RADIATION THERAPY ONCOLOGY GROUP
RTOG 1112

Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy followed by Sorafenib in Hepatocellular Carcinoma

SCHEMA (8/26/14)

<table>
<thead>
<tr>
<th>REGISTRATION</th>
<th>STRATIFY</th>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none)</td>
<td>Arm 1</td>
<td>Daily sorafenib</td>
</tr>
<tr>
<td>Hepatitis B or B and C vs. C vs. other</td>
<td>Arm 2</td>
<td>SBRT alone (27.5 Gy – 50 Gy in 5 fractions)</td>
</tr>
<tr>
<td>North American site vs. Non-North American site</td>
<td></td>
<td>Followed by Sorafenib alone daily</td>
</tr>
<tr>
<td>HCC volume/liver volume (&lt;10% vs. 10-40 vs. &gt;40%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See Section 5.0 for radiation therapy credentialing details. See Section 7.0 for details/doses of sorafenib.

Protocol treatment must begin within 21 days after study registration.

**Patient Population:** (See Section 3.0 for Eligibility)
Unsuitable for resection or transplant or radiofrequency ablation (RFA)
Unsuitable for TACE or refractory to TACE
Barcelona Clinic Liver Cancer Stage (BCLC) Intermediate (B) or Advanced (C)

**Required Sample Size:** 368
RTOG 1112/LU206931  Randomized Phase III Study of Sorafenib Versus Sterotactic Body Radiation Therapy Followed By Sorafenib In Hepatocellular Carcinoma.

Eligibility:

1. Patients must have an HCC diagnosis (initial, recurrent, progressive and/or refractory to other therapies) by at least one criterion listed below ≤360 days prior to study entry
2. Pathologically (histologically or cytologically) proven diagnosis of HCC.
3. At least one solid liver lesion or vascular tumor thrombosis (involving portal vein, IVC and/or hepatic vein) > 1 cm with arterial enhancement and delayed washout on multiphasic computerized tomography (CT) or magnetic resonance imaging (MRI) in the setting of cirrhosis or chronic hepatitis B or C without cirrhosis.
4. For patients whose CURRENT disease is vascular only: Enhancing vascular thrombosis (involving portal vein, IVC and/or hepatic vein) demonstrating early arterial enhancement and delayed washout on multi-phasic CT or MRI, in a patient with known HCC (diagnosed previously < 720 days), using criteria in 3.1.1a or 3.1.1b
5. Measureable hepatic disease and/or presence of vascular tumor thrombosis (involving portal vein, IVC and/or hepatic vein) which may not be measureable as per RECIST, as defined in Section 11.0) on liver CT or MRI, within 28 days of registration
   - Assessment by radiation oncologist and medical oncologist or hepatologist who specializes in treatment of HCC within 28 days prior to study entry
   - Pre-randomization Scan (REQUIRED for All Patients): CT scan chest/abdomen/pelvis with multiphasic liver CT or multiphasic liver MR scan within
6. Zubrod Performance Status 0-2 within 28 days prior to study entry
7. Age ≥ 18
8. All blood work obtained within 14 days prior to study entry with adequate organ marrow function
9. BCLC stage: Intermediate (B) or advanced (C) within 14 days prior to study entry
10. Child-Pugh score A within 14 days prior to study entry
11. Women of childbearing potential and male participants must agree to practice adequate contraception while on study and for at least 6 months following the last dose of RT and for at least 28 days following the last dose of sorafenib (whichever is later).
12. Unsuitable for resection or transplant or radiofrequency ablation (RFA)
13. Unsuitable for or refractory to transarterial hepatic chemo-embolization (TACE) or drug eluting beads (DEB) for any of the following reasons, as described by Raoul et al (2011)
14. Patient must be able to provide study-specific informed consent prior to study entry.
Exclusion Criteria:

1. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 2 years (Note that carcinoma in situ of the breast, oral cavity, or cervix are all permissible)
2. Prior sorafenib use > 60 days. Note that prior chemotherapy for HCC or a different cancer is allowable. See Section 3.2.1.
3. Prior radiotherapy to the region of the liver that would result in excessive doses to normal tissues due to overlap of radiation therapy fields
4. Prior selective internal radiotherapy/hepatic arterial Yttrium therapy, at any time
5. Severe, active co-morbidity, defined as follows:
   - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months before registration
   - Transmural myocardial infarction within the last 6 months prior to study entry
   - Unstable ventricular arrhythmia within the last 6 months prior to study entry
   - Acute bacterial or fungal infection requiring intravenous antibiotics within 28 days prior to study entry
   - Hepatic insufficiency resulting in clinical jaundice, encephalopathy and/or variceal bleed within 60 days prior to study entry
   - Bleeding within 60 days prior to study entry due to any cause, requiring transfusion
   - Thrombolytic therapy within 28 days prior to study entry. Subcutaneous heparin is permitted.
   - Known bleeding or clotting disorder
   - Uncontrolled psychotic disorder

6. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

6. Any one hepatocellular carcinoma > 15 cm
8. Total maximal sum of hepatocellular carcinomas or a single conglomerate HCC > 20 cm
   More than 5 discrete intrahepatic parenchymal foci of HCC
9. Direct tumor extension into the stomach, duodenum, small bowel or large bowel
10. Measureable common or main branch biliary duct involvement with HCC
11. Extrahepatic metastases or malignant nodes (that enhance with typical features of HCC) > 3.0 cm, in sum of maximal diameters (e.g. presence of one 3.4 cm metastatic lymph node or two 2 cm lung lesions). Note that benign non-enhancing periportal lymphadenopathy is not unusual in the presence of hepatitis and is permitted, even if the sum of enlarged nodes is > 2.0 cm.
12. Use of regular phenytoin, carbamzepine, hypericum perforatum [also known as St. John's wort] or Rifampin
13. Use of combination anti-retroviral therapy for HIV, as these agents may modulate cytochrome P450 isozymes
14. Prior liver transplant