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► To cite this version:

Helena Pereira, Mohamed Bouattour, Marco Burgio, Eric Assenat, Jules Grégory, et al.. Health-related quality of life in locally advanced hepatocellular carcinoma treated by either radioembolisation or sorafenib (SARAH trial). *European Journal of Cancer*, 2021, 154, pp.46-56. 10.1016/j.ejca.2021.05.032 . hal-03617608

HAL Id: hal-03617608

<https://hal.science/hal-03617608>

Submitted on 2 Aug 2023

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TITLE PAGE

Title

Health-related quality of life in locally advanced hepatocellular carcinoma treated by either radioembolisation or sorafenib (SARAH trial)

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Keywords

Health-related quality of life, hepatocellular carcinoma, transarterial radioembolisation, Sorafenib.

Electronic word count: 5313

Number of figures and tables: 5

Conflict of interest statement

Valérie Vilgrain reports research grants and personal fees from Sirtex during the conduct of the study. Mohamed Bouattour reports personal fees from Bayer Pharma, Sirtex Medical, Eisai, Roche, AstraZeneca and BMS, outside the submitted work. Jean-Pierre Bronowicki reports personal fees from Bayer, outside the submitted work. The remaining authors have no conflict of interests.

Financial support statement

This study was sponsored by Assistance Publique-Hôpitaux de Paris and was funded by Sirtex Medical, Sydney, Australia. Neither the sponsor nor the funder of the study had any role in study design, data collection, data analysis, or data interpretation, and none of the authors are employees or consultants for this industry. All authors had access to the study data, had control of the data and the information submitted for publication, and approved the final manuscript. Detailed disclosures of the SARAH trial group have been published in the SARAH princeps trial.

Authors' contributions

Valérie Vilgrain was the Coordinating Investigator for the SARAH trial and made substantial contributions to the conception and design of the SARAH trial and participated in collection, analysis, and interpretation of data, and writing and revision of the manuscript. Helena Pereira was the study statistician responsible for the statistical analyses and participated in the analysis, and

interpretation of data, and writing and revision of the manuscript. Gilles Chatellier was the methodologist of the SARAH trial and made substantial contributions to the conception and design of the trial and participated in the analysis, and interpretation of data, and writing and revision of the manuscript. Mohamed Bouattour, Eric Assenat and Jean-Pierre Bronowicki participated in collection, analysis and interpretation of data, and in writing and revision of the manuscript. Marco Dioguardi Burgio and Jules Grégory participated in interpretation of data, and in writing and revision of the manuscript.

Clinical trial number

ClinicalTrials.gov: NCT01482442

ABSTRACT

Background and aims

The aim of this ancillary study of the SARAH trial was to compare health-related quality of life (HRQoL) in patients with locally advanced or inoperable hepatocellular carcinoma (HCC) treated with transarterial radioembolisation (TARE) or sorafenib.

Methods

This study included randomised patients who received either TARE or at least one dose of sorafenib with no major deviation in the protocol and who had at least one quality of life (QoL) follow-up assessment in addition to the baseline evaluation. QoL was assessed from the date of randomisation using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, until disease progression or other reasons for stopping study participation. Data were analysed using linear mixed and time-dependent models.

Results

A total of 285 patients were included (122 and 163, in the TARE and sorafenib groups, respectively). Questionnaire completion rates were similar (77.5% vs. 80.4%, in the TARE and sorafenib groups, respectively, $p=0.25$). Longitudinal HRQoL analysis showed a significant treatment and time effects for fatigue and global health status, and significant treatment, time and treatment by time interaction effects for appetite loss, diarrhoea and social functioning. The median time to deterioration for the global health status was 3.9 months (95% CI: 3.7 to 4.3) vs. 2.6 months (95% CI: 2.0 to 3.0) in the TARE and sorafenib groups, respectively.

Conclusions

HRQoL was preserved longer with TARE than with sorafenib in locally advanced HCC. These data could be used to optimise management of patients with advanced or inoperable HCC.

Electronic word count of the abstract: 250

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the second leading cause of cancer-related death worldwide. An estimated 841,000 new HCCs and 782,000 deaths occurred in 2018.¹ Although all guidelines recommend surveillance programs in at-risk populations, HCC is usually diagnosed at intermediate or advanced stages, which often prevents curative treatment. The prognosis of patients with HCC in palliative care is poor. Systemic treatments are proposed to patients with advanced or progressive HCC following curative or loco-regional therapies.

Until recently, sorafenib, an oral multikinase inhibitor, has been the standard first-line systemic therapy in patients with advanced HCC (Barcelona Clinic Liver Cancer [BCLC] stage C) because it increased overall survival compared to placebo in phase II and phase III trials.²⁻⁴ Nevertheless, adverse events such as diarrhoea, fatigue or hand-and-foot syndrome are frequently observed, altering patient quality of life (QoL). Other systemic treatments including another multikinase inhibitor (lenvatinib) or the association of atezolizumab and bevacizumab have shown similar or better overall survival compared to sorafenib.^{5,6} These systemic treatments also have significant side effects.

