7.9%)
≤1.0 x ULN (1.5 MG/DL)	458 (90.3%)
>1.0-1.5 x ULN (1.5 mg/dL)	6 (1.2%)
>1.5-3.0 x ULN (1.5 mg/dL)	2 (0.4%)
>3.0-6.0 x ULN (1.5 mg/dL)	1 (0.2%)
>6.0 x ULN (1.5 mg/dL)	0 (0.0%)
Corrected Creatinine Clearance	
Missing	383 (75.5%)
≥80 mL/min	68 (13.4%)
<80-60 mL/min	39 (7.7%)
<60-30 mL/min	15 (3.0%)
<30-15 mL/min	2 (0.4%)
<15 mL/min	0 (0.0%)

	Total N=507 n (%)
Albumin (classification 1)	
Missing	60 (11.8%)
≥1.0 x LLN (3.6 g/dL)	261 (51.5%)
<1.0 x LLN(3.6 g/dL) - 3.0 g/dL	129 (25.4%)
<3.0-2.0 g/dL	56 (11.0%)
<2.0 g/dL	1 (0.2%)
Albumin (classification 2)	
Missing	60 (11.8%)
>3.5 g/dL	262 (51.7%)
2.8-3.5 g/dL	152 (30.0%)
<2.8 g/dL	33 (6.5%)
Sodium	
Missing	106 (20.9%)
≥1.0 x LLN (135 mMOL/L)	377 (74.4%)
<1.0 x LLN (135 mMOL/L) - 130 mMOL/L	20 (3.9%)
<130-120 mMOL/L	4 (0.8%)
<120 mMOL/L	0 (0.0%)
Lactate Dehydrogenase	
Missing	329 (64.9%)
Normal (100-250 U/L)	106 (20.9%)
Abnormal	72 (14.2%)
Alpha Fetoprotein	
Missing	137 (27.0%)
<200 ng/mL	276 (54.4%)
≥200-<400 ng/mL	18 (3.6%)
≥400 ng/mL	76 (15.0%)
C Reactive Protein	
Missing	307 (60.6%)
0-<0.1 MG/DL	112 (22.1%)
≥0.1-<0.5 MG/DL	20 (3.9%)
≥0.5-<1.0 MG/DL	12 (2.4%)
≥1.0 MG/DL	56 (11.0%)
Gamma Glutamyl Transferase	
Missing	195 (38.5%)
≤1.0 x ULN (M:50/F:32 U/L)	69 (13.6%)
>1.0-2.5 x ULN (M:50/F:32 U/L)	120 (23.7%)
>2.5-5.0 x ULN (M:50/F:32 U/L)	72 (14.2%)
>5.0-20.0 x ULN (M:50/F:32 U/L)	48 (9.5%)
>20.0 x ULN (M:50/F:32 U/L)	3 (0.6%)

Note 1: the population was denoted “TNE1” in the statistical output.
INR: international normalized ratio, LLN: lower limit of normal, n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization, U: Unit, ULN: upper limit of normal.
Source: Table 14.1.2 / 170

10.2.1.1.2 Baseline disease characteristics

The majority of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (70.8%) were currently treated by a hepatologist as primary treating physician (Table 14.1.2 / 31). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 33, Table 14.1.2 / 35, and Table 14.1.2 / 37, respectively.

Table 11 summarizes the HCC background for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Table 11: HCC background – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507
Time from initial diagnosis to inclusion visit (months)	
n	454
Missing	53
Mean	4.919
SD	15.628
Median	0.000
Min, Max	0.00, 164.83
Symptoms of HCC n (%)	
No	339 (66.9%)
Yes	121 (23.9%)
Unknown	47 (9.3%)
HCC confirmed by biopsy n (%)	
No	399 (78.7%)
Yes	108 (21.3%)
Newly diagnosed n (%)	
No	142 (28.0%)
Yes	365 (72.0%)

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: For newly diagnosed patients, time from initial diagnosis to inclusion visit is derived as 0 (months).
HCC: hepatocellular carcinoma, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 31

Overall, patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) had their inclusion visit shortly after initial diagnosis (mean 4.9 months, median 0.0 months). For the majority of patients, HCC was newly diagnosed (72.0%) and not confirmed by biopsy (78.7%). The majority of patients had no symptoms of HCC (66.9%).

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 33, Table 14.1.2 / 35, and Table 14.1.2 / 37, respectively.

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median time from initial diagnosis to the inclusion visit for patients who were not newly diagnosed was 14.2 months) (Table 14.1.2 / 32). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 34, Table 14.1.2 / 36, and Table 14.1.2 / 38, respectively.

The HCC status at inclusion visit for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) is shown in Table 12.

Table 12: HCC at inclusion visit – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total Total N=507
TNM grading of HCC n (%)	
Missing	71 (14.0%)
Stage I	40 (7.9%)
Stage II	221 (43.6%)
Stage IIIA	153 (30.2%)
Stage IIIB	7 (1.4%)
Stage IIIC	3 (0.6%)
Stage IVA	12 (2.4%)
Stage IVB	0 (0.0%)
Unknown	0 (0.0%)
BCLC stage n (%)	
Missing	31 (6.1%)
Stage 0	0 (0.0%)
Stage A	0 (0.0%)
Stage B	475 (93.7%)
Stage C	1 (0.2%)
Stage D	0 (0.0%)
Child Pugh score	
n	455
Missing	52
Mean	5.8
SD	1.0
Median	5.0
Min, Max	4, 9
Child Pugh classification n (%)	
Missing	48 (9.5%)
A (5-6 points)	363 (71.6%)
B (7-9 points)	96 (18.9%)
C (10-15 points)	0 (0.0%)
ECOG performance status n (%)	
Missing	69 (13.6%)
0 (fully active)	438 (86.4%)
1 (restricted active)	0 (0.0%)
2 (ambulatory and capable of all self-care)	0 (0.0%)
3 (capable of limited self-care)	0 (0.0%)
4 (completely disabled)	0 (0.0%)
5 (dead)	0 (0.0%)

Note 1: the population was denoted “TNE1” in the statistical output.
BCLC: Barcelona Clinic Liver Cancer Staging, ECOG: Eastern Co-Operative Oncology Group, HCC: hepatocellular carcinoma, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization, TNM: tumor, nodes (lymph nodes) and metastases (classification).
Source: Table 14.1.2 / 58

Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) most frequently had an tumor, nodes (lymph nodes) and metastases (TNM) grading of stage II (43.6%), followed by stage IIIA (30.2%). The majority of patients had an BCLC stage of B (93.7%) and a Child Pugh classification of 5-6 points (71.6%; mean 5.8 points). The ECOG performance status was 0 for the majority of patients (86.4%).

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 59, Table 14.1.2 / 60, and Table 14.1.2 / 61, respectively.

Tumor evaluation at inclusion visit for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)was most frequently performed by CT scan (58.8%), followed by MRI (37.9%) (Source: Table 14.1.2 / 72). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 73, Table 14.1.2 / 74, and Table 14.1.2 / 75, respectively.

Tumor evaluation at inclusion visit is shown for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) in Table 13.

Table 13: Tumor evaluation at inclusion visit – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507
Total number of lesions n (%)	
Missing	26 (5.1%)
0	3 (0.6%)
1	118 (23.3%)
2	109 (21.5%)
3	77 (15.2%)
4	56 (11.0%)
5	39 (7.7%)
6	14 (2.8%)
7	20 (3.9%)
8	11 (2.2%)
9	4 (0.8%)
≥10	30 (5.9%)
Longest diameter (mm)	
n	484
Missing	23
Mean	47.302
SD	34.783
Median	39.000
Min, Max	10.00, 432.00
New metastases present n (%)	
Missing	2 (0.4%)
No	505 (99.6%)
Yes	0 (0.0%)
Time from tumor evaluation to inclusion visit (months)	
n	507
Missing	0
Mean	0.716
SD	1.316
Median	0.400
Min, Max	-2.87, 21.93

Note 1: the population was denoted “TNE1” in the statistical output.
Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization .
Source: Table 14.1.2 / 72

Patients in who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) most frequently had between 1 and 3 lesions. The mean longest diameter of the lesions

was 47.302 mm. No new metastases were present in the vast majority of patients (99.6%). The median time from tumor evaluation to inclusion visit was 0.4 months. Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 73, Table 14.1.2 / 74, and Table 14.1.2 / 75, respectively.

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the only disease status criterion present at inclusion visit was advanced liver disease (Child Pugh B/C) (18.7%) (Table 14.1.2 / 86). Please note that some of the criteria that could be recorded at inclusion visit and are present in the overall TACE population (see in Table 24) led to the exclusion from the population of patients who became TACE non-eligible after initial TACE (see section 9.9.2.1).

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 87, Table 14.1.2 / 88, and Table 14.1.2 / 89, respectively.

The history of liver disease is presented in Table 14 for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Table 14: History of liver disease – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507
Liver cirrhosis present n (%)	
Missing	2 (0.4%)
No	104 (20.5%)
Yes	401 (79.1%)
Time from initial diagnosis of liver cirrhosis to inclusion visit (months)	
n	214
Missing	293
Mean	16.688
SD	32.139
Median	1.630
Min, Max	-0.03, 168.77
Findings related to liver cirrhosis (multiple response) n (%)	
Missing	378 (74.6%)
Ascites	59 (11.6%)
Esophageal varices	80 (15.8%)
Gastrointestinal bleeding	27 (5.3%)
Hepatic encephalopathy	7 (1.4%)
Etiology of HCC (multiple response) n (%)	
Missing	3 (0.6%)
Alcohol use	177 (34.9%)
Hepatitis B	141 (27.8%)
Hepatitis C	184 (36.3%)
Aflatoxin	0 (0.0%)
Genetic / metabolic	10 (2.0%)
Nonalcoholic steatohepatitis (NASH)	37 (7.3%)
Primary biliary cirrhosis	0 (0.0%)
Hepatitis D	2 (0.4%)
Steatohepatitis	0 (0.0%)
Unknown	43 (8.5%)
Other	1 (0.2%)

Note 1: the population was denoted “TNE1” in the statistical output.
HCC: hepatocellular carcinoma, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 100

In the majority of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), liver cirrhosis was present (79.1%). The median time from initial diagnosis of liver cirrhosis to inclusion visit was 1.6 months. The most common etiologies were hepatitis C (36.3%), alcohol use (34.9%), and hepatitis B (27.8%).

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 101, Table 14.1.2 / 102, and Table 14.1.2 / 103, respectively.

10.2.1.2 Medical history and concomitant diseases

10.2.1.2.1 Medical history

A total of 300 of 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (59.2%) reported general medical history. The most frequently reported medical history at system organ class (SOC) level were Vascular disorders (34.1%), followed by Metabolism and nutrition disorders (28.0%), and Gastrointestinal disorders (17.0%). At preferred term (PT) level, hypertension (31.8%) and type 2 diabetes mellitus (22.5%) were reported most frequently (Table 14.1.2 / 115). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 117, Table 14.1.2 / 119, and Table 14.1.2 / 121, respectively.

10.2.1.2.2 Concomitant diseases

Overall, 180 of 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (35.5%) reported concomitant diseases. The most frequently reported concomitant disease at SOC level were Gastrointestinal disorders (13.6%), followed by Cardiac disorders (7.1%), Metabolism and nutrition disorders (6.1%), and Infections and infestations (6.1%). At PT level, gastrointestinal ulcer (6.1%), followed by angina pectoris (3.7%), phlebitis (2.6%), and hepatitis C (2.6%) were reported most frequently (Table 14.1.2 / 116). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 118, Table 14.1.2 / 120, and Table 14.1.2 / 122, respectively.

10.2.1.3 Prior and concomitant therapies and medications

10.2.1.3.1 Prior therapeutic procedures for HCC

A total of 81 of 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (16.0%) had any prior therapeutic procedure for HCC (including surgery). Most frequently, hepatectomy (11.2%) and ablation (4.9%) were performed. The most common location of prior procedures was the liver (15.8%) (Table 14.1.2 / 142). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 143, Table 14.1.2 / 144, and Table 14.1.2 / 145, respectively.

10.2.1.3.2 Prior local anti-cancer therapy

A total of 63 of 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (12.4%) had any prior local anti-cancer therapy (except prior surgical procedures and TACE). Most frequently, radio-frequency ablation (10.1%) was performed (Table 14.1.2 / 156). Analyses of the radiological best response and the time of first/last local anti-cancer therapy to time of inclusion by type of local anti-cancer therapy can be found in Table 14.1.2 / 156. Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 157, Table 14.1.2 / 158, and Table 14.1.2 / 159, respectively.

10.2.1.3.3 Prior non-HCC related medication

Overall, 338 of 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (66.7%) reported prior non-HCC related medication. The most frequently reported prior non-HCC related medication at ATC level 1 was alimentary tract and metabolism (49.1%), followed by cardiovascular system (39.8%), and blood and blood forming organs (26.0%) (Table 14.1.2 / 184). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 185, Table 14.1.2 / 186, and Table 14.1.2 / 187, respectively.

10.2.1.3.4 Concomitant non-HCC related medication

A total of 417 of 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (82.2%) reported concomitant non-HCC related medication. The most frequently reported concomitant non-HCC related medication at ATC level 1 was alimentary tract and metabolism (67.9%), followed by cardiovascular system (57.4%), blood and blood forming organs (45.2%), antiinfectives for systemic use (43.8%), and nervous system (43.4%) (Table 14.1.2 / 198). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 199, Table 14.1.2 / 200, and Table 14.1.2 / 201, respectively.

10.2.1.4 Initial TACE treatment

Table 15 presents the initial TACE treatment for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Table 15: Initial TACE treatment – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507
Retrospective TACE n (%)	
No	292 (57.6%)
Yes	215 (42.4%)
Time from informed consent to initial TACE administration for prospectively documented patients (days)	
n	292
Missing	215
Mean	7.8
SD	22.0
Median	1.0
Min, Max	0, 223
Time from retrospective initial TACE administration to informed consent (days)	
n	215
Missing	292
Mean	48.8
SD	69.6
Median	34.0
Min, Max	1, 540
Area of TACE n (%)	
Missing	3 (0.6%)
Whole liver	151 (29.8%)
Left side	66 (13.0%)
Right side	213 (42.0%)
Single segment S1	4 (0.8%)
Single segment S2	6 (1.2%)
Single segment S3	2 (0.4%)
Single segment S4	10 (2.0%)
Single segment S5	9 (1.8%)
Single segment S6	8 (1.6%)
Single segment S7	12 (2.4%)
Single segment S8	23 (4.5%)
Embolization agent (multiple response) n (%)	
Missing	9 (1.8%)
Gelatin foam	179 (35.3%)
Microspheres	59 (11.6%)
Lipiodol	378 (74.6%)
Polyvinyl alcohol	6 (1.2%)
DC-beads	101 (19.9%)
Gelatin sponge	69 (13.6%)
Flax seed oil	2 (0.4%)
Other	2 (0.4%)

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: “Prospectively documented patients” were denoted as “non-retrospective patients” in the statistical output.
Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 212

The initial TACE was documented prospectively for 57.6% of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) and retrospectively for 42.4% of patients. The median time from informed consent to initial TACE administration was 1 day for prospectively documented patients and the median time from retrospective initial TACE administration to informed consent 34 days for retrospective patients. Initial TACE was most frequently performed on the right side (42.0%), followed by the whole liver (29.8%). The most common embolization agent was lipiodol (74.6%), followed by gelatin foam (35.3%).

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 213, Table 14.1.2 / 214, and Table 14.1.2 / 215, respectively.

The drugs used in TACE treatment can be found in Table 14.1.2 / 212 for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.2 / 213, Table 14.1.2 / 214, and Table 14.1.2 / 215, respectively.

10.2.1.5 Disease status summary at time of TACE non-eligibility

The disease status summary at time of TACE non-eligibility is given for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) in Table 16.

Table 16: Disease status summary at time of TACE non-eligibility – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507 n (%)
Most frequent disease status criteria (≥5% of patients)	
ECOG performance status ≥1	228 (45.0%)
BCLC stage C or D	177 (34.9%)
Extrahepatic spread present	63 (12.4%)
Vascular invasion	49 (9.7%)
Two or more consecutive new lesion	45 (8.9%)
Portal vein thrombosis	42 (8.3%)
Two or more consecutive incomplete necrosis	36 (7.1%)
Advanced liver disease (Child Pugh class C)	29 (5.7%)

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: Child Pugh class B is considered as TACE eligible (as of protocol version 3.0).
Note 3: Child Pugh class is derived by CRF section "Child Pugh Classification"
BCLC: Barcelona Clinic Liver Cancer Staging, CRF: case report form, ECOG: Eastern Co-Operative Oncology Group, n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization.
Source: Table 14.1.4 / 1

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the most common disease status criterion at TACE non-eligibility was ECOG performance status ≥1 (45.0%), followed by BCLC stage C or D (34.9%).

In both cohorts ECOG performance status ≥1 and BCLC stage C or D were the most common disease status criteria at TACE non-eligibility. However, the percentages differed. Due to the low number of patients in cohort 1 and heterogeneity in the study cohorts, these results have to be interpreted with caution. Also allocation bias was not corrected for.

Results for the patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.4 / 2,Table 14.1.4 / 3, and Table 14.1.4 / 4, respectively.

The majority of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) had between 1 and 3 follow up visits at the time of TACE non-eligibility (29.6%, 18.7%, and 12.0% of patients, respectively) (Table 14.1.4 / 9).

Selected parameters at time of TACE non-eligibility are presented for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) in Table 17.

Table 17: Selected parameters at time of TACE non-eligibility – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507
Time from initial TACE to TACE non-eligibility (days)	
n	507
Mean	239.5
SD	247.8
Median	146.0
Min, Max	-181, 1337
Number TACE before TACE non-eligibility - n (%)	
0	5 (1.0%)
1	282 (55.6%)
2	107 (21.1%)
3	55 (10.8%)
4	25 (4.9%)
5	14 (2.8%)
6	9 (1.8%)
7	4 (0.8%)
8	6 (1.2%)
10	0 (0.0%)
TNM at time of TACE non-eligibility - n (%)	
Missing	181 (35.7%)
Stage I	28 (5.5%)
Stage II	108 (21.3%)
Stage IIIA	86 (17.0%)
Stage IIIB	36 (7.1%)
Stage IIIC	3 (0.6%)
Stage IVA	21 (4.1%)
Stage IVB	44 (8.7%)
ECOG at time of TACE non-eligibility - n (%)	
Missing	120 (23.7%)
0 (fully active)	171 (33.7%)
1 (restricted active)	189 (37.3%)
2 (ambulatory and capable of all self-care)	17 (3.4%)
3 (capable of limited self-care)	8 (1.6%)
4 (completely disabled)	2 (0.4%)
BCLC at time of TACE non-eligibility - n (%)	
Missing	132 (26.0%)
0 (very early stage)	6 (1.2%)
A (early stage)	30 (5.9%)
B (intermediate stage)	163 (32.1%)
C (advanced stage)	140 (27.6%)
D (end-stage)	36 (7.1%)

	Total N=507
Child Pugh score at time of TACE non-eligibility	
n	329
Missing	178
Mean	6.5
SD	1.9
Median	6.0
Min, Max	4, 14
Child Pugh classification at time of TACE non-eligibility - n (%)	
Missing	179 (35.3%)
A (5-6 points)	214 (42.2%)
B (7-9 points)	85 (16.8%)
C (10-15 points)	29 (5.7%)

Note 1: the population was denoted "TNE1" in the statistical output.
Note 2: For patients who were eligible for TACE prior to the first TACE and became TACE non-eligible before initial TACE, time from initial TACE to TACE non-eligibility was derived as negative duration.
BCLC: Barcelona Clinic Liver Cancer Staging, ECOG: Eastern Co-Operative Oncology Group, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization, TNM: tumor, nodes (lymph nodes) and metastases classification.
Source: Table 14.1.4 / 9

The median time from initial TACE to TACE non-eligibility was 146 days in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol). About half of the patients had 1 TACE before TACE non-eligibility (55.6%). Patients most frequently had an TNM grading of stage II (21.37%), followed by stage IIIA (17.0%). The most common ECOG performance status was restricted active (37.3%) or fully active (33.7%). About half of the patients had an BCLC stage of B (32.1%) or C (27.6%) and about 42.2% had a Child Pugh classification of 5-6 points (mean 6.5 points). Please note that for about a third of patients information on the respective parameters was missing.

A higher proportion of patients in cohort 1 had worse TNM and BCLC gradings compared with cohort 2 (Table 14.1.4 / 9). However, due to the low number of patients in cohort 1 and heterogeneity in the study cohorts, these results have to be interpreted with caution. Also allocation bias was not corrected for.

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.4 / 10,Table 14.1.4 / 11, and Table 14.1.4 / 12, respectively.

The most common treatment decisions at TACE non-eligibility in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) were monitoring only (47.9%), a new TACE (28.6%), other local treatment (7.9%), and new initiation of sorafenib treatment (7.5%) (Table 14.1.4 / 13).

New initiation of sorafenib treatment was the most common treatment decision in cohort 1 (80.9%), while it was not chosen in cohort 2 (as per protocol) (Table 14.1.4 / 13).

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.4 / 14, Table 14.1.4 / 15, and Table 14.1.4 / 16, respectively.

The most common first treatment decisions after TACE non-eligibility (first follow-up visit after TACE non-eligibility) in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) were monitoring only (58.0%) and a new TACE (20.3%)

(Table 14.1.4 / 21). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.4 / 22, Table 14.1.4 /23, and Table 14.1.4 / 24, respectively.

For patients with "new TACE" at TACE non-eligibility, the most common subsequent first treatment decision after TACE non-eligibility was monitoring only (51.8%) and a new TACE (35.3%) (Table 14.1.4 / 25; patients who became TACE non-eligible after initial TACE [protocol specified]). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.4 / 26, Table 14.1.4 /27, and Table 14.1.4 / 28, respectively.

10.2.1.6 Systemic or non-systemic anti-cancer treatments

A total of 9.1% of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) received **systemic anti-cancer treatments** other than sorafenib during follow-up. Most frequently these were other antineoplastic agents (2.4%), an investigational drug (2.4%), and fluorouracil (1.8%) (Table 14.1.6 / 3). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.6 / 4, Table 14.1.6 / 5, and Table 14.1.6 / 6, respectively.

