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A randomised study evaluating the efficacy and safety of sorafenib compared to placebo in metastatic breast cancer

Submission date 10/03/2010	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 06/04/2010	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 06/04/2010	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
FM-B07-01

Study information

Scientific Title

A Multinational Double-Blind, Randomised Phase IIb Cooperative Group Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo when Administered in Combination with Chemotherapy and/or Endocrine Therapy in Patients with Locally Recurrent or Metastatic Breast Cancer

Acronym
SOR

Study objectives
The primary efficacy variable is progression-free survival (PFS). Assuming an exponential distribution for PFS, a median PFS of 7.9 months in the placebo group and 12.2 months in the sorafenib group, a total enrollment of 220 patients will result in the attainment of the targeted 120 PFS events approximately 4 months after completion of enrollment.
In this trial, based on 120 PFS events, an observed HR ≤0.82 would provide evidence that sorafenib is effective. The false positive error rate (one-sided p-value) associated with an observed HR of 0.82 is 0.14. Under the alternative hypothesis that the true HR is 0.65, an observed HR of 0.82 has a false negative error rate of 0.10. The false positive error rate (one-sided) associated with an observed HR of 0.70 is 0.025. Furthermore, under the alternative hypothesis that the HR is 0.65, this trial has power of 66% to achieve a one-sided p-value <0.025 (corresponding to having an observed HR of 0.70).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Independent Ethics Committee of the Istituto Nazionale Tumori of Milano (Coordinating Centre) approved the original protocol on the 20th June 2007. All other centres will seek ethics approval before recruiting participants.

Study design
Multicentre double-blind randomised phase IIb study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Locally recurrent or metastatic breast cancer

Interventions
All patients will be treated with best standard therapy (chemotherapy, endocrine therapy or both) based on clinical status as following:
1. Endocrine therapy if estrogen-receptor positive (ER+) or progesterone receptor-positive (PgR+) and bone or soft tissue disease or both
2. Chemotherapy followed by endocrine therapy after best response to chemotherapy (including stable disease) or excessive toxicity or up to a maximum of 6 cycles if ER+ or PgR+ and visceral lesions (with or without bone/soft tissue). In patients starting chemotherapy and switching to letrozole, the latter will be prescribed starting on day 15-21 of the last cycle of chemotherapy

3. Chemotherapy if triple negative (human epidermal growth factor receptor 2 [HER2] negative, ER negative, and PgR negative) disease
Chemotherapy will consist of:
4. Docetaxel 75 mg/m2 as a 1-hour infusion on day 1 every 21 days
Endocrine therapy will consist of:
5. Letrozole 2.5 mg orally once daily
Patients are randomised to one of two treatment arms.
Arm A: Patients receive sorafenib 400 mg (2 tablets) orally twice daily
Arm B: Patients receive matching placebo (2 tablets) orally twice daily

Intervention Type
Other

Phase
Phase II/III

Primary outcome(s)
The primary objective is to compare progression-free survival (PFS) in patients treated with sorafenib and standard first-line therapy versus patients treated with placebo and standard first-line therapy for locally recurrent or metastatic breast cancer. PFS will be measured from the date of randomisation to the date of first observed disease progression or the date of death due to any cause, if before progression.

Key secondary outcome(s))
1. Comparison of the overall response rate (ORR), duration of response, time to progression (TTP), and overall survival of patients treated with sorafenib and standard first-line therapy versus patients treated with placebo and standard first-line therapy.
2. Comparison of the safety of patients treated with sorafenib and standard first-line therapy versus patients treated with placebo and standard first-line therapy.

Completion date
30/06/2010

Eligibility

Key inclusion criteria
1. Female patients with histologically or cytologically confirmed adenocarcinoma of the breast.
2. Measurable or evaluable locally recurrent or metastatic disease. (Locally recurrent disease must not be amenable to resection with curative intent.) All scans used to document measurable or evaluable disease must be done within 4 weeks prior to randomisation.
3. Age greater than or equal to 18 years . Women who are ER+ or PgR+ and candidates for endocrine therapy, must be post-menopausal as defined below:
3.1. Bilateral oophorectomy; or
3.2. No menses for at least 12 months in patients with an intact uterus, not on gonadatropin suppressing agents; or
3.3. Follicle-stimulating hormone (FSH) in postmenopausal range in patients <60 years without prior hysterectomy; or
3.4. Pre-menopausal women undergoing pharmacological ovarian ablation.
4. Any adjuvant or neoadjuvant taxane therapy must have been completed at least 12 months prior to randomisation should the patient be candidate to start present study treatment with chemotherapy.