Transarterial radioembolisation (TARE) with yttrium-90 (⁹⁰Y) provides targeted delivery of high-dose beta radiation to the liver tumours. TARE has been compared to sorafenib for HCC in two randomized controlled trials, SARAH⁷ and SIRveNIB⁸, which did not demonstrate superiority in overall survival with TARE compared to sorafenib. Nevertheless, patient tolerance and tumour responses were significantly better with TARE than with sorafenib. Furthermore, a recent individual patient meta-analysis pooling SARAH, SIRveNIB, and SORAMIC⁹ showed that TARE was non-inferior to sorafenib for overall survival, suggesting that TARE was an excellent alternative to systemic treatment.

In addition to overall survival, health-related quality of life (HRQoL) is an important goal to assess the clinical benefit of treatment in this vulnerable population.¹⁰ In these patients with cirrhosis,

symptoms that could negatively affect QoL may be related to underlying disease, cancer progression or treatment side effects. Therefore, in addition to increased survival, HRQoL must be taken into consideration when determining treatment strategies.

At present there are no studies comparing HRQoL in patients with locally advanced inoperable HCC treated with TARE or sorafenib. This study reports the findings of an ancillary study of the SARA trial which compares HRQoL in patients treated with TARE and sorafenib using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.¹¹

METHODS

Patients

SARA is a multicentre, randomised, controlled trial performed in 25 centres in France (ClinicalTrials.gov: NCT01482442) between 2011 and 2015. The study was performed in accordance with the Declaration of Helsinki, approved by an ethics committee and complied with the provisions of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice (ICH-GCP). All patients provided written informed consent. The protocol and main results have been published.⁷

The present study reports the detailed results of HRQoL, a secondary endpoint, in the SARA trial. The main inclusion criteria for SARA were a diagnosis of either locally advanced HCC (BCLC stage C) with no extrahepatic disease⁷, new HCC not eligible for surgical resection, liver transplantation, or thermal ablation following previously cured hepatocellular carcinoma, or HCC that failed to respond to two unsuccessful rounds of transarterial chemoembolisation. Eligible patients were ≥ 18 years old, with a life expectancy >3 months, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and a Child-Pugh liver function class A or B score ≤ 7 . The main laboratory tests to assess eligibility were adequate haematological, renal, and hepatic function (including a total bilirubin $\leq 50\mu\text{mol/L}$, aspartate aminotransferase or alanine aminotransferase ≤ 5 times the upper limit of normal, and an international normalized ratio (INR)

≤1.5 in the absence of anticoagulant treatment). Full details of inclusion and exclusion criteria for SARAH are given in Supplementary Tables 1 and 2.

The study sample (QoL population) included all randomised patients who received either TARE or at least one dose of sorafenib with no major deviation in the protocol (per-protocol population of the SARAH trial)⁷ and with at least one follow-up assessment of QoL in addition to the baseline evaluation.

Assessment and outcomes

QoL was assessed using the EORTC QLQ-C30¹¹ questionnaire from the date of randomisation, until the date of disease progression or the date the patient discontinued participation in the study for another reason (e.g., toxicity, completion of the study follow-up period, second line treatment, or death).

The QLQ-C30 is a multidimensional, self-administered, cancer-specific questionnaire. The questionnaire includes five function domains: physical, role, emotional, cognitive, social, and a global QoL scale; three symptom domains: fatigue, nausea and vomiting, and pain, and five single-symptom items: dyspnoea, sleep, appetite, constipation and diarrhoea.

The possible responses for each item range from 1 to 4 except for two items evaluating the global QoL with a range of 1 to 7. The raw score for each functional domain and symptom items are subject to linear transformation to provide a score ranging from 0 to 100 (see appendix chapter 2 for more details). A high score in the functional scales and the global QoL scale of the EORTC QLQ-C30 represents a good level of functioning, while high scores in the symptom scales and single items of the EORTC QLQ-C30 correspond to more severe symptoms.

The questionnaires were given to patients at inclusion, 1 month, 3 months, and every 3 months until the end of the study.

QoL questionnaire completion rates were calculated at two levels. At the patient level, the completion rate was the number of completed questionnaires over the number of expected questionnaires during the entire patient follow-up. At the visit level, the completion rate was the

number of completed questionnaires at a given visit over the number of expected questionnaires at this visit.

To define the patient's QoL response, a 10-point change in the score from baseline was considered to be clinically relevant, based on previous studies.^{12,13} Thus, a patient was considered to have improvement in a functional domain or a symptom score if he/she reported ≥ 10 -point improvement from baseline at any of the time points after baseline. Conversely, in the absence of improvement as defined above, a patient was considered to have a worsened score if he/she reported a ≥ 10 -point decrease from baseline at any time point in QoL assessment. Patients who did not have 10-point changes from baseline during the QoL assessments were considered to be stable. The classification of a patient's QoL response in the symptom domains and single items as improved or worsened were reversed compared to the function domains.