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), 30.8% received **non-systemic anti-cancer therapies** during follow-up (Table 14.1.6 / 13). Most frequently, these were radio-frequency ablation (12.4%), radiotherapy (8.3%), and hepatic artery infusion (6.1%). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.6 / 14, Table 14.1.6 / 15, and Table 14.1.6 / 16, respectively. Please note that patients may have had multiple non-systemic anti-cancer therapies during follow-up.

10.2.2 Descriptive data for the overall TACE population

This section summarizes the demographic and baseline disease characteristics as well as the descriptive data of the overall TACE population, i.e., all patients who received TACE (denoted as TCE in the statistical output). This population is used to analyze secondary objectives regarding TACE treatments including tumor response and practice patterns of the investigators.

10.2.2.1 Demographics and baseline disease characteristics

10.2.2.1.1 Demographic characteristics

Demographic characteristics are summarized for the overall TACE population in Table 18.

Table 18: Demographic and baseline characteristics – Overall TACE population

	Total N=1650
Region n (%)	
China	150 (9.1%)
Japan	233 (14.1%)
Korea	292 (17.7%)
Other Asia	459 (27.8%)
Europe / North America	497 (30.1%)
Central / South America	19 (1.2%)
Sex n (%)	
Male	1332 (80.7%)
Female	318 (19.3%)
Age calculated at date of informed consent (years)	
n	1650
Mean	63.6
SD	12.1
Median	64.0
Min, Max	18, 95
Race n (%)	
Missing	6 (0.4%)
White	344 (20.8%)
Black	1 (<0.1%)
Asian	1062 (64.4%)
Not reported	234 (14.2%)
Multiple	3 (0.2%)
BMI at inclusion visit (kg/m^2)	
n	1477
Missing	173
Mean	24.992
SD	4.294
Median	24.450
Min, Max	15.99, 46.88
Systolic blood pressure at inclusion visit (mmHg)	
n	1434
Missing	216
Mean	127.5
SD	17.2
Median	126.0
Min, Max	84, 216

	Total N=1650
Diastolic blood pressure at inclusion visit (mmHg)	
n	1434
Missing	216
Mean	75.5
SD	10.8
Median	76.0
Min, Max	38, 115
Alcohol use n (%)	
Missing	7 (0.4%)
Abstinent	1040 (63.0%)
Light	283 (17.2%)
Moderate	164 (9.9%)
Heavy	156 (9.5%)
Smoking history n (%)	
Missing	14 (0.8%)
Never	778 (47.2%)
Former	548 (33.2%)
Current	310 (18.8%)

Note 1: the population was denoted “TCE” in the statistical output.
BMI: body mass index, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 1

Most of the patients in the overall TACE population were male (80.7%) and the majority of patients was Asian (64.4%). The mean age was 63.6 years. The majority of patients were abstinent from alcohol (63.0%). Most frequently, patients never (47.2%) or formerly smoked (33.2%).

Patients most frequently were enrolled from the region other Asia (27.8%) and Europe / North America (30.1%).

Regarding countries, patients most frequently were from Korea (17.7%), Japan (14.1%), and France (12.7%) (Table 14.1.2 / 1).

A summary of the demographic data by prospective and retrospective documentation is presented in Table 19.

Table 19: Demography by prospective and retrospective documentation – Overall TACE population

	Prospective documentation N=971	Retrospective documentation N=679
Sex n (%)		
Male	790 (81.4%)	542 (79.8%)
Female	181 (18.6%)	137 (20.2%)
Age calculated at date of informed consent (years)		
n	971	679
Mean	63.3	64.1
SD	12.6	11.2
Median	64.0	64.0
Min, Max	18, 92	18, 95
BCLC stage at inclusion n (%)		
Missing	33 (3.4%)	35 (5.2%)
Stage B	601 (61.9%)	433 (63.8%)
Stage C	326 (33.6%)	203 (29.9%)
Stage D	11 (1.1%)	8 (1.2%)

Note 1: the population was denoted "TCE" in the statistical output.
Note 2: "Prospective documentation" was denoted as "no" and "retrospective documentation" was denoted as "yes" in the statistical output.
BCLC: Barcelona Clinic Liver Cancer Staging, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 15

Of the 1650 patients in the overall TACE population, 679 were enrolled retrospectively and 971 patients were enrolled prospectively. There were no major differences between these patients regarding sex, age and BCLC stage at inclusion.

The last measured laboratory values prior to or at inclusion visit for the overall TACE population are presented in Table 20.

Table 20: Last measured laboratory values prior to or at inclusion visit - Overall TACE population

	Total (N=1650) n (%)
Platelets	
Missing	168 (10.2%)
≥140 Giga/L	672 (40.7%)
<140-75 Giga/L	544 (33.0%)
<75-50 Giga/L	164 (9.9%)
<50-25 Giga/L	63 (3.8%)
<25 Giga/L	39 (2.4%)
Prothrombin INR	
Missing	249 (15.1%)
≤1.0 x ULN (1.22)	1086 (65.8%)
>1.0-1.5 x ULN (1.22)	288 (17.5%)
>1.5-2.5 x ULN (1.22)	23 (1.4%)
>2.5 x ULN (1.22)	4 (0.2%)

	Total (N=1650) n (%)
Bilirubin	
Missing	128 (7.8%)
<2 mg/dL	1342 (81.3%)
2-3 mg/dL	129 (7.8%)
>3 mg/dL	51 (3.1%)
Alanine Aminotransferase	
Missing	134 (8.1%)
≤1.0 x ULN (53 U/L)	999 (60.5%)
>1.0-3.0 x ULN (53 U/L)	459 (27.8%)
>3.0-5.0 x ULN (53 U/L)	40 (2.4%)
>5.0-20.0 x ULN (53 U/L)	17 (1.0%)
>20.0 x ULN (53 U/L)	1 (<0.1%)
Aspartate Aminotransferase	
Missing	212 (12.8%)
≤1.0 x ULN (47 U/L)	641 (38.8%)
>1.0-3.0 x ULN (47 U/L)	687 (41.6%)
>3.0-5.0 x ULN (47 U/L)	81 (4.9%)
>5.0-20.0 x ULN (47 U/L)	28 (1.7%)
>20.0 x ULN (47 U/L)	1 (<0.1%)
Creatinine	
Missing	159 (9.6%)
≤1.0 x ULN (1.5 MG/DL)	1442 (87.4%)
>1.0-1.5 x ULN (1.5 mg/dL)	34 (2.1%)
>1.5-3.0 x ULN (1.5 mg/dL)	5 (0.3%)
>3.0-6.0 x ULN (1.5 mg/dL)	8 (0.5%)
>6.0 x ULN (1.5 mg/dL)	2 (0.1%)
Corrected Creatinine Clearance	
Missing	1286 (77.9%)
≥80 mL/min	206 (12.5%)
<80-60 mL/min	103 (6.2%)
<60-30 mL/min	49 (3.0%)
<30-15 mL/min	5 (0.3%)
<15 mL/min	1 (<0.1%)
Albumin (classification 1)	
Missing	205 (12.4%)
≥1.0 x LLN (3.6 g/dL)	815 (49.4%)
<1.0 x LLN(3.6 g/dL) - 3.0 g/dL	435 (26.4%)
<3.0-2.0 g/dL	184 (11.2%)
<2.0 g/dL	11 (0.7%)
Albumin (classification 2)	
Missing	205 (12.4%)
>3.5 g/dL	832 (50.4%)
2.8-3.5 g/dL	502 (30.4%)
<2.8 g/dL	111 (6.7%)
Sodium	
Missing	379 (23.0%)
≥1.0 x LLN (135 mMOL/L)	1148 (69.6%)
<1.0 x LLN (135 mMOL/L) - 130 mMOL/L	103 (6.2%)
<130-120 mMOL/L	16 (1.0%)
<120 mMOL/L	4 (0.2%)

	Total (N=1650) n (%)
Lactate Dehydrogenase	
Missing	1092 (66.2%)
Normal (100-250 U/L)	309 (18.7%)
Abnormal	249 (15.1%)
Alpha Fetoprotein	
Missing	452 (27.4%)
<200 ng/mL	810 (49.1%)
≥200-<400 ng/mL	66 (4.0%)
≥400 ng/mL	322 (19.5%)
C Reactive Protein	
Missing	1091 (66.1%)
0-<0.1 MG/DL	277 (16.8%)
≥0.1-<0.5 MG/DL	54 (3.3%)
≥0.5-<1.0 MG/DL	25 (1.5%)
≥1.0 MG/DL	203 (12.3%)
Gamma Glutamyl Transferase	
Missing	625 (37.9%)
≤1.0 x ULN (M:50/F:32 U/L)	199 (12.1%)
>1.0-2.5 x ULN (M:50/F:32 U/L)	350 (21.2%)
>2.5-5.0 x ULN (M:50/F:32 U/L)	240 (14.5%)
>5.0-20.0 x ULN (M:50/F:32 U/L)	223 (13.5%)
>20.0 x ULN (M:50/F:32 U/L)	13 (0.8%)

Note 1: the population was denoted "TCE" in the statistical output.
INR: international normalized ratio, LLN: lower limit of normal, n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization, U: Unit, ULN: upper limit of normal.
Source: Table 14.1.2 / 169

10.2.2.1.2 Baseline disease characteristics

The majority of patients in the overall TACE population were currently treated by a hepatologist as primary treating physician (63.7%) (Table 14.1.2 / 29).

Table 21 summarizes the HCC background for patients in the overall TACE population.

Table 21: HCC background - Overall TACE population

	Total N=1650
Time from initial diagnosis to inclusion visit (months)	
n	1498
Missing	152
Mean	3.938
SD	14.436
Median	0.000
Min, Max	0.00, 171.60
Symptoms of HCC n (%)	
No	998 (60.5%)
Yes	516 (31.3%)
Unknown	136 (8.2%)

	Total N=1650
HCC confirmed by biopsy n (%)	
Missing	4 (0.2%)
No	1280 (77.6%)
Yes	366 (22.2%)
Newly diagnosed n (%)	
No	416 (25.2%)
Yes	1234 (74.8%)

Note 1: the population was denoted "TCE" in the statistical output.
Note 2: For newly diagnosed patients, time from initial diagnosis to inclusion visit is derived as 0 (months).
HCC: hepatocellular carcinoma, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 29

Overall, patients in the overall TACE population had their inclusion visit shortly after initial diagnosis (mean 3.9 months, median 0.0 months). For the majority of patients, HCC was newly diagnosed (74.8%) and not confirmed by biopsy (77.6%). The majority of patients had no symptoms of HCC (60.5%).

For patients in the overall TACE population who were not newly diagnosed, the median time from initial diagnosis to the inclusion visit was 11.5 months. Further details on progression and HCC assessment in these patients can be found in Table 14.1.2 / 30.

An overview on the HCC status at inclusion visit for the overall TACE population is given in Table 22.

Table 22: HCC at inclusion visit - Overall TACE population

	Total N=1650
TNM grading of HCC n (%)	
Missing	308 (18.7%)
Stage I	127 (7.7%)
Stage II	540 (32.7%)
Stage IIIA	387 (23.5%)
Stage IIIB	122 (7.4%)
Stage IIIC	48 (2.9%)
Stage IVA	60 (3.6%)
Stage IVB	58 (3.5%)
Unknown	0 (0.0%)
BCLC stage n (%)	
Missing	68 (4.1%)
Stage 0	0 (0.0%)
Stage A	0 (0.0%)
Stage B	1034 (62.7%)
Stage C	529 (32.1%)
Stage D	19 (1.2%)
Child Pugh score	
n	1457
Missing	193
Mean	5.8
SD	1.1
Median	5.0
Min, Max	4, 11

	Total N=1650
Child Pugh classification n (%)	
Missing	185 (11.2%)
A (5-6 points)	1126 (68.2%)
B (7-9 points)	332 (20.1%)
C (10-15 points)	7 (0.4%)
ECOG performance status n (%)	
Missing	210 (12.7%)
0 (fully active)	1103 (66.8%)
1 (restricted active)	294 (17.8%)
2 (ambulatory and capable of all self-care)	36 (2.2%)
3 (capable of limited self-care)	7 (0.4%)
4 (completely disabled)	0 (0.0%)
5 (dead)	0 (0.0%)

Note 1: the population was denoted “TCE” in the statistical output.

BCLC: Barcelona Clinic Liver Cancer Staging, ECOG: Eastern Co-Operative Oncology Group, HCC: hepatocellular carcinoma, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization, TNM: Tumor, Nodes (lymph nodes) and Metastases classification.
Source: Table 14.1.2 / 57

Patients in the overall TACE population most frequently had an TNM grading of stage II (32.7%), followed by stage IIIA (23.5%). The majority of patients had an BCLC stage of B (62.7%) or C (32.1%) and a Child Pugh classification of 5-6 points (68.2%; mean 5.8 points). The ECOG performance status was 0 for the majority of patients (66.8%).

Tumor evaluation at inclusion visit for patients in the overall TACE population was most frequently performed by CT scan (61.9%), followed by MRI (33.6%) (Source: Table 14.1.2 / 71).

Tumor evaluation at inclusion visit for the overall TACE population is shown in Table 23.

Table 23: Tumor evaluation at inclusion visit - Overall TACE population

	Total N=1650
Total number of lesions n (%)	
Missing	88 (5.3%)
0	5 (0.3%)
1	472 (28.6%)
2	360 (21.8%)
3	226 (13.7%)
4	159 (9.6%)
5	123 (7.5%)
6	48 (2.9%)
7	44 (2.7%)
8	26 (1.6%)
9	16 (1.0%)
≥10	83 (5.0%)
Longest diameter (mm)	
n	1570
Missing	80
Mean	55.523
SD	38.993
Median	45.000
Min, Max	0.00, 432.00
New metastases present n (%)	
Missing	3 (0.2%)
No	1525 (92.4%)
Yes	122 (7.4%)
Time from tumor evaluation to inclusion visit (months)	
n	1649
Missing	1
Mean	0.594
SD	1.141
Median	0.270
Min, Max	-3.30, 21.93

Note 1: the population was denoted “TCE” in the statistical output.
Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 71

Patients in the overall TACE population most frequently had between 1 and 3 lesions. The mean longest diameter of the lesions was 55.523 mm. Mostly no new metastases were present (92.4%). The median time from tumor evaluation to inclusion visit was 0.3 months.

Disease status at inclusion visit is summarized for the overall TACE population in Table 24.

Table 24: Disease status summary at inclusion visit - Overall TACE population

	Total N=1650 n (%)
Most frequent disease status criteria (≥5% of patients)	
BCLC stage C or D	547 (33.2%)
ECOG performance status ≥1	342 (20.7%)
Advanced liver disease (Child Pugh B/C)	339 (20.5%)
Vascular invasion	156 (9.5%)
Portal vein thrombosis	123 (7.5%)
Extrahepatic spread present	118 (7.2%)

Note 1: the population was denoted “TCE” in the statistical output.
Note 2: Child Pugh class B is considered as TACE eligible (as of protocol version 3.0)
Note 3: Child Pugh class is derived by CRF section "Child Pugh Classification"
BCLC: Barcelona Clinic Liver Cancer Staging, CRF: case report form, ECOG: Eastern Co-Operative Oncology Group, n: number of patients, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 85

In the overall TACE population, the most frequent disease status criteria were BCLC stage C or D (33.2%), followed by ECOG performance status ≥1 (20.7%) and advanced liver disease (Child Pugh B/C) (20.5%).

The history of liver disease is presented in Table 25 for the overall TACE population.

Table 25: History of liver disease - Overall TACE population

	Total N=1650
Liver cirrhosis present n (%)	
Missing	4 (0.2%)
No	415 (25.2%)
Yes	1231 (74.6%)
Time from initial diagnosis of liver cirrhosis to inclusion visit (months)	
n	645
Missing	1005
Mean	14.044
SD	29.898
Median	1.570
Min, Max	-0.03, 215.23
Findings related to liver cirrhosis (multiple response) n (%)	
Missing	1225 (74.2%)
Ascites	199 (12.1%)
Esophageal varices	284 (17.2%)
Gastrointestinal bleeding	73 (4.4%)
Hepatic encephalopathy	32 (1.9%)

	Total N=1650
Etiology of HCC (multiple response) n (%)	
Missing	5 (0.3%)
Alcohol use	445 (27.0%)
Hepatitis B	548 (33.2%)
Hepatitis C	500 (30.3%)
Aflatoxin	1 (<0.1%)
Genetic / metabolic	43 (2.6%)
Nonalcoholic steatohepatitis (NASH)	111 (6.7%)
Primary biliary cirrhosis	6 (0.4%)
Hepatitis D	3 (0.2%)
Steatohepatitis	0 (0.0%)
Unknown	221 (13.4%)
Other	7 (0.4%)

Note 1: the population was denoted "TCE" in the statistical output.
HCC: hepatocellular carcinoma, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 99

In the overall TACE population, liver cirrhosis was present in the majority of patients (74.6%). The median time from initial diagnosis of liver cirrhosis to inclusion visit was 1.6 months. The most common etiologies were hepatitis B (33.2%), hepatitis C (30.3%), and alcohol use (27.0%).

Table 26 summarizes the prognostic scores for patients to be treated with TACE for the overall TACE population.

Table 26: Prognostic Scores for patients to be treated with TACE - Overall TACE population

	Total N=1650 n (%)
STATE category	
Missing	1138 (69.0%)
<18	131 (7.9%)
≥18	381 (23.1%)
CHIP category	
Missing	233 (14.1%)
0-2	693 (42.0%)
3	350 (21.2%)
4	189 (11.5%)
5	124 (7.5%)
6-7	61 (3.7%)
HAP category	
Missing	581 (35.2%)
0 (HAP A)	1 (<0.1%)
1 (HAP B)	355 (21.5%)
2 (HAP C)	463 (28.1%)
>2 (HAP D)	250 (15.2%)

Note 1: the population was denoted "TCE" in the statistical output.
Note 2: Patients with Child Pugh score > 10 are handled as missing for CHIP category.
CHIP: Chiba HCC in intermediate-stage prognostic score, HAP: hepatoma arterial-embolization prognostic (score), HCC: hepatocellular carcinoma, n: number of patients, N: number of patients in analysis set, STATE: selection for transarterial chemoembolization treatment, TACE: transarterial chemoembolization.
Source: Table 14.1.3 / 1

Patients in the overall TACE population most frequently had a STATE category of ≥18 (23.1%, missing: 69.0%), a CHIP category of 0-2 (42.0%) and a HAP category of 2 (HAP C) (28.1%, missing: 35.2%).

10.2.2.2 Medical history and concomitant diseases

10.2.2.2.1 Medical history

General medical history was reported in 943 of 1650 patients (57.2%) in the overall TACE population. The most frequently reported medical history at SOC level were Vascular disorders (31.8%), followed by Metabolism and nutrition disorders (27.8%), Gastrointestinal disorders (14.5%), and Cardiac disorders (10.8%). At PT level, hypertension (29.9%) and type 2 diabetes mellitus (23.2%) were reported most frequently (Table 14.1.2 / 113).

10.2.2.2.2 Concomitant diseases

Concomitant diseases were reported in 540 of 1650 patients (32.7%) in the overall TACE population. The most frequently reported SOC were Gastrointestinal disorders (11.5%), followed by Cardiac disorders (8.6%), and Infections and infestations (5.8%). At PT level, gastrointestinal ulcer (5.3%), followed by angina pectoris (3.8%), and chronic hepatitis B (2.1%) were reported most frequently (Table 14.1.2 / 114).

10.2.2.3 Prior and concomitant therapies and medications

10.2.2.3.1 Prior therapeutic procedures for HCC

In the overall TACE population, 224 of 1650 patients (13.6%) had any prior therapeutic procedure for HCC (including surgery). Most frequently hepatectomy (9.2%) and ablation (3.8%) were performed. The most common location of prior procedures was the liver (13.4%) (Table 14.1.2 / 141).

10.2.2.3.2 Prior local anti-cancer therapy

In the overall TACE population, 182 of 1650 patients (11.0%) had any prior local anti-cancer therapy (except prior surgical procedures and TACE). Most frequently radio-frequency ablation (8.4%) was performed (Table 14.1.2 / 155). Analyses of the radiological best response and the time of first/last local anti-cancer therapy to time of inclusion by type of local anti-cancer therapy can be found in Table 14.1.2 / 155.

10.2.2.3.3 Prior non-HCC related medication

In the overall TACE population, 994 of 1650 patients (60.2%) reported prior non-HCC related medication. The most frequently reported prior non-HCC related medication at ATC level 1 was alimentary tract and metabolism (44.6%), followed by cardiovascular system (36.7%), blood and blood forming organs (21.9%), nervous system (21.9%), and antiinfectives for systemic use (20.7%) (Table 14.1.2 / 183).

10.2.2.3.4 Concomitant non-HCC related medication

In the overall TACE population, 1288 of 1650 patients (78.1%) reported concomitant non-HCC related medication. The most frequently reported concomitant non-HCC related medication at ATC level 1 was alimentary tract and metabolism (65.2%), followed by cardiovascular system (51.4%), antiinfectives for systemic use (48.3%), and nervous system (44.3%) (Table 14.1.2 / 197).

10.2.2.4 Initial TACE treatment

Table 27 presents the initial TACE treatment in the overall TACE population.

