Post Authorization Safety Study (PASS) Report Addendum – 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
This document is an addendum to CSR v1.0, 29 MAY 2018	
Report version and date	V1.0, 15 OCT 2018
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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®
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, Leverkusen, Germany
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Confidentiality statement:

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1. List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ATC	Anatomical Therapeutic Chemical
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
ECOG	Eastern Co-operative Oncology Group
HCC	Hepatocellular Carcinoma
JSH	Japan Society of Hepatology
NASH	Non-alcoholic steatohepatitis
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
TACE	Transarterial Chemoembolization
TNE	Transarterial Chemoembolization Non-Eligible Population
TNM	Tumor, Nodes (lymph nodes) and Metastases (Classification)
USA	United States of America

2. Rationale

This addendum to the Clinical Study Report (CSR) of the OPTIMIS study presents the additional exploratory analysis of overall survival (OS, as defined in Section 9.1.1 of the CSR) in propensity score matched cohorts of interest.

The OPTIMIS study was a non-interventional study that evaluated outcomes of patients with Hepatocellular carcinoma (HCC) who were treated with Transarterial Chemoembolization (TACE) at the inclusion visit and became TACE non-eligible. Included patients were then assigned to one of 2 cohorts:

- 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.

Assignment to the cohorts was based on the investigators' treatment decisions and therefore represented real-world conditions (see Section 9.9.2.2 of the CSR). According to the original study protocol, it was planned to use a stratified propensity score approach to deal with selection bias and confounding typically present in non-randomized studies (see Sections 9.7.4 and 9.7.8 of the study protocol version 3.0).

However, after the second interim analysis, it was found that in addition to the unexpected low number of patients who were valid for the study population of interest, the allocation of patients into the two cohorts (as defined in Section 9.9.2.2 of the CSR) was imbalanced (cohort 1: cohort 2 = 1: 9). With the low patient numbers in cohort 1, and the poor overlap between the cohorts a primary analysis based on a propensity score approach did not seemed to be appropriate. Therefore based on the steering committee recommendation, the statistical analysis plan was revised not to apply propensity score modeling in order to balance the two cohorts of interest.

The final analysis showed similar findings: imbalance of numbers of patients in the two cohorts and poor overlap in covariate distribution. However, despite these findings, an exploratory analysis based on a propensity score model to attempt to achieve balanced cohorts (with a reduced sample size) was performed.

3. Statistical methods

This analysis consisted of all patients valid for the overall TACE population who were eligible for TACE at the inclusion visit and changed to TACE non-eligibility, with the exception of patients treated with sorafenib or any other systemic anti-cancer treatment prior to time of TACE non-eligibility. TACE non-eligibility was defined using 4 different sets of criteria (see Section 9.9.2.1 of the CSR):

- Criteria 1: Protocol specified
- Criteria 2: American Association for the Study of Liver Diseases (AASLD) based
- Criteria 3: Child-Pugh based
- Criteria 4: Japan Society of Hepatology (JSH) based

The same propensity score model was applied to all of the four populations of interest. A logistic regression was used to estimate the propensity score, which in this study equals the estimated probability of being allocated to cohort 1 (decision for early sorafenib treatment). The covariates elected as possible candidates for the propensity score model are described in Table 1.

To reduce the amount of missing propensity scores, the last non-missing observation prior to time of TACE non-eligibility was used to impute missing values for some of the covariates.

Table 1: Covariate candidates for propensity score model, according to clinical prioritization

Covariate	Categories	Imputation
Priority 1 covariates		
Region	China, Japan, Korea, Other Asia, Europe/ North America, Central/south America	No
BCLC status at TNE	A, B, C, D	Yes
Child-Pugh status at TNE	A, B, C	Yes
Lesion size at TNE	<3cm, 3-<5cm, 5-<10cm, ≥10cm	Yes
Number of lesions at TNE	0, 1, 2-3, 4-5, 6-10, >10	Yes
Response to last TACE prior to TNE	yes, no	No
ECOG at TNE	0, 1, ≥2	Yes
Previous hepatectomy	yes, no	No
Number of TACE before TNE	0, 1, 2, >2	No
Etiology: Hepatitis C	yes, no	No
Etiology: Hepatitis B	yes, no	No
Etiology: Alcohol use	yes, no	No
Etiology: NASH	yes, no	No
Etiology: Hepatitis D	yes, no	No
Etiology: Aflatoxin	yes, no	No
Etiology: Primary biliary cirrhosis	yes, no	No
Vascular invasion at TNE	yes, no	No
Extrahepatic spread at TNE	yes, no	No
Etiology: genetic / metabolic	yes, no	No
Priority 2 covariates		
Age group	<75, ≥75 years	No
Sex	male, female	No
TNM classification at TNE	stage I, II, III, IV	No
Time from initial TACE to TNE	<1 year, ≥ 1 year	No

BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Co-operative Oncology Group, NASH: non-alcoholic steatohepatitis, TACE: transarterial chemoembolization, TNE: TACE non-eligibility, TNM: Tumor, Nodes (lymph nodes) and Metastases (Classification)

Based on the propensity score, patients in cohort 1 were matched to patients in cohort 2 using a 1:2 ratio, with a 8→2 digit greedy match algorithm (1).

No interactions or transformation of covariates were considered. The selection of covariates was mainly based on the number of non-missing values, a covariate could contribute to the final model. In addition, those covariates, which were recognized as a linear combination of other covariates within the model were excluded.

The propensity score modeling was done in an outcome blinded manner: The propensity score modeling and the generation of outcomes were done by two different groups within the same organization.

The matched populations were used to calculate OS from time of TACE non-eligibility, in respect of the four different criteria defining TACE non-eligibility. Descriptive summaries of Kaplan-Meier estimates (including median and 95% Confidence Interval [CI]) and Kaplan-Meier curves were presented for each of the four matched populations.

4. Results

In all 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). The number of patients in each population, corresponding to the criteria are presented in Table 2.

Table 2: Cohort allocation according to the four criteria defining TACE non-eligibility

Criteria definition	Number of patients included in TNE population	Number of patients included - Cohort 1	Number of patients included - Cohort 2
Criteria 1: Protocol specified	507	47	460
Criteria 2: AASLD based	338	46	292
Criteria 3: Child-Pugh based	416	46	370
Criteria 4: JSH based	391	45	346

AASLD: American Association for the Study of Liver Diseases, Cohort 1: patients with early start of sorafenib treatment after TACE, Cohort 2: patients without early start of sorafenib treatment after TACE, JSH: Japan Society of Hepatology, TACE: transarterial chemoembolization, TNE: TACE non-eligible

Table 3 presents the covariates that were included in the final model.

Table 3: Covariates selected for the propensity score model

Covariate	Categories	Imputation
Region	China, Japan, Korea, Other Asia, Europe/ North America, Central/south America	No
BCLC status at TNE	A, B, C, D	Yes
Child-Pugh status at TNE	A, B, C	Yes
Lesion size at TNE	<3cm, 3-<5cm, 5-<10cm, ≥ 10cm	Yes
Number of lesions at TNE	0, 1, 2-3, 4-5, 6-10, >10	Yes
Previous hepatectomy	yes, no	No
Number of TACE before TNE	0, 1, 2, >2	No
Etiology: Hepatitis C	yes, no	No
Etiology: Hepatitis B	yes, no	No
Etiology: Alcohol use	yes, no	No
Vascular invasion at TNE	yes, no	No
Extrahepatic spread at TNE	yes, no	No
Age group	<75, ≥75 years	No
Sex	male, female	No

BCLC: Barcelona Clinic Liver Cancer, TACE: transarterial chemoembolization, TNE: TACE non-eligibility

4.1 Criteria 1: Patients who became TACE non-eligible after initial TACE based on criteria specified in the protocol

4.1.1 Baseline characteristics

Baseline characteristics for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on protocol) are presented in Table 4 for the two cohorts of the unmatched and matched populations. In the unmatched populations, differences in the distribution of parameters between the cohorts were observed, with these differences reduced in most of the parameters in the matched population.

