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Cost-utility of TARE vs Sorafenib for HCC

Cost-utility analysis of transarterial radioembolization with yttrium-90 resin microspheres compared with Sorafenib in locally advanced and inoperable hepatocellular carcinoma

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## Cost-utility of TARE vs Sorafenib for HCC

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### **Authors' contributions**

KZ performed analyses, made substantial contributions to the conception and design of the economic protocol, to writing and revision of the manuscript.

MM collected economic data, performed analyses and made substantial contribution to the writing and revision of the manuscript.

IDZ was the Investigator for the SARA economic study and made substantial contributions to the conception and design of the economic protocol and participated in analysis and interpretation of data, and writing and revision of the manuscript.

VV was the Coordinating Investigator for the SARA trial and made substantial contributions to the conception and design of the SARA economic study and participated in the interpretation of data, and writing and revision of the manuscript.

GC was the methodologist of the SARA trial and participated in the interpretation of data, and writing and revision of the manuscript.

HP was the statistician of the SARA trial contributed to review and to the writing and revision of the manuscript.

## Cost-utility of TARE vs Sorafenib for HCC

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VV reports research grants and personal fees from Sirtex during the conduct of the RCT. All other authors declare no competing interests.

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# Cost-utility analysis of transarterial radioembolization with yttrium-90 resin microspheres compared with Sorafenib in locally advanced and inoperable hepatocellular carcinoma

## 1. Abstract

**Purpose:** The SARAH trial (clinicaltrials.gov, NCT01482442: Transarterial radioembolization with yttrium-90 resin microspheres compared with Sorafenib in locally advanced and inoperable hepatocellular carcinoma) did not show a significant survival benefit for patients treated with transarterial radioembolization (TARE) compared to continuous oral Sorafenib. The improved toxicity profile of patients with TARE in the trial however could result in a quality of life benefit in economic evaluations. Our objective was to perform a cost-utility analysis of TARE versus Sorafenib for locally advanced and inoperable hepatocellular carcinoma.

**Methods:** We used patient-level data of the SARAH trial on resource use, progression-free and overall survival and quality of life for the within-trial period for the patients who received at least one dose of Sorafenib or one treatment with TARE according to their randomization arm, and extrapolated by a partitioned survival model that incorporated costs and health outcomes, measured in life-years and quality-adjusted life-years (QALYs).

**Findings:** The use of TARE resulted in a mean loss of 0.036 Life Years and a gain of 0.006 QALYs compared to Sorafenib. The mean cost for the TARE arm was €17,179 (95% CI: 9,926-24,280) higher than Sorafenib arm, for an ICER of €3,153,086/QALY. The probabilistic sensitivity analysis showed a 50% risk that the TARE strategy was dominated. TARE was consistently dominated by Sorafenib or had an ICER over €450,000/QALY in all sensitivity analyses.

**Implications:** This economic evaluation of SARAH found that using radioembolization with yttrium 90 microspheres (Y90-RE) for the treatment of hepatocellular carcinoma was not a cost-effective option at the usually accepted willingness to pay thresholds.

## **2. Keywords**

cost-utility analysis, survival analysis, Sorafenib, Yttrium Radioisotopes, Hepatocellular Carcinoma

### **3. Introduction**

Based on phase 2 trials, American and European regulatory agencies approved radioembolization with yttrium 90 microspheres (Y90-RE) for the treatment of primary and secondary liver tumors.

The SARAH multicenter, open-label, randomized, controlled, investigator-initiated, phase 3 trial did not show a significant survival benefit for patients with advanced hepatocellular carcinoma treated by elective internal radiotherapy (TARE) with yttrium-90 resin microspheres (Y90-RE) compared to continuous oral Sorafenib (400 mg twice daily) since median overall survival (OS) was 8.0 months in the TARE group vs. 9.9 months in the Sorafenib group in the intention-to-treat population<sup>1</sup>. The SIRveNIB trial also failed to meet the primary endpoint as median OS in the intention-to-treat population was 8.8 and 10.0 months with 90Y-resin microspheres and Sorafenib, respectively. Similarly, no differences in OS were demonstrated in the treated population, OS was prolonged for TARE in the subgroup of patients with advanced HCC from the treated population<sup>2</sup>. A meta analysis of the per protocol populations of the three randomized trials, SARAH, SIRveNIB and SORAMIC found that TARE was non inferior to Sorafenib with a non-inferiority margin of 1.08 in terms of hazard ratio and offered a better safety profile<sup>3</sup>.

The improved toxicity profile of radioembolization could result in a quality life (QoL) benefit evidenced in economic evaluations. A cost-effectiveness study including not only the primary treatment costs (for TARE and Sorafenib) but also subsequent costs and QoL-associated outcomes in both treatment groups was pre-planned as a secondary objective of the trial (NCT registration 01482442).

Our aim was to assess the cost-utility of TARE versus Sorafenib in patients with advanced hepatocellular carcinoma.

### **4. Methods**

#### ***4.1. Target population, setting***

The SARAH trial randomized 467 patients, and 459 were followed at least 12 months in the absence of early interruption of the study: death, medical decision or patient choice. Patients were diagnosed in 25 centers specialized in liver diseases in France with locally advanced hepatocellular carcinoma, or new hepatocellular carcinoma not eligible for curative treatment, or hepatocellular carcinoma with two unsuccessful rounds of transarterial chemoembolization. Patients received either TARE or Sorafenib according to their randomization arm. Our target



population (economic population) included patients who received at least one dose of Sorafenib or one treatment with TARE according to their randomization arm. The reason for this choice was that at the initiation of the SARAH trial several sites had a limited technical experience using TARE which resulted in delays in workup and patients' worsening and dying before treatment was actually administered. The economic population more closely resembles to today's practice. The analysis on the safety population (patients who received at least one dose of Sorafenib or underwent at least one of the TARE workup exams) and on the per-protocol population was also performed in sensitivity analyses.

