

CLINICAL STUDY PROTOCOL

Title:

Phase II, open label, non-randomized study of second line treatment with sorafenib (BAY 43-9006) in patients affected by relapsed high-grade osteosarcoma.

Test Drug: Sorafenib

Sponsor's Name and Address:

Italian Sarcoma Group
c/o Istituti Ortopedici Rizzoli
Via di Barbiano, 1/10 – 40136 Bologna

Sponsor's Telephone Number:

051.6366757

Study Number/Version/Date:

HGosteo-BAY – versione 1.0 del 18.07.2007

Development Phase:

Phase II

Study Authors:

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INVESTIGATOR(S) AND OTHER STUDY PARTICIPANTS

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Inclusion Criteria

1. Patients with histologically documented and not surgically resectable or metastatic high-grade osteosarcoma which progressed after first line treatments.
2. Measurable disease as defined by having at least one lesion that can be accurately measured by means of CT or MRI. Baseline evaluations must be completed within 2 weeks prior to enrollment.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 and an estimated life expectancy of at least 3 months. Patients with and ECOG P.S. 2 are eligible if the P.S.2 depends solely on orthopedic problems
4. Age 15 years.
5. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to start of treatment:

-Hemoglobin ≥ 9.0 g/dl

-Absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$

-Platelet count $\geq 100,000/\mu\text{l}$

-Total bilirubin ≤ 1.5 times the upper limit of normal

-ALT and AST ≤ 2.5 x upper limit of normal (≤ 5 x upper limit of normal for patients with liver involvement of their cancer)

-PT-INR/PTT < 1.5 x upper limit of normal [Patients who are being therapeutically anticoagulated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.]

-Serum creatinine ≤ 1.5 x upper limit of normal.

Written informed consent

Exclusion Criteria

Patients who meet the following criteria at the time of screening will be excluded:

1. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.
2. Coexisting malignancies, except for basal or epithelial cell carcinoma of the skin or other solid tumors curatively treated with no evidence of disease for ≥ 3 years.

3. History of cardiac disease: congestive heart failure >NYHA class 2; active CAD (MI more than 6 months prior to study entry is allowed); cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted) or uncontrolled hypertension.
4. History of HIV infection or chronic hepatitis B or C.
5. Active clinically serious infections (> grade 2 NCI-CTC version 3.0)
6. Symptomatic metastatic brain or meningeal tumors (unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry and is clinically stable with respect to the tumor at the time of study entry)
7. Patients with seizure disorders requiring medication (such as steroids or anti-epileptics)
8. Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must use adequate barrier birth control measures during the course of the trial and two weeks after the completion of trial.
9. Patients with evidence or history of bleeding diathesis
10. Patients undergoing renal dialysis
11. Patients unable to swallow oral medications