Table 4: Baseline characteristics for the unmatched and matched populations – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on protocol)

	Unmatched Population N=507		Matched Population N=93	
	Cohort 1 N=47	**Cohort 2 N=460**	**Cohort 1 N=31**	**Cohort 2 N=62**
Region - n (%)				
China	3 (6.4%)	16 (3.5%)	2 (6.5%)	3 (4.8%)
Japan	20 (42.6%)	74 (16.1%)	11 (35.5%)	14 (22.6%)
Korea	6 (12.8%)	103 (22.4%)	3 (9.7%)	14 (22.6%)
Other Asia	3 (6.4%)	97 (21.1%)	3 (9.7%)	14 (22.6%)
Europe / North America	14 (29.8%)	161 (35.0%)	11 (35.5%)	17 (27.4%)
Central / South America	1 (2.1%)	9 (2.0%)	1 (3.2%)	0
Sex - n (%)				
Male	39 (83.0%)	381 (82.8%)	26 (83.9%)	52 (83.9%)
Female	8 (17.0%)	79 (17.2%)	5 (16.1%)	10 (16.1%)
Age group - n (%)				
<75 years	35 (74.5%)	369 (80.2%)	24 (77.4%)	54 (87.1%)
≥75 years	12 (25.5%)	91 (19.8%)	7 (22.6%)	8 (12.9%)
BCLC status at TNE[a] - n (%)				
Missing	1 (2.1%)	17 (3.7%)	0	0
0 (Very Early Stage)	0	8 (1.7%)	0	0
A (Early Stage)	0	43 (9.3%)	0	1 (1.6%)
B (Intermediate Stage)	18 (38.3%)	243 (52.8%)	17 (54.8%)	34 (54.8%)
C (Advanced Stage)	27 (57.4%)	114 (24.8%)	13 (41.9%)	22 (35.5%)
D (End-Stage)	1 (2.1%)	35 (7.6%)	1 (3.2%)	5 (8.1%)
Child-Pugh status at TNE[a] - n (%)				
Missing	2 (4.3%)	15 (3.3%)	0	0
A (5-6 Points)	39 (83.0%)	305 (66.3%)	25 (80.6%)	54 (87.1%)
B (7-9 Points)	6 (12.8%)	112 (24.3%)	6 (19.4%)	8 (12.9%)
C (10-15 Points)	0	28 (6.1%)	0	0
Lesion size at TNE[a] - n (%)				
Missing	2 (4.3%)	11 (2.4%)	0	0
<3cm	18 (38.3%)	226 (49.1%)	14 (45.2%)	27 (43.5%)
3 - <5cm	11 (23.4%)	100 (21.7%)	7 (22.6%)	15 (24.2%)
5 - <10cm	12 (25.5%)	106 (23.0%)	9 (29.0%)	14 (22.6%)
≥10cm	4 (8.5%)	17 (3.7%)	1 (3.2%)	6 (9.7%)

	Unmatched Population N=507		Matched Population N=93	
	Cohort 1 N=47	**Cohort 2 N=460**	**Cohort 1 N=31**	**Cohort 2 N=62**
Number of lesions at TNE[a] - n (%)				
Missing	1 (2.1%)	4 (0.9%)	0	0
0	2 (4.3%)	45 (9.8%)	2 (6.5%)	4 (6.5%)
1	5 (10.6%)	117 (25.4%)	4 (12.9%)	14 (22.6%)
2-3	18 (38.3%)	145 (31.5%)	11 (35.5%)	13 (21.0%)
4-5	4 (8.5%)	72 (15.7%)	3 (9.7%)	13 (21.0%)
6-10	9 (19.1%)	43 (9.3%)	6 (19.4%)	10 (16.1%)
>10	8 (17.0%)	34 (7.4%)	5 (16.1%)	8 (12.9%)
ECOG at TNE[a,b] - n (%)				
Missing	2 (4.3%)	29 (6.3%)	0	3 (4.8%)
0	31 (66.0%)	243 (52.8%)	20 (64.5%)	38 (61.3%)
1	14 (29.8%)	165 (35.9%)	11 (35.5%)	19 (30.6%)
≥2	0	23 (5.0%)	0	2 (3.2%)
Previous hepatectomy - n (%)				
Yes	9 (19.1%)	48 (10.4%)	4 (12.9%)	6(9.7%)
No	38 (80.9%)	412 (89.6%)	27 (87.1%)	56 (90.3%)
Number of TACE before TNE - n (%)				
0	0	5 (1.1%)		
1	19 (40.4%)	263 (57.2%)	12 (38.7%)	28 (45.2%)
2	10 (21.3%)	97 (21.1%)	8 (25.8%)	14 (22.6%)
>2	18 (38.3%)	95 (20.7%)	11 (35.5%)	20 (32.3%)
Vascular invasion at TNE - n (%)				
Yes	5 (10.6%)	44 (9.6%)	4 (12.9%)	5 (8.1%)
No	42 (89.4%)	416 (90.4%)	27 (87.1%)	57 (91.9%)
Extrahepatic spread at TNE - n (%)				
Yes	15 (31.9%)	48 (10.4%)	6 (19.4%)	13 (21.0%)
No	32 (68.1%)	412 (89.6%)	25 (80.6%)	49 (79.0%)
Etiology - n (%)				
Hepatitis C				
Yes	19 (40.4%)	165 (35.9%)	11 (35.5%)	29 (46.8%)
No	28 (59.6%)	295 (64.1%)	20 (64.5%)	33 (53.2%)
Hepatitis B				
Yes	9 (19.1%)	132 (28.7%)	7 (22.6%)	13 (21.0%)
No	38 (80.9%)	328 (71.3%)	24 (77.4%)	49 (79.0%)
Alcohol Use				
Yes	17 (36.2%)	160 (34.8%)	12 (38.7%)	26 (41.9%)
No	30 (63.8%)	300 (65.2%)	19 (61.3%)	36 (58.1%)
Aflatoxin[b]				
Yes	0	0	0	0
No	47 (100%)	460 (100%)	31 (100%)	62 (100%)
Genetic / metabolic[b]				
Yes	0	10 (2.2%)	0	0
No	47 (100%)	450 (97.8%)	31 (100%)	62 (100%)
NASH[b]				
Yes	5 (10.6%)	32 (7.0%)	4 (12.9%)	2 (3.2%)
No	42 (89.4%)	428 (93.0%)	27 (87.1%)	60 (96.8%)
Primary biliary cirrhosis[b]				
Yes	0	0	0	0
No	47 (100%)	460 (100%)	31 (100%)	62 (100%)
Hepatitis D[b]				

	Unmatched Population N=507		Matched Population N=93	
	Cohort 1 N=47	**Cohort 2 N=460**	**Cohort 1 N=31**	**Cohort 2 N=62**
Yes	0	2 (0.4%)	0	0
No	47 (100%)	458 (99.6%)	31 (100%)	62 (100%)
TNM classification at TNE[b] - n (%)				
Missing	2 (4.3%)	60 (13.0%)	1 (3.2%)	8 (12.9%)
STAGE I	0	46 (10..0%)	0	1 (1.6%)
STAGE II	14 (29.8%)	174 (37.8%)	13 (41.9%)	22 (35.5%)
STAGE III	9 (19.1%)	135 (29.3%)	9 (29.0%)	17 (27.4%)
STAGE IV	22 (46.8%)	45 (9.8%)	8 (25.8%)	14 (22.6%)
Time from initial TACE to TNE[b] - n (%)				
< 365 days	36 (76.6%)	354 (77.0%)	25 (80.6%)	46 (74.2%)
≥ 365 days	11 (23.4%)	106 (23.0%)	6 (19.4%)	16 (25.8%)

Note: the population was denoted “TNE1” in the statistical output.
[a] Last non-missing value prior time of TACE non-eligibility.
[b] Covariate not selected for final propensity score model.
BCLC: Barcelona Clinic Liver Cancer, Cohort 1: patients with early start of sorafenib treatment after TACE, Cohort 2: patients without early start of sorafenib treatment after TACE, ECOG: Eastern Co-operative Oncology Group, n: number of patients, NASH: non-alcoholic steatohepatitis, TACE: transarterial chemoembolization, TNE: TACE non-eligibility, TNM: Tumor, Nodes (lymph nodes) and Metastases (Classification)
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Table 14.1.1/1 and Table 14.1.1/2

4.1.2 OS

Of the patients from the matched population who became TACE non-eligible after initial TACE (TACE non-eligibility based on protocol), those from cohort 1 (with early start of sorafenib treatment based on the investigators' treatment decisions) had a median OS of 16.2 months (95% CI of 10.5;*[1] months) / 494 days (95% CI 320;***Fehler! Textmarke nicht definiert.** days). Cohort 2 patients (those without early start of sorafenib treatment) had a median OS of 12.1 months (95% CI 10.2;22.4 months) / 369 days (95% CI: 310;681 days). The Kaplan-Meier curve is shown in Figure 1.