#### ***4.2. Study design***

A two-step health-economic analysis combining within-trial and modeling of costs and outcomes was performed from the perspective of the French health care provider.

The outcomes collected prospectively were overall survival (OS) defined as the time between the date of randomization and the date of death regardless of the cause or the end date of follow-up, and progression-free survival (PFS) defined as the time between the date of randomization and the date of disease progression or the end of the within-trial follow up in the absence of progression. The quality of life was assessed by EORTC-QLQC-C30 at baseline, 1 month, and every 3 months thereafter up to 12 months. Our analysis was based solely on the within trial and extrapolated data from the patient population included in the SARAH randomized trial comparing TARE to Sorafenib.

#### ***4.3. Estimating resources and costs***

Resource utilization was collected prospectively on all patients during the trial. It comprised protocol-related treatments, disease-related treatments, and adverse events requiring hospital admissions. Admissions for the first and subsequent treatment lines were retrieved by the case report form (CRF) supplemented by routine hospital data via patient-level information and claims systems. Admissions for adverse events were retrieved using both the CRF and the extraction of the linked patients' records from the hospitals' claims database and matching the date of the events in the CRF. Adverse events occurring during an admission for another cause were not valued, nor were adverse events not requiring an admission. Second and third line treatments were identified by their diagnostic and

procedural codes. Admissions for other causes and end of life care were recorded separately from the hospitals' claims database (Table S1.1. Supplementary Material)

In the TARE arm, we used microcosting to estimate the full cost of the procedure which comprised:

- Work-up: arteriography procedure, hospital stay and control scintigraphy;
- Initial admission radioembolization: procedure, hospital stay and control scintigraphy

Three work-ups and five radioembolizations were observed in three different centers: Beaujon university hospital (three workups and three radioembolizations); Nancy university hospital (one radioembolization) and Grenoble university hospital (one radioembolization). We applied the time-driven activity-based costing method by adjusting the costs collected according to the duration of the procedure. Additional workups and radioembolization were added based upon the CRF information.

In the Sorafenib arm, the cost of treatment was calculated from the total number of tablets, including wastage in the sensitivity analysis.

Costs of hospital admissions were calculated using DRG-specific production costs adjusted to the actual length of stay of trial participants and based on the latest available schedule of reference costs. Device and drugs unit costs were sourced from the manufacturer and list prices (Tables S1.2 and S1.3). We used 2017 costs in €.

#### ***4.4. The model***

We used the trial outcomes (overall survival and progression-free survival) and costs in a partitioned survival model using patient-level data to extrapolate trial results beyond the end of the follow up period<sup>4</sup>. The model contained three health states: progression-free, progressed, and dead.

The proportion of patients in each health state over time was calculated from PFS and OS curves. The model time horizon was 5 years, which was sufficient to capture the predicted lifetime of almost all patients in the cohort from treatment initiation to death. Model time was divided into increments (model cycles). At the end of each time increment, the proportion of patients in each health state was counted, the costs incurred and the life-years (LYs) and quality-adjusted life-years (QALYs) accrued. A model cycle length of 1 day was used in order to ensure that differences in time to progression could be precisely modeled as well as longer-term events such as death. Patients entered the model at the initiation of therapy and were assigned to the Progression-free health state.

The ICER was computed as the ratio between the cost difference and the QALYs difference between the two arms, the reference being the Sorafenib arm.

The Model was built using R version 3.6.4, and using the heemod package<sup>5</sup>.

#### ***4.4.1. Modeling PFS and OS Estimates***

Since the PFS and OS Kaplan–Meier curves from the trial ended in plateaus and the amount of censoring was not negligible (for PFS: 4.8% and 6.0% patients in the TARE and Sorafenib arms, respectively, for OS: 17.7% and 20.7%), modeling and extrapolating of the curves beyond the follow-up period was required in order to estimate health outcomes and costs over the entire lifetime of all patients<sup>6</sup>.

We used the cumulative hazard plots of both arms to visually determine the presence of proportional hazards<sup>7</sup>. For the PFS, the slopes of the survival curve of both arms were identical until 1 year after randomization, and changed afterwards. For OS, the slopes were parallel during almost the entire follow-up. We therefore decided to model the survival in two parts (piecewise model): one part before 365 days and one beyond 365 days. This ensured that the curves could cross, as was the case with the Kaplan Meier PFS curves. In the first part, we right-censored the follow-up time to 365 days by truncating the time and assigning a value of 0 to subsequent events. In the second part, we only kept patients who had no event at 365 days and then subtracted 365 from the follow-up time. Each part had its own parameter estimates.

We considered several survival functions: Exponential, Weibull, Gompertz and log-normal. Goodness of fit was assessed with visual inspection of the Kaplan Meier curves together with the modeled curve<sup>7</sup>. We validated our models with the 5-year survival rate of locally advanced hepatocellular carcinoma treated with Sorafenib published in the literature. The most appropriate long-term OS rate identified for this validation was around 3%<sup>8</sup>.

Consequently, we considered as adequate a model with a 5-year survival rate below 5%. We chose the exponential function which was the simplest, had a good fit with the Kaplan Meier curve visually, and resulted in a 5-years survival rate below 5%.