If there was a 10-point decrease in the function domain or a 10-point increase in the symptom score from randomisation, the patient's QoL in that domain or for that symptom was considered to be deteriorated as of the time point the deterioration was first recorded. The event of deterioration was defined as a composite of the deteriorated QoL, disease progression or death. In patients with no recorded deterioration but with documented disease progression (PD) or who died, the date of PD or death was considered to be the date of deteriorated QoL. All other patients were censored at the date of the final QoL assessment. When using competing risk analysis, QoL deterioration was analysed as the event of interest and disease progression and death were treated as the competing events.

Statistical analysis

Analyses were performed in the QoL population. Baseline characteristics were compared between the TARE and sorafenib groups using the Student t-test for continuous variables and the Chi-square test or Fisher test for categorical variables.

A response analysis was performed between the two groups using the Chi-square test to compare the distribution of data in the three categories (improved, worsened and stable domain/item).

A linear mixed model was used to explore the overall impact of time and the potential interaction between treatment allocation and time (at inclusion and 1, 3, 6, 9 and 12 months after treatment initiation).

Time-to-deterioration analyses were performed for the global QoL scale and function domains (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning). Time-to-deterioration was analysed with a two-sided log-rank test, the hazard ratio (HR) with the two-sided 95% confidence interval (CI) based on a Cox proportional-hazards model and the associated Kaplan-Meier survival estimates. The proportional hazards assumption was assessed by testing the interaction between covariates and time.

Multivariate time-to-deterioration analysis was performed using a Cox proportional-hazards model and univariate analysis followed by a stepwise variable selection procedure (with a significance level of 0.2 when deciding to enter a predictor into the stepwise model).

Time-to deterioration was also analysed with a competing risk method. QoL deterioration was defined as the event of interest and radiographic disease progression and death, the competing events. The cumulative incidences of time-to-deterioration were compared with the Gray test.¹⁴

Treatment effect was estimated with the Fine and Gray model.¹⁵ Results are presented as subdistribution HRs and their 95% CIs.

A post-hoc subgroup analysis was performed in patients with macroscopic vascular invasion. SAS software version 9.4 was used for all analyses. A p value <0.05 was considered to be significant. No formal adjustment of p-values was made for the multiple testing.

RESULTS

Patient characteristics

Between December 2011 and March 2015, 380 out of 467 patients randomly assigned to the SARA trial were included in the per-protocol population (174 [45.8%] in the TARE group and 206 [54.2%] in the sorafenib group). A total of 285 patients were included in the QoL analysis (122

[42.8%] in the TARE group and 163 [57.2%] in the sorafenib group) after excluding 95 patients with no QoL assessment at baseline or follow-up (Figure 1). Median follow-up was 29.2 months (IQR 21.9–34.8) in the TARE group and 29.6 months (21.4–35.1) in the sorafenib group.

The two groups were well-balanced at baseline and no clinically relevant differences were observed between the groups (Table 1). There were statistically significant differences between patients excluded from the per-protocol population and those in our study sample for some known prognostic factors such Child-Pugh liver function ($p=0.045$), tumour burden $>25\%$ ($p=0.012$), and ALBI grade ($p=0.005$) (Supplementary Table 3). The median overall survival of the SARAH trial per-protocol population, was 9.9 months (95% CI 8.0–12.7) in the SIRT group versus 9.9 months (9.0–11.6) in the sorafenib group (HR 0.99 [95% CI 0.79–1.24]). Similar results were observed for the QOL population, HR 0.96 [95% CI 0.73–1.25].

Questionnaire completion rates

The questionnaire completion rates at the patient level were similar between the two groups (77.5% in the TARE group vs. 80.4% in the sorafenib group, $p=0.25$). One month after treatment initiation, the completion rate was 87.7% in the TARE group (107/122) vs. 89.0% in the sorafenib group (145/163). The completion rate declined comparably between the 2 groups at the following visits: 75.0%, 62.1%, 44.7% and 39.7% vs. 81.5%, 67.7%, 46.2% and 40.0%, respectively, 3, 6, 9 and 12 months after treatment initiation. The number of patients in the study decreased rapidly over time due to disease progression or death.

Longitudinal analysis

The mean baseline scores for the two treatment groups were similar for global health status, as well as all symptom and function domains except that emotional functioning was better in the TARE group than in the sorafenib group, 77.4 vs. 71.0 respectively, $p=0.024$ (Supplementary Table 4). Although there was a significant treatment effect ($p=0.006$), and a significant time effect ($p<0.0001$) on global health status, no treatment by time interaction was observed ($p=0.12$). A significant treatment effect, time effect and a treatment by time interaction effect was observed for

social functioning ($p < 0.0001$, $p < 0.0001$ and $p = 0.003$, respectively). A significant treatment effect, time effect and a treatment by time interaction effect was observed for the symptoms of appetite loss ($p < 0.0001$, $p < 0.0001$ and $p = 0.0002$, respectively) and diarrhoea ($p < 0.0001$, $p < 0.0001$ and $p < 0.0001$, respectively). There was a significant treatment effect ($p = 0.007$), and time effect ($p < 0.0001$) for fatigue. However, no treatment time interaction was observed ($p = 0.10$). The results for all the other domains are presented in Table 2. These results were similar for patients with macroscopic vascular invasion (Supplementary Table 5). Figure 2 illustrates the evolution in time of the mean scores for each treatment and for each domain.