Table 27: Initial TACE treatment - Overall TACE population

	Total N=1650
Retrospective TACE n (%)	
No	971 (58.8%)
Yes	679 (41.2%)
Time from informed consent to initial TACE administration for prospectively documented patients (days)	
n	971
Missing	679
Mean	6.2
SD	16.9
Median	1.0
Min, Max	0, 223
Time from retrospective initial TACE administration to informed consent (days)	
n	679
Missing	971
Mean	48.4
SD	66.2
Median	33.0
Min, Max	1, 679
Area of TACE n (%)	
Missing	6 (0.4%)
Whole liver	461 (27.9%)
Left side	205 (12.4%)
Right side	753 (45.6%)
Single segment S1	12 (0.7%)
Single segment S2	12 (0.7%)
Single segment S3	10 (0.6%)
Single segment S4	28 (1.7%)
Single segment S5	24 (1.5%)
Single segment S6	34 (2.1%)
Single segment S7	33 (2.0%)
Single segment S8	72 (4.4%)
Embolization agent (multiple response) n (%)	
Missing	37 (2.2%)
Gelatin foam	561 (34.0%)
Microspheres	204 (12.4%)
Lipiodol	1238 (75.0%)
Polyvinyl alcohol	70 (4.2%)
DC-beads	269 (16.3%)
Gelatin sponge	207 (12.5%)
Flax seed oil	30 (1.8%)
Other	4 (0.2%)

Note 1: the population was denoted “TCE” in the statistical output.
Note 2: “Prospectively documented patients” were denoted as “non-retrospective patients” in the statistical output.
Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.1.2 / 211

The initial TACE was documented prospectively for 58.8% of patients in the overall TACE population and retrospectively for 41.2% of patients. The median time from informed consent to initial TACE administration was 1 day for prospectively documented patients and the median time from retrospective initial TACE administration to informed consent 33 days for retrospective patients. Initial TACE was most frequently performed on the right side (45.6%), followed by the whole liver (27.9%). The most common embolization agent was lipiodol (75.0%), followed by gelatin foam (34.0%).

The drugs used in TACE treatment can be found in Table 14.1.2 / 211 for the overall TACE population.

10.2.2.5 Systemic or non-systemic anti-cancer treatments

Overall, 6.8% of patients in overall TACE population received **systemic anti-cancer treatments other than sorafenib** during follow-up. Most frequently these were other antineoplastic agents (2.3%), fluorouracil (1.6%) or an investigational drug (1.3%) (Table 14.1.6 / 1).

A total of 25.0% of patients in the overall TACE population received **non-systemic anti-cancer therapies** during follow-up. Most frequently these were radio-frequency ablation (10.7%), radiotherapy (5.2%), hepatic artery infusion (3.1%), and transarterial embolization (3.0%) (Table 14.1.6 / 11). Please note that patients may have had multiple non-systemic anti-cancer therapies during follow-up.

10.2.3 Descriptive data for the sorafenib treated patients

This section summarizes the demographic and baseline disease characteristics as well as the descriptive data of the sorafenib population, i.e. all patients who received sorafenib (denoted as SOAP in the statistical output). This population is used to analyze safety parameters regarding sorafenib treatment and the secondary objective "OS, PFS, TTP, tumor response and AEs from start of sorafenib treatment".

10.2.3.1 Demographics and baseline disease characteristics

10.2.3.1.1 Demographic characteristics

Demographic characteristics are summarized for sorafenib treated patients in Table 28.

Table 28: Demographic and baseline characteristics – Sorafenib treated patients

	Total N=515
Region n (%)	
China	73 (14.2%)
Japan	81 (15.7%)
Korea	54 (10.5%)
Other Asia	137 (26.6%)
Europe / North America	164 (31.8%)
Central / South America	6 (1.2%)
Sex n (%)	
Male	420 (81.6%)
Female	95 (18.4%)

	Total N=515
Age calculated at date of informed consent (years)	
n	515
Mean	62.3
SD	12.6
Median	63.0
Min, Max	18, 88
Race n (%)	
Missing	1 (0.2%)
White	97 (18.8%)
Asian	339 (65.8%)
Not reported	78 (15.1%)
BMI at inclusion visit (kg/m^2)	
n	469
Missing	46
Mean	25.226
SD	4.362
Median	24.540
Min, Max	16.38, 46.88
Systolic blood pressure at inclusion visit (mmHg)	
n	464
Missing	51
Mean	129.4
SD	18.2
Median	129.0
Min, Max	90, 216
Diastolic blood pressure at inclusion visit (mmHg)	
n	464
Missing	51
Mean	76.8
SD	10.1
Median	77.0
Min, Max	50, 109
Alcohol use n (%)	
Missing	2 (0.4%)
Abstinent	314 (61.0%)
Light	95 (18.4%)
Moderate	52 (10.1%)
Heavy	52 (10.1%)
Smoking history n (%)	
Missing	4 (0.8%)
Never	246 (47.8%)
Former	155 (30.1%)
Current	110 (21.4%)

Note 1: the population was denoted “SOAP” in the statistical output.
BMI: body mass index, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation.
Source: Table 14.1.2 / 14

In sorafenib treated patients, most of the patients were male (81.6%) and the majority of patients was Asian (65.8%). The mean age was 62.3 years. The majority of patients were abstinent from alcohol

(61.0%). Most frequently, patients never (47.8%) or formerly smoked (30.1%). Patients most frequently were enrolled from the region Europe / North America (31.8%) and other Asia (26.6%).

In sorafenib treated patients most frequently were from Japan (15.7%), France (14.2%), and China (14.2%). For more details on the countries of origin in each set, see Table 14.1.2 / 1 to Table 14.1.2 / 14.

Of the 515 sorafenib treated patients, 220 were enrolled retrospectively and 291 patients were enrolled prospectively. Four patients had no initial TACE documented and therefore information regarding retrospective or prospective enrollment was missing. There were no major differences between these patients regarding sex, age and BCLC stage at inclusion (Table 14.1.2 / 28).

The last measured laboratory values prior to or at inclusion visit for sorafenib treated patients are presented in Table 29.

Table 29: Last measured laboratory values prior to or at inclusion visit - Sorafenib treated patients

	Total N=515 n (%)
Platelets	
Missing	40 (7.8%)
≥140 Giga/L	266 (51.7%)
<140-75 Giga/L	153 (29.7%)
<75-50 Giga/L	37 (7.2%)
<50-25 Giga/L	9 (1.7%)
<25 Giga/L	10 (1.9%)
Prothrombin INR	
Missing	79 (15.3%)
≤1.0 x ULN (1.22)	362 (70.3%)
>1.0-1.5 x ULN (1.22)	67 (13.0%)
>1.5-2.5 x ULN (1.22)	7 (1.4%)
>2.5 x ULN (1.22)	0 (0.0%)
Bilirubin	
Missing	27 (5.2%)
<2 mg/dL	435 (84.5%)
2-3 mg/dL	33 (6.4%)
>3 mg/dL	20 (3.9%)
Alanine Aminotransferase	
Missing	33 (6.4%)
≤1.0 x ULN (53 U/L)	310 (60.2%)
>1.0-3.0 x ULN (53 U/L)	150 (29.1%)
>3.0-5.0 x ULN (53 U/L)	18 (3.5%)
>5.0-20.0 x ULN (53 U/L)	3 (0.6%)
>20.0 x ULN (53 U/L)	1 (0.2%)
Aspartate Aminotransferase	
Missing	49 (9.5%)
≤1.0 x ULN (47 U/L)	195 (37.9%)
>1.0-3.0 x ULN (47 U/L)	236 (45.8%)
>3.0-5.0 x ULN (47 U/L)	30 (5.8%)
>5.0-20.0 x ULN (47 U/L)	4 (0.8%)
>20.0 x ULN (47 U/L)	1 (0.2%)

	Total N=515 n (%)
Creatinine	
Missing	39 (7.6%)
≤1.0 x ULN (1.5 MG/DL)	463 (89.9%)
>1.0-1.5 x ULN (1.5 mg/dL)	8 (1.6%)
>1.5-3.0 x ULN (1.5 mg/dL)	1 (0.2%)
>3.0-6.0 x ULN (1.5 mg/dL)	1 (0.2%)
>6.0 x ULN (1.5 mg/dL)	3 (0.6%)
Corrected Creatinine Clearance	
Missing	409 (79.4%)
≥80 mL/min	63 (12.2%)
<80-60 mL/min	34 (6.6%)
<60-30 mL/min	8 (1.6%)
<30-15 mL/min	1 (0.2%)
<15 mL/min	0 (0.0%)
Albumin (classification 1)	
Missing	66 (12.8%)
≥1.0 x LLN (3.6 g/dL)	292 (56.7%)
<1.0 x LLN(3.6 g/dL) - 3.0 g/dL	115 (22.3%)
<3.0-2.0 g/dL	42 (8.2%)
<2.0 g/dL	0 (0.0%)
Albumin (classification 2)	
Missing	66 (12.8%)
>3.5 g/dL	299 (58.1%)
2.8-3.5 g/dL	127 (24.7%)
<2.8 g/dL	23 (4.5%)
Sodium	
Missing	103 (20.0%)
≥1.0 x LLN (135 mMOL/L)	379 (73.6%)
<1.0 x LLN (135 mMOL/L) - 130 mMOL/L	30 (5.8%)
<130-120 mMOL/L	1 (0.2%)
<120 mMOL/L	2 (0.4%)
Lactate Dehydrogenase	
Missing	323 (62.7%)
Normal (100-250 U/L)	110 (21.4%)
Abnormal	82 (15.9%)
Alpha Fetoprotein	
Missing	111 (21.6%)
<200 ng/mL	245 (47.6%)
≥200-<400 ng/mL	28 (5.4%)
≥400 ng/mL	131 (25.4%)
C Reactive Protein	
Missing	336 (65.2%)
0-<0.1 MG/DL	81 (15.7%)
≥0.1-<0.5 MG/DL	11 (2.1%)
≥0.5-<1.0 MG/DL	9 (1.7%)
≥1.0 MG/DL	78 (15.1%)
Gamma Glutamyl Transferase	
Missing	171 (33.2%)
≤1.0 x ULN (M:50/F:32 U/L)	55 (10.7%)
>1.0-2.5 x ULN (M:50/F:32 U/L)	115 (22.3%)
>2.5-5.0 x ULN (M:50/F:32 U/L)	87 (16.9%)
>5.0-20.0 x ULN (M:50/F:32 U/L)	82 (15.9%)
>20.0 x ULN (M:50/F:32 U/L)	5 (1.0%)

	Total N=515 n (%)

Note 1: the population was denoted “SOAP” in the statistical output.
INR: international normalized ratio, LLN: lower limit of normal, n: number of patients, N: number of patients in analysis set, U: Unit, ULN: upper limit of normal.
Source: Table 14.1.2 / 182

10.2.3.1.2 Baseline disease characteristics

More than half of the sorafenib treated patients were currently treated by a hepatologist as primary treating physician (55.3%) (Table 14.1.2 / 55).

Overall, sorafenib treated patients had their inclusion visit shortly after initial diagnosis (mean 3.9 months, median 0.0 months). For the majority of patients, HCC was newly diagnosed (72.6%) and not confirmed by biopsy (72.0%). The majority of patients had no symptoms of HCC (56.1%) (Table 14.1.2 / 55).

For sorafenib treated patients who were not newly diagnosed, the median time from initial diagnosis to the inclusion visit was 10.2 months. Further details on progression and HCC assessment in these patients can be found in Table 14.1.2 / 56.

An overview on the HCC status at inclusion visit for sorafenib treated patients is given in Table 30.

Table 30: HCC at inclusion visit - Sorafenib treated patients

	Total N=515
TNM grading of HCC n (%)	
Missing	100 (19.4%)
Stage I	21 (4.1%)
Stage II	118 (22.9%)
Stage IIIA	135 (26.2%)
Stage IIIB	60 (11.7%)
Stage IIIC	22 (4.3%)
Stage IVA	29 (5.6%)
Stage IVB	30 (5.8%)
Unknown	0 (0.0%)
BCLC stage n (%)	
Missing	22 (4.3%)
Stage 0	0 (0.0%)
Stage A	0 (0.0%)
Stage B	267 (51.8%)
Stage C	219 (42.5%)
Stage D	7 (1.4%)
Child Pugh score	
n	467
Missing	48
Mean	5.8
SD	1.1
Median	5.0
Min, Max	4, 11

	Total N=515
Child Pugh classification n (%)	
Missing	46 (8.9%)
A (5-6 points)	370 (71.8%)
B (7-9 points)	96 (18.6%)
C (10-15 points)	3 (0.6%)
ECOG performance status n (%)	
Missing	47 (9.1%)
0 (fully active)	337 (65.4%)
1 (restricted active)	115 (22.3%)
2 (ambulatory and capable of all self-care)	14 (2.7%)
3 (capable of limited self-care)	2 (0.4%)
4 (completely disabled)	0 (0.0%)
5 (dead)	0 (0.0%)

Note 1: the population was denoted "SOAP" in the statistical output.

BCLC: Barcelona Clinic Liver Cancer Staging, ECOG: Eastern Co-Operative Oncology Group, HCC: hepatocellular carcinoma, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TNM: Tumor, Nodes (lymph nodes) and Metastases classification.
Source: Table 14.1.2 / 70

Sorafenib treated patients most frequently had an TNM grading of stage IIIA (26.2%), followed by II (22.9%). The majority of patients had an BCLC stage of B (51.8%), followed by C (42.5%,) and a Child Pugh classification of 5-6 points (71.8%; mean 5.8 points). The most common ECOG performance status was 0 (65.4%), followed by 1 (22.3%).

Tumor evaluation at inclusion visit for sorafenib treated patients was most frequently performed by CT scan (61.4%), followed by MRI (32.6%) (Source: Table 14.1.2 / 84).

Sorafenib treated patients most frequently had between 1 and 4 lesions. The mean longest diameter of the lesions was 64.910 mm. Mostly no new metastases were present (87.8%). The median time from tumor evaluation to inclusion visit was 0.2 months (Table 14.1.2 / 84).

In sorafenib treated patients, the most frequent disease status criteria at inclusion visit were BCLC stage C or D (43.9%), followed by ECOG performance status ≥1 (25.6%) and advanced liver disease (Child Pugh B/C) (19.0%) (Table 14.1.2 / 98).

In sorafenib treated patients, liver cirrhosis was present in the majority of patients (64.5%). The median time from initial diagnosis of liver cirrhosis to inclusion visit was 1.5 months. The most common etiologies were hepatitis B (37.1%), alcohol use (26.4%), and hepatitis C (25.6%) (Table 14.1.2 / 112).

10.2.3.2 Medical history and concomitant diseases

10.2.3.2.1 Medical history

A total of 277 of 515 sorafenib treated patients (53.8%) reported general medical history. The most frequently reported medical history at SOC level were Vascular disorders (30.9%), followed by Metabolism and nutrition disorders (24.7%), and Gastrointestinal disorders (11.7%). At PT level, hypertension (29.5%) and type 2 diabetes mellitus (20.2%) were reported most frequently (Table 14.1.2 / 139).

10.2.3.2.2 Concomitant diseases

Overall, 167 of 515 sorafenib treated patients (32.4%) reported concomitant diseases. The most frequently reported SOC were Gastrointestinal disorders (10.1%), followed by Infections and infestations (8.2%), and Cardiac disorders (7.4%). At PT level, gastrointestinal ulcer (4.3%) and angina pectoris (3.3%) were reported most frequently (Table 14.1.2 / 140).

10.2.3.3 Prior and concomitant therapies and medications

10.2.3.3.1 Prior therapeutic procedures for HCC

A total of 87 of 515 sorafenib treated patients (16.9%) had any prior therapeutic procedure for HCC (including surgery). Most frequently hepatectomy (13.2%) and ablation (3.1%) were performed. All procedures were performed at the liver (16.9%) (Table 14.1.2 / 154).

10.2.3.3.2 Prior local anti-cancer therapy

A total of 48 of 515 sorafenib treated patients (9.3%) had any prior local anti-cancer therapy (except prior surgical procedures and TACE). Most frequently radio-frequency ablation (6.2%) was performed (Table 14.1.2 / 168). Analyses of the radiological best response and the time of first/last local anti-cancer therapy to time of inclusion by type of local anti-cancer therapy can be found in Table 14.1.2 / 168.

10.2.3.3.3 Prior non-HCC related medication

Overall, 275 of 515 sorafenib treated patients (53.4%) reported prior non-HCC related medication. At ATC level 1, the most frequently reported prior non-HCC related medication was alimentary tract and metabolism (38.4%), followed by cardiovascular system (31.8%) (Table 14.1.2 / 196).

10.2.3.3.4 Concomitant non-HCC related medication

A total of 397 of 515 sorafenib treated patients (77.1%) reported concomitant non-HCC related medication. The most frequently reported concomitant non-HCC related medication at ATC level 1 was alimentary tract and metabolism (63.9%), followed by cardiovascular system (46.8%), nervous system (37.9%), antiinfectives for systemic use (37.5%), and blood and blood forming organs (36.9%) (Table 14.1.2 / 210).

10.2.3.4 Systemic or non-systemic anti-cancer treatments

Overall, 14.6% of sorafenib treated patients received **systemic anti-cancer treatments other than sorafenib** during follow-up. Most frequently these were fluorouracil (4.1%), followed by other antineoplastic agents (3.9%), and an investigational drug (3.7%) (Table 14.1.6 / 2).

In sorafenib treated patients, 23.9% received **non-systemic anti-cancer therapies** during follow-up. Most frequently these were radiotherapy (6.8%), hepatic artery infusion (6.6%), and radio-frequency ablation (6.2%) (Table 14.1.6 / 12). Please note that patients may have had multiple non-systemic anti-cancer therapies during follow-up.

10.2.3.5 Sorafenib treatment

Table 31 summarizes the exposure to sorafenib in sorafenib treated patients.

Table 31: Exposure to sorafenib - Sorafenib treated patients

	Total N=515
Initial dose of sorafenib - n (%)	
200 mg	17 (3.3%)
400 mg	172 (33.4%)
600 mg	12 (2.3%)
800 mg	314 (61.0%)
Duration of sorafenib exposure (days)	
n	515
Mean	233.1
SD	264.3
Median	131.0
Min, Max	1, 1416
Cumulative person time (years)	328.64
Actual days on sorafenib (days)	
n	515
Mean	219.9
SD	256.3
Median	124.0
Min, Max	1, 1416
Average total daily dose of sorafenib (mg)	
n	515
Mean	609.09
SD	197.39
Median	671.47
Min, Max	200.0, 800.0
Sorafenib dose modification (multiple response)	
Missing	86 (16.7%)
Reduction	108 (21.0%)
Interruption or delay	127 (24.7%)
Escalation	87 (16.9%)
Drug withdrawn	376 (73.0%)
Dose restart	124 (24.1%)

Note 1: the population was denoted “SOAP” in the statistical output.
Note 2: Duration of sorafenib was defined as days from first sorafenib to the day of permanent discontinuation.
Note 3: Actual days on sorafenib was defined as days between date of first treatment and date of last treatment.
Note 4: Average total daily dose of sorafenib was defined as sum of total daily doses divided by actual days on sorafenib.
Note 5: Cumulative person time in years was calculated as sum of duration of sorafenib divided by 365.25.
Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation.
Source: Table 14.1.5 / 1

In sorafenib treated patients, the most frequently, the initial dose of sorafenib was 800 mg (61.0%), followed by 400 mg (33.4%). The median duration of sorafenib exposure was 131 days, with a median of 124 actual days on sorafenib. The cumulative person time was 328.64 years. The most common dose modification was “drug withdrawn” (73.0%).

The most common reasons for discontinuation from sorafenib treatment were “adverse event per protocol” (27.6%), “progression, recurrence/relapse of cancer under study” (23.7%), and “death” (10.9%; missing: 27.4%) (Table 14.1.5 / 1).

10.3 Outcome data

The number of documented patients across the categories of the main outcomes are provided in section 10.2 for demographic and disease characteristics, in section 10.4.1 for the primary objectives, in section 10.4.2 for the secondary objectives, and in section 10.6 for the safety parameters.

Results regarding TACE non-eligibility and outcome of patients in relation to the timing of initiation of sorafenib can be found in section 10.4.1, section 10.4.2.1, section 10.4.2.2, section 10.4.2.3, and section 10.4.2.4. Details on TACE treatments are provided in section 10.4.2.5, section 10.4.2.6, and section 10.4.2.7 and a description on the practice patterns of the investigators can be found in section 10.4.2.8 and section 10.4.2.9.

10.4 Main results

10.4.1 Analysis of primary outcome variables

The primary objective of this study was to evaluate OS from time of TACE non-eligibility in two cohorts of special interest (see section 9.9.2.2) not only overall but also by study region. Individual analyses for the regions China, Japan, Korea, Other Asia, and Europe / North America are provided as stand-alone documents in Annex 1 and are available upon request. Analyses for the region Central / South America was not performed due to the low number of subjects (N=19).

The OS from TACE non-eligibility for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) is provided in Table 32 and a Kaplan-Meier curve is presented in Figure 3.