#### ***4.4.2. Modeling the costs***

Four linear regressions were performed to model the costs, after checking that the validity conditions were met. For each treatment arm, we modeled the pre-progression cost as a function of time in pre-progression, and the post-progression cost as a function of time in progression. In the TARE arm, we added the initial cost in the term of the linear regression of the pre-progression period. Removing the intercept improved the models performance ( $R^2$ , AIC and BIC). We input the results of the regression models into the partitioned survival model to estimate the increment of cost at any time in the model.

#### ***4.4.3. Modeling the Quality of Life***

The Longworth response-mapping model was used to map the trial EORTC-QLQ-C30 summary scores to probabilities of EQ-5D scores on each domain, which were then weighted according to EQ-5D preferences from the French general population to calculate an estimated EQ-5D utility<sup>9,10</sup>. We set up a predictive linear mixed regression model relating the EQ-5D score with time since randomization and other covariates, by a forward stepwise selection. We found that the EQ-5D score had the lowest AIC with baseline score, time since randomization, presence of progression, ECOG score 1 or 2 and if the patient received a first-line Sorafenib treatment. We used the results of this regression model into the partitioned survival model to estimate the utility scores.

Both costs and QALYs incurred in the second and subsequent years after randomization were discounted at a 4% rate, as recommended by the Health Authority<sup>11</sup> in France.

#### ***4.5. Sensitivity analyses***

We performed 2 deterministic sensitivity analyses (DSA): one regarding the cost difference between the arms within trial in order to determine the main cost drivers, and one regarding the ICER using the model. For the former, we considered the cost components likely to have an impact on the cost difference, based on expert opinion:

- The number of procedures: a single work-up and radioembolization procedures per patient in the TARE arm
- A single hospital stay for both work-up and radioembolization, without using coils in work-up procedure, which corresponds to the practice today
- The Y90-RE consumables price: 20% cost reduction

- The Y90-RE interventions duration: minimum = 4.4 hours and maximum = 6.3 hours for both work-up and treatment
- Including the Sorafenib wastage in the calculation of Sorafenib costs

For the latter, we considered all costs components included the first DSA, and added the variables influencing survival and utilities:

- The population: *the per-protocol population*, i.e. all patients completing the study without major protocol deviations, and the *safety population* which included all patients with at least one workup for TARE, regardless of final TARE administration.
- The time horizon (10 years vs 5 years)
- The survival distribution : full exponential, Weibull and lognormal vs piecewise exponential
- The discount rate (0-5%)

The variability surrounding incremental survival, costs and QALYs (exponential distribution for survival, linear regression for costs and QALYs) was assessed by non-parametric bootstrap, a probabilistic sensitivity analysis whereby 1,000 replicate samples were generated by resampling. For each of these samples, we obtained estimates of survival rates, costs, and quality of life and their predictors. We then ran the partitioned survival model on each sample using with these new parameters. Bootstrapped 95% CIs were estimated for mean incremental costs and incremental QALYs, respectively, while their joint distribution was plotted on a cost-effectiveness plane.

#### **4.6. Model validation**

We computed the average progression-free and overall survivals using restricted means at 500 days and 1000 days, and the pre- and post-progression costs at the same time horizon, that we compared to the model outcome at 500 and 1000 days in order to assess internal validity. Cross-validity (comparison of results with other models analyzing the same decision problem) could not be performed because no study comparing cost and effectiveness of radioembolization vs Sorafenib with a randomized controlled trial was identified. As an external validation, we compared the 5-years survival rates of locally advanced hepatocellular carcinoma found in our model with that of another study, for a treatment with Sorafenib and TARE <sup>8</sup>.

## 5. Results

Of the 459 patients randomized in the study, 237 were randomized to the TARE arm and 222 to the Sorafenib arm. 226 underwent the TARE workup, 184 received TARE and 216 Sorafenib (Figure 1); the 400 patients constituted the population for the economic evaluation with 90% men; the average age was 65 years.

### 5.1. Costs

Disaggregated resource use and costs are shown in the **Table 1**.

#### *Costs in the TARE arm*

The total average within-trial cost in the TARE arm was €42,699 ( $\pm 18,874$ ) including first and subsequent treatment lines and hospitalizations for adverse events or other cause. The pre- and post-progression costs were €32,211 ( $\pm 12,925$ ) and €10,488 ( $\pm 16,292$ ) respectively (Table 2).

Detailed costs for the initial TARE are presented in the Supplementary Material 1, table S1.4. During the first admission, 30 patients required a repeated workup. Seventy five patients had at least one additional workup after the first admission and 69 patients at least one additional radioembolization. Seventy one patients received a second-line treatment (Table S1.5 Supplementary Material): 18 with a liver-targeted therapy and 53 with a systemic treatment (52 with Sorafenib), with an average cost of (N=71) €10,298 ( $\pm 14,511$ ). 20 patients received a third-line treatment for an average cost of (N=20) €6,995 ( $\pm 6,428$ ).

128 hospitalizations for adverse event occurred in 79 patients during the within trial follow-up period. The average length of stay was 7.37 ( $\pm 7.33$ ) days and the average cost for patients with severe adverse event (SAE) (N=79) was €7,357 ( $\pm 5,063$ ).

96 patients were hospitalized for causes other than SAE, second or third line treatment. The average length of stay was 2.32 ( $\pm 2.83$ ) days and the average cost (N=96) was €4,353 ( $\pm 4,653$ ).

