A Double-Blind, Randomized Phase II Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Ovarian Epithelial Cancer or Primary Peritoneal Cancer Patients who have achieved a Complete Clinical Response after Standard Platinum/Taxane Containing Chemotherapy

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The objective of this phase IIb is to compare the efficacy and safety of sorafenib to placebo of patients with ovarian epithelial or primary peritoneal cancers stage IIIb and IV who have achieved a complete clinical response after standard platinum/...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ovarian and fallopian tube disorders
Study type	Interventional

Summary

ID

NL-OMON33786

Source
ToetsingOnline

Brief title
IMP 12007

Condition

- Ovarian and fallopian tube disorders

Synonym
Peritoneal Cancer and Ovarian Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer B.V.

Intervention

Keyword: Ovarian Epithelial cancer, Primary Peritoneal Cancer, safety and efficacy, Sorafenib

Outcome measures

Primary outcome

The primary objective is to compare the treatment groups in terms of progression

free survival (PFS), the time to CT-documented relapse.

Secondary outcome

- Time to first pathologic CA125 serum levels (needs to be confirmed with a

second measurement within 14 days) and

- Overall survival (OS).

Other efficacy evaluations will include:

- Ovarian cancer symptom response and

- General health status.

Evaluation of safety will include assessment of adverse events and

abnormalities in

laboratory parameters.

Study description

Background summary

See protocol versie 5 (30 July 2008) page 7 - 16.

Study objective

The objective of this phase IIb is to compare the efficacy and safety of sorafenib to placebo of patients with ovarian epithelial or primary peritoneal cancers stage IIIb and IV who have achieved a complete clinical response after standard platinum/taxane containing chemotherapy.

STUDY OBJECTIVES
Primary:
The primary objective is to compare the treatment groups in terms of progression free survival (PFS), the time to CT-documented relapse.
Secondary:
The secondary objectives are to compare the sorafenib and placebo treatment groups in terms of:
· Time to first pathologic CA125 serum levels (needs to be confirmed with a second measurement within 14 days) and
· Overall survival (OS).

Study design

A Double-Blind, Randomized Phase II Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Ovarian Epithelial Cancer or Primary Peritoneal Cancer Patients who have achieved a Complete Clinical Response after Standard Platinum/Taxane Containing Chemotherapy:

Patients will be randomized in a double-blind fashion using a 1:1 allocation of patients to either sorafenib or matching placebo groups.
. Sorafenib Group- Sorafenib 400 mg po (per os, taken orally) bid, continuous dosing
. Placebo Group- Matching placebo 400 mg po bid, continuous dosing.
Patients will be stratified according to:
1. The degree of residual disease following initial diagnosis and surgical debulkment: optimal surgical cytoreduction (any/each lesion remaining after surgery <=1 cm) or suboptimal surgical cytoreduction (any/each lesion remaining after surgery > 1cm).
2. The presence or absence of any IP chemotherapy before enrollment into the study.
During the treatment period, patients will be assessed for safety every 28 days and for efficacy every 56 days.

Patients will continue on treatment until disease progression, unacceptable toxicity or non-compliance. Following the completion of End of Treatment assessment, patients will be followed-up for overall survival every three months. The duration of the trial is expected to be 27.2 months from the time the first patient is randomized until the number of PFS events is achieved.

Intervention

See protocol page 57 - 58 (study flowchart)

Study burden and risks

Blood collection or venipuncture risks:

- Frequent blood samples will be collected during this study. Patient may experience pain, bleeding from the puncture site or in tissues surrounding the puncture site, blood clot formation, or local infection and inflammation in the vicinity of the puncture site (very rare).

CT (Computerized Tomography) Scan:
- Patients may have claustrophobic feeling and will be exposed to radiation during this test. In addition, there are the risks of veni-puncture (above) when the contrast medium is injected during the CT scan. Patient may experience nausea, flushing, warmth, and a salty taste. Some patients might be allergic to the contrast medium.