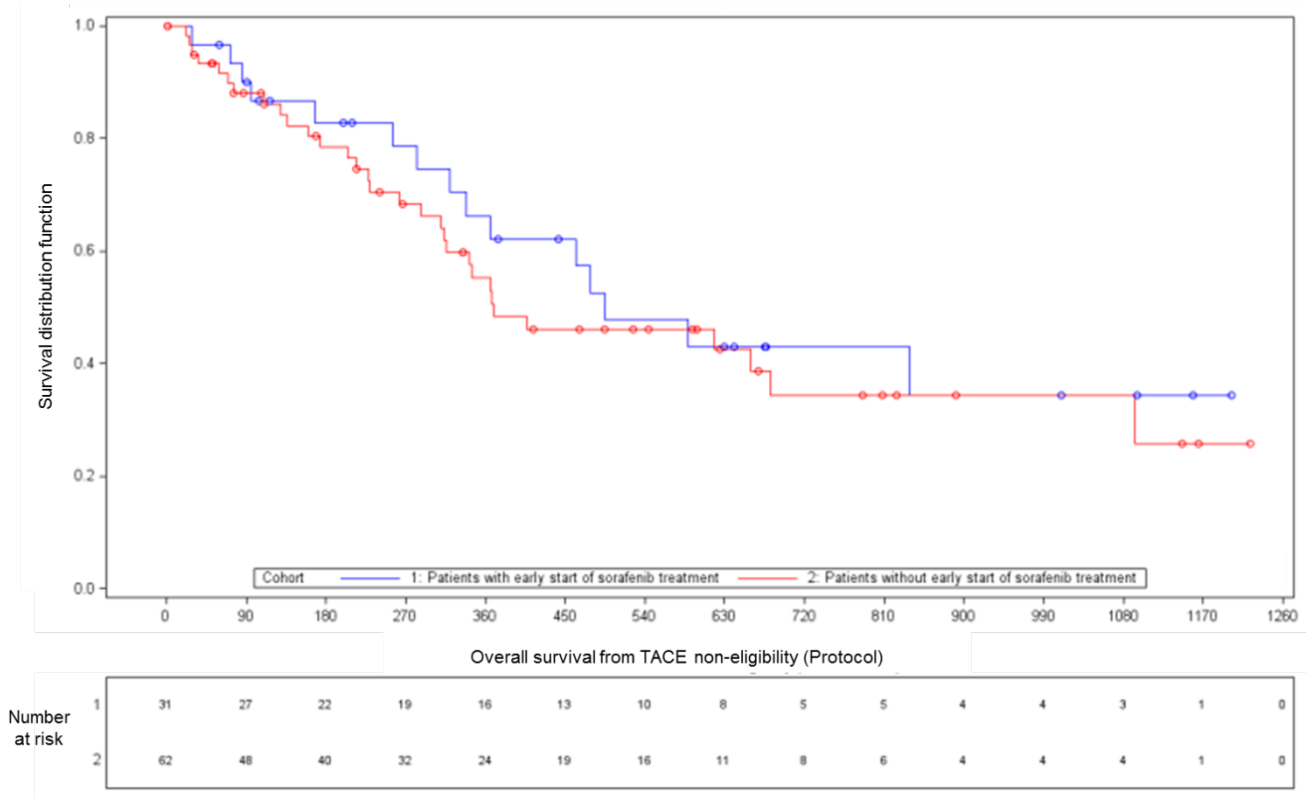

Figure 1: Kaplan-Meier curve of OS by cohort from TACE non-eligibility for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on protocol)
Note 1: the population was denoted "TNE1" in the statistical output.
TACE: transarterial chemoembolization
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Figure 14.1.1/1

[1] * presents censored observation or unestimable value due to censored data

4.2 Criteria 2: Patients who became TACE non-eligible after initial TACE based on AASLD criteria

4.2.1 Baseline Characteristics

Baseline characteristics for the patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on AASLD criteria) are presented in Table 5 for the two cohorts of the unmatched and matched populations. In the unmatched populations, differences in the distribution of parameters between the cohorts were observed, with these differences reduced in most of the parameters in the matched population.

Table 5: Baseline characteristics for the unmatched and matched populations – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on AASLD criteria)

	Unmatched Population N=338		Matched Population N=90	
	Cohort 1 N=46	**Cohort 2 N=292**	**Cohort 1 N=30**	**Cohort 2 N=60**
Region - n (%)				
China	1 (2.2%)	4 (1.4%)	0	0
Japan	17 (37.0%)	57 (19.5%)	9 (30.0%)	17 (28.3%)
Korea	9 (19.6%)	67 (22.9%)	6 (20.0%)	17 (28.3%)
Other Asia	4 (8.7%)	63 (21.6%)	3 (10.0%)	6 (10.0%)
Europe / North America	15 (32.6%)	97 (33.2%)	12 (40.0%)	18 (30.0%)
Central / South America	0	4 (1.4%)	0	2 (3.3%)
Sex - n (%)				
Male	36 (78.3%)	244 (83.6%)	24 (80.0%)	48 (80.0%)
Female	10 (21.7%)	48 (16.4%)	6 (20.0%)	12 (20.0%)
Age group - n (%)				
<75 years	36 (78.3%)	237 (81.2%)	23 (76.7%)	45 (75.0%)
≥75 years	10 (21.7%)	55 (18.8%)	7 (23.3%)	15 (25.0%)
BCLC status at TNE[a] - n (%)				
Missing	1 (2.2%)	10 (3.4%)	0	0
0 (Very Early Stage)	0	5 (1.7%)	0	0
A (Early Stage)	0	15 (5.1%)	0	3 (5.0%)
B (Intermediate Stage)	9 (19.6%)	82 (28.1%)	8 (26.7%)	19 (31.7%)
C (Advanced Stage)	35 (76.1%)	135 (46.2%)	21 (70.0%)	31 (51.7%)
D (End-Stage)	1 (2.2%)	45 (15.4%)	1 (3.3%)	7 (11.7%)
Child-Pugh status at TNE[a] - n (%)				
Missing	1 (2.2%)	11 (3.8%)	0	0
A (5-6 Points)	39 (84.8%)	168 (57.5%)	24 (80.0%)	44 (73.3%)
B (7-9 Points)	6 (13.0%)	85 (29.1%)	6 (20.0%)	15 (25.0%)
C (10-15 Points)	0	28 (9.6%)	0	1 (1.7%)
Lesion size at TNE[a] - n (%)				
Missing	2 (4.3%)	5 (1.7%)	0	0
<3cm	17 (37.0%)	145 (49.7%)	14 (46.7%)	27 (45.0%)
3 - <5cm	9 (19.6%)	65 (22.3%)	4 (13.3%)	19 (31.7%)
5 - <10cm	14 (30.4%)	66 (22.6%)	10 (33.3%)	11 (18.3%)
≥10cm	4 (8.7%)	11 (3.8%)	2 (6.7%)	3 (5.0%)

	Unmatched Population N=338		Matched Population N=90	
	Cohort 1 N=46	**Cohort 2 N=292**	**Cohort 1 N=30**	**Cohort 2 N=60**
Number of lesions at TNE[a] - n (%)				
Missing	1 (2.2%)	3 (1.0%)		
0	2 (4.3%)	26 (8.9%)	2 (6.7%)	2 (3.3%)
1	7 (15.2%)	83 (28.4%)	5 (16.7%)	12 (20.0%)
2-3	16 (34.8%)	83 (28.4%)	13 (43.3%)	17 (28.3%)
4-5	2 (4.3%)	42 (14.4%)	1 (3.3%)	10 (16.7%)
6-10	10 (21.7%)	27 (9.2%)	6 (20.0%)	10 (16.7%)
>10	8 (17.4%)	28 (9.6%)	3 (10.0%)	9 (15.0%)
ECOG at TNE[a,b] n (%)				
Missing	2 (4.3%)	14 (4.8%)	0	2 (3.3%)
0	31 (67.4%)	172 (58.9%)	20 (66.7%)	46 (76.7%)
1	12 26.1%)	67 (22.9%)	10 (33.3%)	9 (15.0%)
≥2	1 (2.2%)	39 (13.4%)	0	3 (5.0%)
Previous hepatectomy - n (%)				
Yes	8 (17.4%)	33 (11.3%)	3 (10.0%)	11 (18.3%)
No	38 (82.6%)	259 (88.7%)	27 (90.0%)	49 (81.7%)
Number of TACE before TNE - n (%)				
1	15 (32.6%)	140 (47.9%)	12 (40.0%)	22 (36.7%)
2	11 (23.9%)	80 (27.4%)	6 (20.0%)	19 (31.7%)
>2	20 (43.5%)	72 (24.7%)	12 (40.0%)	19 (31.7%)
Vascular invasion at TNE - n (%)				
Yes	8 (17.4%)	54 (18.5%)	6 (20.0%)	13 (21.7%)
No	38 (82.6%)	238 (81.5%)	24 (80.0%)	47 (78.3%)
Extrahepatic spread at TNE n (%)				
Yes	21 (45.7%)	59 (20.2%)	9 (30.0%)	25 (41.7%)
No	25 (54.3%)	233 (79.8%)	21 (70.0%)	35 (58.3%)
Etiology - n (%)				
Hepatitis C				
Yes	19 (41.3%)	94 (32.2%)	11 (36.7%)	28 (46.7%)
No	27 (58.7%)	198 (67.8%)	19 (63.3%)	32 (53.3%)
Hepatitis B				
Yes	10 (21.7%)	92 (31.5%)	7 (23.3%)	14 (23.3%)
No	36 (78.3%)	200 (68.5%)	23 (76.7%)	46 (76.7%)
Alcohol Use				
Yes	13 (28.3%)	99 (33.9%)	10 (33.3%)	17 (28.3%)
No	33 (71.7%)	193 (66.1%)	20 (66.7%)	43 (71.7%)
Aflatoxin[b]				
Yes	0	0	0	0
No	46 (100%)	292 (100%)	30 (100%)	60 (100%)
Genetic / metabolic[b]				
Yes	0	4 (1.4%)	0	0
No	46 (100%)	288 (98.6%)	30 (100%)	60 (100%)
NASH[b]				
Yes	5 (10.9%)	19 (6.5%)	3 (10.0%)	5 (8.3%)
No	41 (89.1%)	273 (93.5%)	27 (90.0%)	55 (91.7%)
Primary biliary cirrhosis[b]				
Yes	0	0	0	0
No	46 (100%)	292 (100%)	30 (100%)	60 (100%)

	Unmatched Population N=338		Matched Population N=90	
	Cohort 1 N=46	**Cohort 2 N=292**	**Cohort 1 N=30**	**Cohort 2 N=60**
Hepatitis D[b]				
Yes	0	2 (0.7%)	0	0
No	46 (100%)	290 (99.3%)	30 (100%)	60 (100%)
TNM classification at TNE[b] - n (%)				
Missing	2 (4.3%)	32 (11.0%)	1 (3.3%)	1 (1.7%)
STAGE I	0	31 (10.6%)	0	3 (5.0%)
STAGE II	9 (19.6%)	89 (30.5%)	8 (26.7%)	19 (31.7%)
STAGE III	8 (17.4%)	92 (31.5%)	7 (23.3%)	20 (33.3%)
STAGE IV	27 (58.7%)	48 (16.4%)	14 (46.7%)	17 (28.3%)
Time from initial TACE to TNE[b] - n (%)				
< 365 days	30 (65.2%)	206 (70.5%)	19 (63.3%)	38 (63.3%)
≥ 365 days	16.(34.8%)	86 (29.5%)	11 (36.7%)	22 (36.7%)

Note: the population was denoted “TNE2” in the statistical output.
[a] Last non-missing value prior time of TACE non-eligibility.
[b] Covariate not selected for final propensity score model.
BCLC: Barcelona Clinic Liver Cancer, Cohort 1: patients with early start of sorafenib treatment after TACE, Cohort 2: patients without early start of sorafenib treatment after TACE, ECOG: Eastern Co-operative Oncology Group, n: number of patients, NASH: non-alcoholic steatohepatitis, TACE: transarterial chemoembolization, TNE: TACE non-eligibility, TNM: Tumor, Nodes (lymph nodes) and Metastases (Classification)
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Table 14.1.2/1 and Table 14.1.2/2

4.2.2 OS

Of patients from the matched population who became TACE non-eligible after initial TACE (TACE non-eligibility based on AASLD criteria), those from cohort 1 (with early start of sorafenib treatment based on the investigators' treatment decisions) had a median OS of 27.6 months (95%CI: 10.5;*[2] months) / 839 days (95% CI: 321;*[2] days). Cohort 2 patients (those without early start of sorafenib treatment) had a median OS of 12.4 months (95%CI: 8.0;13.9 months) / 378 days (95% CI: 242;422 days). The Kaplan-Meier curve is shown in Figure 2.

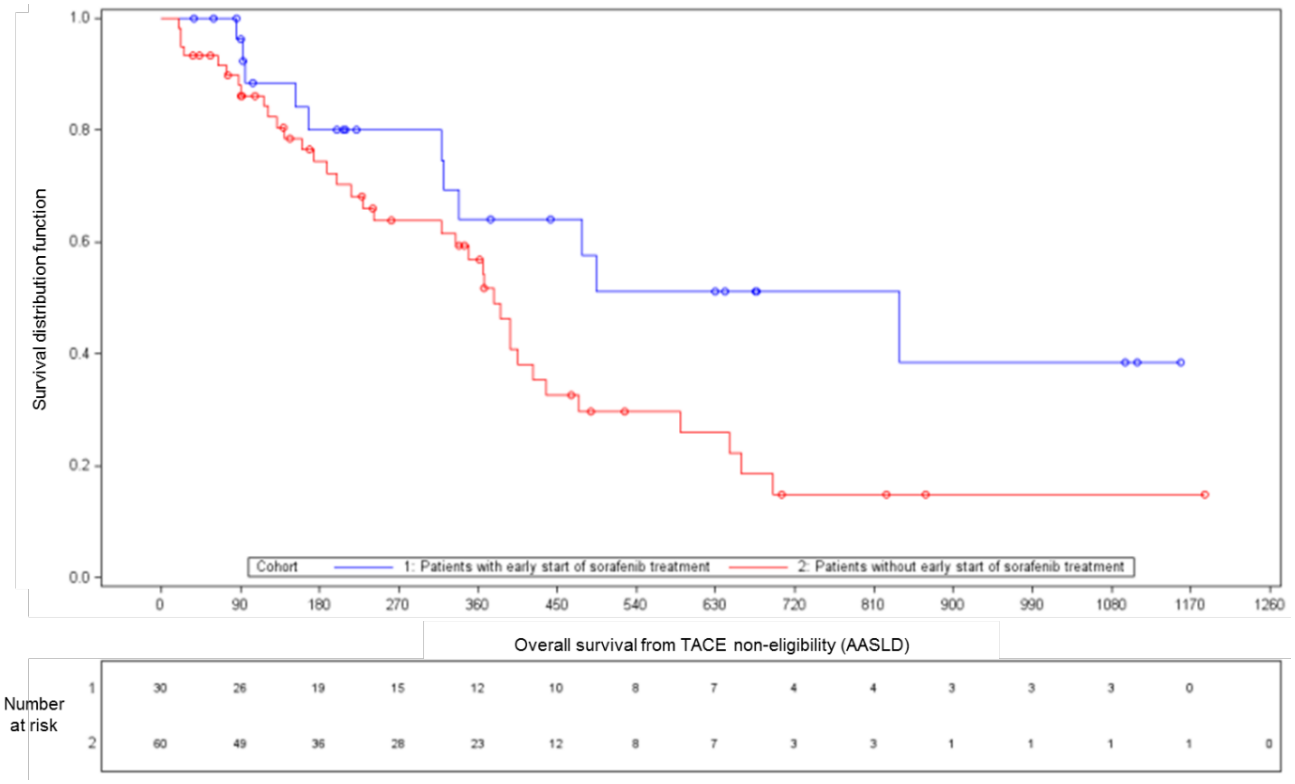

Figure 2: Kaplan-Meier curve of OS by cohort from TACE non-eligibility for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on AASLD criteria)
Note: the population was denoted "TNE2" in the statistical output.
TACE: transarterial chemoembolization
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Figure 14.1.2/1

[2] * presents censored observation or unestimable value due to censored data

4.3 Criteria 3: Patients who became TACE non-eligible after initial TACE based on Child-Pugh criteria

4.3.1 Baseline Characteristics

Baseline characteristics for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on Child-Pugh criteria) are presented in Table 6 for the two cohorts of the unmatched and matched populations. In the unmatched populations, differences in the distribution of parameters between the cohorts were observed, with these differences reduced in most of the parameters in the matched population.

Table 6: Baseline characteristics for the unmatched and matched populations – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on Child-Pugh criteria)

	Unmatched Population N=416		Matched Population N=108	
	Cohort 1 N=46	Cohort 2 N=370	Cohort 1 N=36	Cohort 2 N=72
Region - n (%)				
China	1 (2.2%)	4 (1.1%)	0	1 (1.4%)
Japan	20 (43.5%)	68 (18.4%)	15 (41.7%)	24 (33.3%)
Korea	8 (17.4%)	82 (22.2%)	6 (16.7%)	22 (30.6%)
Other Asia	3 (6.5%)	86 (23.2%)	3 (8.3%)	10 (13.9%)
Europe / North America	14 (30.4%)	124 (33.5%)	12 (33.3%)	15 (20.8%)
Central / South America	0	6 (1.6%)	0	0
Sex - n (%)				
Male	39 (84.8%)	308 (83.2%)	31 (86.1%)	63 (87.5%)
Female	7 (15.2%)	62 (16.8%)	5 (13.9%)	9 (12.5%)
Age group - n (%)				
<75 years	35 (76.1%)	304 (82.2%)	27 (75.0%)	54 (75.0%)
≥75 years	11 (23.9%)	66 (17.8%)	9 (25.0%)	18 (25.0%)
BCLC status at TNE[a] - n (%)				
Missing	2 (4.3%)	13 (3.5%)	0	0
0 (Very Early Stage)	0	7 (1.9%)	0	0
A (Early Stage)	0	30 (8.1%)	0	2 (2.8%)
B (Intermediate Stage)	13 (28.3%)	148 (40.0%)	13 (36.1%)	23 (31.9%)
C (Advanced Stage)	30 (65.2%)	129 (34.9%)	22 (61.1%)	40 (55.6%)
D (End-Stage)	1 (2.2%)	43 (11.6%)	1 (2.8%)	7 (9.7%)
Child-Pugh status at TNE[a] - n (%)				
Missing	1 (2.2%)	13 (3.5%)	0	0
A (5-6 Points)	40 (87.0%)	238 (64.3%)	31 (86.1%)	63 (87.5%)
B (7-9 Points)	5 (10.9%)	85 (23.0%)	5 (13.9%)	7 (9.7%)
C (10-15 Points)	0	34 (9.2%)	0	2 (2.8%)
Lesion size at TNE[a] - n (%)				
Missing	2 (4.3%)	6 (1.6%)	0	0
<3cm	21 (45.7%)	186 (50.3%)	18 (50.0%)	34 (47.2%)
3 - <5cm	9 (19.6%)	84 (22.7%)	6 (16.7%)	15 (20.8%)
5 - <10cm	11 (23.9%)	81 (21.9%)	10 (27.8%)	20 (27.8%)
≥10cm	3 (6.5%)	13 (3.5%)	2 (5.6%)	3 (4.2%)

	Unmatched Population N=416		Matched Population N=108	
	Cohort 1 N=46	**Cohort 2 N=370**	**Cohort 1 N=36**	**Cohort 2 N=72**
Number of lesions at TNE[a] - n (%)				
Missing	1 (2.2%)	3 (0.8%)	0	0
0	2 (4.3%)	31 (8.4%)	2 (5.6%)	4 (5.6%)
1	6 (13.0%)	93 (25.1%)	5 (13.9%)	6 (8.3%)
2-3	19 (41.3%)	111 (30.0%)	15 (41.7%)	21 (29.2%)
4-5	2 (4.3%)	61 (16.5%)	2 (5.6%)	13 (18.1%)
6-10	9 (19.6%)	37 (10.0%)	8 (22.2%)	15 (20.8%)
>10	7 (15.2%)	34 (9.2%)	4 (11.1%)	13 (18.1%)
ECOG at TNE[a,b] - n (%)				
Missing	2 (4.3%)	28 (7.6%)	0	2 (2.8%)
0	33 (71.7%)	241 (65.1%)	26 (72.2%)	53 (73.6%)
1	10 (21.7%)	66 (17.8%)	10 (27.8%)	13 (18.1%)
≥2	1 (2.2%)	35 (9.5%)	0	4 (5.6%)
Previous hepatectomy - n (%)				
Yes	9 (19.6%)	40 (10.8%)	6 (16.7%)	11 (15.3%)
No	37 (80.4%)	330 (89.2%)	30 (83.3%)	61 (84.7%)
Number of TACE before TNE - n (%)				
1	17 (37.0%)	191 (51.6%)	13 (36.1%)	26 (36.1%)
2	10 (21.7%)	93 (25.1%)	8 (22.2%)	19 (26.4%)
>2	19 (41.3%)	86 (23.2%)	15 (41.7%)	27 (37.5%)
Previous hepatectomy - n (%)				
Yes	9 (19.6%)	40 (10.8%)	6 (16.7%)	11 (15.3%)
No	37 (80.4%)	330 (89.2%)	30 (83.3%)	61 (84.7%)
Vascular invasion at TNE - n (%)				
Yes	7 (15.2%)	52 (14.1%)	5 (13.9%)	12 (16.7%)
No	39 (84.8%)	318 (85.9%)	31 (86.1%)	60 (83.3%)
Extrahepatic spread at TNE - n (%)				
Yes	16 (34.8%)	53 (14.3%)	9 (25.0%)	19 (26.4%)
No	30 (65.2%)	317 (85.7%)	27 (75.0%)	53 (73.6%)
Etiology - n (%)				
Hepatitis C				
Yes	19 (41.3%)	133 (35.9%)	14 (38.9%)	28 (38.9%)
No	27 (58.7%)	237 (64.1%)	22 (61.1%)	44 (61.1%)
Hepatitis B				
Yes	9 (19.6%)	105 (28.4%)	8 (22.2%)	19 (26.4%)
No	37 (80.4%)	265 (71.6%)	28 (77.8%)	53 (73.6%)
Alcohol Use				
Yes	17 (37.0%)	129 (34.9%)	14 (38.9%)	29 (40.3%)
No	29 (63.0%)	241 (65.1%)	22 (61.1%)	43 (59.7%)
Aflatoxin[b]				
Yes	0	0	0	0
No	46 (100%)	370 (100%)	36 (100%)	72 (100%)
Genetic / metabolic[b]				
Yes	0	7 (1.9%)	0	1 (1.4%)
No	46 (100%)	363 (98.1%)	36 (100%)	71 (98.6%)
NASH[b]				
Yes	5 (10.9%)	25 (6.8%)	3 (8.3%)	2 (2.8%)
No	41 (89.1%)	345 (93.2%)	33 (91.7%)	70 (97.2%)