The average within-trial cost of follow-up in the TARE population was €10,164 ( $\pm 13,751$ ).

The extrapolated 5-year cost for the TARE arm was €44,345 [CI95 39,793-50,065] (tables S2.1-2.4 Supplementary Material).

### ***Cost in the SORAFENIB arm***

The average within-trial cost of the Sorafenib population was €25,407 ( $\pm 20,626$ ), including first and subsequent treatment lines and hospitalizations for adverse events or other cause. The pre- and post-progression costs were €15,550 ( $\pm 15,514$ ) and €9,857 ( $\pm 14,349$ ) respectively. The mean number of the Sorafenib tablets during the within trial period recorded in the CRF was 661 ( $\pm 623$ ) per patient.

Thirty-eight patients received a second-line treatment (Table S1.8): 10 had a liver-targeted therapy and 28 a systemic treatment, for an average cost of (N=38) €7,588 ( $\pm \text{€}11,815$ ). 11 patients received a third-line treatment for an average cost of (N=12) €7,515 ( $\pm \text{€}5,635$ ).

122 hospitalizations for adverse event occurred in 82 patients within trial follow-up period. The average length of stay was 9.57 ( $\pm 11.2$ ) days and the average cost for patients with SAE (N=82) was €7,948 ( $\pm \text{€}6,609$ ). 70 patients were hospitalized for other causes. The average length of stay was 2 ( $\pm 3.2$ ) days and the average cost (N=70) was €3,690 ( $\pm \text{€}3,884$ ).

The average within-trial cost of follow-up in the Sorafenib arm was €5,966 ( $\pm \text{€}9,454$ ).

The extrapolated 5-year cost for the Sorafenib arm was €27,166 [CI95 22,856-32,174] (tables S2.1-2.4 Supplementary Material).

### ***5.2. Survival analysis and QALYs***

In the within-trial period, the median overall survival (OS) and progression-free survival (PFS) were 9.7 [CI95 8.2; 13.0] months versus 9.9 [CI95 9.2; 11.8] months ( $p=0.9$ ) and 4.4 [CI95 3.9; 5.7] months versus 3.7 [CI95 3.3; 5.6] months ( $p=0.6$ ) for the TARE and Sorafenib arms.

The overall survival rate at the end of the within-trial period was 7.2% in the TARE arm and 11.6% for the Sorafenib arm (Figure 2).

When extrapolating with the partitioned survival model over 5 years, the median OS and PFS were 11.4 [CI95 9.9; 13.3] months versus 11.4 [CI95 9.9; 13.2] months and 4.9 [CI95 4.2; 5.7] months versus 4.6 [CI95 3.9; 5.3] months for TARE and Sorafenib, respectively. The 5-year overall survival rate was 0.9% for TARE and 1.6% for Sorafenib. Progressed patients had worse estimated utility than pre-progression patients (Table S2.5 Supplementary Material).

5-year discounted QALYs were 0.803 (CI95 0.70-0.93) and 0.797 (CI95 0.69 – 0.92) in the TARE and Sorafenib arms, respectively.

### **5.3. Cost utility analyses**

The ICER point estimate was €3,153,086/QALY

### **5.4. Sensitivity analyses**

The main cost driver for the TARE arm was the number of workups and radioembolization (Fig S2.1 in the Supplementary Material 2): limiting the number of procedures to 1 reduced the cost to €35,939(-€6,763).

No parameter among all analyzed in the deterministic sensitivity analysis resulted in an ICER less than €450,000/QALY (Table 3).

The results of the probabilistic sensitivity analyses are shown on the cost-effectiveness plane (Figure 3). There was a probability of 50% that the Sorafenib arm dominated the TARE arm over 5 years.

### **5.5. Model validation**

The average overall survival times at 1,000 days in the model and within trial were 415 days in the TARE arm and 418 days in the Sorafenib arm vs 420 in the TARE arm of the trial and 417 in the Sorafenib arm, respectively (Table S2.6 Supplementary Material). The average costs at 1,000 days in the model and within trial were €42,788 vs €42,166 in the TARE arm (+€622) and €25,186 vs €25,195 in the Sorafenib arm (-€9), respectively.

## **6. Discussion**

Despite its better safety profile, TARE failed to demonstrate a strong QALY advantage over Sorafenib. The initial utility benefit in the TARE arm was offset by the longer duration of survival in the Sorafenib arm. Although Sorafenib was an expensive comparator, the lack of sustained improvement in outcomes obtained with TARE resulted in high ICER. The lower post-progression life expectancy in the TARE arm was the main driver of the result. The SARA trial found a clear advantage for TARE regarding adverse events. This advantage did not translate into a difference in costs, which can be explained by 1) the fact that several events can be combined into



one single admission, 2) events occurring during an admission for another cause (e.g. disease progression) are not counted as a separate cost, 3) the exclusion of non-hospital costs.

Few cost-effectiveness analyses of radioembolization for HCC vs Sorafenib have been published. Rognoni's study was based on real-life data collected at three oncology centers in Italy, and found transarterial radioembolization to be cost-effective, and even dominant in advanced hepatocellular carcinoma<sup>12</sup>. The following reasons can explain the differences: a) We did not use the per protocol population in the baseline analysis; b) we only considered locally advanced and inoperable hepatocellular carcinoma; c) we modeled the survival with fewer than 5% patients alive after 5 years<sup>8</sup>. Sorafenib is a very expensive molecule, the extension of the treatment beyond 5 years had an important influence on the cost of the Sorafenib arm, which could not be observed in our model ; d) a different study design and data collection: we estimated cost of procedures with a microcosting approach, that permitted us to be closer to the production cost, which was consistent with the costs of radioembolization found in another study in the setting of the US healthcare system (between \$31,000 and \$48,000)<sup>13</sup>; e) a different modeling method: we used partitioned survival models instead of other modeling techniques as being the simplest to have an extrapolation of cost and utilities beyond the time horizon of the trial when working on individual survival data<sup>6</sup>.