Response analysis

The QoL-response analysis confirmed the above results. Thus, more patients reported worsening nausea and vomiting in the sorafenib group than in the TARE group (47.2% vs. 33.6%, $p = 0.012$, respectively), worsening appetite loss (69.1% vs. 41.0%, $p < 0.0001$, respectively) and worsening diarrhoea (70.8% vs. 26.4%, $p < 0.0001$). More patients in the sorafenib group complained of worsened social functioning than in the TARE group (66.5% vs. 46.7%, $p = 0.004$). There were no significant differences between the two groups for other function and symptom domains. These results were also observed in patients with macroscopic vascular invasion (data not shown).

Time-to-deterioration analysis

The median time to deterioration of global health status was 3.9 months (95% CI: 3.7 to 4.3) in the TARE group and 2.6 months (95% CI: 2.0 to 3.0) in the sorafenib group. The risk of deterioration was significantly lower in the TARE group than in the sorafenib group (HR 0.59 [95% CI 0.47 to 0.76]; $p < 0.0001$, respectively Figure 3A). The influence of clinical, laboratory and tumoural factors on deterioration on univariate Cox regression analysis is shown in Supplementary Table 6.

Multivariate analysis showed TARE treatment and tumour burden $\leq 25\%$ to be independent factors for a lower risk of deterioration of HRQoL (HR 0.61 [95% CI 0.48 to 0.78]; $p < 0.0001$ and HR 0.73 [95% CI 0.56 to 0.95]; $p = 0.019$, respectively, Supplementary Table 6 and supplementary Figure 1).

When disease progression and death were considered to be competing risks, the cumulative incidence of deteriorated QoL for global health status was significantly lower in the TARE group than in the sorafenib group (sub-distribution HR 0.64 [95% CI 0.48 to 0.87]; p=0.006; figure 3B). The risk of deterioration in physical, role and social functioning was also significantly lower in the TARE group than in the sorafenib group (Supplementary Figure 2). The median time to deterioration in global health status in patients with macroscopic vascular invasion was 3.9 months (95% CI: 3.6 to 4.3) in the TARE group vs. 2.3 months (95% CI: 1.6 to 3.0) in the sorafenib group. The risk of deterioration was also significantly lower in the TARE group than in the sorafenib group (HR 0.55 [95% CI 0.40 to 0.75]; p=0.0002).

DISCUSSION

The results of this multicentre randomised controlled trial (RCT) head-to-head comparison of TARE and sorafenib in locally advanced or inoperable HCC show that preservation of HRQoL was significantly better with TARE than sorafenib, and that the median time to deterioration was significantly longer in the TARE arm than the sorafenib arm. Although there was no difference in survival with the two treatments, the superiority of TARE in HRQoL confirms the importance of this treatment in locally advanced HCC treatment.

Assessment of HRQoL has become increasingly important in oncology and is critical in advanced diseases such as inoperable or advanced HCC. HRQoL metrics are now considered to be as important as overall survival when considering treatment strategies to optimize clinical benefit to patients.¹⁶⁻¹⁹

There are very few studies and no RCT reporting HRQoL in HCC patients treated with TARE. The present large study including patients with macrovascular invasion confirms that HRQoL was stable and even improved after TARE.²⁰⁻²²

There are more results in HCC patients treated with sorafenib. Two pivotal phase III trials (SHARP trial⁴ and the Asia-Pacific trial³) showed a benefit to overall and progression-free survival with first-

line sorafenib compared to placebo in patients with advanced HCC as well as significantly more frequent serious drug-related adverse events in the sorafenib arm than in the placebo arm.^{3,4} Studies on HRQoL have shown a significant decrease in QoL with sorafenib,^{23,24} in particular physical well-being scores. Our study also showed a decrease in HRQoL in longitudinal studies with marked and significant changes found one month after the initiation of treatment, especially diarrhoea, fatigue, appetite loss, and pain.

More importantly, our study provides a longitudinal comparison of HRQoL in patients treated with sorafenib and TARE. The questionnaire completion rate was approximately 80% per patient with no between-group difference, thus providing an unbiased comparison. Indeed, as observed in other studies,²⁵ the completion rate was higher at one month than later in the follow-up.

