A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (HCC).

Published: 16-08-2016
Last updated: 17-04-2024

The objective of the study is to evaluate TheraSphere in the treatment of patients with unresectablehepatocellular carcinoma in whom treatment with standard-of-care sorafenib therapy is planned.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50334

Source
ToetsingOnline

Brief title
TheraSphere® in Unresectable Hepatocellular Carcinoma (HCC). STOP-HCC

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
hepatocellular carcinoma, liver cancer

Research involving
Human

Sponsors and support

Primary sponsor: Biocompatibles UK Ltd.

Source(s) of monetary or material Support: Biocompatibles UK Ltd

Intervention

Keyword: Hepatocellular carcinoma, TheraSphere

Outcome measures

Primary outcome

Overall Survival (OS) from time of randomization.

Secondary outcome

- Time to progression (TTP) from time of randomization based on investigator assessment according RECIST criteria v 1.1

- Time to untreatable progression (TTUP) from the time of randomization based one or more of the following: investigator assessment according to RECIST criteria v 1.1, contraindication to protocol treatments based on package insert or patient performance status.

- Time to symptomatic progression (TTSP) from the time of randomization to ECOG performance status > 1 with or without tumor progression based on investigator assessment according to RECIST criteria v 1.1. Deterioration in performance status is to be confirmed at two subsequent evaluations at 8 week intervals.

- Tumor response according to RECIST v 1.1 criteria based on investigator assessment

- Quality of life Assessments (including the Functional Assessment of Cancer Therapy - Hepatobiliary Questionnaire - FACT-Hep)

- Adverse events (NCI-CTAE v 4.0)

Study description

Background summary

According to the international Agency for Research on Cancer (IARC), primary liver cancer is a major health problem worldwide.
Globally, it is the sixth most commonly diagnosed cancer, with more than 749,000 new cases in 20011. It is the third leading cause of cancer death in men and sixth among women. In North America and Western or Northern Europe, areas with historically low rates, the
incidence of liver cancer is increasing, possibly due to increased prevalence of hepatitis C.

In 2007, the FDA approved sorafenib tosylate (Nexavar®), a small molecule Raf kinase and VEGF receptor
kinase inhibitor, for the treatment of patients with unresectable hepatocellular carcinoma (HCC).
The approval was based on the results of an international, multicenter, randomized, double-blind,
placebo-controlled trial (SHARP trial) in patients with unresectable, biopsy-proven hepatocellular
carcinoma.

Sorafenib is the standard-of-care (SOC) therapy for patients with advanced HCC, guidelines recommend the use of sorafenib in this cohort of patient. One such guideline, the Barcelona Clinic Liver Cancer (BCLC) classification system recommends use of sorafenib in patient with a classification of stage C HCC.

Moreover, s orafenib is included in the NCCN Clinical Practice Guidelines in Oncology (NCCN- Hepatobiliary cancersV.1.2010 - HCC5) as one of the possible treatments for patients with unresectable HCC and extensive liver disease who are not candidates for transplantation.

Although sorafenib is a SOC in the treatment of patients with HCC, it is associated with only a modest improvement in median survival as compared to best supportive care. Further, sorafenib treatment is
associated with significant toxicity. Salem et al recently published their long-term experience of TheraSphere in the treatment of patients
with HCC.Hilgard et al report treatment of 108 consecutive patients with advanced HCC using TheraSphere.
At the International Liver Cancer Association conference in September 2010, Metrakos et al reported
preliminary results of a Phase II investigation of the safety, tolerability and efficacy of administering
TheraSphere and Nexavar (sorafenib) treatment in patients with HCC.
As illustrated by these published reports, there is now an extensive clinical

experience demonstrating the safety of TheraSphere in the management of patients with unresectable HCC.

In this trial (STOP-HCC), all patients with unresectable HCC eligible for treatment with SOC sorafenib may be considered for study participation. Patients who meet the entry criteria will be randomized to either the patient*s planned SOC sorafenib therapy (Control group), or to TheraSphere administered prior to the patient*s SOC sorafenib therapy (Treatment group). The primary outcome measure for this trial is overall survival.