5. Patients must have discontinued other adjuvant chemotherapy at least 3 weeks prior to randomisation.
6. Adjuvant aromatase inhibitors must have been completed at least 3 months prior to randomisation.
7. Adjuvant tamoxifen must have been completed at least 4 weeks prior to randomisation
8. Prior radiation therapy is allowed but must be completed at least 3 weeks prior to randomisation, with all acute toxicities recovered to baseline status. Previously radiated area(s) must not be the only site of disease and must not correspond to more than 25% of the bone marrow producing areas for patients who are candidate for chemotherapy.
9. ECOG Performance Status of 0 or 1
10. Adequate bone marrow, liver, and renal function as assessed by the following:
10.1. Haemoglobin equal or greater than 9.0 g/dl
10.2. Absolute neutrophil count (ANC) equal or greater than 1,500 x 10^9/L
10.3. Platelet count equal or greater than 100,000 x 10^9/L
10.4. Total bilirubin lesser than or equal to 1.5 times the upper limit of normal (ULN)
10.5. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) lesser than or equal to 2.5 x ULN (lesser than or equal to 5 x ULN for patients with liver involvement)
10.6. International Normalised Ratio for Prothrombin Time (PT-INR) lesser than or equal to 1.5 and activated prothrombin time (aPTT) within normal limits.
10.7. Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin may be allowed to participate. For patients on warfarin, the INR should be measured prior to initiation of sorafenib/placebo and monitored at least weekly, or as defined by the local standard of care, until INR is stable.
10.8. Creatinine lesser than or equal to 1.5 times the upper limit of normal.
11. Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to randomisation, and patients must agree to use adequate contraception (barrier method of birth control) prior to randomisation, for the duration of study participation, and for 28 days after the last dose of study treatment.
12. Patients must be willing and able to sign a written informed consent. A signed informed consent must be appropriately obtained prior to any study specific procedures.
13. Patients must be able to swallow, retain, and absorb whole oral tablets.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Key exclusion criteria
1. Patients with breast cancer over-expressing human epidermal growth factor receptor 2 (HER2) [gene amplification by fluorescence in situ hybridisation (FISH) or 3+ over-expression by immunohistochemistry (IHC)]. Patients with unknown HER-2 status are not eligible.

2. Patients with active brain metastases. Patients with neurological symptoms must undergo a contrast CT scan or MRI of the brain to exclude active brain metastasis. Patients with treated brain metastases are eligible provided they have no evidence of disease and are off definitive therapy (including steroids) at least 3 months prior to randomisation.
3. Prior chemotherapy or endocrine therapy for locally recurrent or metastatic breast cancer.
4. Patients with unknown hormone receptor status.
5. Patients who are ER+ or PgR+ and are pre-menopausal and unwilling to undergo pharmacological ovarian ablation
6. Women who are pregnant or breast-feeding.
7. Major surgery, open biopsy, or significant traumatic injury within 4 weeks of randomisation.
8. Evidence or history of bleeding diathesis or coagulopathy.
9. Serious, non-healing wound, ulcer, or bone fracture.
10. Substance abuse or medical, psychological, or social condition that may interfere with the patients participation in the study or evaluation of the study results.
11. Pre-existing peripheral neuropathy equal to or greater than grade 2.
12. Use of cytochrome P450 enzyme-inducing anti-epileptic drugs (such as phenytoin, carbamazepine, or phenobarbital) is not allowed.
13. Cardiac disease:
13.1. Congestive heart failure >class II New York Heart Association (NYHA) or
13.2. Unstable angina (anginal symptoms at rest), or new-onset angina (begun within the last 3 months), or myocardial infarction within the 6 months prior to randomisation, or
13.3. Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.
14. Uncontrolled hypertension (systolic blood pressure greater than 150 mm Hg or diastolic pressure greater than 90 mm Hg) despite optimal medical management.
15. Thrombolic, embolic, venous, or arterial events, such as a cerebrovascular accident including transient ischemic attacks within the past 6 months.
16. Pulmonary haemorrhage/bleeding event greater than National Cancer Institute (NCI-CTCAE) Grade 2 within 4 weeks of first dose of study drug.
17. Any other haemorrhage/bleeding event greater than NCI-CTCAE Grade 3 within 4 weeks of randomisation.
18. Active clinically serious infection greater than NCI-CTCAE Grade 2.
19. Known human immunodeficiency virus (HIV) infection or chronic hepatitis B or C.
20. Previous or concurrent cancer that is distinct in primary site or histology from breast cancer EXCEPT cervical cancer in-situ, treated basal cell carcinoma, superficial bladder tumours [Ta and Tis], or any cancer curatively treated >5 years prior to randomisation.
21. Known or suspected allergy to sorafenib, letrozole or hypersensitivity to docetaxel or drugs using the vehicles polysorbate 80 or ethanol.
22. Prior or concurrent use of St. Johns Wort or rifampin (rifampicin) within 1 week of randomisation.
23. Prior or concurrent treatment with any agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors (VEGFR) (licensed or investigational).
24. Use of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding randomisation.

Date of first enrolment
22/11/2007

Date of final enrolment
30/06/2010

Locations

Countries of recruitment
Germany

Italy

Poland

Russian Federation

Study participating centre
Fondazione IRCC Istituto Nazionale Tumori di Milano
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Sponsor information

Organisation
Fondazione Michelangelo (Italy)

ROR
https://ror.org/014vaxq24

Funder(s)

Funder type
Charity

Funder Name
Fondazione Michelangelo (Italy)

Funder Name
Onyx Pharmaceuticals Inc (USA) - provided free sorfenib/placebo as well as an unrestricted research grant

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration