Sorafenib and Micro-therapy Guided by Primovist Enhanced MRI in Patients With Inoperable Liver Cancer (SORAMIC)

Purpose

The purpose of this study is to evaluate Sorafenib and local microtherapy guided by Primovist enhanced MRI in patients with inoperable liver cancer (HCC).

Methodology:

Patients with a diagnosis of hepatocellular carcinoma will receive either:

- local ablation therapy of liver lesions by radiofrequency ablation followed by sorafenib or placebo (local ablation group), or
- radioembolization (SIRT) + sorafenib or sorafenib alone (palliative treatment group).

In each study group, patients will be randomized to one of the 2 treatment arms following a pre-defined randomization plan. Randomization will be on a 1:1 basis in the local ablation group and on the basis of 10 (sorafenib only) : 11 (SIRT + sorafenib) in the palliative treatment group.

Patients in the local ablation group will be followed at 2 months intervals for recurrence and overall survival, patients in the palliative treatment group will be followed for overall survival. Follow-up in each study group will end 24 months after inclusion of the last patient into the respective study group.

The assignment of patients to the local ablation or palliative study group will be based on the ablative potential of RFA (local ablation if \( \leq 4 \) tumors, each \( \leq 5 \) cm in size). Diagnostic imaging will be used to guide this decision. The assignment to the local ablation or the palliative treatment group will be made by the local investigator.

As a sub-study, all patients will undergo Primovist®-enhanced MRI in addition to contrast-enhanced CT before assignment to one treatment group. The goal of the sub-study is to assess the value of Primovist®-enhanced MRI to correctly stratify patients for a local ablation or palliative treatment strategy. Primovist®-enhanced MRI will be compared with contrast-enhanced multislice CT using a truth panel assessment as the standard of reference. In addition, Primovist-enhanced MRI and contrast-enhanced CT will be obtained during follow-up of patients in the local ablation group to assess its potential for detection of recurrence.
Further study details as provided by University of Magdeburg:

### Primary Outcome Measures:
- **time to recurrence** [Time Frame: 13-18 months (average time to recurrence)] [Designated as safety issue: Yes]
  - In patients in whom local ablation therapy is appropriate, to determine if the sorafenib in combination with radiofrequency ablation (RFA) prolongs the time-to-recurrence (TTR) in comparison with RFA + placebo.
- **overall survival** [Time Frame: 10-15 months (average survival)] [Designated as safety issue: Yes]
  - In patients in whom RFA is NOT appropriate (palliative treatment group), to determine if the combination of yttrium-90 microspheres (SIRT) + sorafenib improves the overall survival (OS) in comparison to sorafenib alone.
  - Interim analyses will be conducted after 60 and 180 deaths and a final analysis after 240 deaths.
- **Primovist©-enhanced MRI is non-inferior or superior compared with contrast-enhanced multislice CT** [Time Frame: 3 years] [Designated as safety issue: No]
  - To confirm in a 2-step procedure that Primovist©-enhanced MRI is non-inferior (first step) or superior (second step) compared with contrast-enhanced multislice CT for assignment of patients to a palliative vs. local ablation treatment strategy.
  - The overall study is successful, if the primary objectives 1 OR 2 are met, AND Primovist-enhanced MRI is at least non-inferior to contrast-enhanced CT for treatment stratification.

### Secondary Outcome Measures:
- **quality of life** [Time Frame: 3 years] [Designated as safety issue: No]
  - Assess health-related quality of life via ECOG questionnaire
- **safety of RFA** [Time Frame: 3 years] [Designated as safety issue: Yes]
  - To assess the safety of the combination of RFA + sorafenib in comparison to RFA + placebo
- **safety of SIR Spheres** [Time Frame: 3 years] [Designated as safety issue: Yes]
  - To assess the safety of the combination of SIR-Spheres therapy and sorafenib in comparison to sorafenib alone.