Our outcome assumption in the Control group is based on the SHARP trial, with a median overall survival of 10.7 months for patients treated with sorafenib. We assume a median overall survival of 15 months in the Treatment group, (hazard ratio = 0.71). However, due to uncertainty in the expected treatment effect, a sample size re-estimation is planned, which would allow the sample size to increase in order to detect a smaller increase in median OS time, from 10.7 months in the sorafenib arm to 14.0 months in the TheraSphere arm (ie, hazard ratio = 0.76).

Study objective

The objective of the study is to evaluate TheraSphere in the treatment of patients with unresectable hepatocellular carcinoma in whom treatment with standard-of-care sorafenib therapy is planned.

Study design

This study is an open-label, prospective, multi-center, randomized clinical trial.

Intervention

The Control group will receive planned standard-of-care therapy sorafenib in accordance with the approved product labeling.
The Treatment group will receive TheraSphere prior to the initiation of standard-of-care sorafenib treatment. All liver tumors observed at baseline that are amenable to treatment with TheraSphere should be treated with TheraSphere prior to the initiation of treatment with sorafenib. In cases where disease progression amenable to treatment with TheraSphere is observed after sorafenib treatment has been initiated, TheraSphere should be administered in a

sorafenib treatment window.

Study burden and risks

An overview of all study visits and related study procedures can be found in section 3 of the protocol (pages 16-17). A complete description of the study visits and procedures can be found in section 9 of the protocol (pages 25-39). Please see summary below:
Screening Period
The following screening and enrollment evaluations should be performed within 14 days prior to randomization:
• ICF (before any study required tests are performed),
• Physical examination,
. Medical history,
• Child-Pugh assessment of chronic liver disease
• Assessment of liver function, including presence/absence of portal hypertension and normal/abnormal bilirubin levels
• ECOG Performance Status assessment
• Triple phase spiral CT/MRI to assess liver tumor presentation, estimate tumor burden in the liver.
• Chest CT/MRI to rule out extra-hepatic metastases
• FACT-Hep quality of life questionnaire
• Required laboratory blood work plus α-feto protein (AFP)
Randomization
Upon meeting eligibility for study participation in accordance with the Eligibility criteria, patients will be randomized 1:1 between the Treatment and Control groups.
In order to balance the treatment groups, patients will be stratified at randomization on the basis of Region (North America and Europe vs Asia), ECOG Performance Status (0 vs 1), presence or absence of branch portal vein thrombosis.
Control Group (Sorafenib)
All patients randomized to the Control group should start their planned standard-of-care treatment with sorafenib as soon as possible after randomization.
Patients will follow standard dosing for sorafenib according to the product label information as prescribed by the investigator. Medically appropriate dose adjustments and drug holidays due to adverse events and toxicity are allowable.
Treatment Group (TheraSphere followed by Sorafenib)
As soon as possible after randomization, hepatic angiography will be performed to assess hepatic vascular anatomy and tumor hypervascularity, followed by a 99mTc-MAA scan to rule-out gastrointestinal flow or unacceptable lung shunting. Embolization may be performed, if necessary, to close off gastrointestinal flow so that the patient can qualify for treatment with TheraSphere. The lobe with the highest tumor burden should be scheduled for first treatment with TheraSphere.
Patients will not be able to receive TheraSphere if the potential radiation

dose to the lungs exceeds 30 Gy for a single treatment or cumulative 50 Gy or embolization cannot be performed to effectively block GI blood flow from the hepatic arterial system. If radiation exposure to the lungs exceeds 30 Gy (or 50 Gy cumulative), dose reduction of TheraSphere is permitted (minimum dose allowed is 90 Gy ± 10%).
If after consideration of dose reduction, radiation exposure to the lung continues to be greater than 30 Gy (or 50 Gy cumulative), sorafenib treatment will be initiated as soon as possible and 99mTc-MAA will be repeated after 4 weeks of continuous treatment with sorafenib. If radiation exposure to the lung is less than 30Gy for a single treatment or 50Gy cumulative within a target dose of 90-120 Gy +10% , the patient may commence treatment with TheraSphere. In such instances, sorafenib should be discontinued at least 7 days prior to the administration of TheraSphere and resume sorafenib at least 2 weeks after the administration of TheraSphere. If radiation exposure to the lung is outside of the permitted range, treatment with sorafenib should be continued.
In the case where TheraSphere could not be delivered at at target dose of 120 Gy ± 10% within 28 days of randomization, these patients will be included in the Treatment Group Intent-to-Treat analysis, but not in the Treatment Group Per-Protocol analysis.