The strength of our work lies in the fact that the study was based on an RCT with prospective patient-level collection of cost data. Thus, we were able to input all the parameters necessary for the partitioned survival model by follow-up duration and progression. As the survival of locally advanced and inoperable hepatocellular carcinoma is low (5-year survival : <5%), we did not have to extrapolate results over a longer time horizon. The extrapolated part constituted a small fraction of the results – the survival rates were 6.2% and 11.6% at the end of the trial, in TARE and Sorafenib arms; the parameters uncertainty was therefore lower than in other modeling studies. The uncertainty of the model was explored by a deterministic and a probabilistic sensitivity analyzes with non-parametric bootstrap. A different patient management (a single day hospitalization for treatment and work-up exam), without the need to repeat the procedure and no protocol driven costs, would reduce the €17,000 difference in cost between the two arms. We studied 3 patientpopulations in the TARE arm, the patients who did receive at least course of treatment, the per-protocol population and the safety population and found consistent results.

The study had good internal and external validity, with 5-year survival near 0, and similar average survival and costs at 500 and 1000 days post-randomization between what was found in the trial and what we modeled.

#### Limitations:

Although RCTs provide the highest level of evidence for individual studies, they require standardization of procedures. The protocol for patient follow-up was not necessarily the one that would be performed in real world. We found that hospital readmission data for any cause was not consistent across centers: in the Sorafenib arm, 21/26 of patients treated in one center were readmitted vs 1/25 patients treated in another center. Such discrepancies were not observed in the TARE arm; this could reflect differences in the management of patients during the trial, with patients in the Sorafenib arm being treated in outpatient settings. Sorafenib administration costs could include routine outpatient interactions between patients and hepatologists/nurses for the monitoring and management of adverse events – these costs would not be captured.

Treatment was proposed according to the level of evidence at the time, which is regularly updated. Since it is not possible to modify the treatment that the patient would have received had he or she been treated today, we presented deterministic sensitivity analysis of the change most likely to influence the results (which are those affecting a large proportion of patients), namely a single hospitalization for both work-up exam and treatment.

Other limitations of the study result from the modeling: we used survival curves with proportional risks between the two groups rather than independent curves. Yet, we were unable to fit the survival by a single parametric survival function and needed a piecewise model. We used linear regression to estimate incremental costs for 1 day. However, it is generally recommended to use a generalized linear model using a log link and gamma family<sup>14</sup>. We could not model cost that way, because the model needed to be additive and not multiplicative. We checked that the conditions for a linear model were satisfied, which was the case.

There were several modeling steps to express the utility as a function of time: a) mapping EORTC - QLQ-C30 to EQ5D-3L (response mapping)<sup>9</sup>, b) using utility weights for the French population<sup>10</sup>, c) model utility in function of the time. Each of these steps is a simplification of the real world, and increased the uncertainty of the model.

This study was conducted in a French population from the perspective of a French provider. Extrapolating results from one country to one another is always difficult because of different mortality rates, test costs, medical visits costs, and hospital management costs. However, even if we significantly changed the parameters of the study,

including the different costs in each arm, our sensitivity analyses were consistent and still showed a very high incremental cost-effectiveness ratio for the TARE arm (Table S3.2 Supplementary Material 3)

## **7. Conclusions**

This economic evaluation of SARAH found that using radioembolization with yttrium 90 microspheres (Y90-RE) for the treatment of hepatocellular carcinoma was not a cost-effective option, with 50% probability of being dominated by Sorafenib in the population of patients receiving at least one treatment of their randomization arm, and a point estimate for the ICER over €3,000,000/QALY. Given the paucity of economic evaluations of radioembolization for the treatment of hepatocellular carcinoma and the large variability of the few ones that do exist, further studies are needed to improve the accuracy of the findings.

## 8. Disclosure of Funding Support

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## 9. Figure Captions

Figure 1: Flowchart of the randomized controlled trial ; from Vilgrain et al<sup>1</sup>

