Phase IB-II, open label, multicentre feasibility study of pazopanib in combination with Paclitaxel and Carboplatin in patients with platinumrefractory/ resistant ovarian, fallopian tube or peritoneal carcinoma.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON45226

Source
ToetsingOnline

Brief title
Pazopanib and weekly paclitaxel/carboplatin in ovarian cancer

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
fallopian tube cancer, ovarian cancer

Research involving

Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC;Novartis,Novartis

Intervention

Keyword: ovarian cancer, pazopanib, platinum-resistant, weekly paclitaxel carboplatin

Outcome measures

Primary outcome

Primary end point: PFS defined by RECIST 1.1 at 1 year.

Secondary outcome

Secondary end points:

- Response Rate

- Overall Survival/ Progression Free Survival

- Safety and tolerability of the combination, according to CTCAE 4.0

- Predictive biomarkers

- Age related subanalysis for toxicity and efficacy (cut-off 65 years)

Study description

Background summary

Title: Phase IB-II, open label, multicentre feasibility study of pazopanib in combination with paclitaxel and carboplatin in patients with platinum refractory/ resistant ovarian, fallopian tube or peritoneal carcinoma.

In 2002 the estimated number of new cases worldwide was 204 000 with 125 000 cancer deaths, ranking ovarian cancer as the 6th most common cancer in women, and 7th most common cause of cancer death. About 90% of cases are epithelial carcinomas, and more than 75% of patients present at an advanced stage. Ovarian cancer responds well to chemotherapy, with complete response rates to first

line platinum containing chemotherapy in up to 45% of patients. Unfortunately, after a median progression-free interval of 18 months most patients relapse, and will ultimately die of their disease. The prognosis is poor for patients who relapse less than 6 months since the last platinum containing therapy (considered platinum-resistant) or who progress within 4 weeks of platinum administration (platinum-refractory) The use of weekly paclitaxel in combination with 3-weekly carboplatin has been recently shown to be superior as first- line therapy in a randomized study of the Japanese GOG. In addition several studies have shown the promising activity of dose dense or weekly paclitaxel/carboplatin in recurrent, even platinum-resistant, ovarian carcinoma. The dosages used in the weekly scheme (carboplatin AUC 2.7/week and Paclitaxel 60mg/m²/week) are higher than that of most studies using weekly paclitaxel carboplatin combination in ovarian cancer, but have been shown to be well tolerated and effective.

Pazopanib (GW786034) is an orally active, multi-target tyrosine kinase inhibitor (TKI) with a potent and selective in vitro activity against VEGF receptors (VEGF receptor-1, -2, and -3), platelet-derived growth factor (PDGF) receptor-* and -*, and stem cell factor receptor (CD-117 or c-Kit ligand). In preclinical models of ovarian cancer, anti- VEGF therapy has been shown to inhibit ascites formation, slow tumor growth and synergy with cytotoxic agents. Several retrospective clinical studies in ovarian cancer have also demonstrated that intratumoral VEGF and VEGFR-2 expression are independent poor prognostic factors. Approximately 3000 subjects with cancer have been enrolled in clinical studies of pazopanib. Data from these studies show that oral pazopanib at a dose of 800 mg daily is associated with an acceptable patient safety profile and established efficacy in various tumor types. Pazopanib has shown efficacy in renal cell carcinoma, soft tissue sarcoma, non-small cell lung cancer, breast cancer, cervical cancer and ovarian cancer. Pazopanib has received US Food and Drug Administration approval for two indications: renal cell carcinoma (RCC) and soft-tissue sarcomas.
Experience with pazopanib is increasing, several phase I/II studies have shown promising results. Recently, results of the phase III AGO-OVAR-16 study of maintenance pazopanib in 940 women with advanced newly diagnosed EOC showed a benefit for maintenance therapy with pazopanib for 24 months compared to placebo. All patients had previously achieved a clinical response with first-line platinum-based therapy. Median PFS was significantly longer in the pazopanib group (17.9 versus 12.3, HR 0.77, 95% CI 0.64*0.91, P=0.0021). The first OS interim analysis (20% of OS events) showed no difference between arms. In breast cancer a phase Ib study is being performed with dosages escalating for paclitaxel from 70-90 mg/m2, carboplatin at a fixed dose of AUC 2 and pazopanib at a dose ranging from 400 to 800 mg daily. However, the ovarian weekly regimen needs to be adapted because in ovarian cancer the dose of carboplatin should be higher and the paclitaxel seems to be less important than in breast cancer. In addition, the complications * especially bowel perforation * are different in ovarian cancer than in breast cancer and will be further documented in this study. The combination at a dose of at least 400mg pazopanib