TheraSphere Treatment #1: TheraSphere treatment should occur within 28 days of randomization, and prior to the initiation of sorafenib. The number of infusions required to achieve lobar treatment will be determined by the Investigator, based on the hepatic vascular anatomy.
Patients will receive 120 Gy ± 10% of TheraSphere to the treated lobe of the liver and may be administered in multiple infusions to address vascular abnormalities.
TheraSphere Treatment #2: Patients who have bilobar disease at randomization should have TheraSphere administered to the untreated lobe. If needed, a second angiogram and/or 99mTc-MAA scan should be performed. Such treatments typically take place 28 days after the treatment to the first lobe.
From 2 to 6 weeks following TheraSphere treatment of all treatable liver tumors observed at the time of randomization, patients should initiate standard-of-care sorafenib treatment in accordance with the sorafenib label directions.
Re-treatment of the same patient with further cycles of TheraSphere is permitted if a treatable progression is detected during follow-up evaluations. Any re-treatment should take place a minimum of 28 days from the last TheraSphere treatment administered to that lobe. A maximum of 2 re-treatments are permitted in any patient.

Study Visits and Follow up
Screening evaluations should be completed within 14 days prior to randomization. For patients randomized to sorafenib, study visits will take place every 8 weeks for as long as the patient remains on the trial. Additional visits may be scheduled as needed when initiating sorafenib treatment, and to manage any adverse events and adjustments to sorafenib dosing.

For Patients randomized to TheraSphere, the pre-treatment evaluations and TheraSphere treatment to the first lobe should take place during the first 3 to 4 weeks following randomization. For patients with bilobar disease, the evaluations and TheraSphere treatment to the 2nd lobe should take place during weeks 5 to 8 weeks following randomization. After TheraSphere treatment, subsequent study visits will take place every 8 weeks from randomization for as long as the patient remains on the trial.
After start of sorafenib therapy, patients may have additional visits as needed to adjust sorafenib dosing. Dosing of sorafenib should be consistent with the relevant label instructions, with allowance for appropriate adjustments based on the investigators medical judgment.
In general, follow up visits take place approximately every 8 weeks from randomization until one of the study discontinuation criteria is met (see 9.2.19). The following assessments take place at the follow-up visit:
. ECOG Performance Status assessment
. Standard laboratory blood draw for CBC, differential, electrolytes, BUN, glucose, liver function test, coagulation panel, and α-fetoprotein biomarker
. Triple phase spiral abdomen CT/MRI scan and spiral CT/MRI scan of chest and pelvis
. Child-Pugh Status
. QOL questionnaire
. Adverse event reporting

Contacts

Public
Biocompatibles UK Ltd.

Farnham Business Park, Weydon Lane -
Farnham GU9 8QL
GB
Scientific
Biocompatibles UK Ltd.

Farnham Business Park, Weydon Lane -
Farnham GU9 8QL
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Must have signed informed consent prior to any study-related evaluation
2. Must be male or female patients over 18 years of age
3. Must have unresectable HCC confirmed by histology or by non-invasive AASLD10 criteria
4. Must have measurable disease defined as at least one uni-dimensional measurable lesion by CT
or MRI (according to RECIST 1.1)
5. Must have a Child Pugh score <= 7 points
6. Must have an ECOG Performance Status score of <= 1
7. Must have a Life expectancy of 12 weeks or more
8. Must have be eligible to receive SOC sorafenib
9. Must have Platelet count > 50 x 109/L or > 50% prothrombin activity
10. Must have Hemoglobin >= 8.5 g/dL
11. Must have Bilirubin <= 2.5 mg/dL
12. ALT and AST must be < 5X upper limit of normal
13. Amylase or lipase must be <= 2X upper limit of normal
14. Serum creatinine must be <= 1.5X upper limit of normal
15. INR must be <= 2.0