Table 32: Summary of OS from TACE non-eligibility - Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	N	Number failed	Number censored	Median (days)	95% CI Median (days)
Total	507	227 (44.8%)	280 (55.2%)	590	[474;695]

Note 1: the population was denoted “TNE1” in the statistical output.
CI: confidence interval, N: number of patients in analysis set, OS: overall survival, TACE: transarterial chemoembolization.
Source: Table 14.2 / 1

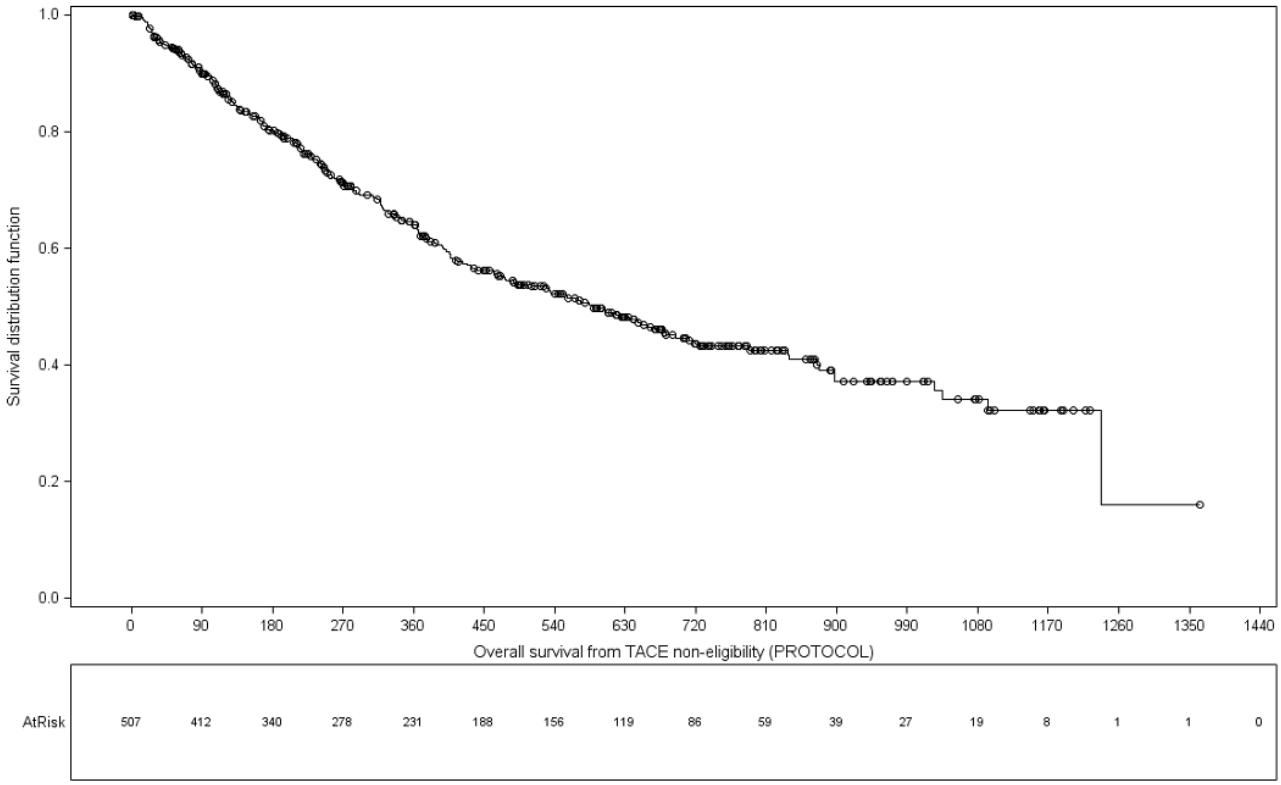

Figure 3: Kaplan-Meier curve of OS from TACE non-eligibility – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)
Note 1: the population was denoted "TNE1" in the statistical output.
OS: overall survival, TACE: transarterial chemoembolization.
Source: Figure: 14.2 / 1

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median OS was 590 days (95% CI: 474; 695 days).

In cohort 1, the median OS was 494 days (95% CI: 318;* days[12]) and in cohort 2, the median OS was 604 days (95% CI: 474;711 days) (Table 14.2 / 1). Please note that due to the low number of patients in cohort 1 and heterogeneity in the study cohorts, these results have to be interpreted with caution. Also allocation bias was not corrected for.

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.2 / 4, Table 14.2 / 7, and Table 14.2 / 10, respectively. Kaplan-Meier curves can be found in Figure 14.2 / 3 to Figure 14.2 / 8.

[12] * presents censored observation or unestimable due to censored data.

A summary of OS from TACE non-eligibility by number of previous TACE is given in Table 33 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Table 33: Summary of OS from TACE non-eligibility by number of previous TACE – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

Previous TACE	N	Number failed	Number censored	Median (days)	95% CI Median (days)
0	5	3 (60.0%)	2 (40.0%)	877	[109;*]
1	282	125 (44.3%)	157 (55.7%)	668	[534;897]
2	107	53 (49.5%)	54 (50.5%)	477	[314;681]
3	55	25 (45.5%)	30 (54.5%)	529	[320;839]
4 - 5	39	16 (41.0%)	23 (59.0%)	407	[205;*]
≥6	19	5 (26.3%)	14 (73.7%)	342	[263;*]

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: For patients who were eligible for TACE prior to the first TACE and became TACE non-eligible before initial TACE, number of TACE before TACE non-eligibility was calculated as 0
Note 3: "*" presents censored observation or unestimable due to censored data
CI: confidence interval, N: number of patients, OS: overall survival, TACE: transarterial chemoembolization.
Source: Table 14.2 / 2

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median OS tended to decrease with increasing number of TACEs.

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.2 / 5, Table 14.2 / 8, and Table 14.2 / 11, respectively.

The OS from TACE non-eligibility by best radiological response to the first TACE is summarized in Table 34 for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Table 34: Summary of OS from TACE non-eligibility by best radiological response to the first TACE – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	N	Number failed	Number censored	Median (days)	95% CI Median (days)
Complete response	88	35 (39.8%)	53 (60.2%)	874	[618;*]
Partial response	153	57 (37.3%)	96 (62.7%)	605	[407;1238]
Stable disease	114	50 (43.9%)	64 (56.1%)	718	[462;1093]
Progressive disease	104	64 (61.5%)	40 (38.5%)	377	[291;584]
Not evaluable	4	2 (50.0%)	2 (50.0%)	457	[232;682]
Missing	44	19 (43.2%)	25 (56.8%)	407	[238;*]

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: "*" presents censored observation or unestimable due to censored data
CI: confidence interval, N: number of patients, OS: overall survival, TACE: transarterial chemoembolization
Source: Table 14.2 / 3

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median OS was lower in patients with progressive disease as best radiological response than in patients with complete response, partial response, or stable disease.

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.2 / 6, Table 14.2 / 9, and Table 14.2 / 12, respectively.

10.4.2 Analysis of secondary outcome variables

10.4.2.1 Progression-free survival and time to progression from time of TACE non-eligibility

A secondary objective of the study was the evaluation of PFS, TTP, tumor response, and AE from time of TACE non-eligibility.

The time to event (PFS and TTP) in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) is summarized in Table 35. Kaplan-Meier curves are presented in Figure 4 (PFS) and Figure 5 (TTP).

Table 35: Summary of PFS and TTP – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	N	Number failed	Number censored	Median (days)	95% CI Median (days)
PFS	507	381 (75.1%)	126 (24.9%)	103	[91;126]
TTP	507	354 (69.8%)	153 (30.2%)	45	[3;86]

Note 1: the population was denoted “TNE1” in the statistical output.
CI: confidence interval, N: number of patients, PFS: progression free survival, TACE: transarterial chemoembolization, TTP: time to progression.
Source: Table 14.3.1 / 2

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median PFS was 103 days (95% CI: 91;126 days) and the median TTP was 45 days (95% CI: 3;86 days).

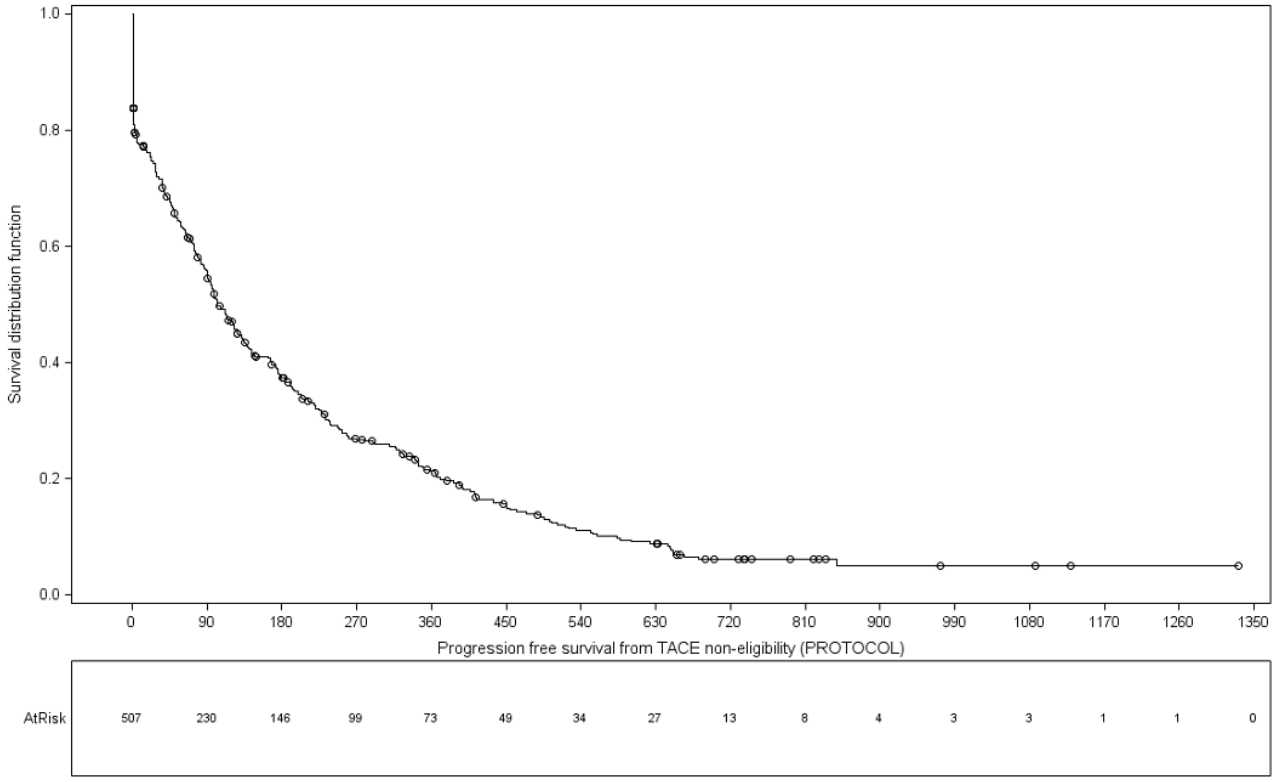

Figure 4: Kaplan-Meier curve of PFS from TACE non-eligibility – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)
Note 1: the population was denoted “TNE1” in the statistical output.
PFS: progression free survival, TACE: transarterial chemoembolization.
Source: Figure: 14.3.1 / 4

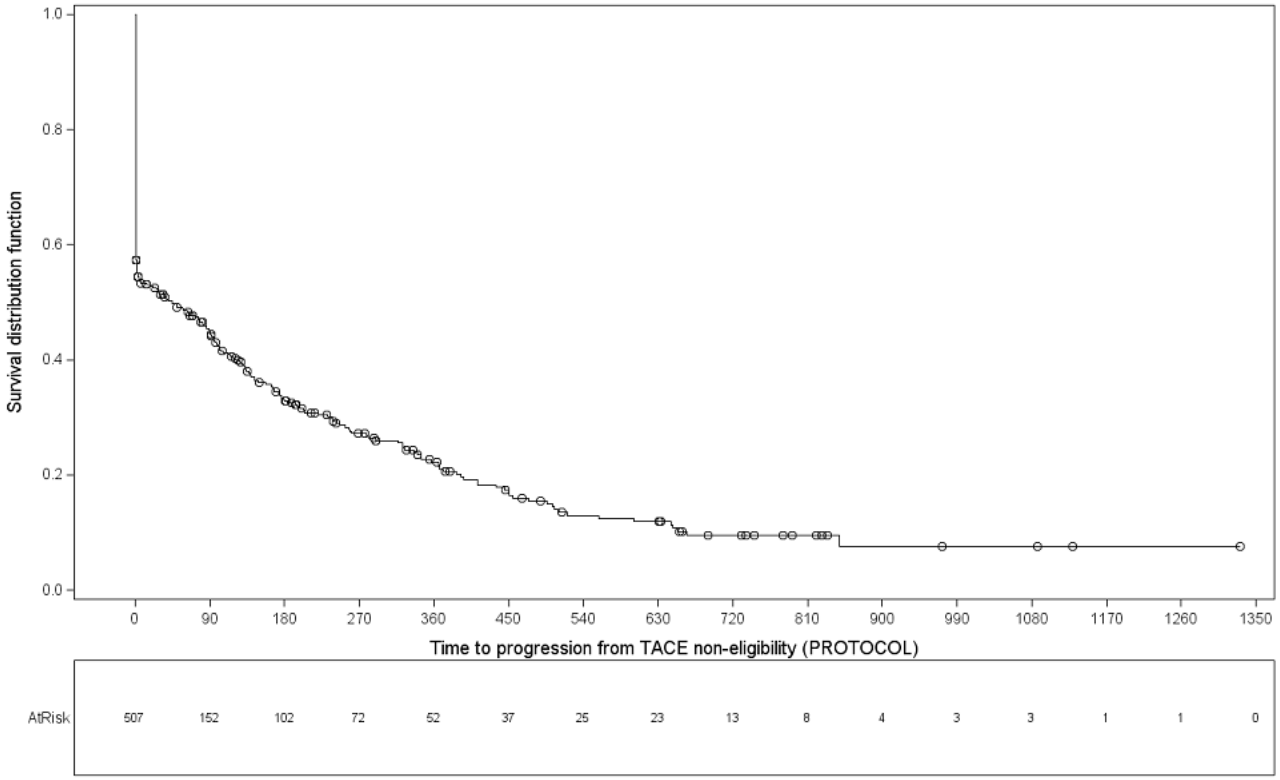

Figure 5: Kaplan-Meier curve of TTP from TACE non-eligibility – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)
Note 1: the population was denoted "TNE1" in the statistical output.
TACE: transarterial chemoembolization, TTP: time to progression.
Source: Figure: 14.3.1 / 14

Results for the cohorts of patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) can be found in Table 14.3.1 / 2 (Summary of PFS and TTP), Figure 14.3.1 / 5 (Kaplan-Meier curve of PFS), and Figure 14.3.1 / 15 (Kaplan-Meier curve of TTP).

Results for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on JSH) can be found in Table 14.3.1 / 5 (Summary of PFS and TTP), Figure 14.3.1 / 4 (Kaplan-Meier curve of PFS), Figure 14.3.1 / 11 (Kaplan-Meier curve of PFS, cohorts), Figure 14.3.1 / 20 (Kaplan-Meier curve of TTP), and Figure 14.3.1 / 21 (Kaplan-Meier curve of TTP, cohorts).

Results for patients who became TACE non-eligible after initial TACE (AASLD based) can be found in Table 14.3.1 / 3 (Summary of PFS and TTP), Figure 14.3.1 / 6 (Kaplan-Meier curve of PFS), Figure 14.3.1 / 7 (Kaplan-Meier curve of PFS, cohorts), Figure 14.3.1 / 16 (Kaplan-Meier curve of TTP), and Figure 14.3.1 / 17 (Kaplan-Meier curve of TTP, cohorts).

Results for patients who became TACE non-eligible after initial TACE (Child Pugh based) are provided in Table 14.3.1 / 4 (Summary of PFS and TTP), Figure 14.3.1 / 6 (Kaplan-Meier curve of PFS), Figure 14.3.1 / 8 (Kaplan-Meier curve of PFS), Figure 14.3.1 / 9 (Kaplan-Meier curve of PFS, cohorts), Figure 14.3.1 / 18 (Kaplan-Meier curve of TTP), and Figure 14.3.1 / 19 (Kaplan-Meier curve of TTP, cohorts).

Tumor response from time of TACE non-eligibility also was part of the present secondary objective. As the number of patients who became TACE non-eligible after initial TACE was low and tumor assessments did not always match visits dates, tumor response from time of TACE non-eligibility

would have been available for only few patients. Therefore, it was decided to exclude this part objective from the analysis.

The incidence of AEs from time of TACE non-eligibility can be found in Table 47.

10.4.2.2 Overall survival, progression-free survival, time to progression, and tumor response from start of sorafenib treatment

Evaluation of OS, PFS, TTP, tumor response and AE from start of sorafenib treatment were also a secondary objective of the study.

The time to event (OS, PFS, and TTP) in sorafenib treated patients is summarized in Table 36. Kaplan-Meier curves are presented in Figure 6 (OS), Figure 7 (PFS) and Figure 8 (TTP).

Table 36: Summary of OS, PFS, and TTP - Sorafenib treated patients

	N	Number failed	Number censored	Median (days)	95% CI Median (days)
OS	515	266 (51.7%)	249 (48.3%)	362	[313;444]
PFS	515	404 (78.4%)	111 (21.6%)	90	[81;100]
TTP	515	285 (55.3%)	230 (44.7%)	96	[86;111]

Note 1: the population was denoted “SOAP” in the statistical output.
Note 2: "*" presents censored observation or unestimable due to censored data
CI: confidence interval, N: number of patients, OS: overall survival, PFS: progression free survival, TTP: time to progression.
Source: Table 14.3.1 / 6

In sorafenib treated patients, the median OS was 362 days (95% CI: 313; 444 days), the median PFS was 90 days (95% CI: 81; 100 days), and the median TTP was 96 days (95% CI: 86; 111 days).

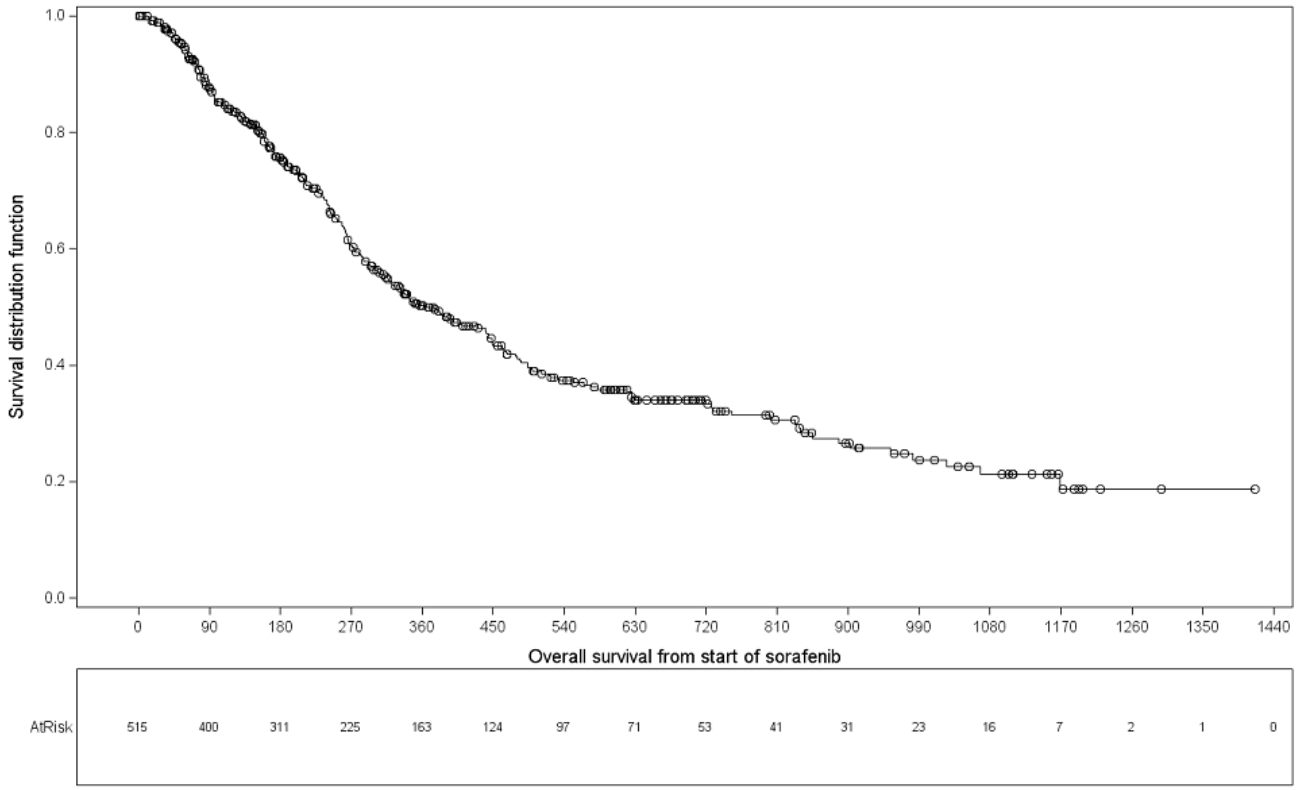

Figure 6: Kaplan-Meier curve of OS from start of sorafenib – Sorafenib treated patients
Note 1: the population was denoted “SOAP” in the statistical output.
OS: overall survival.
Source: Figure: 14.3.1 / 2

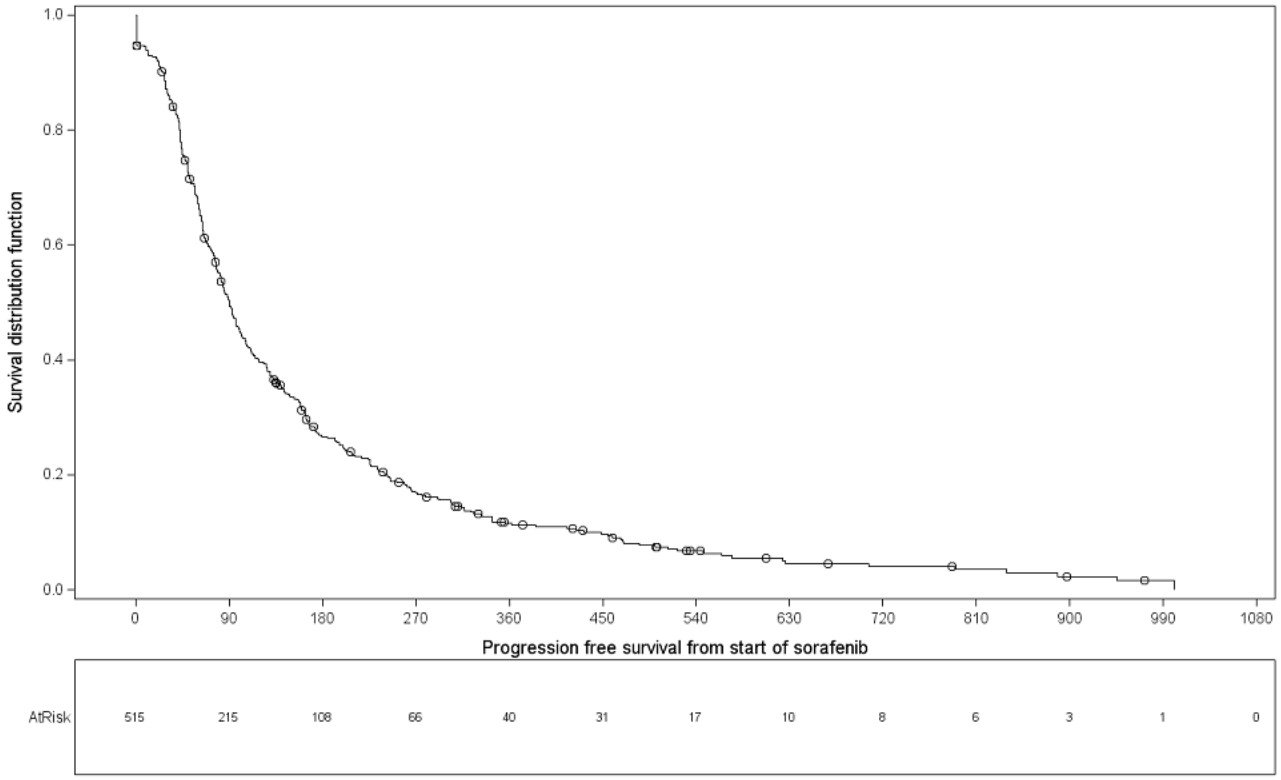

Figure 7: Kaplan-Meier curve of PFS from start of sorafenib – Sorafenib treated patients
Note 1: the population was denoted “SOAP” in the statistical output.
PFS: progression free survival.
Source: Figure: 14.3.1 / 12

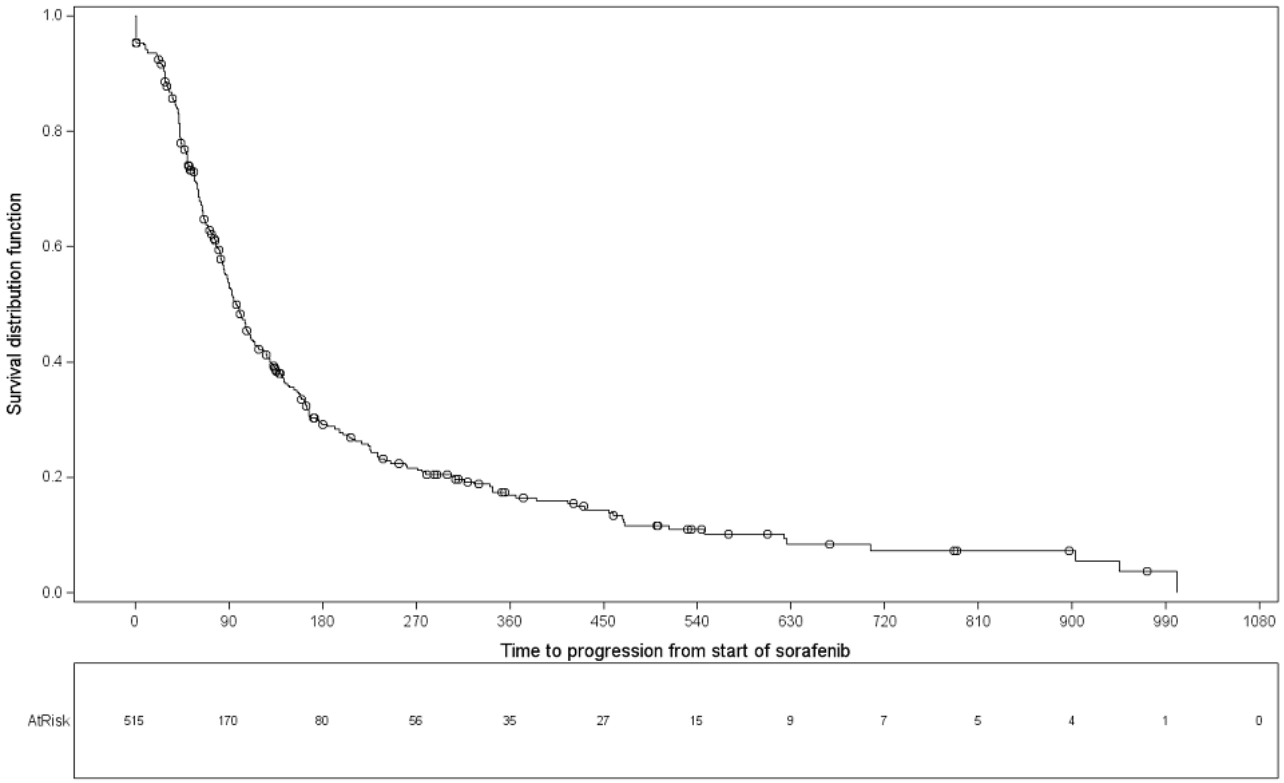

Figure 8: Kaplan-Meier curve of TTP from start of sorafenib – Sorafenib treated patients
Note 1: the population was denoted "SOAP" in the statistical output.
TTP: time to progression.
Source: Figure: 14.3.1 / 22

For tumor response from start of sorafenib, the latest radiological tumor response compared to start of sorafenib was evaluated (Table 37).

Table 37: Latest radiological tumor response compared to start of sorafenib - Sorafenib treated patients

	Total N=515 n (%)
Tumor response	
n	515 (100.0%)
Missing	233 (45.2%)
Complete response	6 (1.2%)
Partial response	24 (4.7%)
Stable disease	58 (11.3%)
Progressive disease	189 (36.7%)
Not evaluable	5 (1.0%)

Note 1: the population was denoted "SOAP" in the statistical output.
Note 2: In case latest radiological tumor response was assessed by multiple assessment types, the best assessment was considered.
n: number of patients, N: number of patients in analysis set.
Source: Table 14.3.4 / 42

Most frequently, the latest radiological tumor response compared to start of sorafenib was progressive disease (36.7%), followed by stable disease (11.3%). However, assessment was missing in nearly half of the patients (45.2%).

The latest radiological tumor response compared to start of sorafenib by type of assessment in sorafenib treated patients is provided in Table 14.3.4 / 43.

The incidence of AEs from start of sorafenib treatment can be found in Table 46.

10.4.2.3 Duration of treatment of sorafenib after TACE

Another secondary objective was to determine duration of treatment of sorafenib after TACE with respect to the start of sorafenib treatment (early vs. not early).

The duration of treatment of sorafenib treatment in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) is given in Table 38.

Table 38: Duration of treatment of sorafenib – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507	Cohort 1 N=47	Cohort 2 N=460
Duration of sorafenib exposure (days)			
n	144	47	97
Missing	363	0	363
Mean	201.0	294.6	155.7
SD	225.7	300.7	161.9
Median	117.0	157.0	106.0
Min, Max	7, 1197	7, 1197	9, 895
Time from first TACE non-eligibility to first sorafenib in days			
n	144	47	97
Missing	363	0	363
Mean	155.0	10.8	224.9
SD	187.3	14.3	192.4
Median	77.5	6.0	151.0
Min, Max	1, 684	1, 60	14, 684

Note 1: the population was denoted “TNE1” in the statistical output.
Note 2: Duration of sorafenib was defined as days from first sorafenib to the day of permanent discontinuation of sorafenib + 1. For patients who did not take any sorafenib, the duration of sorafenib was considered missing.
Note 3: Time to initiation of sorafenib was defined as days from TACE non-eligibility to date of sorafenib initiation + 1.
Note 4: Cohort 1 includes patients with early start of sorafenib treatment based on the investigators’ treatment decisions.
Note 5: Cohort 2 includes patients without early start of sorafenib treatment based on the investigators’ treatment decisions.
Max: maximum, Min: minimum, n: number of patients, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.3.2 / 1

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median duration of sorafenib exposure was 117 days and was longer in cohort 1 (median 157 days) than in cohort 2 (median 106 days). Please note that only 97 of 460 patients in cohort 2 received sorafenib.

The median time from first TACE non-eligibility to first sorafenib in days was 77.5 days overall, 6 days in cohort 1, and 151 days in cohort 2. Please note that cohort 1 comprises all patients for whom the investigator decided at the time of TACE non-eligibility to choose sorafenib as the next treatment option, while cohort 2 includes patients with TACE non-eligibility for whom the decision to treat with sorafenib was made by the investigator at a later point in time, patients who were never treated with sorafenib as well as patients for whom another systemic cancer treatment was chosen.

Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.3.2 / 2, Table 14.3.2 / 3, and Table 14.3.2 / 4, respectively.

10.4.2.4 Time to meet TACE non-eligibility criteria from initial TACE

Another secondary objective was to determine time to meet TACE non-eligibility criteria from initial TACE according to the guidelines.

The median time from initial TACE to TACE non-eligibility was 146 days in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) (Table 17). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.1.4 / 10, Table 14.1.4 / 11, and Table 14.1.4 / 12, respectively.

10.4.2.5 Evaluation of tumor response to TACE by number of TACEs

The tumor response to TACE by number of TACEs was evaluated as a secondary objective in this study.

The radiological tumor response to the first four TACEs for the overall TACE population is shown in Table 39.

Table 39: Radiological tumor response to the first four TACEs – Overall TACE population

	Total N=1650 n (%)
First TACE	
Complete response	226 (13.7%)
Partial response	433 (26.2%)
Stable disease	368 (22.3%)
Progressive disease	304 (18.4%)
Not evaluable	23 (1.4%)
Missing	296 (17.9%)
Second TACE	
Complete response	103 (10.3%)
Partial response	158 (15.8%)
Stable disease	191 (19.1%)
Progressive disease	213 (21.3%)
Not evaluable	9 (0.9%)
Missing	328 (32.7%)
Third TACE	
Complete response	56 (9.7%)
Partial response	84 (14.5%)
Stable disease	111 (19.1%)
Progressive disease	147 (25.3%)
Not evaluable	12 (2.1%)
Missing	170 (29.3%)
Fourth TACE	
Complete response	28 (8.3%)
Partial response	59 (17.5%)
Stable disease	70 (20.7%)
Progressive disease	92 (27.2%)
Not evaluable	2 (0.6%)
Missing	87 (25.7%)

Note 1: the population was denoted “TCE” in the statistical output.
Note 2: The summary is based on the best responses over all types of assessment of the first tumor evaluation after each TACE.
n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization.
Source: Table 14.3.4 / 1

After the first TACE, patients in the overall TACE population, most frequently showed partial response (26.2%) and stable disease (22.3%). A total of 18.4% of patients had progressive disease and 13.7% had complete response. After the second, third and fourth TACE, the proportion of patients with progressive disease gradually increased to 27.2% in the fourth TACE, while the proportion of patients with complete response decreased to 8.3% in the fourth TACE. However, for about 20% of patients to a third of patients radiological tumor response was missing. Up to 15 TACEs were reported in this study. Results for these subsequent TACEs can be found in Table 14.3.4 / 1.

Please note that these results have to be interpreted with caution, as the number of patients with TACEs decreased.

The radiological tumor response to each TACE by type of assessment can be found in Table 14.3.4 / 14 for the overall TACE population.

Results for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) can be found in Table 14.3.4 / 2 and Table 14.3.4 / 15. Results for patients who became TACE non-eligible after initial TACE (AASLD based) can be found in Table 14.3.4 / 3 and Table 14.3.4 / 16, results for patients who became TACE non-eligible after initial TACE (Child Pugh based) in Table 14.3.4 / 4 and Table 14.3.4 / 17, and results for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on JSH) in Table 14.3.4 / 5 and Table 14.3.4 / 18.

The non-radiological tumor response to the first four TACEs in the overall TACE population is presented in Table 40.

Table 40: Non-radiological tumor response to the first four TACEs – Overall TACE population

	Total N=1650
	n (%)
First TACE	
No clinical progressive disease	1221 (74.0%)
Clinical progressive disease	134 (8.1%)
Missing	295 (17.9%)
Second TACE	
No clinical progressive disease	604 (60.3%)
Clinical progressive disease	58 (5.8%)
Missing	340 (33.9%)
Third TACE	
No clinical progressive disease	355 (61.2%)
Clinical progressive disease	44 (7.6%)
Missing	181 (31.2%)
Fourth TACE	
No clinical progressive disease	215 (63.6%)
Clinical progressive disease	28 (8.3%)
Missing	95 (28.1%)

Note 1: the population was denoted “TCE” in the statistical output.
Note 2: The summary is based on the best responses over all types of assessment of the first tumor evaluation after each TACE.
n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization.
Source: Table 14.3.4 / 27

After the first, second, third, and fourth TACE, the majority of patients (ranging from 74.0% after the first TACE to 60.3% after the second TACE) in the overall TACE population had no clinical progressive disease based on non-radiological assessment.

Results for patients who became TACE non-eligible after initial TACE can be found in Table 14.3.4 / 28 (TACE non-eligibility specified based on protocol), Table 14.3.4 / 29 (TACE non-eligibility based on AASLD), Table 14.3.4 / 30 (TACE non-eligibility based on Child Pugh), and Table 14.3.4 / 31 (TACE non-eligibility based on JSH).

Latest radiological tumor response compared to inclusion visit for the overall TACE population is given in Table 41.

Table 41: Latest radiological tumor response compared to inclusion visit - Overall TACE population

	Total N=1650 n (%)
Tumor response	
Missing	295 (17.9%)
Complete response	186 (11.3%)
Partial response	227 (13.8%)
Stable disease	283 (17.2%)
Progressive disease	631 (38.2%)
Not evalable	28 (1.7%)

Note 1: the population was denoted "TCE" in the statistical output.
Note2: In case latest radiological tumor response was assessed by multiple assessment types, the best assessment was considered.
TACE: transarterial chemoembolization.
Source: Table 14.3.4 / 40

Most frequently, the latest radiological tumor response compared to inclusion visit in the overall TACE population was progressive disease (38.2%), followed by stable disease (17.2%) and partial response (13.8%; missing: 17.9%). Complete response was reported in 11.3% of patients.

The latest radiological tumor response compared to inclusion visit by type of assessment in the overall TACE population is provided in Table 14.3.4 / 41.

10.4.2.6 Deterioration of liver dysfunction

A further secondary objective was to evaluate deterioration of liver dysfunction in the course of TACE treatment and thereafter.

Assessment of liver function was assessed based on laboratory parameters (alanine aminotransferase, albumin, aspartate aminotransferase, bilirubin, prothrombin INR).

The pre-TACE period was defined as 30 days before TACE to the day of TACE. The acute period was defined as the time interval from the day of TACE up to 30 days after TACE and the chronic period was defined as the time interval between 31 to 90 days after the day of TACE (see Figure 1).

Liver related laboratory parameters for each TACE in the overall TACE population are given for the pre-TACE period in Table 14.3.6 / 1, for the acute period in Table 14.3.6 / 2, and for the chronic period in Table 14.3.6 / 3. Box plots for all liver related laboratory data in the TACE relevant periods can be found in Figure 14.3.6 / 1 to Figure 14.3.6 / 5.

Additionally, liver related laboratory parameters were provided for the subset of patients with pre, acute and chronic values. These can be found in Table 14.3.6 / 4 (pre-TACE period), Table 14.3.6 / 5 (acute period), and Table 14.3.6 / 6 (chronic period). Box plots for all liver related laboratory parameters in these patients are given in Figure 14.3.6 / 6 to Figure 14.3.6 / 10.

Changes from pre-TACE period to the acute period in the overall TACE population are summarized in Table 42 for the first four TACEs.

Table 42: Changes from pre-TACE period to the acute and to the chronic period- Overall TACE population (N=1650)

	Changes from pre-TACE period to the acute period [1]				Changes from pre-TACE period to the chronic period [2]			
	n	Mean	SD	Median	n	Mean	SD	Median
First TACE								
Alanine aminotransferase (U/L)	690	46.77	188.75	7.00	884	-7.60	474.57	0.00
Albumin (g/dL)	579	-0.29	1.24	-0.20	816	-0.05	2.10	-0.10
Aspartate aminotransferase (U/L)	650	47.30	182.46	4.00	836	5.29	388.12	2.60
Bilirubin (mg/dL)	678	0.26	1.60	0.10	874	-9.39	252.88	0.10
Prothrombin INR	487	0.06	0.19	0.04	715	-0.10	4.20	0.02
Second TACE								
Alanine aminotransferase (U/L)	279	37.16	171.76	7.40	296	14.50	154.35	-1.00
Albumin (g/dL)	231	0.00	2.75	-0.20	269	-0.12	0.34	-0.10
Aspartate aminotransferase (U/L)	270	32.72	113.68	5.00	285	13.43	77.11	2.00
Bilirubin (mg/dL)	270	0.18	0.56	0.10	288	0.20	0.65	0.10
Prothrombin INR	216	0.04	0.10	0.02	216	0.04	0.18	0.01
Third TACE								
Alanine aminotransferase (U/L)	111	34.82	110.05	4.00	137	20.63	85.69	1.00
Albumin (g/dL)	98	-0.26	0.37	-0.20	125	-0.10	0.40	-0.10
Aspartate aminotransferase (U/L)	109	32.23	97.88	3.00	131	22.81	70.00	3.00
Bilirubin (mg/dL)	111	0.11	1.37	0.10	133	0.44	1.79	0.10
Prothrombin INR	88	0.03	0.10	0.03	105	0.01	0.12	0.01
Fourth TACE								
Alanine aminotransferase (U/L)	49	48.49	120.04	16.00	61	22.57	70.31	2.00
Albumin (g/dL)	45	-0.29	0.39	-0.30	58	-0.14	0.42	-0.10
Aspartate aminotransferase (U/L)	48	66.17	279.48	5.50	59	33.49	132.32	3.00
Bilirubin (mg/dL)	47	0.58	1.50	0.24	61	0.46	0.96	0.10
Prothrombin INR	39	0.06	0.09	0.06	45	0.03	0.08	0.02

[1] Table includes only patients who have all data for respective lab parameter during pre- and acute-period.
[2] Table includes only patients who have all data for respective lab parameter during pre- and chronic-period.
Note: the population was denoted "TCE" in the statistical output.
INR: international normalized ratio; Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization, U: unit.
Source: Table 14.3.6 / 7, Table 14.3.6 / 8

Alanine aminotransferase, aspartate aminotransferase, bilirubin, prothrombin INR increased in the **acute period** compared to the pre-TACE period for the first four TACEs, while albumin decreased after the first, third and fourth TACE and remained stable after the second TACE.

Changes from pre-TACE period to the acute period for the subset of patients with pre, acute and chronic values can be found in Table 14.3.6 / 9.

In the **chronic period**, alanine aminotransferase decreased in the chronic period compared to the pre-TACE period of the first TACE and increased for the second to fourth TACE. These increases were smaller than in the acute phase.

Albumin decreased in the chronic period compared to the pre-TACE period of the first four TACEs. The magnitude of these decreases was slightly lower than in the acute period.

Aspartate aminotransferase slightly increased in the chronic period compared to the pre-TACE period for the first four TACEs. The magnitude of these increases was lower than in the acute period.

Bilirubin decreased in the chronic period compared to the pre-TACE period of the first TACE and increased for the second to fourth TACE. For the third and fourth TACE these increases were smaller than in the acute phase.

Prothrombin INR decreased in the chronic period compared to the pre-TACE period of the first TACE and slightly increased for the second to fourth TACE. These increases were comparable to those of the acute phase.

Changes from pre-TACE period to the chronic period for the subset of patients with pre, acute and chronic values can be found in Table 14.3.6 / 10.

Overall, no clinically relevant changes from pre-TACE period to the acute period or from pre-TACE period to the chronic period were observed.

Changes from pre-TACE of the first TACE to the chronic period of the last TACE is provided in Table 14.3.6 / 11 for the overall TACE population and in Table 14.3.6 / 12 for the subset of patients with pre, acute and chronic values.

Alanine aminotransferase, albumin, bilirubin and prothrombin INR were graded normal for the majority of patients in the overall TACE population in the pre-TACE period of the first four TACEs. Aspartate aminotransferase was graded normal for the pre-TACE period in 45% of patients for the first TACE and for the majority of patients for the second to fourth TACE (Table 14.3.6 / 13). In the acute period, the proportion of patients with normal values in the first four TACEs mostly decreased (Table 14.3.6 / 14) and then mostly increased again in the chronic period of the first four TACEs compared to the acute period, with the exception of bilirubin. However, for bilirubin the proportion of patients with normal values was already >80% for the first four TACEs in all periods (Table 14.3.6 / 15).

Results for the subset of patients with pre, acute and chronic values can be found in Table 14.3.6 / 16, Table 14.3.6 / 17, and Table 14.3.6 / 18.

Deteriorations of liver dysfunction for the overall TACE population and for the subset of patients with available pre, acute and chronic values was evaluated by the following subgroups:

- by pre TACE grade: Table 14.3.6 / 19 and Table 14.3.6 / 20
- by area of TACE: Table 14.3.6 / 21 and Table 14.3.6 / 22
- by BCLC stage at inclusion: Table 14.3.6 / 23 and Table 14.3.6 / 32
- by lesion size at inclusion: Table 14.3.6 / 24 and Table 14.3.6 / 33
- by number of lesions at inclusion: Table 14.3.6 / 25 and Table 14.3.6 / 34
- by TACE non-eligibility at inclusion (criterion 1: Protocol): Table 14.3.6 / 26 and Table 14.3.6 / 35
- by TACE non-eligibility at inclusion (criterion 2: AASLD): Table 14.3.6 / 27 and Table 14.3.6 / 36
- by TACE non-eligibility at inclusion (criterion 3: Child Pugh B): Table 14.3.6 / 28 and Table 14.3.6 / 37
- by TACE non-eligibility at inclusion (criterion 4: JSH): Table 14.3.6 / 29 and Table 14.3.6 / 38
- by bilirubin grade at inclusion: Table 14.3.6 / 30 and Table 14.3.6 / 39
- by up to seven criteria at inclusion (i.e., if the sum of longest diameter of liver lesion and total number of lesions is ≤7 or >7): Table 14.3.6 / 31 and Table 14.3.6 / 40

10.4.2.7 Overall survival from initial TACE

OS from initial TACE for all patients in the study irrespective of their treatment after TACE was analyzed as secondary objective. Results are presented in Table 43 and Figure 9.

Table 43: Summary of OS, PFS, and TTP from initial TACE - Overall TACE population

	N	Number failed	Number censored	Median (days)	95% CI Median (days)
OS	1650	690 (41.8%)	960 (58.2%)	877	[789;989]
PFS	1650	1212 (73.5%)	438 (26.5%)	198	[187;213]
TTP	1650	927 (56.2%)	723 (43.8%)	240	[218;263]

Note 1: the population was denoted “TCE” in the statistical output.
Note 2: "*" presents censored observation or unestimable due to censored data
CI: confidence interval, OS: overall survival, PFS: progression free survival, TACE: transarterial chemoembolization, TPP: time to progression.
Source: Table 14.3.1 / 1

In the overall TACE population, the median OS from initial TACE was 877 days (95% CI: 789;989 days). Additionally PFS and TTP were analyzed. The median PFS from initial TACE was 198 days (95% CI: 187;213 days), and the median TTP from initial TACE was 240 days (95% CI: 218;263 days).