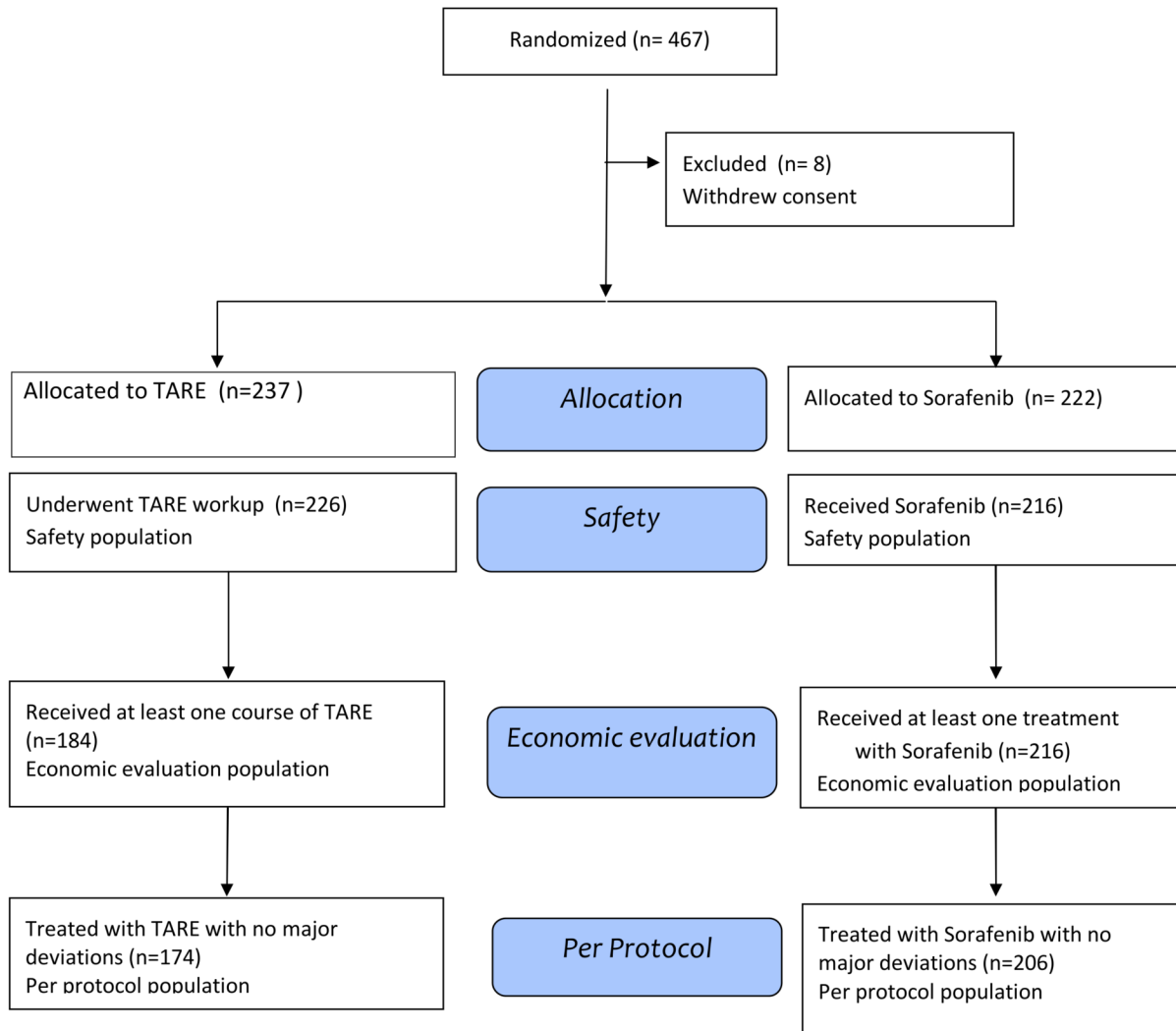
Figure 2: Progression-free survival and b) overall survival curves. The plain lines represent the within-trial survival curves computed with Kaplan Meier estimator ; the dashed lines represent the parametric survival curves (piecewise exponential)