We observed a significant treatment effect, time effect and a treatment by time interaction effect for social functioning, appetite loss, and diarrhoea, and a significant treatment effect and time effect for global health status and fatigue in the TARE group, with worsening of HRQoL in these domains in patients in the sorafenib group. This highly important evaluation has never been performed in a published RCT. The only HRQoL data in patients treated with sorafenib or radioembolisation are from a global quality of life survey in HCC patients in which these were the most frequently used treatments.²⁶ In that survey, the time since the diagnosis of HCC was highly variable: one third of those who responded had been diagnosed with HCC less than one year before completing the survey, while one third had had HCC for 1–3 years. Moreover, there was no longitudinal evaluation of HRQoL. Their results are similar to ours, as HRQoL was more frequently rated poor in patients receiving sorafenib than in those treated with radioembolisation (42% vs. 22%). Also, 81% of patients whose most recent treatment was sorafenib reported a negative effect on their HRQoL, while 56% of those receiving TARE reported an improvement in their HRQoL.

All symptoms do not have the same influence on HRQoL. For example, fatigue has been shown to have a greater impact on HRQoL than appetite loss in HCC patients.²⁶ This shows the importance of using a questionnaire that evaluates symptoms, functional and global health HRQoL such as that

used in our study. This type of questionnaire allows researchers to show that the presence of severe diarrhoea, for example, may affect a patient's physical and social HRQoL scales.

Patients were asked to fill out the questionnaire at different time points (at inclusion, 1 and 3 months, and every 3 months after treatment initiation until study completion), which showed that in the sorafenib group most of the deterioration of HRQoL was observed one month after treatment initiation, while changes were minimal during follow-up for most scales in the TARE group. We also showed that time to deterioration was significantly longer in the TARE arm than in the sorafenib arm (3.9 months vs. 2.6 months, respectively) and we searched for other independent factors besides TARE with a lower risk of deterioration of HRQoL on multivariate analysis. The only significant variable identified besides TARE was tumour burden $\leq 25\%$. Time-to-event models such as the time to deterioration have recently been proposed in oncology.²⁷⁻²⁹ Both approaches (linear mixed model and time-to-deterioration model), measure different concepts and provide complementary ways of summarizing HRQoL data.²⁹ The definition of difference must be clinically meaningful. Like others, significant changes were defined in our study as a minimal 10-point difference from baseline in the function domains or the symptom scores.

Moreover, like in other oncological studies, we defined deterioration as a composite outcome that included a deterioration in QoL as well as radiographic disease progression or death.^{30,25} Finally, when death and disease progression were considered to be competing risks, the cumulative incidence of a deterioration in QoL was still significantly higher in the sorafenib group than in the TARE group.

The present study has several limitations. First, the evaluation of QoL is not standardised. In particular, several questionnaires are currently used in HCC patients: EORTC QLQ-C30, EORTC QLQ-HCC18, SF-36, FACT-Hep, FACT-TOI, EQ-5D, etc. We chose the EORTC QLQ-C30, which is one of the most commonly used in HCC patients treated either with locoregional or systemic treatment.³¹ We also excluded patients with no baseline or follow-up assessment of QoL, which may have influenced our estimates of HRQoL results since it excluded patients with the most

severe liver disease and the highest tumour burden. Nevertheless, patients in the TARE group included in the present study did not differ from those included in the sorafenib group. Third, the questionnaire completion rate and patient censoring due to death could influence results. However, this bias is probably minimal, because the survival and questionnaire completion rates were comparable in the 2 groups. This completion rate decreased over time, which is commonly observed in longitudinal HRQoL evaluations of severely ill patients.^{32,33}

In conclusion, this longitudinal evaluation of HRQoL in an ancillary SARAH study shows that the preservation of quality of life in patients treated with TARE was significantly better for both symptoms and function compared to that in patients receiving sorafenib. Moreover, the time to deterioration was significantly longer in the TARE arm than in the sorafenib arm. These data should play a role in defining the optimal treatment strategy in patients with locally advanced HCC.

ABBREVIATIONS

⁹⁰Y, yttrium-90; ALBI, albumin-bilirubin; BCLC, Barcelona clinic liver cancer; BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; HRQoL, health-related quality of life; INR, international normalized ratio; IQR, Interquartile range; PD, progression disease; QoL, quality of life; RCT, randomized controlled trial; SD, standard deviation; TACE, trans-arterial chemoembolization; TARE, transarterial radioembolisation.

ACKNOWLEDGEMENTS

We would like to thank Pascaline Aucouturier and Aurelia Dinut at the Clinical Research Unit, Hôpital européen Georges-Pompidou, for their help in managing the study. We would also like to thank all clinical research associates for data monitoring and data collection and to the clinical research technicians and nurses from each centre. We thank the patients, their caregivers, and the

investigators who participated in this study. The SARAH investigators are listed in the Supplementary Materials.

ETHICS APPROVAL

The present study was conducted in accordance with the Declaration of Helsinki, approved by an ethics committee (Ethics Approval N° 11051), and compliant with the provisions of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for good clinical practice. All patients provided written informed consent.