	Unmatched Population N=416		Matched Population N=108	
	Cohort 1 N=46	**Cohort 2 N=370**	**Cohort 1 N=36**	**Cohort 2 N=72**
Primary biliary cirrhosis[b]				
Yes	0	0	0	0
No	46 (100%)	370 (100%)	36 (100%)	72 (100%)
Hepatitis D[b]				
Yes	0	2 (0.5%)	0	0
No	46 (100%)	368 (99.5%)	36 (100%)	72 (100%)
TNM classification at TNE[b] - n (%)				
Missing	2 (4.3%)	46 (12.4%)	1 (2.8%)	3 (4.2%)
STAGE I	0	36 (9.7%)	0	1 (1.4%)
STAGE II	14 (30.4%)	131 (35.4%)	13 (36.1%)	18 (25.0%)
STAGE III	7 (15.2%)	110 (29.7%)	7 (19.4%)	31 (43.1%)
STAGE IV	23 (50.0%)	47 (12.7%)	15 (41.7%)	19 (26.4%)
Time from initial TACE to TNE[b] - n (%)				
< 365 days	32 (69.6%)	268 (72.4%)	24 (66.7%)	46 (63.9%)
≥ 365 days	14 (30.4%)	102 (27.6%)	12 (33.3%)	26 (36.1%)

Note: the population was denoted “TNE3” in the statistical output.
[a] Last non-missing value prior time of TACE non-eligibility.
[b] Covariate not selected for final propensity score model.
BCLC: Barcelona Clinic Liver Cancer, Cohort 1: patients with early start of sorafenib treatment after TACE, Cohort 2: patients without early start of sorafenib treatment after TACE, ECOG: Eastern Co-operative Oncology Group, n: number of patients, NASH: non-alcoholic steatohepatitis, TACE: transarterial chemoembolization, TNE: TACE non-eligibility, TNM: Tumor, Nodes (lymph nodes) and Metastases (Classification)
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Table 14.1.3/1 and Table 14.1.3/2

4.3.2 OS

Of patients from the matched population who became TACE non-eligible after initial TACE (TACE non-eligibility based on Child-Pugh criteria), those from cohort 1 (with early start of sorafenib treatment based on the investigators' treatment decisions) had a median OS of 19.3 months (95% CI: 12.0;*[3] months) / 588 days (95% CI: 365;*[3] days). Cohort 2 patients (those without early start of sorafenib treatment) had a median OS of 13.0 months (95% CI: 8.8;22.4 months) / 396 days (95% CI: 267;681 days). The Kaplan-Meier curve is shown in Figure 3.

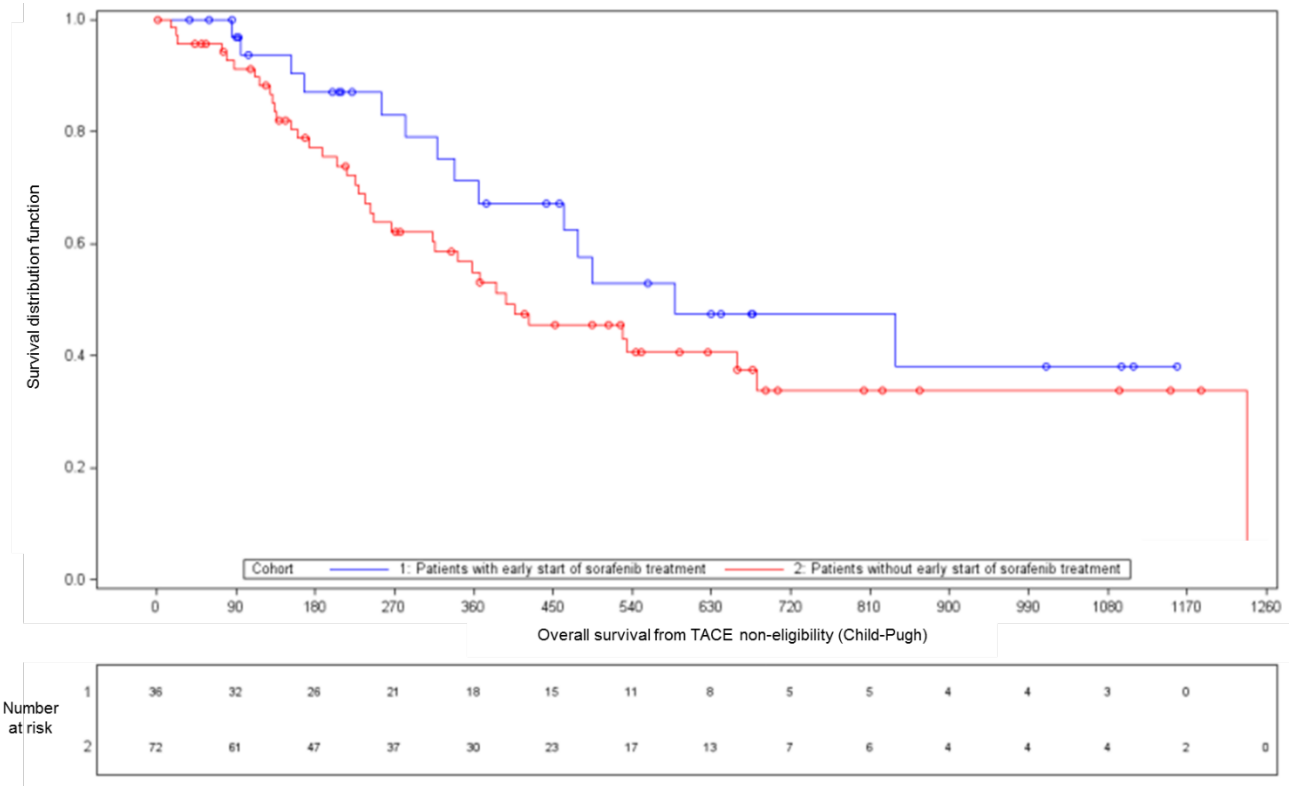

Figure 3: Kaplan-Meier curve of OS by cohort from TACE non-eligibility for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on Child-Pugh criteria)
Note: the population was denoted "TNE3" in the statistical output.
TACE: transarterial chemoembolization
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Figure 14.1.3/1

[3] * presents censored observation or unestimable value due to censored data

4.4 Criteria 4: Patients who became TACE non-eligible after initial TACE based on JSH criteria

4.4.1 Baseline Characteristics

Baseline characteristics for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on JSH criteria) are presented in Table 7 for the two cohorts of the unmatched and matched populations. In the unmatched populations, differences in the distribution of parameters between the cohorts were observed, with these differences reduced in most of the parameters in the matched population.

Table 7: Baseline characteristics for the unmatched and matched populations – Patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on JSH criteria)

