Purpose

To evaluate and compare the efficacy and safety of regorafenib versus placebo in subjects with colorectal cancer (CRC) after curative resection of liver metastasis and completion of all planned chemotherapy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Neoplasms</td>
<td>Drug: Regorafenib (Stivarga, BAY73-4506)</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Drug: Placebo</td>
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</tbody>
</table>

Resource links provided by NLM:

MedlinePlus related topics: Cancer Colorectal Cancer

Drug Information available for: Regorafenib

Genetic and Rare Diseases Information Center resources: Liver Cancer

Primary Outcome Measures:

- Disease Free Survival (DFS) as assessed by investigator [ Time Frame: Every 3 months for approximately 50 months ]
  [ Designated as safety issue: No ]
  DFS is defined as the time (in days) from date of randomization to date of first observed disease recurrence or death

Secondary Outcome Measures:

- Overall Survival (OS) [ Time Frame: Up to 90 months ] [ Designated as safety issue: No ]
  Overall Survival (OS) is defined as the time from the date of randomization /starting treatment to death due to any cause.

- Number of participants with adverse events as a measure of safety and tolerability [ Time Frame: Approximately 50 months ]
Regorafenib as Adjuvant Therapy for Colorectal Cancer (CRC) With R...

Estimated Enrollment: 750
Study Start Date: December 2013
Estimated Study Completion Date: September 2021
Estimated Primary Completion Date: March 2018 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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</thead>
<tbody>
<tr>
<td>Experimental: Regorafenib</td>
<td>4 regorafenib tablets taken orally in the morning daily, followed by a low fat meal for 3 weeks on off treatment followed by 1 week off without treatment, Treatment 21 days. Drug: Regorafenib (Stivarga, BAY73-4506) Four tablets of 40mg taken orally daily in the morning, dose of 160 mg for 21 days of treatment followed by 7 days without treatment</td>
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<tr>
<td>Placebo Comparator: Placebo</td>
<td>4 placebo tablets taken orally in the morning daily, followed by a low fat meal for 3 weeks on off treatment followed by 1 week off without treatment, Treatment 21 days. Drug: Placebo Four tablets taken in the morning orally daily for 21 days of treatment followed by 7 days without treatment</td>
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Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Have a diagnosis of Stage IV CRC with metastases to the liver only and have undergone one of the following three treatment regimens:
  - A primary CRC lesion(s) in the colon and/or rectum and synchronous liver metastases, which were treated with surgery with curative intent for both primary and metastatic lesions and at least 3 months of neoadjuvant, adjuvant, or perioperative chemotherapy including a fluoropyrimidine and either oxaliplatin or irinotecan. Total chemotherapy administered, including that administered prior to and after liver resection, should not exceed 6 months.
  - A primary CRC lesion(s) in the colon and/or rectum, treated with surgery and at least 3 months of adjuvant chemotherapy with a) a fluoropyrimidine or b) a fluoropyrimidine and oxaliplatin or c) a fluoropyrimidine and irinotecan and > 6 months after completing treatment for primary CRC, developed liver metastases, which were treated with surgery with curative intent and a second course of chemotherapy lasting at least 3 months, including a fluoropyrimidine and either oxaliplatin or irinotecan.
  - A primary CRC lesion(s) in the colon and/or rectum, treated with surgery and at least 3 months of chemotherapy, including a) a fluoropyrimidine, b) fluoropyrimidine and oxaliplatin, or c) fluoropyrimidine and irinotecan, and developed liver metastases ≤6 months after completing treatment for primary CRC which were treated with surgery with curative intent.
- Prior to randomization, have histological confirmation that all CRC lesions were adenocarcinoma.
- Have pathology-proven complete removal of all primary and liver metastatic CRC lesions. Subjects with positive margins will not be eligible for the study.
- Have adequate bone marrow function, liver function, and renal function, as measured by the following laboratory assessments conducted within 7 days prior to the initiation of study treatment:
  - Total bilirubin ≤1.5 times the upper limit of normal (ULN)
  - Alanine aminotransferase and aspartate aminotransferase ≤3 times the ULN
  - Lipase ≤1.5 times the ULN
  - Serum creatinine ≤1.5 times the ULN
  - Carcinoembryonic antigen (CEA) ≤3 times the ULN
  - Glomerular filtration rate ≥30 mL/min/1.73 m² according to the Modified Diet in Renal Disease abbreviated formula
  - International normalized ratio of prothrombin time and activated partial thromboplastin time ≤1.5 times the ULN. Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate if no underlying abnormality in coagulation parameters exists per medical history.
  - Platelet count ≥100,000 /mm³, hemoglobin ≥9 g/dL, absolute neutrophil count ≥1500/mm³ without transfusions or granulocyte colony stimulating factor and other hematopoietic growth factors
  - Alkaline phosphatase ≤2.5 times the ULN
- Have had a CT or MRI scan (chest, abdomen, pelvis and other suspected sites as applicable) to determine eligibility for randomization within 4 weeks prior to randomization (hereafter referred to as the "eligibility scan")
- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 14 days prior to the initiation of study treatment
- If female and of childbearing potential, or if male, agree to use adequate contraception (eg, abstinence, intrauterine device, oral contraceptive, or double barrier method) based on the judgment of the investigator or a designated associate from the date on which the ICF is signed until 8 weeks after the last dose of study drug.
- Abstinence is only acceptable as 'true abstinence': when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and
withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

- Are taking strong cytochrome P (CYP) CYP3A4 inhibitors (eg, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort).
- Have used biologic response modifiers, such as granulocyte-colony stimulating factor, within 3 weeks of study entry.
- Have had prior treatment with regorafenib or any other VEGFR-targeting kinase inhibitor.
- Have had anti-cancer treatment following liver resection that exceeded a duration of 6 months.
- Have been treated with biologics (eg, antibodies targeting VEGFR or EGFR) after liver resection unless the administration of the biologic started prior to liver resection and continued after liver resection only to complete a pre-specified number of cycles.
- Completed their last dose of chemotherapy or had their last cancer surgery more than 8 weeks, whichever came later, prior to randomization.
- Have extra-hepatic metastatic disease. Suspicious lesions should be rigorously evaluated with other imaging techniques and/or biopsy.
- Have had systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and/or hormonal therapy within 4 weeks prior to initiation of study treatment.
- Are pregnant and or breast feeding.
- Have had prior or concurrent cancer distinct in primary site or histology from CRC within 5 years prior to randomization EXCEPT for curatively treated cervical cancer in situ, nonmelanoma skin cancer, or superficial bladder tumors classified as noninvasive tumor (Ta), carcinoma in situ (Tis), or tumor invades lamina propria (T1).
- Have congestive heart failure classified as New York Heart Association Class 2 or higher. Have had unstable angina (angina symptoms at rest) or new-onset angina greater than 3 months prior to screening. Have had a myocardial infarction greater than 6 months prior to initiation of study treatment.
- Have had arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 6 months prior to the initiation of study treatment.
- Have cardiac arrhythmias requiring anti-arrhythmic therapy, with the exception of beta blockers or digoxin.
- Have uncontrolled hypertension (systolic blood pressure [SBP] greater than 140 mmHg or diastolic blood pressure [DBP] greater than 90 mmHg) despite optimal medical management.
- Have pheochromocytoma.
- Have had a hemorrhage or a bleeding event >/=Grade 3 (NCI-CTCAE v 4.0) within 4 weeks prior to the initiation of study treatment.
- Have any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the subject and/or his/her compliance with study procedures, or may interfere with the subject's participation in the study or evaluation of the study results.