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TABLES

Table 1. Baseline characteristics of patients in the QoL analysis population.

Variables	TARE (n=122)	Sorafenib (n=163)	p-value
Median age, years	67 (61-72)	64 (57-71)	0.07
Sex			
Male	112 (92%)	149 (91%)	0.91
Female	10 (8%)	14 (9%)	
Mean BMI (kg/m ²)	27.2 (5.2)	27.7 (4.8)	0.41
Cirrhosis	109 (89.3%)	147 (90.2%)	0.82
Cause of disease*			
Alcohol	81 (66.4%)	97 (59.5%)	0.16
Hepatitis C virus	22 (18.0%)	35 (21.5%)	0.48
Hepatitis B virus	4 (3.3%)	8 (4.9%)	0.57
Non-alcoholic steatohepatitis	27 (22.1%)	43 (26.4%)	0.48
Other	12 (9.8%)	16 (9.8%)	0.98
Unknown	12 (9.8%)	15 (9.2%)	0.86
ECOG performance status			0.74
0	74 (60.7%)	102 (62.6%)	
1	48 (39.3%)	61 (37.4%)	
BCLC stage			0.65
A	5 (4.1%)	7 (4.3%)	
B	38 (31.1%)	43 (26.4%)	
C	79 (64.8%)	113 (69.3%)	
Child-Pugh liver function class			0.34
A5 + A6	105 (86.1%)	148 (90.8%)	
B7	16 (13.1%)	15 (9.2%)	

Unknown	1 (0.8%)	0 (0.0%)	
Unsuccessful TACE†	65 (53.3%)	73 (44.8%)	0.16
Tumor number			0.38
Single	58 (47.5%)	69 (42.3%)	
Multiple	64 (52.5%)	94 (57.7%)	
Tumor Involvement			0.18
Unilobar	94 (77.0%)	136 (83.4%)	
Bilobar	28 (23.0%)	27 (16.6%)	
Median tumor burden	14.0 (6.0-25.0)	15.0 (5.0-30.0)	0.73
Tumor burden >25%	30 (24.6%)	48 (29.4%)	0.36
Tumor differentiation			0.52
No biopsy	71 (58.2%)	98 (60.1%)	
Poorly differentiated	4 (3.3%)	7 (4.3%)	
Moderately differentiated	22 (18.0%)	20 (12.3%)	
Well differentiated	20 (16.4%)	28 (17.2%)	
Not assessable	5 (4.1%)	10 (6.1%)	
Macroscopic vascular invasion‡	74 (60.7%)	91 (55.8%)	0.41
Portal venous invasion			0.59
Main portal vein	18/70 (25.7%)	25/84 (29.8%)	
Main portal branch (right or left)	33/70 (47.1%)	42/84 (50.0%)	
Segmental	19/70 (27.1%)	17/84 (20.2%)	
Pattern of occlusion in the main portal vein§			0.66
Complete	7/17 (41.2%)	12/25 (48.0%)	
Incomplete	10/17 (58.8%)	13/25 (52.0%)	
Laboratory values			

Mean total bilirubin (mg/dL)	1.0 (0.7)	1.0 (0.5)	0.68
Mean albumin (g/L)	36.7 (4.8)	37.0 (5.1)	0.64
ALBI grade			0.32
A1	36/117 (30.8%)	56/160 (35.0%)	
A2	80/117 (68.4%)	99/160 (61.9%)	
A3	1/117 (0.9%)	5/160 (3.1%)	
Median platelet count ($\times 10^3$ per mm ³)	152.0 (106.0-208.0)	136.0 (101.0-204.0)	0.48
Median INR	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.99
Median α -fetoprotein (ng/mL)	66.0 (11.0-942.0)	58.0 (8.0-668.0)	0.67

Data are median (IQR), mean (SD), or n (%), unless otherwise stated. QoL, quality of life. TARE, transarterial radioembolization. BMI, body-mass index. ECOG, Eastern Cooperative Oncology Group. BCLC, Barcelona Clinic Liver Cancer. TACE, trans-arterial chemoembolization. ALBI, albumin-bilirubin. INR, international normalized ratio.

*The same patient could have several causes of disease. †Some patients had both BCLC stage C and unsuccessful TACE (28 in the TARE group and 33 in the sorafenib group). ‡Some patients had hepatic venous invasion and no portal vein invasion (4 in the TARE group and 7 in the sorafenib group). § The pattern of portal vein occlusion was not assessable for one patient in the TARE group.

Table 2. Linear mixed modelling for interaction between treatment (TARE vs sorafenib) and time for global health status, functional scales and symptoms scales/items of the EORTC QLQC30 questionnaire.