Contacts

Public
Bayer

Energieweg 1
3641 RT Mijdrecht
NL
Scientific
Bayer

Energieweg 1
3641 RT Mijdrecht
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must be able and willing to sign a written informed consent. A signed informed consent must be appropriately obtained prior to any study specific procedures.
· Age > 18 years.
· Histologically confirmed FIGO stage (57) III or IV ovarian epithelial cancer or primary peritoneal cancer at presentation. Patients must have achieved a clinical complete response (disappearance of all clinical and radiological evidence of tumor) after only one regimen (4-8 cycles) of platinum and taxane-containing standard chemotherapy received after tumor debulkment. Details for chemotherapy and surgical debulkment are as follows:
- Standard debulking surgery: Surgery followed by one regimen (4-8 cycles) of platinum and taxane-containing standard chemotherapy received after tumor debulkment.
- Interval surgical debulkment: Interval debulking will be defined as debulking surgery that is performed after a minimum of 2 cycles of platinum/taxane containing chemotherapy, or after a maximum of 6 cycles of chemotherapy. All patients who undergo interval debulking must subsequently complete at least 2 additional cycles of chemotherapy after debulking, and all must complete the required 4-8 cycles of chemotherapy.
- There is to be only one debulking procedure per patient.
- The taxane and platinum compounds used for either intravenous or intraperitoneal treatment can be replaced with another taxane or platinum compound, respectively. Dosing and timing of the treatment cycles (e.g. 3-weekly or 4 weekly) may vary at the discretion of the clinical investigator.
- Intraperitoneal chemotherapy is not allowed for patients undergoing interval debulking. For patients with optimally debulked residual disease following standard debulking surgery (largest tumor nodule <= 1.0 cm), intraperitoneal chemotherapy can be applied.
- No more than 6 intraperitoneal treatment cycles are allowed.

- Cross-over from intraperitoneal chemotherapy to standard intravenous taxane/platinum chemotherapy is allowed at any time. However, the total number of treatment cycles, no matter what modality, must not exceed 8.
- Complete clinical response will be documented via an eligibility scan that is performed after completion of required chemotherapy. No previous chemotherapy can be administered except for the one regimen of IV/IP chemotherapy for ovarian or primary peritoneal cancer.
· Normal serum CA125 level within 14 days prior to first dose of the study drug.
· Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
· All scans used to document complete response must be done within 42 days prior to randomization.
· Eligibility scan must be completed within 60 days of the date of the last dose of chemotherapy.
· Patients must be able to swallow and retain oral medication.
· Life expectancy of at least 12 weeks.
· Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 14 days prior to randomization:
. Hemoglobin >= 8.5 g/dl
- Absolute neutrophil count (ANC) >=1,500/ul
- Platelet count >= 75,000/ul
. Total bilirubin <= 1.5 times the upper limit of normal
. Alanine aminotransaminase (ALT) and Aspartate aminotransferase (AST) <= 2.5 x upper limit of normal
. Alkaline phosphatase <= 4 x upper limit of normal (ULN)
. Prothrombin time (PT) as measured in international normalized ratio (INR) and partial thromboplastin time (PTT) < 1.5 x ULN
. Serum creatinine <= 1.5 x ULN.
· Women of childbearing potential must have a negative serum pregnancy test performed within 14 days prior to the start of treatment. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
· Women of childbearing potential must agree to use adequate contraception (barrier method of birth control) prior to study entry and for the duration of study participation

Exclusion criteria

· Patients with any residual cancer tissue after the completion of chemotherapy detectable by standard CT or magnetic resonance imaging (MRI).
· Prior local radiotherapy, neoadjuvant chemotherapy or hormonal or any other systemic treatment other than that specified in the protocol for any current or prior diagnosis of ovarian or primary peritoneal cancer. Single-agent weekly paclitaxel will not be considered standard for the purpose of this trial, and is therefore excluded.
· Male sex.

· Patients with more than one surgical procedure for ovarian or peritoneal cancer. This does not refer to diagnostic biopsies, but does exclude second-look operations.
· Histologic subtypes of ovarian cancer other than epithelial (i.e. sarcoma, lymphoma, germ cell).
· Major surgery, open biopsy, or significant traumatic injury within 30 days prior to randomization.
· Non-healing wound, ulcer, or bone fracture.
· Evidence or history of bleeding diathesis or coagulopathy.
· Clinically significant cardiac disease including congestive heart failure > class II New York Heart Association (NYHA) (see Appendix 10.6), unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months) or myocardial infarction within the past 6 months prior to randomization.
· Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy or uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg) despite optimal medical management.
· Thrombotic or embolic venous or arterial events, such as a cerebrovascular accident, including transient ischemic attacks and pulmonary embolism within the past 6 months.
· Hemorrhage/bleeding event ³ NCI-Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 within 30 days of randomization.
· Infection > NCI-CTCAE Grade 2.
· Known human immunodeficiency virus infection or infection with hepatitis B or C.
· Previous or concurrent cancer that is distinct in primary site or histology from ovarian or primary peritoneal cancer within 5 years prior to randomization EXCEPT cervical cancer in situ, treated basal cell carcinoma and superficial bladder tumors [Ta (Non invasive tumor), Tis (Carcinoma in situ) and T1 (Tumor invades lamina propria)].
· Known or suspected allergy to sorafenib or hypersensitivity to sorafenib or any agent given in the course of this trial.
· Patients with seizure disorder requiring medication (such as steroids or antiepileptics).
· Patients undergoing renal dialysis.
· Substance abuse, medical, psychological or social conditions that may interfere with the patient*s participation in the study or evaluation of the study results.
· Unresolved toxicity (i.e. neurotoxicity) attributed to the required chemotherapy higher than NCI-CTCAE (version 3) Grade 2 (excluding cases of alopecia).
· Patients unable to swallow oral medications.
· Any malabsorption condition.
· Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study.
· Known brain metastasis. Patients with unexplained neurological symptoms will undergo a CT scan/MRI of the brain to exclude brain metastasis.
· Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within 14 days of the start of treatment, and must use adequate birth control measures during the course of the trial. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate.
Excluded therapies and medications, previous and concomitant:

· Anticancer chemotherapy, radiotherapy or immunotherapy during the study or prior to study entry for any current or prior diagnosis of ovarian or primary peritoneal cancer except for the one prior platinum/taxane containing regimen administered following surgery to treat ovarian or primary peritoneal cancer. Mitomycin C or nitrosureas will not be given within 45 days of study entry. Anticancer therapy is defined as any agent or combination of agents with clinically proven anticancer activity administered by any route with the purpose of affecting the cancer, either directly or indirectly, including palliative and therapeutic endpoints.
· Use of St. John*s Wort or rifampin (rifampicin) within 7 days of randomization.
· Use of cytochrome P450 enzyme-inducing drugs.
· Prior or concomitant treatment with bevacizumab or any other drugs (licensed or investigational) that target VEGF or VEGFR.
· Autologous bone marrow transplant or stem cell rescue within 4 months of study.
· Use of biologic response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 21 days of study entry. [G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator; however they may not be substituted for a required dose reduction].
· Investigational drug therapy outside of this trial during or within 30 days prior to randomization.
· Prior exposure to the study drug.
· Therapeutic anticoagulation with vitamin K antagonists such as warfarin or with heparins and heparinoids.
. Low dose warfarin (1mg po qd) with INR £ 1.5 is permitted.
. Low dose of aspirin is permitted £ 100 mg daily.
. Prophylactic doses of heparins are permitted

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-06-2009
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-12-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-04-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2009
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-08-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-10-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-10-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-04-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-05-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	19-07-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-004429-41-NL
CCMO	NL25894.003.08