### Estimated Enrollment:
665

### Study Start Date:
December 2010

### Estimated Study Completion Date:
February 2014

### Estimated Primary Completion Date:
February 2014 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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<tr>
<td>local ablation group</td>
<td>Procedure: RFA</td>
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<tr>
<td>Local ablation group: Potentially curative treatment of early HCC includes surgical resection and local ablation (RFA, PEI, BT). Recurrence rates after such approaches are reported to amount to 50% at 3 years and 70% at 5 years. Tumor recurrence may be either due to de novo development of new primary tumors or due to intrahepatic (unrecognized) metastases. Prevention of recurrence after local ablation is an important strategy to improve overall survival. So far, adjuvant chemembolization and chemotherapy have not proven to be effective in preventing recurrences. There is, however, a strong rationale to assume that sorafenib will be of value in the adjuvant treatment of HCC as sorafenib has a dual mechanism of action (inhibition of tumor proliferation and antiangiogenesis) and has proven efficacy in HCC.</td>
<td>A max.of 2 percutaneous RFA sessions is permitted per patient with a max.of 2 liver lesions treated in each RFA session. Randomization to sorafenib or placebo is performed after completion of RFA. Percutaneous RFA is to be performed according to the manufacturer's instructions and following as far as possible routine procedures of the participating hospital. Typically, RFA will be performed under conscious sedation, general anesthesia is permitted. After local anesthesia of the site of puncture, the applicator is positioned in the center of the lesion using ultrasound-, CT- or MR-guidance. The success of ablation is to be controlled directly after RFA using ultrasound, contrast-enhanced CT, or MR imaging. If for any reason RFA is deemed incomplete within the immediate follow-up (up to 2 weeks after the initial ablation), RFA is to be repeated once (in this case, the total (max.) number of RFA sessions will be three). The study procedure guide will contain further instructions for RFA. Other Name: Sorafenib (Nexavar 200 mg film-coated tablets),marketing authorization no.: EU/1/06/342/001</td>
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<td>Active Comparator: palliative treatment group</td>
<td>Procedure: Radioembolization (SIRT)</td>
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<td>Radioembolization has been reported to be effective in patients with</td>
<td>One SIRT prescription consists of the pre-treatment assessment followed</td>
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unresectable HCC with preserved liver function from a number of trials. Successful downstaging of disease rendering patients eligible for potentially curative therapies, and even histologically confirmed complete responses of unresectable HCC, have repeatedly been reported providing the rationale to evaluate SIRT+sorafenib in comparison to sorafenib alone.

The impact of cirrhosis as a concomitant disease in most patients with HCC is that it limits the ability of many patients to tolerate chemotherapy and is an independent cause of death in HCC patients. Thus, the historical difficulty in demonstrating an effect of therapy on survival in patients with advanced-stage, unresectable HCC (the majority). A new therapy that is effective in controlling hepatic disease, is less toxic than traditional chemotherapy, and improves the quality of life for patients in the advanced stages of HCC could represent an alternative.

The aim of pre-treatment assessment is to ensure delivery of the microspheres to the target. Evaluation includes a determination of the arterial location and any consequent necessity for coil-embolization of the gastroduodenal artery, right gastric artery and any other accessory arteries to prevent inadvertent administration of microspheres into the gastrointestinal tract or pancreas. In addition, parasitic extrahepatic supply should be coil-embolized. Patients in whom the shunt fraction indicates potential exposure to the lung to an absorbed radiation dose of more than 30 Gy should be excluded from treatment with SIR-Spheres. Patients who are randomized to receive SIRT but who are not regarded as eligible for SIRT after the pre-treatment assessment will be switched to the sorafenib only group within the palliative treatment arm.

Other Names:
- SIR Spheres Microspheres
- Sorafenib (Nexavar)

### Eligibility

**Ages Eligible for Study:** 18 Years to 85 Years

**Genders Eligible for Study:** Both

**Accepts Healthy Volunteers:** No

**Criteria**

**Inclusion Criteria:**
- Age: 18-85 years
- Diagnosis of hepatocellular carcinoma
- If primary diagnosis of HCC: diagnosis based on the following criteria:
  - cyto-histological criteria, OR
  - radiological criteria: Focal lesion >1 cm with arterial hypervascularization in 2 coincident imaging techniques (CT, MRI, or US), OR
  - combined criteria: one imaging technique showing a focal lesion 1-2 cm with arterial hypervascularization AND AFP levels >400 ng/mL, OR
  - combined criteria: one imaging technique showing a focal lesion >2 cm with arterial hypervascularization AND AFP levels >200 ng/mL
- If extrahepatic metastases: liver-dominant disease
- Stage BCLC A, B, or C
- Child-Pugh A, Child-Pugh B up to 7 points (in patients receiving anticoagulant therapy: Child-Pugh score up to 5 points; INR category not regarded for calculation of the Child-Pugh score)
- Willing to comply with all study procedures
- Has voluntarily given written informed consent