	Unmatched Population N=391		Matched Population N=93	
	Cohort 1 N=45	**Cohort 2 N=346**	**Cohort 1 N=31**	**Cohort 2 N=62**
Region - n (%)				
China	1 (2.2%)	11 (3.2%)	1 (3.2%)	3 (4.8%)
Japan	16 (35.6%)	54 (15.6%)	10 (32.3%)	17 (27.4%)
Korea	5 (11.1%)	67 (19.4%)	3 (9.7%)	10 (16.1%)
Other Asia	4 (8.9%)	82 (23.7%)	4 (12.9%)	6 (9.7%)
Europe / North America	19 (42.2%)	126 (36.4%)	13 (41.9%)	24 (38.7%)
Central / South America	0	6 (1.7%)	0	2 (3.2%)
Sex - n (%)				
Male	38 (84.4%)	292 (84.4%)	27 (87.1%)	53 (85.5%)
Female	7 (15.6%)	54 (15.6%)	4 (12.9%)	9 (14.5%)
Age group - n (%)				
<75 years	33 (73.3%)	282 (81.5%)	23 (74.2%)	47 (75.8%)
≥75 years	12 (26.7%)	64 (18.5%)	8 (25.8%)	15 (24.2%)
BCLC status at TNE[a] - n (%)				
Missing	2 (4.4%)	13 (3.8%)	0	0
0 (Very Early Stage)	0	9 (2.6%)	0	0
A (Early Stage)	1 (2.2%)	32 (9.2%)	1 (3.2%)	6 (9.7%)
B (Intermediate Stage)	13 (28.9%)	154 (44.5%)	13 (41.9%)	28 (45.2%)
C (Advanced Stage)	28 (62.2%)	89 (25.7%)	16 (51.6%)	20 (32.3%)
D (End-Stage)	1 (2.2%)	49 (14.2%)	1 (3.2%)	8 (12.9%)
Child-Pugh status at TNE[a] - n (%)				
Missing	1 (2.2%)	10 (2.9%)	0	0
A (5-6 Points)	35 (77.8%)	221 (63.9%)	23 (74.2%)	50 (80.6%)
B (7-9 Points)	9 (20.0%)	85 (24.6%)	8 (25.8%)	8 (12.9%)
C (10-15 Points)	0	30 (8.7%)	0	4 (6.5%)
Lesion size n at TNE[a] - n (%)				
Missing	1 (2.2%)	6 (1.7%)	0	0
<3cm	17 (37.8%)	158 (45.7%)	14 (45.2%)	30 (48.4%)
3 - <5cm	11 (24.4%)	81 (23.4%)	6 (19.4%)	14 (22.6%)
5 - <10cm	12 (26.7%)	78 (22.5%)	9 (29.0%)	15 (24.2%)
≥10cm	4 (8.9%)	23 (6.6%)	2 (6.5%)	3 (4.8%)

	Unmatched Population N=391		Matched Population N=93	
	Cohort 1 N=45	**Cohort 2 N=346**	**Cohort 1 N=31**	**Cohort 2 N=62**
Number of lesions at TNE[a] - n (%)				
Missing	0	1 (0.3%)	0	0
0	2 (4.4%)	28 (8.1%)	2 (6.5%)	7 (11.3%)
1	8 (17.8%)	86 (24.9%)	5 (16.1%)	14 (22.6%)
2-3	18 (40.0%)	106 (30.6%)	13 (41.9%)	15 (24.2%)
4-5	5 (11.1%)	59 (17.1%)	3 (9.7%)	7 (11.3%)
6-10	5 (11.1%)	36 (10.4%)	4 (12.9%)	8 (12.9%)
>10	7 (15.6%)	30 (8.7%)	4 (12.9%)	11 (17.7%)
ECOG at TNE[a,b] - n (%)				
Missing	2 (4.4%)	24 (6.9%)	0	2 (3.2%)
0	27 (60.0%)	207 (59.8%)	20 (64.5%)	43 (69.4%)
1	13 (28.9%)	68 (19.7%)	10 (32.3%)	13 (21.0%)
≥2	3 (6.7%)	47 (13.6%)	1 (3.2%)	4 (6.5%)
Previous hepatectomy – n (%)				
Yes	7 (15.6%)	36 (10.4%)	4 (12.9%)	10 (16.1%)
No	38 (84.4%)	310 (89.6%)	27 (87.1%)	52 (83.9%)
Number of TACE before TNE - n (%)				
1	21 (46.7%)	178 (51.4%)	15 (48.4%)	30 (48.4%)
2	7 (15.6%)	89 (25.7%)	6 (19.4%)	13 (21.0%)
>2	17 (37.8%)	79 (22.8%)	10 (32.3%)	19 (30.6%)
Vascular invasion at TNE - n (%)				
Yes	11 (24.4%)	70 (20.2%)	7 (22.6%)	16 (25.8%)
No	34 (75.6%)	276 (79.8%)	24 (77.4%)	46 (74.2%)
Extrahepatic spread at TNE - n (%)				
Yes	24 (53.3%)	71 (20.5%)	12 (38.7%)	22 (35.5%)
No	21 (46.7%)	275 (79.5%)	19 (61.3%)	40 (64.5%)
Etiology - n (%)				
Hepatitis C				
Yes	16 (35.6%)	124 (35.8%)	11 (35.5%)	23 (37.1%)
No	29 (64.4%)	222 (64.2%)	20 (64.5%)	39 (62.9%)
Hepatitis B				
Yes	6 (13.3%)	97 (28.0%)	6 (19.4%)	10 (16.1%)
No	39 (86.7%)	249 (72.0%)	25 (80.6%)	52 (83.9%)
Alcohol Use				
Yes	18 (40.0%)	119 (34.4%)	11 (35.5%)	26 (41.9%)
No	27 (60.0%)	227 (65.6%)	20 (64.5%)	36 (58.1%)
Aflatoxin[b]				
Yes	0	0	0	0
No	45 (100%)	346 (100%)	31 (100%)	62 (100%)
Genetic / metabolic[b]				
Yes	1 (2.2%)	8 (2.3%)	1 (3.2%)	1 (1.6%)
No	44 (97.8%)	338 (97.7%)	30 (96.8%)	61 (98.4%)
NASH[b]				
Yes	5 (11.1%)	24 (6.9%)	3 (9.7%)	8 (12.9%)
No	40 (88.9%)	322 (93.1%)	28 (90.3%)	54 (87.1%)
Primary biliary cirrhosis[b]				
Yes	0	0	0	0
No	45 (100%)	346 (100%)	31 (100%)	62 (100%)

	Unmatched Population N=391		Matched Population N=93	
	Cohort 1 N=45	**Cohort 2 N=346**	**Cohort 1 N=31**	**Cohort 2 N=62**
Hepatitis D[b]				
Yes	0	2 (0.6%)	0	0
No	45 (100%)	344 (99.4%)	31 (100%)	62 (100%)
TNM classification at TNE[b] - n (%)				
Missing	4 (8.9%)	49 (14.2%)	3 (9.7%)	4 (6.5%)
STAGE I	1 (2.2%)	33 (9.5%)	0	4 (6.5%)
STAGE II	12 (26.7%)	117 (33.8%)	11 (35.5%)	25 (40.3%)
STAGE III	8 (17.8%)	102 (29.5%)	7 (22.6%)	16 (25.8%)
STAGE IV	20 (44.4%)	45 (13.0%)	10 (32.3%)	13 (21.0%)
Time from initial TACE to TNE[b] - n (%)				
< 365 days	35 (77.8%)	257 (74.3%)	24 (77.4%)	45 (72.6%)
≥ 365 days	10 (22.2%)	89 (25.7%)	7 (22.6%)	17 (27.4%)

Note: the population was denoted “TNE4” in the statistical output.
[a] Last non-missing value prior time of TACE non-eligibility.
[b] Covariate not selected for final propensity score model.
BCLC: Barcelona Clinic Liver Cancer, Cohort 1: patients with early start of sorafenib treatment after TACE, Cohort 2: patients without early start of sorafenib treatment after TACE, ECOG: Eastern Co-operative Oncology Group, n: number of patients, NASH: non-alcoholic steatohepatitis, TACE: transarterial chemoembolization, TNE: TACE non-eligibility, TNM: Tumor, Nodes (lymph nodes) and Metastases (Classification)
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Table 14.1.4/1 and Table 14.1.4/2

4.4.2 OS

Of patients from the matched population who became TACE non-eligible after initial TACE (TACE non-eligibility based on JSH criteria), those from cohort 1 (with early start of sorafenib treatment based on the investigators' treatment decisions) had a median OS of 15.2 months (95% CI: 5.4;27.6 months) / 462 days (95% CI: 164;839 days). Cohort 2 patients (those without early start of sorafenib treatment) had a median OS of 11.8 months (95% CI: 7.4;13.4 months) / 360 days (95% CI: 226;407 days). The Kaplan-Meier curve is shown in Figure 4.