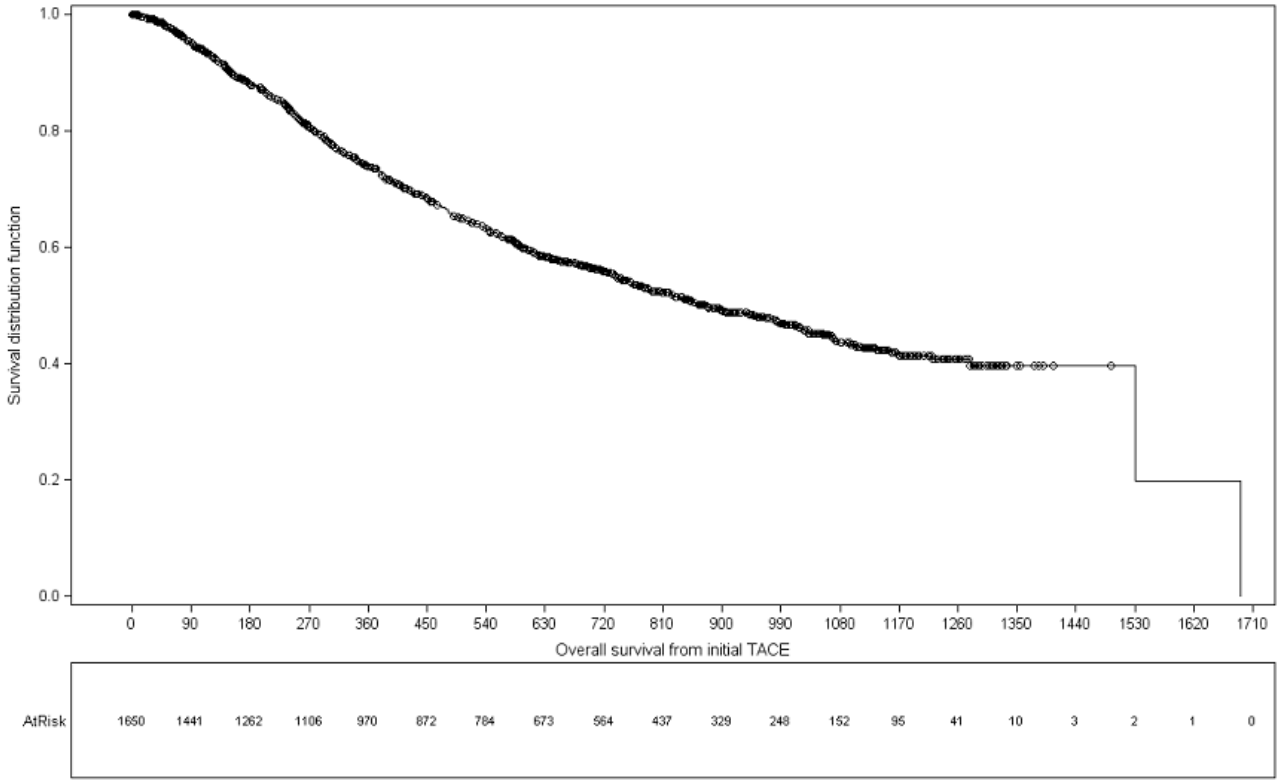

Figure 9: Kaplan-Meier curve of OS from initial TACE – Overall TACE population
Note 1: the population was denoted “TCE” in the statistical output.
OS: overall survival, TACE: transarterial chemoembolization.
Source: Figure: 14.3.1 / 1

Kaplan-Meier curves for PFS and TTP can be found in Figure 14.3.1 / 3 and Figure 14.3.1 / 13, respectively.

10.4.2.8 Deviations from recommendations for TACE

Another secondary objective was to evaluate deviations from recommendations for TACE use in the treatment guidelines for TACE use.

In this study different sets of criteria were applied to evaluate TACE non-eligibility (see also Table 4):

- Criteria 1: Protocol specified
- Criteria 2: AASLD based
- Criteria 3: Child Pugh based
- Criteria 4: JSH based

Of the 1676 patients enrolled in this study, about 40% of patients received TACE although they were already TACE non-eligible prior to the first TACE according to the non-eligibility criteria 1-3 (protocol specified: 37.9%, AASLD based: 37.6%, Child Pugh based: 37.9%) and about 20% were already TACE non-eligible at the inclusion visit based on JSH (22.0%) (Table 6).

Additionally, the first treatment decision after inclusion was "new TACE" in more than 20% of these patients (protocol specified: 23.1%, AASLD based: 23.3%, Child Pugh based: 23.1%, JSH based: 22.5%) (Table 14.1.4 / 17, Table 14.1.4 / 18, Table 14.1.4 / 19, Table 14.1.4 / 20).

About 20 to 30% of patients enrolled in this study became TACE non-eligible after initial TACE (protocol specified: 30.3%, AASLD based: 20.2%, Child Pugh based: 24.8%, JSH: based 23.3%) (Table 6).

Of these 20 to 30% of patients had the treatment decision "new TACE" at the time of TACE non-eligibility either alone or in combination with other treatments (protocol specified: 30.6%; AASLD based: 22.5%, Child Pugh based: 28.4%, JSH based: 24.0%) (Table 14.1.4 / 13, Table 14.1.4 / 14, Table 14.1.4 / 15, Table 14.1.4 / 16).

Furthermore, about 20% of patients had "new TACE" as the first treatment decision after TACE non-eligibility (first follow-up visit after TACE non-eligibility) (protocol specified: 20.3%; AASLD based: 16.3%, Child Pugh based: 18.9%, JSH based: 17.9%) (Table 14.1.4 / 21, Table 14.1.4 / 22, Table 14.1.4 / 23, Table 14.1.4 / 24).

For patients with "new TACE" at TACE non-eligibility, a new TACE was the subsequent first treatment decision in more than a third of patients (protocol specified: 35.3%, AASLD based: 33.8%, Child Pugh based: 37.5%, JSH based: 37.2%) (Table 14.1.4 / 25, Table 14.1.4 / 26, Table 14.1.4 /27, Table 14.1.4 / 28).

10.4.2.9 Practice patterns of the investigators

In addition, practice patterns of the investigators involved in the care of patients with HCC under real-life conditions were evaluated as secondary objective.

The exposure to TACE in the overall TACE population is presented in Table 44.

Table 44: Exposure to TACE - Overall TACE population

	Total N=1650
Duration of TACE treatment (days)	
n	1650
Mean	209.7
SD	284.6
Median	78.0
Min, Max	1, 1374
Cumulative person time (years)	947.47
Number of TACE treatments n (%)	
1	648 (39.3%)
2	422 (25.6%)
3	242 (14.7%)
4-5	214 (13.0%)
≥6	124 (7.5%)
Radiofrequency ablation in combination with TACE n (%)	
No	1572 (95.3%)
Yes	78 (4.7%)

Note 1: the population was denoted "TCE" in the statistical output.
Note 2: Duration of TACE was defined as the time interval from first TACE to last TACE plus one.
Note 3: Cumulative person time in years was calculated as sum of duration of TACE divided by 365.25.
Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, SD: standard deviation, TACE: transarterial chemoembolization.
Source: Table 14.3.3 / 1

The median duration of TACE treatments in the overall TACE population was 78 days, resulting in a cumulative person time of 947.47 years. Patients most frequently had 1 (39.3%) or 2 (25.6%) TACE treatments. Only few patients (4.7%) received radiofrequency ablation in combination with TACE.

Results for the patients who became TACE non-eligible after initial TACE can be found in Table 14.3.3 / 6 (TACE non-eligibility specified based on protocol), Table 14.3.3 / 7 (TACE non-eligibility based on AASLD), Table 14.3.3 / 8 (TACE non-eligibility based on Child Pugh), and Table 14.3.3 / 9 (TACE non-eligibility based on JSH).

The median time between TACE treatments in the overall TACE population was 80 days for the time between first and second TACE, 95 days for the time between second and third TACE, and 97 days for the time between third and fourth TACE (Table 14.3.3 / 14).

Additional information on the area of TACE, used drug and embolization agent for the TACE by number of procedure in the overall TACE population can be found in Table 14.3.3 / 14.

Results for patients who became TACE non-eligible after initial TACE can be found in Table 14.3.3 / 15 (TACE non-eligibility specified based on protocol), Table 14.3.3 / 16 (TACE non-eligibility based on AASLD), Table 14.3.3 / 17 (TACE non-eligibility based on Child Pugh), and Table 14.3.3 / 18 (TACE non-eligibility based on JSH).

Treatment flows for sorafenib and other systemic and non-systemic anti-cancer treatments are presented in Table 45 for the overall TACE population.

Table 45: Treatment flows - Overall TACE population

	Total N=1650 n (%)
Switch to sorafenib	
Before initial TACE	6 (1.2%)
After one TACE	259 (50.7%)
After two TACEs	104 (20.4%)
After more than two TACEs	142 (27.8%)
Switch to other systemic anti-cancer treatment	
After one TACE	43 (38.1%)
After two TACEs	31 (27.4%)
After more than two TACEs	39 (34.5%)
Switch to other non-systemic anti-cancer treatment	
Before initial TACE	4 (1.0%)
After one TACE	181 (43.9%)
After two TACEs	121 (29.4%)
After more than two TACEs	105 (25.5%)
Missing or partial date of local anti-cancer therapy	1 (0.2%)

Note 1: the population was denoted “TCE” in the statistical output.
Note 2: Local or systemic anti-cancer treatments initiated at date of TACE were considered after respective TACE.
Note 3: Switch was calculated as actual start of respective treatment, independent from treatment decision.
n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization.
Source: Table 14.3.5 / 1

A total of 511 of 1650 patients in the overall TACE population switched to sorafenib treatment. Patients in the overall TACE population who switched to sorafenib most frequently switched after one TACE (50.7%), followed by after more than two TACEs (27.8%).

A switch to other systemic anti-cancer therapy was reported in 113 of 1650 patients in the overall TACE population. Patients most frequently switched after one TACE (38.1%), followed by after more than two TACEs (34.5%).

A switch to other non-systemic anti-cancer treatment was reported in 412 of 1650 patients in the overall TACE population. Patient most frequently switched after one TACE (43.9%), followed by after two TACEs (29.4%).

10.5 Other analyses

The Assessment for Retreatment with TACE (ART) score was performed as a separate stand-alone analysis (see SAP section 4.6.6 and 6.3.9). Results are provided in Table 14.3.7 / 1 to Table 14.3.7 / 3.

10.6 Adverse events/adverse reactions

10.6.1 Adverse events

Please note that all analyses were performed by CTCAE worst grade, i.e., patients with more than one AE were counted with worst respective grade.

10.6.1.1 Brief Summary of Adverse Events

An overview of TEAEs in sorafenib treated patients is provided in Table 46.

Table 46: Overview of TEAEs - Sorafenib treated patients

	Total N=515 n (%)
TEAE	400 (77.7%)
TEAE related to sorafenib	271 (52.6%)
TESAE	211 (41.0%)
TESAE related to sorafenib (all grades)	44 (8.5%)
TEAE resulting in sorafenib withdrawal, interruption, or dose reduction	300 (58.3%)
TEAE resulting in inpatient hospitalization or prolongation of existing hospitalization	110 (21.4%)
TEAE with CTCAE worst grade - 1	45 (8.7%)
TEAE with CTCAE worst grade – 2	97 (18.8%)
TEAE with CTCAE worst grade – 3	96 (18.6%)
TEAE with CTCAE worst grade – 4	17 (3.3%)
TEAE with CTCAE worst grade – 5	145 (28.2%)
TEAE related to sorafenib with CTCAE worst grade – 1	56 (10.9%)
TEAE related to sorafenib with CTCAE worst grade - 2	121 (23.5%)
TEAE related to sorafenib with CTCAE worst grade – 3	79 (15.3%)
TEAE related to sorafenib with CTCAE worst grade - 4	6 (1.2%)
TEAE related to sorafenib with CTCAE worst grade – 5	9 (1.7%)

Note 1: the population was denoted “SOAP” in the statistical output.
Note 2: Treatment-emergent: Any event arising or worsening after start of sorafenib until 30 days after last intake.
Note 3: This table presents counts of patients.
Note 4: Relation: Events with missing relationship classification were considered as causally related to treatment.
Note 5: Serious: Events with missing serious classification were considered as serious AEs, as worst case assumption.
CTCAE: common terminology criteria for adverse events, n: number of patients, N: number of patients in analysis set, TEAE: treatment-emergent adverse event, TESAE: treatment-emergent serious adverse event.
Source: Table 14.4.2 / 1

Of the 515 sorafenib treated patients, 400 patients (77.7%) experienced TEAEs, i.e., events that arose or worsened after the start of sorafenib until 30 days after the last intake. In 52.6% of patients, the TEAEs were related to sorafenib treatment. Treatment-emergent serious AEs (TESAEs, all grades) were experienced by 41.0% of patients and in 8.5% of patients, the TESAEs were related. TEAEs resulting in sorafenib withdrawal, interruption, or dose reduction were observed in 58.3% of patients and TEAEs resulting in inpatient hospitalization or prolongation of existing hospitalization were reported in 21.4% of patients.

CTCAE grade 1 (worst grade) TEAEs were documented in 8.7% of patients, 18.8% of patients had CTCAE grade 2 TEAEs, 18.6% of patients had CTCAE grade 3 TEAEs, 3.3% of patients had CTCAE grade 4 TEAEs and 28.2% of patients had CTCAE grade 5 TEAEs.

A total of 10.9% of patients had grade 1 (worst grade) sorafenib-related TEAEs, 23.5% of patients had grade 2 sorafenib-related TEAEs, 15.3% of patients had grade 3 sorafenib-related TEAEs,1.2% of patients had grade 4 sorafenib-related TEAEs, and 1.7% had grade 5 sorafenib-related TEAEs.

An overview of the safety data in the overall TACE population can be found in Table 14.4.2 / 2.

Evaluation of AEs from time of TACE non-eligibility was a secondary objective of this study. Table 47 shows a summary of AEs in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Table 47: Overview of AEs – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol)

	Total N=507 n (%)
Total number of patients	507 (100.0%)
AE	374 (73.8%)
SAE	284 (56.0%)
AE resulting in inpatient hospitalization or prolongation of existing hospitalization	154 (30.4%)
AE with CTCAE worst grade – 1	21 (4.1%)
AE with CTCAE worst grade – 2	51 (10.1%)
AE with CTCAE worst grade – 3	75 (14.8%)
AE with CTCAE worst grade - 4	9 (1.8%)
AE with CTCAE worst grade – 5	218 (43.0%)

Note 1: the population was denoted "TNE1" in the statistical output.
Note 2: This table includes only AEs starting on or after date of TACE non-eligibility.
Note 3: This table presents counts of patients.
Note 4: Serious: Events with missing serious classification were considered as serious AEs, as worst case assumption.
AE: adverse event, CTCAE: common terminology criteria for adverse events, n: number of patients, N: number of patients in analysis set, SAE: serious adverse event, TACE: transarterial chemoembolization.
Source: Table 14.4.2 / 3

Of the 507 patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), 73.8% of patients experienced AEs and 56.0% experienced serious AEs (SAEs). AEs resulting in inpatient hospitalization or prolongation of existing hospitalization were reported in 30.4% of patients. CTCAE worst grade 1 AEs were documented in 4.1% of patients and worst grade 2 AEs were experienced by 10.1% of patients. CTCAE worst grade 3, 4 and 5 AEs were documented in 14.8%, 1.8%, and 43.0% of patients, respectively.

Results for the patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.4.2 / 4, Table 14.4.2 / 5, and Table 14.4.2 / 6, respectively.

10.6.1.2 Display of Treatment Emergent Adverse Events

Incidences of TEAEs occurring in ≥1% of sorafenib treated patients in the are presented in Table 48. A cut-off of ≥1% of patients was chosen to avoid very long in-text tables. Incidences of all TEAEs without cut-off can be found in Table 14.4.2 / 7.

Table 48: Incidences of TEAEs (≥1% of patients) - Sorafenib treated patients

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Any TEAE	96 (18.6%)	17 (3.3%)	145 (28.2%)	400 (77.7%)
Blood and lymphatic system disorders	6 (1.2%)	0 (0.0%)	0 (0.0%)	17 (3.3%)
Anemia	4 (0.8%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
Cardiac disorders	2 (0.4%)	0 (0.0%)	6 (1.2%)	10 (1.9%)
Endocrine disorders	1 (0.2%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Gastrointestinal disorders	49 (9.5%)	4 (0.8%)	9 (1.7%)	198 (38.4%)
Abdominal distension	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Abdominal pain	9 (1.7%)	0 (0.0%)	0 (0.0%)	43 (8.3%)
Anorexia	2 (0.4%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
Ascites	15 (2.9%)	1 (0.2%)	3 (0.6%)	39 (7.6%)
Constipation	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (3.1%)
Diarrhea	13 (2.5%)	0 (0.0%)	0 (0.0%)	95 (18.4%)
Esophageal varices hemorrhage	5 (1.0%)	0 (0.0%)	2 (0.4%)	11 (2.1%)
Gastrointestinal disorders - other, specify	1 (0.2%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Mucositis oral	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (5.0%)
Upper gastrointestinal hemorrhage	5 (1.0%)	1 (0.2%)	0 (0.0%)	9 (1.7%)
Vomiting	2 (0.4%)	0 (0.0%)	0 (0.0%)	10 (1.9%)
General disorders and administration site conditions	14 (2.7%)	4 (0.8%)	18 (3.5%)	106 (20.6%)
Death NOS	0 (0.0%)	0 (0.0%)	8 (1.6%)	8 (1.6%)
Edema limbs	2 (0.4%)	0 (0.0%)	0 (0.0%)	17 (3.3%)
Fatigue	11 (2.1%)	0 (0.0%)	0 (0.0%)	39 (7.6%)
Fever	0 (0.0%)	3 (0.6%)	0 (0.0%)	29 (5.6%)
General disorders and administration site conditions – other, specify	3 (0.6%)	1 (0.2%)	6 (1.2%)	15 (2.9%)
Malaise	1 (0.2%)	0 (0.0%)	0 (0.0%)	9 (1.7%)
Pain	1 (0.2%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
Hepatobiliary disorders	9 (1.7%)	2 (0.4%)	41 (8.0%)	65 (12.6%)
Hepatic failure	1 (0.2%)	0 (0.0%)	38 (7.4%)	39 (7.6%)
Hepatic pain	2 (0.4%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
Hepatobiliary disorders- other, specify	3 (0.6%)	1 (0.2%)	2 (0.4%)	10 (1.9%)
Portal vein thrombosis	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Infections and infestations	10 (1.9%)	6 (1.2%)	8 (1.6%)	38 (7.4%)
Lung infection	1 (0.2%)	1 (0.2%)	1 (0.2%)	5 (1.0%)
Peritoneal infection	2 (0.4%)	1 (0.2%)	2 (0.4%)	6 (1.2%)
Sepsis	3 (0.6%)	3 (0.6%)	4 (0.8%)	10 (1.9%)
Injury, poisoning and procedural complications	1 (0.2%)	0 (0.0%)	0 (0.0%)	7 (1.4%)
Investigations	19 (3.7%)	6 (1.2%)	0 (0.0%)	58 (11.3%)
Aspartate aminotransferase increased	1 (0.2%)	1 (0.2%)	0 (0.0%)	9 (1.7%)
Blood bilirubin increased	10 (1.9%)	4 (0.8%)	0 (0.0%)	27 (5.2%)
Investigations other, specify	4 (0.8%)	0 (0.0%)	0 (0.0%)	11 (2.1%)
Weight loss	1 (0.2%)	0 (0.0%)	0 (0.0%)	17 (3.3%)
Metabolism and nutrition disorders	12 (2.3%)	1 (0.2%)	0 (0.0%)	43 (8.3%)
Anorexia	6 (1.2%)	0 (0.0%)	0 (0.0%)	29 (5.6%)
Hypoalbuminemia	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Musculoskeletal and connective tissue disorders	7 (1.4%)	0 (0.0%)	0 (0.0%)	38 (7.4%)
Back pain	4 (0.8%)	0 (0.0%)	0 (0.0%)	16 (3.1%)
Pain in extremity	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Neoplasms benign malignant and unspecified (incl cysts and polyps)	5 (1.0%)	1 (0.2%)	55 (10.7%)	69 (13.4%)
Neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify	4 (0.8%)	0 (0.0%)	55 (10.7%)	66 (12.8%)
Nervous system disorders	9 (1.7%)	1 (0.2%)	3 (0.6%)	38 (7.4%)
Encephalopathy	6 (1.2%)	1 (0.2%)	3 (0.6%)	18 (3.5%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.4%)
Paresthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Other	1 (0.2%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
No code in CTCAE	1 (0.2%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Psychiatric disorders	3 (0.6%)	0 (0.0%)	0 (0.0%)	9 (1.7%)
Renal and urinary disorders	2 (0.4%)	1 (0.2%)	5 (1.0%)	18 (3.5%)
Acute kidney injury	1 (0.2%)	0 (0.0%)	5 (1.0%)	7 (1.4%)
Renal and urinary disorders – other, specify	0 (0.0%)	1 (0.2%)	0 (0.0%)	5 (1.0%)
Respiratory, thoracic and mediastinal disorders	8 (1.6%)	3 (0.6%)	7 (1.4%)	44 (8.5%)
Cough	1 (0.2%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
Dyspnea	4 (0.8%)	0 (0.0%)	1 (0.2%)	10 (1.9%)
Pleural effusion	1 (0.2%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Respiratory failure	0 (0.0%)	2 (0.4%)	4 (0.8%)	6 (1.2%)
Skin and subcutaneous tissue disorders	26 (5.0%)	2 (0.4%)	0 (0.0%)	140 (27.2%)
Alopecia	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (2.5%)
Pain of skin	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Palmar-plantar erythrodysesthesia syndrome	19 (3.7%)	1 (0.2%)	0 (0.0%)	91 (17.7%)
Pruritus	2 (0.4%)	0 (0.0%)	0 (0.0%)	10 (1.9%)
Rash acneiform	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Rash maculo-papular	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (1.7%)
Skin and subcutaneous tissue disorders – other, specify	2 (0.4%)	0 (0.0%)	0 (0.0%)	25 (4.9%)
Vascular disorders	6 (1.2%)	0 (0.0%)	0 (0.0%)	25 (4.9%)
Hypertension	6 (1.2%)	0 (0.0%)	0 (0.0%)	21 (4.1%)

Note 1: the population was denoted “SOAP” in the statistical output.
Note 2: Treatment-emergent: Any event arising or worsening after start of sorafenib until 30 days after last intake.
Note 3: CTCAE Terms are sorted alphabetically and not by frequency.
Note 4: This table presents counts of patients. Patients with more than one AE were counted with worst respective grade. In addition to the total (including all grades), only grade 3, 4, and 5 are shown in this table, for grade 1, grade 2, and grade missing please refer to the source table.
Note 5: NCI-CTCAE version 4.0 was used.
CTCAE: common terminology criteria for adverse events, n: number of patients, N: number of patients in analysis set, NCI: National Cancer Institute, NOS: not otherwise specified, TEAE: treatment-emergent adverse event.
Source: Table 14.4.2 / 7

A total of 77.7% of the 515 sorafenib treated patients experienced any TEAE, 18.6% had grade 3 (worst grade), 3.3% had grade 4, and 28.2% had grade 5 TEAEs.