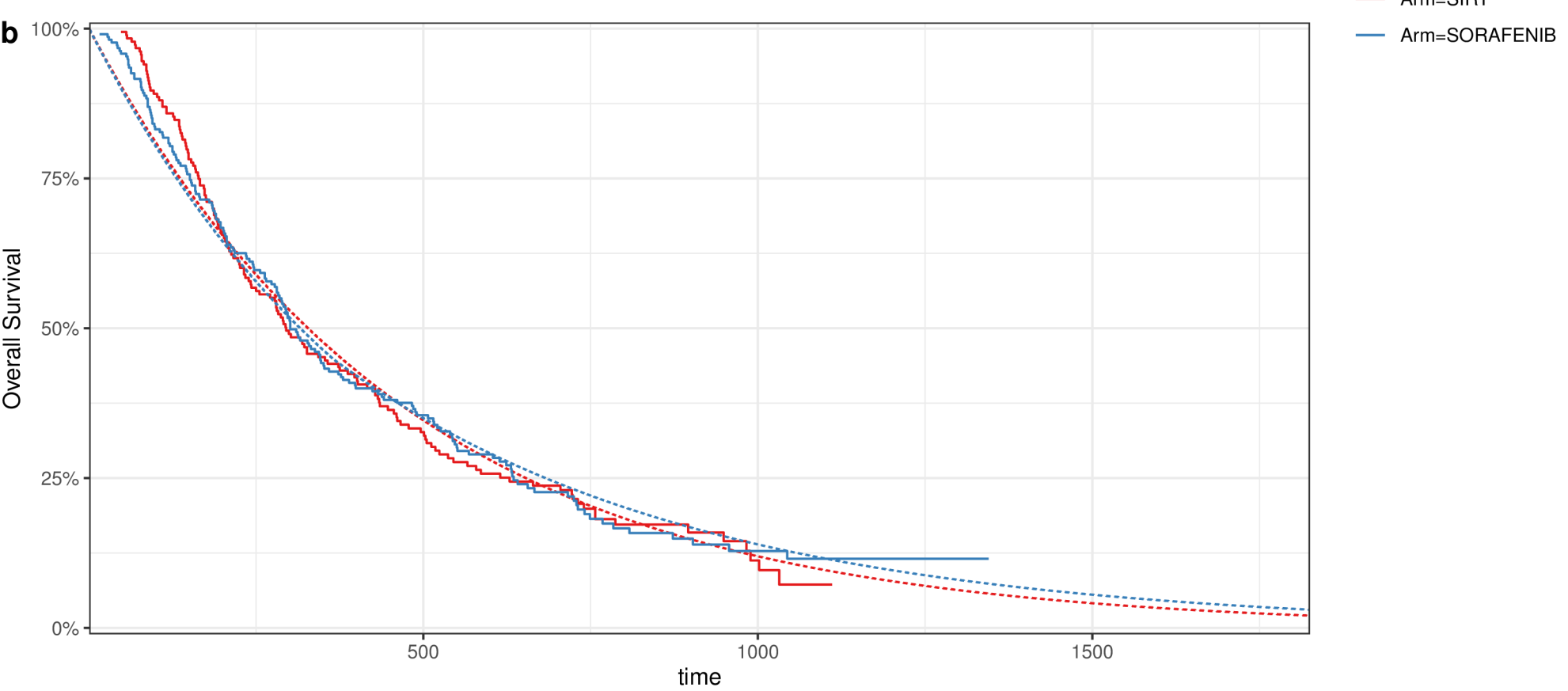
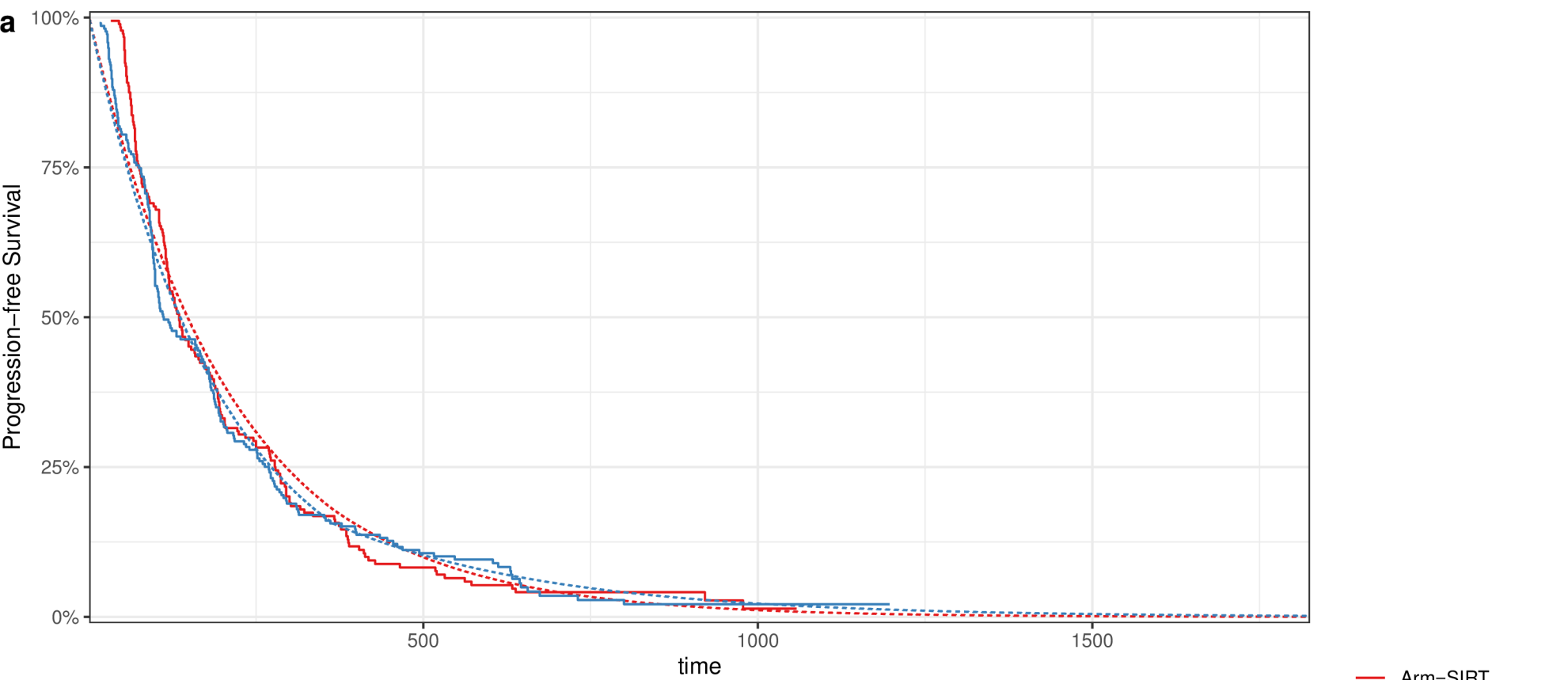
Figure 3: Cost-utility plane of TARE vs Sorafenib. Each point is the result of a bootstrap replication and represents the difference in average between the TARE and Sorafenib arms.