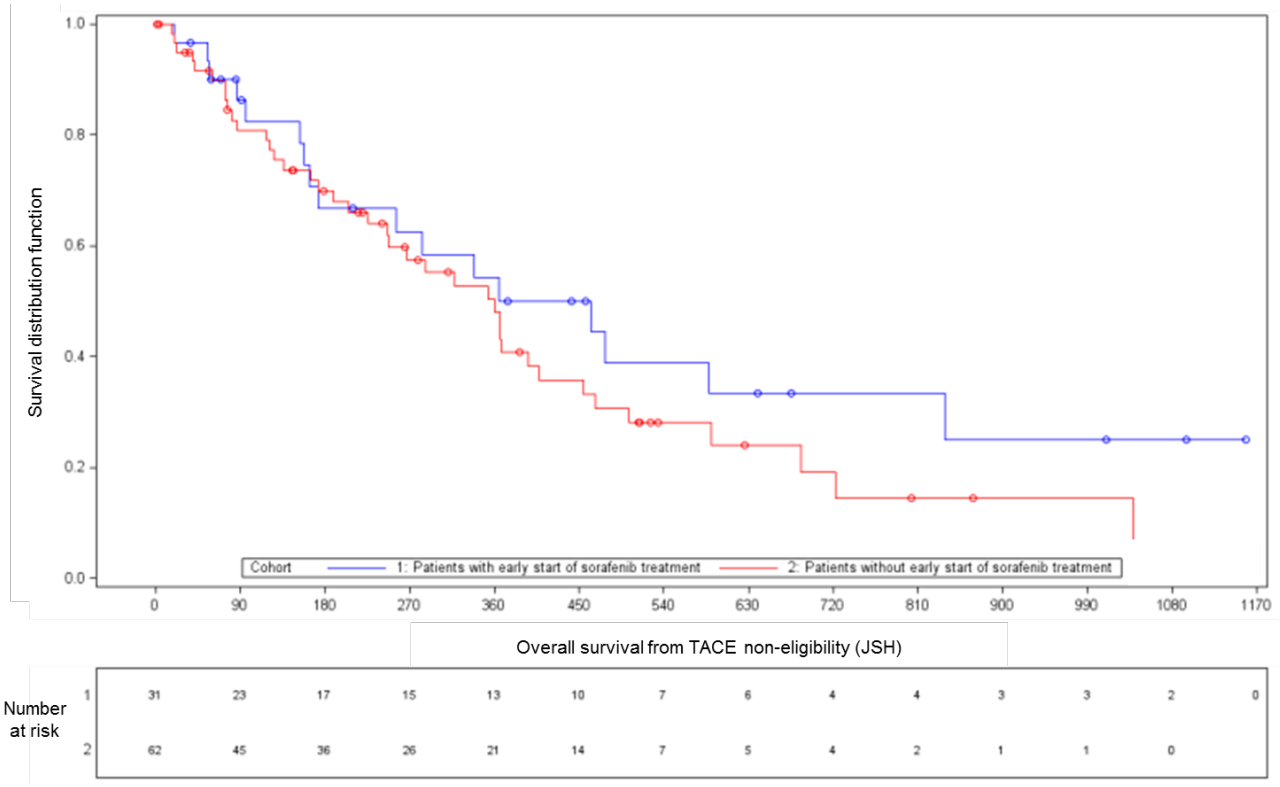

Figure 4: Kaplan-Meier curve of OS by cohort from TACE non-eligibility for patients who became TACE non-eligible after initial TACE (TACE non-eligibility based on JSH criteria)
Note: the population was denoted "TNE4" in the statistical output.
TACE: transarterial chemoembolization
Source: 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Figure 14.1.4/1

5. Summary of OS of the four criteria for the unmatched and matched populations

The analysis of OS described in this addendum is summarized in Table 8 (matched populations). For completeness, the reference to the results out of the main analysis (unmatched populations) is given.

Table 8: Summary of OS over the different criteria

	Unmatched Populations			Matched Populations		
Cohort	**N**	**Number failed**	**OS median [95% CI] (months)**	**N**	**Number failed**	**OS median [95% CI] (months)**
Criteria 1: Protocol specified						
Total	507	227 (44.8%)	19.4 [15.6 ; 22.8]	93	46 (49%)	15.2 [11.2; 22.4]
Cohort 1	47	21 (44.7%)	16.2 [10.5 ; *]	31	15 (48%)	16.2 [10.5 ; *]
Cohort 2	460	206 (44.8%)	19.9 [15.6 ; 23.4]	62	31 (50%)	12.1 [10.2 ; 22.4]
Criteria 2: AASLD based						
Total	338	178 (52.7%)	12.4 [10.5 ; 13.9]	90	47 (52%)	13.1 [11.1 ; 16.2]
Cohort 1	46	18 (39.1%)	16.2 [10.5 ; *]	30	11 (37%)	27.6 [10.6 ; *]
Cohort 2	292	160 (54.8%)	12.1 [10.3 ; 13.6]	60	36 (60%)	12.4 [8.0 ; 13.9]
Criteria 3: Child Pugh based						
Total	416	201 (48.3%)	14.3 [12.7 ; 18.2]	108	52 (48%)	15.7 [11.8 ; 22.4]
Cohort 1	46	19 (41.3%)	19.3 [11.1 ; *]	36	14 (39%)	19.3 [12.0 ; *]
Cohort 2	370	182 (49.2%)	13.6 [12.3 ; 17.6]	72	38 (53%)	13.0 [8.8 ; 22.4]
Criteria 4: JHS based						
Total	391	204 (52.2%	13.3 [11.7 ; 15.7]	93	56 (60%)	12.0 [8.4 ; 15.2]
Cohort 1	45	24 (53.3%)	11.1 [7.0 ; 27.6]	31	17 (55%)	15.2 [5.4 ; 27.6]
Cohort 2	346	180 (52.0%)	13.3 [11.7 ; 16.8]	62	39 (63%)	11.8 [7.4 ; 13.4]

AASLD: American Association for the Study of Liver Diseases, CI: confidence interval, Cohort 1: patients with early start of sorafenib treatment after TACE, Cohort 2: patients without early start of sorafenib treatment after TACE, JSH: Japan Society of Hepatology, N: number of patients, OS: overall survival, TACE: transarterial chemoembolization
Source: 16560_OPTIMIS_TLF_V1.2_2018-05-17, Table 14.2/1, Table 14.2/4, Table 14.2/7, Table 14.2/10 and 16560_OPTIMIS_FA_ADD_B1_2018-05-07, Table 14.1.1 / 3, Table 14.1.2 / 3, Table 14.1.3 / 3, Table 14.1.4 / 3

6. Discussion

The different criteria determining TACE non-eligibility might define a patient as TACE non-eligible at a different point in time, which has not only an impact on the covariate value, used for the propensity score model, but also on length of OS from time of TACE-non-eligibility. This results in different matched populations (especially differences in patient selection for cohort 2) as well as in different length of OS in the matched populations.

The same propensity score model was applied for all of the 4 different populations. Covariate selection separately for each of the four populations could have resulted in other propensity score

models and therefore in differences in the estimated propensity scores as well as in the matched populations.

The generalizability of the results is questionable, not only because of the purely descriptive nature of this additional exploratory analysis, but also because of the remaining number of patients due to the poor overlap between the two cohorts of interest. This poor overlap results in limited number of matched patients, as well as not perfectly balanced cohorts after matching. Approximately 1/3 of patients from cohort 1 were lost as no match from cohort 2 was found. Also, bias might have been introduced as a high number of missing values in many parameters was observed.

In addition, a general limitation of the propensity score method is that if there are important covariates that are not measured and/or used in the estimation of the propensity score, then there is residual bias, which needs to be taken into account when interpreting analyses utilizing propensity scores.

7. References

1 Parsons LS. Performing a 1:N Case-Control Match on Propensity Score. SUGI 29 Proceedings: SAS Users Group International Conference, May 9-12, 2004, Palais Des Congrès de Montréal, Montréal, Canada. Paper 165-29.

Annex 1: List of stand-alone documents

Document Name	**Final version and date (if available)**
Statistical Specification	27-AUG-2018
Statistical output 16560_OPTIMIS_FA_ADD_B1_2018-05-07	07 MAY 2018
Statistical output 16560_OPTIMIS_TLF_V1.2_2018-05-17	17 MAY 2018
Optimis_Addendum_stat_attachment_20181001	01 OCT 2018