Overall, the most frequently reported TEAEs were diarrhea (18.4%), palmar-plantar erythrodysesthesia syndrome (17.7%), and neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (12.8%).

The most common grade 3 (worst grade) TEAEs were palmar-plantar erythrodysesthesia syndrome (3.7%), followed by ascites (2.9%), diarrhea (2.5%), and fatigue (2.1%). All grade 4 TEAEs occurred in less than 1% of patients. Grade 5 TEAEs that were documented in more than 1% of patients included neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (10.7%), hepatic failure (7.4%), death NOS (1.6%), and general disorders and administration site conditions – other, specify (1.2%).

Incidences of TEAEs related to sorafenib treatment

Incidences of treatment-emergent sorafenib-related AEs occurring in ≥1% of sorafenib treated patients are presented in Table 49. A cut-off of ≥1% of patients was chosen to avoid long in-text tables. Incidences of all TEAEs without cut-off can be found in Table 14.4.2 / 8.

Table 49: Incidences of TEAEs related to sorafenib (≥1% of patients) - Sorafenib treated patients

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Any AE	79 (15.3%)	6 (1.2%)	9 (1.7%)	271 (52.6%)
Blood and lymphatic system disorders	3 (0.6%)	0 (0.0%)	0 (0.0%)	10 (1.9%)
Gastrointestinal disorders	27 (5.2%)	0 (0.0%)	2 (0.4%)	137 (26.6%)
Abdominal pain	3 (0.6%)	0 (0.0%)	0 (0.0%)	16 (3.1%)
Anorexia	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Ascites	5 (1.0%)	0 (0.0%)	1 (0.2%)	7 (1.4%)
Diarrhea	11 (2.1%)	0 (0.0%)	0 (0.0%)	88 (17.1%)
Mucositis oral	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.4%)
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (2.9%)
Vomiting	2 (0.4%)	0 (0.0%)	0 (0.0%)	7 (1.4%)
General disorders and administration site conditions	10 (1.9%)	0 (0.0%)	2 (0.4%)	51 (9.9%)
Fatigue	10 (1.9%)	0 (0.0%)	0 (0.0%)	34 (6.6%)
Fever	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (1.2%)
General disorders and administration site conditions – other, specify	0 (0.0%)	0 (0.0%)	1 (0.2%)	5 (1.0%)
Malaise	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.4%)
Hepatobiliary disorders	4 (0.8%)	0 (0.0%)	4 (0.8%)	13 (2.5%)
Hepatic failure	1 (0.2%)	0 (0.0%)	4 (0.8%)	5 (1.0%)
Infections and infestations	4 (0.8%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
Investigations	10 (1.9%)	2 (0.4%)	0 (0.0%)	35 (6.8%)
Aspartate aminotransferase increased	1 (0.2%)	0 (0.0%)	0 (0.0%)	7 (1.4%)
Blood bilirubin increased	5 (1.0%)	1 (0.2%)	0 (0.0%)	15 (2.9%)
Weight loss	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (1.9%)
Metabolism and nutrition disorders	6 (1.2%)	0 (0.0%)	0 (0.0%)	24 (4.7%)
Anorexia	3 (0.6%)	0 (0.0%)	0 (0.0%)	21 (4.1%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (1.9%)
Nervous system disorders	1 (0.2%)	0 (0.0%)	0 (0.0%)	18 (3.5%)
Encephalopathy	1 (0.2%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	1 (0.2%)	1 (0.2%)	10 (1.9%)

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Skin and subcutaneous tissue disorders	23 (4.5%)	2 (0.4%)	0 (0.0%)	130 (25.2%)
Alopecia	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (2.5%)
Pain of skin	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Palmar-plantar erythrodysesthesia syndrome	19 (3.7%)	1 (0.2%)	0 (0.0%)	90 (17.5%)
Pruritus	1 (0.2%)	0 (0.0%)	0 (0.0%)	6 (1.2%)
Rash maculo-papular	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (1.2%)
Skin and subcutaneous tissue disorders – other, specify	1 (0.2%)	0 (0.0%)	0 (0.0%)	17 (3.3%)
Vascular disorders	5 (1.0%)	0 (0.0%)	0 (0.0%)	19 (3.7%)
Hypertension	5 (1.0%)	0 (0.0%)	0 (0.0%)	18 (3.5%)

Note 1: the population was denoted “SOAP” in the statistical output.
Note 2: Treatment-emergent: Any event arising or worsening after start of sorafenib until 30 days after last intake
Note 3: Relation: Events with missing relationship classification were considered as causally related to treatment.
Note 4: CTCAE Terms are sorted alphabetically and not by frequency.
Note 5: This table presents counts of patients. Patients with more than one AE were counted with worst respective grade. In addition to the total (including all grades), only grade 3, 4, and 5 are shown in this table, for grade 1, grade 2, and grade missing please refer to the source table.
Note 6: NCI-CTCAE version 4.0 was used.
CTCAE: common terminology criteria for adverse events, n: number of patients, N: number of patients in analysis set, NCI: National Cancer Institute, TEAE: treatment-emergent adverse event.
Source: Table 14.4.2 / 8

Sorafenib-related TEAEs in sorafenib treated patients were experienced by 52.6% of the 515 patients overall, 15.3% had grade 3 (worst grade), 1.2% had grade 4, and 1.7% had grade 5 TEAEs.

Overall, the most frequently reported sorafenib-related TEAEs were palmar-plantar erythrodysesthesia syndrome (17.5%) and diarrhea (17.1%). With the exception of fatigue (6.6%), all other TEAEs occurred in less than 5% of patients.

The most common grade 3 (worst grade) sorafenib-related TEAEs were palmar-plantar erythrodysesthesia syndrome (3.7%), followed by diarrhea (2.1%), fatigue (1.9%), and ascites, blood bilirubin increased and hypertension (1.0% each). All other TEAEs occurred in less than 1% of patients. The only grade 4 TEAEs reported were blood bilirubin increased, lipase increased, renal and urinary disorders – other, specify, pneumonitis, erythema multiforme, and palmar-plantar erythrodysesthesia syndrome (0.2% each). Most frequently documented grade 5 TEAEs included hepatic failure (0.8%), ascites, esophageal varices hemorrhage, death NOS, general disorders and administration site conditions – other, specify, and respiratory failure (0.2% each) (Table 14.4.2 / 8).

Incidences of TEAEs and TACE-related TEAEs in the overall TACE population can be found in Table 14.4.2 / 11 and Table 14.4.2 / 12. Incidences of AEs in patients who became TACE non-eligible after initial TACE can be found in Table 14.4.2 / 15 (TACE non-eligibility specified based on protocol), Table 14.4.2 / 17 (TACE non-eligibility based on AASLD), Table 14.4.2 / 19 (TACE non-eligibility based on Child Pugh), and Table 14.4.2 / 21 (TACE non-eligibility based on JSH).

Incidences of TEAEs and sorafenib-related TEAEs in sorafenib treated patients classified by MedDRA can be found in Table 14.4.2 / 23 and Table 14.4.2 / 24. Incidences of TEAEs and TACE-related TEAEs in the overall TACE population classified by MedDRA can be found in Table 14.4.2 / 27 and Table 14.4.2 / 28. Incidences of AEs classified by MedDRA in patients who became TACE non-eligible after initial TACE can be found in Table 14.4.2 / 31 (TACE non-eligibility specified based on protocol), Table 14.4.2 / 33 (TACE non-eligibility based on AASLD),

Table 14.4.2 / 35 (TACE non-eligibility based on Child Pugh), and Table 14.4.2 / 37 (TACE non-eligibility based on JSH).

Incidences of TEAEs by worst grade

Incidences of TEAEs in sorafenib treated patients are presented by worst grade in Table 50.

Table 50: Incidences of TEAE by worst grade - Sorafenib treated patients

	Grade 1 N=515 n (%)	Grade 2 N=515 n (%)	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
TEAE	45 (8.7%)	97 (18.8%)	96 (18.6%)	17 (3.3%)	145 (28.2%)	400 (77.7%)
TEAE related to sorafenib	56 (10.9%)	121 (23.5%)	79 (15.3%)	6 (1.2%)	9 (1.7%)	271 (52.6%)
TESAE	0 (0.0%)	9 (1.7%)	40 (7.8%)	17 (3.3%)	145 (28.2%)	211 (41.0%)
TESAE related to sorafenib	0 (0.0%)	7 (1.4%)	23 (4.5%)	5 (1.0%)	9 (1.7%)	44 (8.5%)

Note 1: the population was denoted “SOAP” in the statistical output.
Note 2: Treatment-emergent: Any event arising or worsening after start of sorafenib until 30 days after last intake.
Note 3: This table presents counts of patients.
Note 4: Relation: Events with missing relationship classification were considered as causally related to treatment.
Note 5: Serious: Events with missing serious classification were considered as serious AEs, as worst case assumption.
Note 6: NCI-CTCAE version 4.0 was used.
CTCAE: common terminology criteria for adverse events, n: number of patients, N: number of patients in analysis set, NCI: National Cancer Institute, TEAE: treatment-emergent adverse event, TESAE: treatment-emergent serious adverse event.
Source: Table 14.4.2 / 7, Table 14.4.2 / 8, Table 14.4.2 / 9, Table 14.4.2 / 10

Grade 5 (worst grade) TEAEs were observed in 28.2% of patients, grade 4 TEAEs in 3.3% of patients, grade 3 TEAEs in 18.6% of patients, grade 2 TEAEs in 18.8% of patients, and grade 1 in 8.7%.

The majority of sorafenib-related TEAEs was grade 1, 2 and 3 (worst grade).

10.6.1.3 Deaths, other serious adverse events, and other significant adverse events

10.6.1.3.1 Deaths

Table 51 displays a summary of deaths and primary causes of deaths in sorafenib treated patients.

Table 51: Deaths and causes of death - Sorafenib treated patients

	Total N=515 n (%)
Cause of death – primary reason	267 (51.8%)
Cancer-related	167 (32.4%)
Not cancer-related	17 (3.3%)
Liver-related	25 (4.9%)
Cancer- and liver-related	36 (7.0%)
Cancer- and liver-related and other	1 (0.2%)
Not cancer-related and other	2 (0.4%)
Not cancer-related and liver related	3 (0.6%)
Other	11 (2.1%)
Missing	5 (1.0%)

Note 1: the population was denoted “SOAP” in the statistical output.
n: number of patients, N: number of patients in analysis set.
Source: Table 14.4.1 / 6

A total of 51.8% of sorafenib treated patients died during the study. The most commonly reported primary reason of death was cancer-related (32.4%), followed by cancer- and liver-related death (7.0%), liver-related death (4.9%), not cancer-related death (3.3%), and other (2.1%).

A summary of deaths and primary causes of deaths in the overall TACE population is presented in Table 52.

Table 52: Deaths and causes of death - Overall TACE population

	Total N=1650 n (%)
Cause of death – primary reason	694 (42.1%)
Cancer-related	375 (22.7%)
Not cancer-related	48 (2.9%)
Liver-related	116 (7.0%)
Cancer- and liver-related	85 (5.2%)
Cancer- and liver-related and other	1 (<0.1%)
Cancer-related and other	1 (<0.1%)
Not cancer-related and other	5 (0.3%)
Liver-related and other	1 (<0.1%)
Not cancer-related and liver-related	9 (0.5%)
Other	33 (2.0%)
Missing	20 (1.2%)

Note 1: the population was denoted "TCE" in the statistical output.
n: number of patients, N: number of patients in analysis set, TACE: transarterial chemoembolization.
Source: Table 14.4.1 / 1

In overall TACE population, 42.1% of patients died during the study. The most commonly reported primary reason of death was cancer-related (22.7%), followed by liver-related death (7.0%), cancer- and liver-related death (5.2%), not cancer-related death (2.9%), and other (2.0%).

Results for patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol) were in line with the overall TACE population (Table 14.4.1 / 2). Results for patients who became TACE non-eligible after initial TACE based on AASLD, based on Child Pugh based, and based on JSH can be found in Table 14.4.1 / 3, Table 14.4.1 / 4, and Table 14.4.1 / 5).

10.6.1.3.2 Serious adverse events

Incidences of TESAEs occurring in ≥1% of patients in sorafenib treated patients are shown in Table 53. A cut-off of ≥1% of patients was chosen to avoid long in-text tables. Incidences of all TEAEs without cut-off can be found in Table 14.4.2 / 9.

Table 53: Incidences of TESAEs (≥1% of patients) - Sorafenib treated patients

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Any TESAE	40 (7.8%)	17 (3.3%)	145 (28.2%)	211 (41.0%)
Cardiac disorders	1 (0.2%)	0 (0.0%)	6 (1.2%)	8 (1.6%)
Gastrointestinal disorders	27 (5.2%)	4 (0.8%)	9 (1.7%)	47 (9.1%)
Ascites	9 (1.7%)	1 (0.2%)	3 (0.6%)	17 (3.3%)
Esophageal varices hemorrhage	3 (0.6%)	0 (0.0%)	2 (0.4%)	7 (1.4%)
Upper gastrointestinal hemorrhage	4 (0.8%)	1 (0.2%)	0 (0.0%)	6 (1.2%)
General disorders and administration site conditions	3 (0.6%)	4 (0.8%)	18 (3.5%)	32 (6.2%)
Death NOS	0 (0.0%)	0 (0.0%)	8 (1.6%)	8 (1.6%)
Fever	0 (0.0%)	3 (0.6%)	0 (0.0%)	9 (1.7%)
General disorders and administration site conditions – other, specify	1 (0.2%)	1 (0.2%)	6 (1.2%)	8 (1.6%)

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Hepatobiliary disorders	6 (1.2%)	2 (0.4%)	41 (8.0%)	52 (10.1%)
Hepatic failure	0 (0.0%)	0 (0.0%)	38 (7.4%)	38 (7.4%)
Portal vein thrombosis	2 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Infections and infestations	9 (1.7%)	6 (1.2%)	8 (1.6%)	23 (4.5%)
Peritoneal infection	2 (0.4%)	1 (0.2%)	2 (0.4%)	5 (1.0%)
Sepsis	2 (0.4%)	3 (0.6%)	4 (0.8%)	9 (1.7%)
Investigations	3 (0.6%)	5 (1.0%)	0 (0.0%)	10 (1.9%)
Blood bilirubin increased	2 (0.4%)	4 (0.8%)	0 (0.0%)	7 (1.4%)
Metabolism and nutrition disorders	6 (1.2%)	1 (0.2%)	0 (0.0%)	9 (1.7%)
Musculoskeletal and connective tissue disorders	4 (0.8%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Neoplasms benign malignant and unspecified (incl cysts and polyps)	2 (0.4%)	1 (0.2%)	55 (10.7%)	58 (11.3%)
Neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify	2 (0.4%)	0 (0.0%)	55 (10.7%)	57 (11.1%)
Nervous system disorders	5 (1.0%)	1 (0.2%)	3 (0.6%)	16 (3.1%)
Encephalopathy	4 (0.8%)	1 (0.2%)	3 (0.6%)	13 (2.5%)
Renal and urinary disorders	2 (0.4%)	1 (0.2%)	5 (1.0%)	9 (1.7%)
Acute kidney injury	1 (0.2%)	0 (0.0%)	5 (1.0%)	7 (1.4%)
Respiratory, thoracic and mediastinal disorders	6 (1.2%)	3 (0.6%)	7 (1.4%)	16 (3.1%)
Respiratory failure	0 (0.0%)	2 (0.4%)	4 (0.8%)	6 (1.2%)
Skin and subcutaneous tissue disorders	3 (0.6%)	2 (0.4%)	0 (0.0%)	6 (1.2%)

Note 1: the population was denoted “SOAP” in the statistical output.
Note 2: Treatment-emergent: Any event arising or worsening after start of sorafenib until 30 days after last intake.
Note 3: CTCAE Terms are sorted alphabetically and not by frequency.
Note 4: This table presents counts of patients. Patients with more than one AE were counted with worst respective grade. In addition to the total (including all grades), only grade 3, 4, and 5 are shown in this table, for grade 1, grade 2, and grade missing please refer to the source table.
Note 5: NCI-CTCAE version 4.0 was used.
CTCAE: common terminology criteria for adverse events, n: number of patients, N: number of patients in analysis set, NCI: National Cancer Institute, NOS: not otherwise specified, TESAE: treatment-emergent adverse event.
Source: Table 14.4.2 / 9

A total of 41.0% of the 515 sorafenib treated patients experienced any TESAE, 7.8% had grade 3 (worst grade), 3.3% had grade 4, and 28.2% had grade 5 TEAEs.

Overall, the most frequently reported TESAEs were neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (11.1%) and hepatic failure (7.4%). All other TEAEs occurred in less than 5% of patients.

The most common grade 3 (worst grade) TESAE was ascites (1.7%); all other grade 3 TESAEs occurred in less than 1% of patients. Likewise, all grade 4 TEAEs occurred in less than 1% of patients. Grade 5 TEAEs that were documented in more than 1% of patients included neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (10.7%), hepatic failure (7.4%), death NOS (1.6%), and general disorders and administration site conditions – other, specify (1.2%).

Incidences of TESAEs related to sorafenib treatment

Table 54 displays the incidences of sorafenib-related TESAEs in sorafenib treated patients.

Table 54: Incidences of TESAEs related to sorafenib - Sorafenib treated patients

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Any TESAE	23 (4.5%)	5 (1.0%)	9 (1.7%)	44 (8.5%)
Gastrointestinal disorders	11 (2.1%)	0 (0.0%)	2 (0.4%)	16 (3.1%)
Abdominal distention	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Anal fistula	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Anorexia	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Ascites	4 (0.8%)	0 (0.0%)	1 (0.2%)	6 (1.2%)
Diarrhea	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Esophageal hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Esophageal varices hemorrhage	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
Stomach pain	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Upper gastrointestinal hemorrhage	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vomiting	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
General disorders and administration site conditions	1 (0.2%)	0 (0.0%)	2 (0.4%)	4 (0.8%)
Death NOS	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
Fever	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
General disorders and administration site conditions – other, specify	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
Oral hemorrhage	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hepatobiliary disorders	2 (0.4%)	0 (0.0%)	4 (0.8%)	8 (1.6%)
Hepatic failure	0 (0.0%)	0 (0.0%)	4 (0.8%)	4 (0.8%)
Hepatic hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hepatic infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hepatic pain	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Portal vein thrombosis	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Infections and infestations	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Infections and infestations – other, specify	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Peritoneal infection	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Investigations	0 (0.0%)	1 (0.2%)	0 (0.0%)	2 (0.4%)
Blood bilirubin increased	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Weight loss	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Metabolism and nutrition disorders	4 (0.8%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Anorexia	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Dehydration	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hyponatremia	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Nervous system disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Encephalopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
Lethargy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Other	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
No code in CTC-AE	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Renal and urinary disorders	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Renal and urinary disorders – other, specify	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)

CTCAE Term	Grade 3 N=515 n (%)	Grade 4 N=515 n (%)	Grade 5 N=515 n (%)	Total N=515 n (%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.6%)
Pneumonitis	1 (0.2%)	1 (0.2%)	0 (0.0%)	2 (0.4%)
Respiratory failure	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
Skin and subcutaneous tissue disorders	2 (0.4%)	2 (0.4%)	0 (0.0%)	5 (1.0%)
Bullous dermatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Erythema multiforme	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Palmar-plantar erythrodysesthesia syndrome	1 (0.2%)	1 (0.2%)	0 (0.0%)	2 (0.4%)
Skin infection	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Surgical and medical procedures	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Surgical and medical procedures – other, specify	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Note 1: the population was denoted "SOAP" in the statistical output.
Note 2: Treatment-emergent: Any event arising or worsening after start of sorafenib until 30 days after last intake.
Note 3: Relation: Events with missing relationship classification were considered as causally related to treatment.
Note 4: CTCAE Terms are sorted alphabetically and not by frequency.
Note 5: This table presents counts of patients. Patients with more than one TESAE were counted with worst respective grade. In addition to the total (including all grades), only grade 3, 4, and 5 are shown in this table, for grade 1, grade 2, and grade missing please refer to the source table.
Note 6: NCI-CTCAE version 4.0 was used.
CTCAE: common terminology criteria for adverse events, n: number of patients, N: number of patients in analysis set, NCI: National Cancer Institute, NOS: not otherwise specified, TESAE: treatment-emergent serious adverse event.
Source: Table 14.4.2 / 10

Sorafenib-related TESAEs were experienced by 8.5% of the 515 sorafenib treated patients overall, 4.5% had grade 3 (worst grade), 1.0% had grade 4, and 1.7% had grade 5 TESAEs.

The only sorafenib-related TESAE that occurred in more than 1% of patients overall was ascites (1.2%).