Exclusion criteria

16. Must not have main PVT (branch portal vein thrombosis is permissible).
17. Must not be eligible for curative treatment (e.g ablation or transplantation)
18. Must not have a history of previous or concurrent cancer other than HCC unless treated curatively 5 or more years prior to entry
19. Must not have confirmed presence of extra-hepatic disease with the exception of lung nodules
and mesenteric or portal lymph nodes <= 2.0 cm each
20. Must not be at risk of hepatic or renal failure
21. Must not have tumor replacement >70% of total liver volume based on visual

estimation by the
investigator OR must not have tumor replacement >50% of total liver volume in the presence of
albumin <3 g/dL
22. Must not have any history of severe allergy or intolerance to contrast agents, narcotics sedatives
or atropine that cannot be managed medically
23. Must not have any contraindications to angiography and selective visceral catheterization
24. Must not have history of organ allograft
25. Must not have any known contraindications to sorafenib including allergic reaction, pill-swallowing difficulty, evidence of severe or uncontrolled
systemic diseases, uncontrolled severe hypertension or cardiac arrhythmias, congestive heartcardiac failure >New York Heart Association (NYHA) class 2, myocardial infarct within 6 months, prolonged QT/QTc >450ms, evidence of torsades de
pointe, or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial , significant GI bleed within 30 days, metastatic brain disease, renal failure requiring dialysis.
26. Must not be taking any of the following: Rifampicin, St. John*s Wort, phenytoin, carbamazepine,
phenobarbital, and dexamethasone
27. Must not be taking any other systemic anticancer agent (e.g docetaxel, doxorubicin, irinotecan etc)
28. Must not be taking substrate agents for CYP2B6 (buproprion, cyclophosphamide, efavirenz,
ifosfamide, methadone, pacilitaxel, amodiaquine, repaglinide)
29. Must not be taking UGT 1A1 and UGT 1A9 substrates (e.g., irinotecan)
30. Must not be taking P-Gp substrates (e.g., Digoxin)
31. Any prior liver resection must have taken place > 2 months prior to randomization
32 Treatment with other locoregional therapies (other than study treatment) has not been planned
for the duration of the clinical study period
33 Has not received any prior external beam radiation treatment to the chest, liver or abdomen
34. Has not received any prior yttrium-90 microsphere treatment to the liver
35. Prior treatment with transarterial chemoembolization (TACE) or bland embolization must have
occurred > 2 months prior to randomization and must have been applied to a treatment field
and/or lobe that is not to be treated under this protocol. For patients with tumor progression in the treatment field and/or lobe previously treated with TA(C)E, vessels feeding the tumor(s) must
be assessed for adequate blood flow using angiography (cone beam computerized tomography (CBCT) strongly recommended), and the TACE or bland embolization

must have been applied >6 months prior to randomization.
36. Has not received any anti-cancer therapy or any treatment with an investigational agent within
30 days prior to randomization
37. Must not have any adverse effect due to prior therapy that is unresolved at randomization
38. Has not received any prior systemic therapy for the treatment of HCC, including sorafenib given for more than 4 weeks during the 2 previous months prior to randomisation; no prior sorafenib related toxicity
39. No evidence of pulmonary insufficiency or inadequately treated moderate grade or severe/very severe grade chronic obstructive pulmonary disease.
40. Must not have undergone any intervention for, or compromise of, the Ampulla of Vater
41. Must not have any clinically evident ascites (trace ascites on imaging is acceptable)
42. Must not be pregnant or breast-feeding
43. Women of childbearing potential must have a negative serum pregnancy test within 14 days
prior to randomization
44. Must not have any disease or condition that would preclude the safe use of TheraSphere,
including concurrent dialysis treatment, or unresolved serious infections.
Patients infected with HIV can be considered, however, they must be wellmanaged and well controlled with an undetectable viral load.
45. Must not be participating in concurrent clinical trials evaluating treatment intervention(s).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-11-2016
Enrollment:	38
Type:	Actual

Medical products/devices used

Generic name:	TheraSphere
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	16-08-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01556490
CCMO	NL53905.018.16