with 3-weekly paclitaxel/carboplatin (paclitaxel at 175 mg/m2, carboplatin at AUC 5 or 6) was not feasible in two Phase I studies (VEG105427 part II and VEG110190). In this Phase I study conducted with the triplet in subjects with gynaecologic malignancies, two of 6 subjects experienced DLTs at 800 mg pazopanib, and 2 of 6 subjects had DLTs at 400 mg pazopanib. On the other hand, in the other Phase I study conducted with the triplet in pre-treated subjects with solid tumors, pazopanib increased mean paclitaxel and carboplatin AUC and/or Cmax by at least 30%, vs when paclitaxel and carboplatin were administered without pazopanib.

The EORTC proposed a phase Ib/II study to establish the maximum tolerated dose for pazopanib and evaluate the effectiveness in terms of progression free survival and safety of pazopanib in addition to paclitaxel and carboplatin given weekly in a group of patients with platinum-refractory or -resistant ovarian, fallopian tube or peritoneal carcinoma. The phase Ib part of this study enrolled 28 patients between August, 24th 2012 and January 22nd 2014 by 3 institutions. Of those 28, 23 were evaluable for DLT assessment (i.e. eligible and received at least one course of protocol treatment).The dose evaluation procedure was completed on February 27th 2014 and transition to the phase II part approved by the Trial Steering Committee.

The current version protocol pertains to the phase II part of the study

Study objective

The primary objective of the phase II is to determine the progression free survival (PFS) at 1 year according to the RECIST 1.1 of the combination of pazopanib with weekly paclitaxel and carboplatin in platinum-resistant ovarian, fallopian tube or peritoneal carcinoma.

The secondary objectives are: To evaluate the RR, overall survival (OS) and PFS, To determine and evaluate predictive biomarkers. To evaluate safety and adverse event profiles.

Study design

Randomized Open label, multi-center, Phase II trial.

A total of 60 patients (40 in experimental arm and 20 in standard arm) will be randomized in the phase II part of the study.

Translational research part: Plasma markers for pazopanib response (plasma samples at baseline, 4 weeks and 12 weeks of treatment), and Tumor DNA biomarkers for pazopanib response, Germline DNA biomarkers for side effects to pazopanib, Biobanking

Intervention

Treatment in the experimental arm: Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 400 mg daily. Patients randomized to the experimental arm will continue pazopanib (at the standard dose of 800 mg per day) after the planned 18 courses of paclitaxel-carboplatin weekly until documented disease progression, unacceptable toxicity or patient refusal.
Treatment in the standard arm: carboplatin AUC 2.7 weekly and paclitaxel 60mg/m² weekly for 18 courses. Or paclitaxel 80 mg/m² weekly (maximum 18 courses). Or paclitaxel 80 mg/m² weekly (maximum 18 courses) in combination with bevacizumab 15 mg/kg 3-weekly, followed by maintenance therapy with bevacizumab.

Study burden and risks

weekly visits to the hospital for treatment during 18 weeks
possible side effects

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83
Brussel 1200
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Female subjects of age 18 years or older
- Histologically confirmed diagnosis of ovarian, fallopian tube, or peritoneal carcinoma with recurrent disease
- All patients with at least one earlier platinum treatment can be included but should be platinum resistant (progression between 28 days and 6 months after last platinum dose). There is no restriction on the number of prior lines. Non-platinum treatment after proven platinumresistance disease is allowed
- Evaluable (measurable or non-measurable) disease by RECIST version 1.1 (CT or MRI from thorax, abdomen and pelvis: within 3 weeks before randomization)
- Patient must be able to receive the infusions (paclitaxel, carboplatin and if applicable bevacizumab) and swallow the tablets (pazopanib)
-WHO Performance status must be * 2
-LVEF assessed by ECHO or MUGA scan of the heart > 50%, if clinically indicated
-Adequate organ function, see table page 19
-Patients with childbearing potential should have a negative serum pregnancy test, within 1 week before first day of treatment and use effective contraceptive methods for the whole duration of the study and for 6 months after discontinuing treatment
-Patients who are lactating should discontinue nursing prior to the first dose
-Patients must be able and willing to discontinue use of prohibited medications for at least 14 days (28 days for drugs with a longer half-life) prior to the first dose of study drug and for the duration of the study
-Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations

Exclusion criteria

- prior treatment for recurrence with weekly paclitaxel (with or without weekly carboplatin). Prior bevacizumab is allowed
-known metastatic disease to the brain or leptomeninges
-other prior malignancies treated primarily or for recurrence within 2 years prior to inclusion in this study, except for completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma of the skin or cervix of the uterus
- treatment with any of the following anti-cancer therapies:
* Radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of study drug
* previous radiotherapy to the pelvis

* chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days (28 days for drugs with a longer half-life) prior to the first dose of study drug
-Patients with ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity, except alopecia and * Grade 2 peripheral neuropathy
-Patients with known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs similar or related to paclitaxel, carboplatin, bevacizumab and pazopanib. Mild infusion related reactions are allowed (see protocol)
-Patients with unstable or serious condition e.g. uncontrolled infection requiring systemic therapy
-prior major surgery or trauma within 28 days prior to the first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement and diagnostic endoscopic procedures not considered to be major)
-history of any of the following cardiovascular conditions within 6 months before randomisation: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, class II or greater congestive heart failure, as defined by the NYHA
- inadequately controlled hypertension (systolic blood pressure (SBP) >150 mmHg, or diastolic blood pressure (DBP) >100 mmHg) despite intensive medical management or prior history of hypertensive crisis or hypertensive encephalopathy. Antihypertensive medication is allowed. Initiation or adjustment of blood pressure medication is permitted prior to the study entry . Initiation or adjustment of blood pressure medication is permitted prior to the study entry.
- prolonged corrected QT interval (QTc) defined as >480 msecs using Bazett*s formula
- history of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT), aorta-aneurysm requiring surgical repair or recent peripheral arterial thrombosis within 6 months prior to randomisation
- evidence of active bleeding or bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation). Current or recent (within 10 days) use of dipyridamole, ticlopidine, clopidrogel, cilostazol, prasugrel, ticagrelor, or use of full dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purpose. HOWEVER prophylactic anticoagulation of venous access devices is allowed, provided PT, INR and aPTT is within normal limits within 1 week prior to randomization. Profylactic or therapeutic use of LMWH is allowed;- Obvious signs or risks of gastrointestinal fistula formation or perforation such as:
- history of abdominal or tracheo-esophageal fistula or perforation within 6 months prior to randomization
- clinical signs or symptoms of GI obstruction or requirement for routine parenteral hydration, parenteral nutrition or tube feeding
- history of bowel obstruction (excluding postoperative within 4 weeks) or other GI condition with increased risk of perforation such as clear infiltration of the rectosigmoid, colon or small bowel.
- clinically significant gastro-intestinal tract abnormalities that may increase the risk for GI bleeding including but not limited to: active peptic ulcer disease, known intraluminal metastatic lesion/s with risk of bleeding, inflammatory bowel disease (e.g. ulcerative colitis, Crohn*s disease)
-clinically significant gastrointestinal abnormalities that may affect absorption of

investigational product including, but not limited to: malabsorption syndrome, major resection of stomach or small bowel. Clinically sign evidence of tumor invading up to the mucosa of the GI tract (esophagus, stomach, small or large bowel, rectum or anus)
- known endobronchial lesions and/or lesions infiltrating major pulmonary vessels
- hemoptysis in excess of 2.5mL (one half tea spoon) within 8 weeks prior to first dose of study drug.
- poor oral hygiene or invasive dental or orofacial procedures within 28 days before the first dose of study drug
- any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-09-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Votrient
Generic name:	Pazopanib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-03-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-08-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-024077-39-NL
ClinicalTrials.gov	NCT01402271
CCMO	NL51891.078.15