**Exclusion Criteria:**
- If female, pregnant or breast feeding (females of child-bearing potential must use adequate contraception and must have a negative pregnancy test performed within 7 days prior to inclusion into this study)
- If male, not using adequate birth control measures
- One or more of the following:
  - Hemoglobin <10g/dL,
  - WBC <2,500 cells/mm3,
  - ANC <1,500 cells/mm3,
  - platelets <50,000/mm3,
  - ECOG performance status >2
- Life expectancy <16 weeks
- Extrahepatic metastases (except metastases to bone, lymph nodes, and adrenal glands which do not constitute an exclusion criterion)
- Patients with known GFR <30 mL/min/1.73m2
- PT-INR/PTT >1.5 times the upper limit of normal (patients on anticoagulation therapy will be allowed to participate provided that no prior evidence exists of an underlying abnormality in anticoagulation)
- uncontrolled infections at the time of microtherapy
- Child-Pugh score >7 points; in patients receiving anticoagulant therapy: Child-Pugh score >5 points (INR category not regarded for calculation of the Child-Pugh score)
- Uncontrolled ascites
- tumor load of the whole liver >70%
• Contraindications for study medications according to product labeling or procedures (sorafenib, Primovist®, x-ray contrast agents, SIR-Spheres®, RFA, MRI, CT) incl. any contraindication to the trans-arterial interventional procedure (e.g., allergy against x-ray contrast agents, uncontrolled hyperthyroidism)
• Prior resection of the papilla of Vater (e.g., Whipple procedure) or bile duct stent across the papilla
• Significant cardiovascular disease; e.g., myocardial infarction within 6 months of inclusion, chronic heart failure (New York Heart Association class III or IV), unstable coronary artery disease
• Uncontrolled hypertension
• Thrombotic or embolic events including transient ischemic attacks within the past 6 months
• History of hemorrhage / bleeding events of grade 3 or worse
• Previous variceal bleeding within the past 3 months
• Previous malignancy other than carcinoma in situ of the skin or the cervix uteri within 5 years prior to inclusion
• History of organ transplant (including prior liver transplantation)
• HIV, congenital immune defect, any immunosuppressive therapy for autoimmune disease (rheumatoid arthritis) or inflammatory bowel disease
• Mental conditions rendering the subject incapable to understand the nature, scope, and consequences of the trial
• Close affiliation with the investigational site; e.g. first-degree relative of the investigator.
• Participating in another therapeutic clinical trial or has completed study participation in another therapeutic clinical trial within 30 days of enrolment into this trial
• Having been previously enrolled in this clinical trial

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01126645

Contacts

Contact: Benjamin Etschmann 0049 30 6322270 0 mailto:soramic@pharmtrace.com
Contact: Friederike Sattler, M.A. 0049 391 67 15591 mailto:soramic@med.ovgu.de

Locations

Germany

University of Magdeburg Recruiting
Magdeburg, Germany, 39120
Contact: Jens Ricke, Prof. Dr. 0049 391 67 13030 mailto:jens.ricke@med.ovgu.de

Sponsors and Collaborators

University of Magdeburg
Bayer
Sirtex Medical

Investigators

Study Director: Jens Ricke, Prof. Dr. University of Magdeburg
Study Director: Peter Malfertheiner, Prof. Dr. University of Magdeburg

More Information

Additional Information:
web page of SORAMIC clinical trial

No publications provided

Responsible Party: Prof. Dr. Jens Ricke, University of Magdeburg
ClinicalTrials.gov Identifier: NCT01126645 History of Changes
Other Study ID Numbers: RAD85, 2009-012676-27
Study First Received: May 17, 2010
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Health Authority: Germany: Federal Institute for Drugs and Medical Devices
Germany: Federal Office for Radiation Protection

Keywords provided by University of Magdeburg:
Liver
HCC

Additional relevant MeSH terms:
Carcinoma Digestive System Diseases
Carcinoma, Hepatocellular
Neoplasms, Glandular and Epithelial
Neoplasms by Histologic Type
Neoplasms
Adenocarcinoma
Liver Neoplasms
Digestive System Neoplasms
Neoplasms by Site

Liver Diseases
Sorafenib
Antineoplastic Agents
Therapeutic Uses
Pharmacologic Actions
Protein Kinase Inhibitors
Enzyme Inhibitors
Molecular Mechanisms of Pharmacological Action

ClinicalTrials.gov processed this record on October 22, 2012