Effect	Effect		
	Treatment	Time	Treatment x time
Global health status /			
QoL	0.006	<0.0001	0.12
Physical functioning	0.22	<0.0001	0.32
Role functioning	0.003	<0.0001	0.23
Emotional functioning	0.0004	0.94	0.26
Cognitive functioning	0.21	0.001	0.75
Social functioning	<0.0001	<0.0001	0.003
Fatigue	0.007	<0.0001	0.10
Nausea and vomiting	0.05	<0.0001	0.07
Pain	0.030	<0.0001	0.16
Dyspnea	0.30	0.003	0.12
Insomnia	0.70	0.40	0.66
Appetite loss	<0.0001	<0.0001	0.0002
Constipation	0.72	0.31	0.70
Diarrhoea	<0.0001	<0.0001	<0.0001
Financial difficulties	0.27	0.003	0.14

QoL, quality of life.

FIGURES LEGENDS

Fig. 1. Study profile.

TARE, transarterial radioembolization. QoL, quality of life.

Fig. 2. Longitudinal analysis of EORTC QLQC30 questionnaire for global QoL scale, functional domains, and symptom domains for the QoL population.

TARE, transarterial radioembolisation. QoL, quality of life. (A) Global QoL scale and functional domains: Physical, Role, Emotional, Cognitive, Social. A high score for the global health status / QoL represents a high QoL and a high score for a functional scale represents a high / healthy level of functioning. (B) Symptom domains: Fatigue, Nausea and Vomiting, and Pain, and single-symptom items: Dyspnoea, Sleep, Appetite, Constipation and Diarrhoea. A high score for a symptom scale / item represents a high level of symptomatology / problems.

Data are observed means (SD).

Fig. 3. Kaplan-Meier curves and cumulative incidence of deterioration of global QoL scale of the EORTC QLQ-C30 questionnaire for the QoL population.

(A) Kaplan-Meier curve for deterioration of global QoL scale. (B) Cumulative incidence for deterioration of Global QoL scale considering disease progression and death as competing risks. p values correspond to a log-rank test for part A, and to the Gray test for parts B. TARE, transarterial radioembolisation. QoL, quality of life.

380 Patients in the **per-protocol population** of the SARAH trial

174 patients treated with
TARE
(per-protocol population)

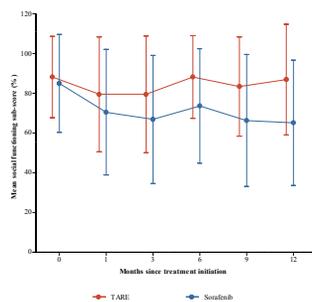
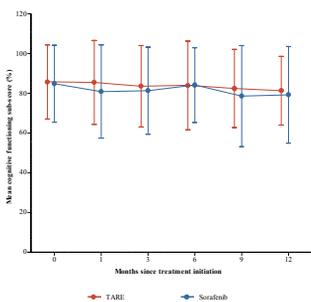
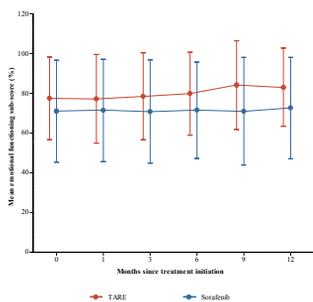
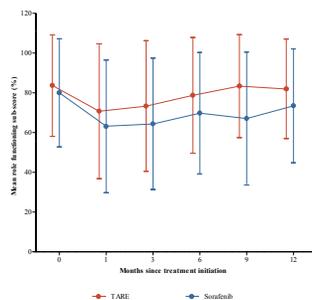
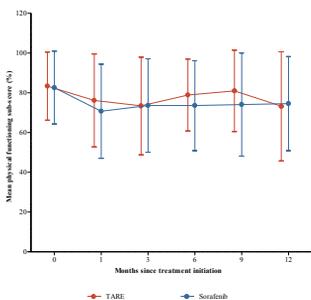
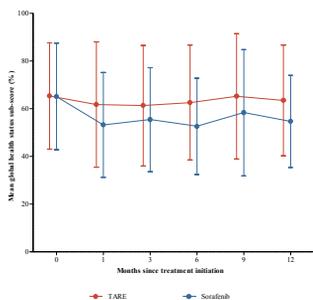
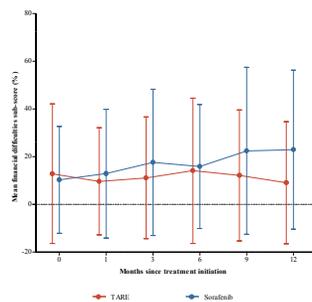
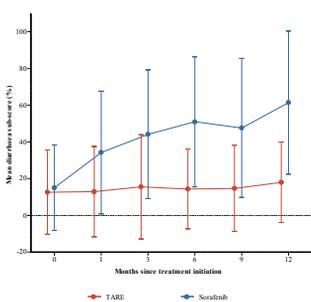
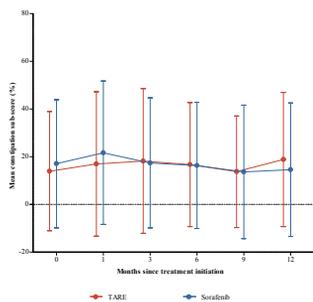
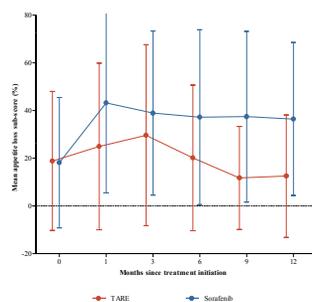
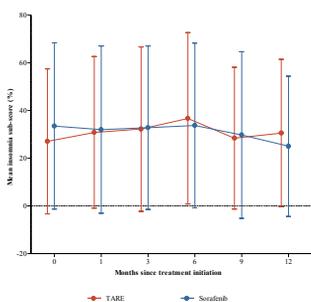
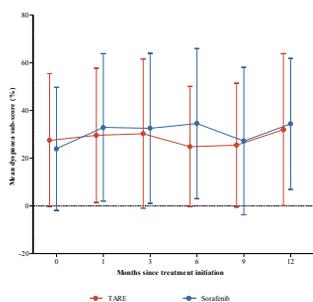
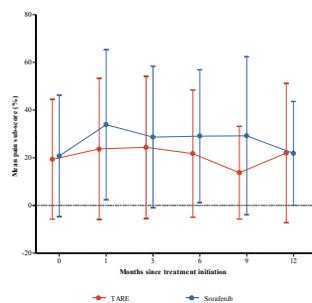
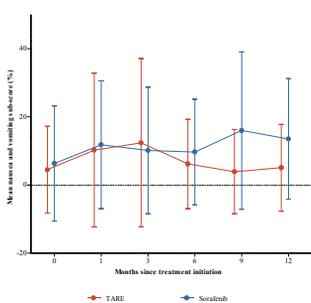
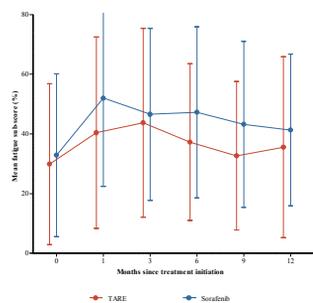
206 patients treated with
sorafenib
(per-protocol population)