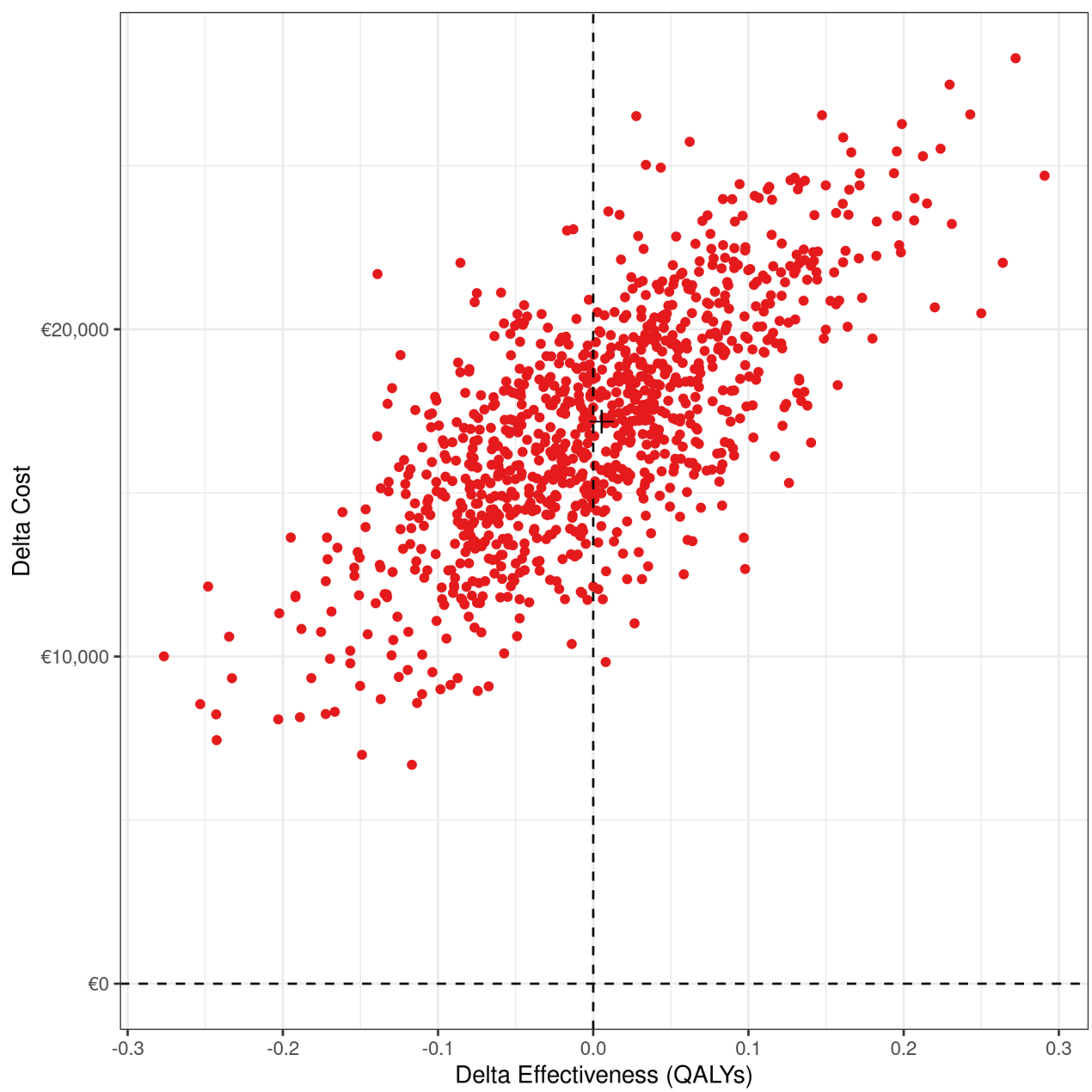
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**Table 1:** Within-trial initial and follow-up cost in the TARE and Sorafenib arms

	TARE Arm	Sorafenib Arm
	N=184	N=216
Procedural and initial costs	Mean cost (SD) (€)	Mean cost (SD) (€)
Initial workup	6,420 (±2,161)	0
Initial Radioembolization	16,320 (±359)	0
Additional workup	2,740 (±3,771)	0
Additional Radioembolization	7,054 (±9,818)	0
Sorafenib	0	19,441 (±18,476)
Total Procedural and initial costs	32,534 (±13,411)	19,441 (±18,476)
Follow-up costs	Mean cost (SD) (€)	Mean cost (SD) (€)
Second-line treatments	3,974 (±10,287)	1,335 (±5,693)
Third-line treatments	760 (±3,010)	418 (±2,145)
Admissions for SAEs	3,159 (±4,925)	3,017 (±5,604)
Other admissions	2,271 (±3,999)	1,196 (±2,800)
Total follow up costs	10,164 (±13,751)	5,966 (±9,454)
Total cost per patient	<b>42,699 (±18,874)</b>	<b>25,407 (±20,626)</b>
SAE: Serious adverse events		

**Table 2:** Within trial pre- and post-progression cost per patient in the TARE and Sorafenib arms

	TARE	Sorafenib	P-value
	N=184	N=216	
Pre-progression			
Mean cost (SD) (€)	32,211 (±12,925)	15,550 (±15,514)	<0.001
Post-progression			
Mean cost (SD) (€)	10,488 (±16,292)	9,857 (±14,349)	0.68

**Table 3:** Average (discounted at 4%) Life Years and QALYs obtained by modeling at 5 years time horizon, differences in costs and outcomes for the safety and per protocol populations. ICER was not calculated since TARE dominated in the safety population.

	TARE	Sorafenib	Difference
	N=184	N=216	
<i>Mean total Life Years</i>	1.212	1.248	-0.036
Mean Life Years Progression-free	0.585	0.584	+0.001
Mean Life Years post Progression	0.627	0.664	-0.04
<i>Mean total QALYs</i>	0.803	0.797	+0.006
Mean QALYs Progression-free	0.407	0.393	+0.014
Mean QALYs post Progression	0.396	0.404	-0.008
<i>Mean total cost</i>	€44,345	€27,166	€17,179
<b>Incremental cost effectiveness ratio</b>	<b>€3,153,086/QALY</b>		