No grade 3 (worst grade), grade 4, or grade 5 sorafenib-related TESAEs occurred in more than 1% of patients. The most frequent grade 3 sorafenib-related TESAE was ascites (0.8%); all other sorafenib-related TESAEs occurred in less than 0.5% of patients. Grade 4 sorafenib-related TESAEs included blood bilirubin increased, renal and urinary disorders – other, specify, pneumonitis, erythema multiforme, and palmar-plantar erythrodysesthesia syndrome (0.2% each). The most common grade 5 sorafenib-related TEAEs was hepatic failure (0.8%); all other sorafenib-related TESAEs, i.e., ascites, esophageal varices hemorrhage, death NOS, general disorders and administration site conditions – other, specify, and respiratory failure occurred in 0.2% of patients each.

Incidences of TESAEs and TACE-related TESAEs in the overall TACE population can be found in Tables 14.4.2 / 13 and Table 14.4.2 / 14. Incidences of SAEs in patients who became TACE non-eligible after initial TACE can be found in Table 14.4.2 / 16 (TACE non-eligibility specified based on protocol), Table 14.4.2 / 18 (TACE non-eligibility based on AASLD), Table 14.4.2 / 20 (TACE non-eligibility based on Child Pugh), and Table 14.4.2 / 22 (TACE non-eligibility based on JSH).

Incidences of TESAEs and sorafenib-related TESAEs in sorafenib treated patients classified by MedDRA can be found in Table 14.4.2 / 25 and Table 14.4.2 / 26. Incidences of TESAEs and TACE-related TESAEs in the overall TACE population classified by MedDRA can be found in Table 14.4.2 / 29 and Table 14.4.2 / 30. Incidences of SAEs be classified MedDRA in patients who became TACE non-eligible after initial TACE can be found in Table 14.4.2 / 32 (TACE non-eligibility specified based on protocol), Table 14.4.2 / 34 (TACE non-eligibility based on AASLD),

Table 14.4.2 / 36 (TACE non-eligibility based on Child Pugh), and Table 14.4.2 / 38 (TACE non-eligibility based on JSH).

10.6.2 Other safety analyses

10.6.2.1 Change in ALBI Grade

By means of changes in the ALBI grade, the liver function in the overall TACE population was assessed pre-TACE, in the acute and in the chronic period (for definitions, please see section 9.9.2.5). The ALBI grade is based on albumin and bilirubin values. For the definition of the ALBI grades 1 to 3, please refer to section 4.6.5 of the SAP (provided as a stand-alone document to be found in Annex 1 and available upon request).

In overall TACE population , the pre-TACE ALBI grade was 2 in more than 50% of patients (ranging from 52.3% to 59.8%), more than 30% of patients had grade 1 (ranging from 33.6% to 41.5%), and roughly 5% of patients had grade 3 (ranging from 3.8% to 6.6%) for the first 4 TACEs. In the acute period, the percentage of patients with ALBI grade 2 increased to around 70% (ranging from 68.6% to 72.4%), while the percentage of ALBI grade 1 patients decreased to less than 22% (ranging from 13.8% to 21.9%); the remaining patients had an ALBI grade of 3 (ranging from 6.3% to 13.8%). In the chronic period, the distribution of grades was roughly comparable to the pre-TACE results (Table 14.4.3 / 1).

From the fifth TACE onwards, the number of patients was too small to allow for reliable comparisons (Table 14.4.3 / 1).

10.6.2.2 Summary of laboratory parameters

Deteriorations of liver dysfunction in sorafenib treated patients were evaluated throughout the study based on the laboratory parameters[13] listed in section 9.4.4.

In sorafenib treated patients, there were no major changes in laboratory parameters within follow up visit 1 to 20. From follow up visit 21 onwards, the number of patients with assessments was too low to allow for reliable comparisons (Table 14.4.4 / 2).

Please note that the proportion of missing values was quite high for some of the individual parameters.

A summary of laboratory parameters during the course of the study for the overall TACE population is provided in Table 14.4.4 / 1.

10.6.2.3 Summary of blood pressure

Systolic and diastolic blood pressure were assessed at the initial visit and at the follow up visits.

There were no major changes in mean systolic or diastolic blood pressure or changes from baseline within follow up visit 1 to 20. From follow up visit 21 onwards, the number of patients with assessments of blood pressure was too low to allow for reliable comparisons (Table 14.4.4 / 4).

Blood pressure during the course of the study for the overall TACE population is provided in Table 14.4.4 / 3.

[13] Only values between the first Sorafenib administration and the last Sorafenib administration plus 30 days were included.

11. Discussion

11.1 Key results

This study was an international, prospective, open-label, multi-center, non-interventional study. A total of 1676 patients were enrolled

Description for the results focused on the following analysis sets:

- Overall TACE population
- TACE administered patients who became non-eligible for TACE after initial TACE and before end of the study based on the TACE non-eligibility criteria specified in the protocol
- Patients treated with sorafenib

A total of 1650 patients received TACE (overall TACE population).

The population of patients who became TACE non-eligible after initial TACE included 507 patients. Patients in this population were additionally stratified according to their sorafenib treatment: cohort 1 (treated with sorafenib early based on the investigators' treatment decisions) included less than 50 patients, while the remaining patients were in cohort 2 (not treated with sorafenib early based on the investigators' treatment decisions)[14]. Overall, a higher proportion of patients in cohort 1 had worse TNM and BCLC gradings compared with cohort 2. However, due to the low number of patients in cohort 1 and heterogeneity in the study cohorts, these results have to be interpreted with caution.

A total of 515 patients (30.7% of enrolled patients) received sorafenib. In this group, most frequently, the initial dose of sorafenib was 800 mg (61.0%), followed by 400 mg (33.4%). The median duration of sorafenib exposure was 131 days, with a median of 124 actual days on sorafenib. The cumulative person time was 328.64 years. The most common dose modification was "drug withdrawn" (73.0%).

Overall, most of the patients were male and the majority of patients were Asian. The mean age was over 60 years.

The **primary objective** of this study was to evaluate OS from time of TACE non-eligibility in two cohorts of special interest (i.e. patients with early start of sorafenib treatment vs. patients without early start of sorafenib treatment including no sorafenib treatment, each based on the investigators' treatment decisions) not only overall but also by study region[15].

In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median OS was 590 days (95% CI: 474;695 days). In cohort 1 (patients treated with sorafenib early based on the investigators' treatment decisions), the median OS was 494 days (95% CI: 318;* days[16]) and in cohort 2 (patients not treated with sorafenib early based on the investigators' treatment decisions), the median OS was 604 days (95% CI: 474;711 days). Please note that due to the low number of patients in cohort 1 and heterogeneity in the study cohorts, these results have to be interpreted with caution. Also allocation bias was not corrected for.

[14] Please note that cohort 1 comprises all patients for whom the physician decided at the time of TACE non-eligibility to choose sorafenib as the next treatment option, while cohort 2 includes patients with TACE non-eligibility for whom the decision to treat with sorafenib was made at a later point in time, patients who were never treated with sorafenib as well as patients for whom another systemic cancer treatment was chosen.

[15] Analyses for the regions are provided as stand-alone documents in in Annex 1 and are available upon request.

[16] * presents censored observation or unestimable due to censored data.

The median OS tended to decrease with increasing number of TACEs and was lower in patients with progressive disease as best radiological response than in patients with complete response, partial response, or stable disease.

The following secondary objectives were assessed in this study:

Evaluation of PFS, TTP, tumor response, and AE from time of TACE non-eligibility: patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median PFS was 103 days (95% CI: 91;126 days) and the median TTP was 45 days (95% CI: 3;86 days).

The incidence of AEs from time of TACE non-eligibility was 73.8% in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Please note that tumor response from time of TACE non-eligibility also was part of the present secondary objective but was not analyzed.

OS, PFS, TTP, tumor response and AE from start of sorafenib treatment: In sorafenib treated patients, the median OS was 362 days (95% CI: 313;444 days), the median PFS was 90 days (95% CI: 81;100 days), and the median TTP was 96 days (95% CI: 86;111 days). Most frequently, the latest radiological tumor response compared to start of sorafenib was progressive disease (36.7%), followed by stable disease (11.3%). However, assessment was missing in nearly half of the patients (45.2%). The incidence of AEs from start of sorafenib treatment was 77.7%.

Duration of treatment of sorafenib after TACE with respect to the start of sorafenib treatment (early vs. not early): In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median duration of sorafenib exposure was 117 days and was longer in cohort 1 (median 157 days; treated with sorafenib early based on the investigators' treatment decisions) than in cohort 2 (median 106 days; not treated with sorafenib early based on the investigators' treatment decisions).

Determine time to meet TACE non-eligibility criteria from initial TACE according to the guidelines: The median time from initial TACE to TACE non-eligibility was 146 days in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol).

Response to TACE by number of TACEs: After the first TACE patients in the overall TACE population most frequently showed partial response (26.2%) and stable disease (22.3%). A total of 18.4% of patients had progressive disease and 13.7% had complete response. After the second, third and fourth TACE, the proportion of patients with progressive disease gradually increased to 27.2% in the fourth TACE, while the proportion of patients with complete response decreased to 8.3% in the fourth TACE.

After the first four TACEs, the majority of patients (ranging from 74.0% after the first TACE to 60.3% after the second TACE) in the overall TACE population had no clinical progressive disease based on non-radiological assessment.

Deterioration of liver dysfunction in the course of TACE treatment: Assessment of liver dysfunction was assessed based on laboratory parameters (alanine aminotransferase, albumin, aspartate aminotransferase, bilirubin, prothrombin INR). Overall, no clinically relevant changes from pre-TACE period to the acute period or from pre-TACE period to the chronic period were observed.

Alanine aminotransferase, albumin, bilirubin and prothrombin INR were graded normal for the majority of patients in the overall TACE population in the pre-TACE period of the first four TACEs.

Aspartate aminotransferase was graded normal for the pre-TACE period in 45% of patients for the first TACE and for the majority of patients for the second to fourth TACE. In the acute period, the proportion of patients with normal values in the first four TACEs mostly decreased and then mostly increased again in the chronic period of the first four TACEs compared to the acute period, with the exception of bilirubin. However, for bilirubin the proportion of patients with normal values was already >80% for the first four TACEs in all periods.

OS from initial TACE: In the overall TACE population, the median OS was 877 days (95% CI: 789;989 days). The median PFS from initial TACE was 198 days (95% CI: 187;213 days), and the median TTP from initial TACE was 240 days (95% CI: 218;263 days).

Deviations from recommendations for TACE use:. Of the 1676 patients enrolled in this study, about 40% of patients received TACE although they were already TACE non-eligible prior to the first TACE based on the non-eligibility criteria 1-3 (protocol specified, AASLD based, Child Pugh based) and about 20% were already TACE non-eligible at the inclusion visit based on the non-eligibility criteria 4 (TACE non-eligibility based on JSH). Additionally, the first treatment decision after inclusion was "new TACE" in more than 20% of these patients. In patients who became TACE non-eligible after initial TACE, more than 20% of patients had the treatment decision "new TACE" after they became non-eligible.

Practice patterns of the investigators involved in the care of patients with HCC under real-life conditions: The median duration of TACE treatments in the overall TACE population was 78 days. Patients most frequently had 1 (39.3%) or 2 (25.6%) TACE treatments. Only few patients (4.7%) received radiofrequency ablation in combination with TACE. The median time between TACE treatments was 80 days for the time between first and second TACE, 95 days for the time between second and third TACE, and 97 days for the time between third and fourth TACE.

A total of 511 of 1650 patients in the overall TACE population switched to sorafenib treatment. Patients who switched to sorafenib most frequently switched after one TACE (50.7%), followed by after more than two TACEs (27.8%). A switch to other systemic anti-cancer therapy was reported in 113 of 1650 patients. Patient most frequently switched after one TACE (38.1%), followed by after more than two TACEs (34.5%). A switch to other non-systemic anti-cancer treatment was reported in 412 of 1650 patients. Patient most frequently switched after one TACE (43.9%), followed by after two TACEs (29.4%).

Adverse events

Of the 515 sorafenib treated patients, 400 patients (77.7%) experienced **TEAEs**, i.e., events that arose or worsened after the start of sorafenib until 30 days after the last intake. In 52.6% of patients, the TEAEs were related to sorafenib treatment. TESAEs were experienced by 41.0% of patients and in 8.5% of patients, the TESAEs were related. TEAEs resulting in sorafenib withdrawal, interruption, or dose reduction were observed in 58.3% of patients and TEAEs resulting in inpatient hospitalization or prolongation of existing hospitalization were reported in 21.4% of patients. CTCAE grade 1 (worst grade) TEAEs were documented in 8.7% of patients, 18.8% of patients had CTCAE grade 2 TEAEs, 18.6% of patients had CTCAE grade 3 TEAEs, 3.3% of patients had CTCAE grade 4 TEAEs and 28.2% of patients had CTCAE grade 5 TEAEs. A total of 10.9% of patients had grade 1 (worst grade) sorafenib-related TEAEs, 23.5% of patients had grade 2 sorafenib-related TEAEs, 15.3% of patients had grade 3 sorafenib-related TEAEs,1.2% of patients had grade 4 sorafenib-related TEAEs, and 1.7% had grade 5 sorafenib-related TEAEs.

Overall, the most frequently reported TEAEs were diarrhea (18.4%), palmar-plantar erythrodysesthesia syndrome (17.7%), and neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (12.8%). The most frequently reported sorafenib-related TEAEs were palmar-plantar erythrodysesthesia syndrome (17.5%) and diarrhea (17.1%). With the exception of fatigue (6.6%), all other TEAEs occurred in less than 5% of patients.

A total of 51.8% of the 515 patients who received sorafenib died before end of the study. The most commonly reported primary reason of death was cancer-related (32.4%), followed by cancer- and liver-related death (7.0%), liver-related death (4.9%), not cancer-related death (3.3%), and reason other (2.1%). Overall, only few patients (1.7%) died due to sorafenib-related TEAEs (grade 5).

The most frequently reported TESAEs were neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (11.1%) and hepatic failure (7.4%). All other TESAEs occurred in less than 5% of patients. The only sorafenib-related TESAE that occurred in more than 1% of patients overall was ascites (1.2%).

In sorafenib treated patients, there were no major changes in laboratory parameters within follow up visit 1 to 20. From follow up visit 21 onwards, the number of patients with assessments was too low to allow for reliable comparisons.

11.2 Limitations

This study was a 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. Since the number of relevant covariates was presumably very high, a pure descriptive statistical approach may not be sufficient to fully interpret the results. However, due to low number of patients in cohort 1 and multiple covariates, a comparison based on a propensity score matched population was not appropriate.

Results from this study were 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 were inherent and result from the non-interventional character and the fact of voluntary participation of investigators and patients.

11.3 Interpretation

This study was a non-interventional, prospective, open-label, multi-center study to evaluate outcomes of all patients who are treated with TACE followed by sorafenib and patients who did not receive sorafenib after TACE.

The primary objective of this study was to evaluate OS from time of TACE non-eligibility in two cohorts of special interest not only overall but also by study region[17]. In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), the median OS was 590 days (95% CI: 474;695 days).

[17] Analyses for the regions are provided as stand-alone documents in in Annex 1 and are available upon request.

This study was designed to evaluate outcomes of all patients with early start of sorafenib treatment after TACE (cohort 1) and patients without early start of sorafenib treatment after TACE (cohort 2), each based on the investigators' treatment decisions. However, with the low patient numbers in cohort 1, as well as multiple covariates, a comparison based on a propensity score matched population was not appropriate. Cohort 1 includes all patients for whom the investigator made the treatment decision for sorafenib immediately at time of TACE non-eligibility, while cohort 2 includes patients for whom the decision to treat with sorafenib was made at a later points in time, patients who were never treated with sorafenib as well as patients for whom another systemic cancer treatment had been chosen. Data indicate that the two cohorts are different from each other with patients in cohort 1 having worse TNM and BCLC gradings compared with cohort 2 and a lower OS in cohort 1 might be expected. As allocation bias was not corrected for, no comparison between the cohorts can be made.

The median OS from start of sorafenib treatment in patients who received sorafebnib was 362 days (95% CI: 313;444 days), the median PFS was 90 days (95% CI: 81;100 days), and the median TTP was 96 days (95% CI: 86;111 days). These data are in line with what was observed with the past studies.

Overall, the median time from initial TACE to TACE non-eligibility was 146 days in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol). However, results showed that despite of being non-eligible for TACE as specified based on the protocol, many patients received further TACE treatments. Of the 1676 patients enrolled in this study, about 40% of patients received TACE although they were already TACE non-eligible prior to the first TACE based on the protocol. Additionally, the first treatment decision after inclusion was "new TACE" in more than 20% of these patients. In patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol), more than 20% of patients had the treatment decision "new TACE" after they became non-eligible.

The response to TACE based on radiological and non-radiological assessments were evaluated in this study. The proportion of patients with progressive disease gradually increased in the overall TACE population based on radiological assessment with increasing number of TACEs, while the proportion of patients with complete response decreased. The majority of patients had no clinical progressive disease based on non-radiological assessment.

Analysis of the practice patterns of the investigators involved in the care of patients with HCC under real-life conditions showed a median duration of TACE treatments in the overall TACE population of 78 days. Patients most frequently had 1 (39.3%) or 2 (25.6%) TACE treatments. The median time between TACE treatments was 80 days for the time between first and second TACE, 95 days for the time between second and third TACE, and 97 days for the time between third and fourth TACE. A total of 511 of 1650 patients in the overall TACE population switched to sorafenib treatment. Patients who switched to sorafenib most frequently switched after one TACE (50.7%), followed by after more than two TACEs (27.8%). A switch to other systemic anti-cancer therapy was reported in 113 of 1650 patients. Patient most frequently switched after one TACE (38.1%), followed by after more than two TACEs (34.5%). A switch to other non-systemic anti-cancer treatment was reported in 412 of 1650 patients. Patients most frequently switched after one TACE (43.9%), followed by after two TACEs (29.4%). Overall, no clinically relevant deterioration of liver dysfunction was observed after TACE.

Overall, it could be shown that TACE treatment varies greatly between patients and did not necessarily adhere to treatment guidelines with respect to TACE non-eligibility.

The overall safety profile of sorafenib observed in this study is in line with the known profile. Of the 515 patients who received sorafenib, 400 patients (77.7%) experienced **TEAEs**, i.e., events that arose or worsened after the start of sorafenib until 30 days after the last intake. In 52.6% of patients, the TEAEs were related to sorafenib treatment. Overall, the most frequently reported TEAEs were diarrhea (18.4%), palmar-plantar erythrodysesthesia syndrome (17.7%), and neoplasms benign malignant and unspecified (incl cysts and polyps) – other, specify (12.8%). The incidence of deaths due to sorafenib-related TEAEs (grade 5) was low (1.7%) and in line with previous studies. No new safety concern was identified.

11.4 Generalizability

The small number of inclusion and exclusion criteria allowed the enrollment of a heterogeneous patient population with regard to demographic and disease characteristics and, thus, the patient population in this study is assumed to reflect the real-life situation in patients with HCC who were treated with TACE followed or not followed by sorafenib.

Patients were treated according to daily practice conditions. The non-interventional nature of the study allowed to collect real-life data on real-life treatment to help to get a clearer picture of the clinical practice in HCC and on the influence this might have on patients' OS, without influencing the investigators' treatment decisions.

This study was performed in 25 countries and analyzed 1650 patients. Therefore, it is considered to produce generalizable results in patients with HCC who were treated with TACE.

12. Other information

Individual analyses for the regions China, Japan, Korea, Other Asia, and Europe / North America were prepared (provided as stand-alone documents in Annex 1 and available upon request). Analyses for the region Central / South America will not be performed due to the low number of subjects (N=19).

13. Conclusion

This non-interventional study evaluated outcomes of all patients with early start of sorafenib treatment after TACE (cohort 1) and patients without early start of sorafenib treatment after TACE (cohort 2), each based on the investigators' treatment decisions under real-world conditions.

The primary objective of this study was to evaluate OS from time of TACE non-eligibility in two cohorts of special interest not only overall but also by study region[18]. The median OS was 590 days (95% CI: 474;695 days) in patients who became TACE non-eligible after initial TACE (TACE non-eligibility specified based on protocol). As allocation bias was not corrected for, no comparison between the cohorts can be made.

The study indicated multiple TACE treatments prior to sorafenib therapy in a substantial number of patients. Overall, it could be shown that TACE treatment varies greatly between patients and did not necessarily adhere to treatment guidelines with respect to TACE non-eligibility.

The overall safety profile of sorafenib observed in this study is in line with the known profile.

[18] Analyses for the regions are provided as stand-alone documents in in Annex 1 and are available upon request

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Appendices

Annex 1: List of stand-alone documents

Table 55: List of stand-alone documents

Document Name	Final version and date (if available)*
Investigator list	29 MAY 2018
Steering Committee Members	12 JUN 2014
Steering Committee Charter	12 JUN 2014
Study protocol version 3.0	03 SEP 2015
SAP version 1.1	07 NOV 2017
List of IEC or IRB approvals	11 APR 2018
Data Management Plan version 1.0	19 SEP 2013
Quality Review Plan version 1.0	04 SEP 2014
Final Quality Review Report version 1.0	06 FEB 2018
Medical Review Plan version 1.0	06 AUG 2015
Medical Review Report version 1.0	13 DEC 2017
Statistical output version 1.2	17 MAY 2018
Region analysis - Japan version 1.1	13 APR 2018
Region analysis – Korea version 1.1	13 APR 2018
Region analysis - Other Asia version 1.2	18 MAY 2018
Region analysis – China version 1.1	13 APR 2018
Region analysis - Europe / North America version 1.2	18 MAY 2018

Annex 2 Additional information

Not applicable.

Annex 3 Signature Pages

Signature Page - [redacted]

Title	OPTIMIS - **O**utcomes of HCC **p**atients treated with TACE followed or not followed by sorafenib and the influence of **tim**ing to **i**nitiate sorafenib
Report version and date	v1.0, 29 MAY 2018
IMPACT study number	16560
Study type / Study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4564
Medicinal product / Active substance	Nexavar®/ ATC L01XE - Protein kinase inhibitors, sorafenib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

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