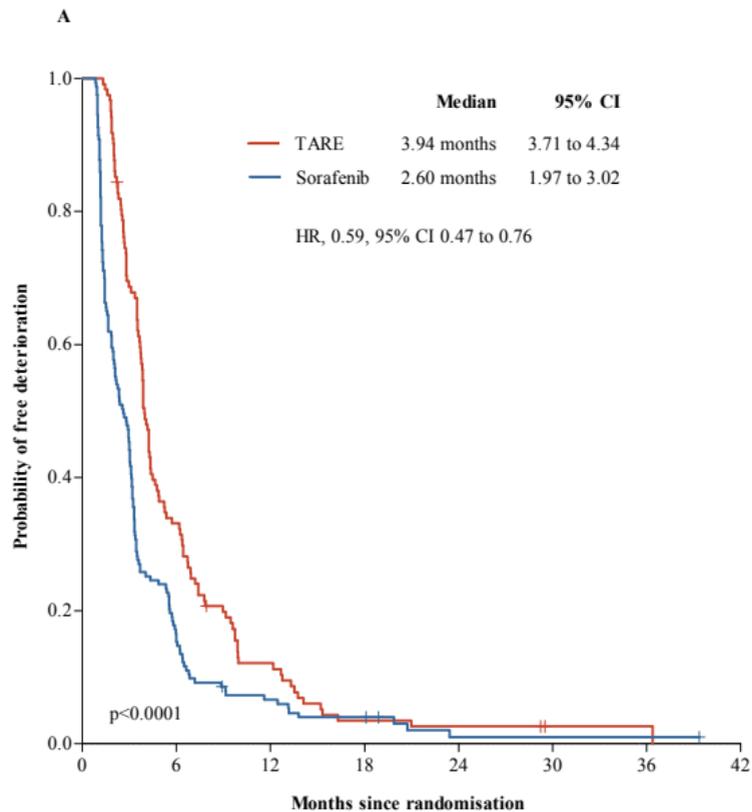
52 Excluded
24 no baseline assessment
of QOL
18 no follow-up assessment
of QOL
10 no baseline and follow-
up assessment of QOL

43 Excluded
13 no baseline assessment
of QOL
24 no follow-up assessment
of QOL
6 no baseline and follow-up
assessment of QOL

122 patients treated with
TARE with QOL assessment
(QOL population)

163 patients treated with
sorafenib with QOL
assessment
(QOL population)

A**B**



Number at risk (number censored)

TARE	122 (0)	40 (1)	14 (2)	4 (2)	3 (2)	1 (4)	1 (4)	0 (4)
Sorafenib	163 (0)	25 (0)	10 (1)	6 (1)	1 (3)	1 (3)	1 (3)	0 (4)

