Purpose

Indication:

Treatment of subjects with advanced (FIGO stage IVB) or recurrent cervical cancer, prior radiochemotherapy or neo-adjuvant chemotherapy is allowed.

Study design:

This is a phase II randomized, double blind and placebo controlled trial evaluating the efficacy of Nintedanib/placebo in combination with the standard of 6 cycles 3 weekly carboplatin and paclitaxel followed by Nintedanib/placebo maintenance in the treatment of patients with advanced or recurrent cervical cancer.

A total of 120 patients will be randomized between the experimental and control arm in a 1:1 ratio. Randomization will be stratified for 1 previous therapy (chemo-radiotherapy or neoadjuvant chemotherapy: no, >6 months since last platin course) and 2 disease status (Stage IVB primary versus recurrent disease).

Experimental arm: Subjects will receive 6 cycles of 3-weekly carboplatin (AUC 5) + paclitaxel (175 mg/m2) and Nintedanib 200 mg BID followed by Nintedanib maintenance until progression or for a total maximum duration of 120 weeks.

Control arm: Subjects will receive 6 cycles of 3-weekly carboplatin (AUC 5) + paclitaxel (175 mg/m2) and placebo 200 mg BID followed by placebo maintenance until progression or for a total maximum duration of 120 weeks.

Subjects without evidence of disease progression after completion or discontinuation of the study treatment will be followed until radiographic disease progression, withdrawal of consent or death.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine Cervical Neoplasms</td>
<td>Drug: Nintedanib</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Drug: Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional  
Study Design: Randomized  
Allocation: Randomized  
Endpoint Classification: Safety/Efficacy Study  
Intervention Model: Parallel Assignment  
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)  
Primary Purpose: Treatment  

Official Title: BGOG-cx1/ENGOT-cx1: "Randomized Double-blind Phase II Study Comparing 3-weekly Carboplatin + Paclitaxel With or Without Concomitant and Maintenance Nintedanib (NINTEDANIB) in Advanced or Recurrent Cervical Carcinoma."

Resource links provided by NLM:  
MedlinePlus related topics: Cancer  Cervical Cancer
Further study details as provided by Belgian Gynaecological Oncology Group:

Primary Outcome Measures:
- Progression free survival [Time Frame: 1.5 years after LPI] [Designated as safety issue: No]
  Primary objective: The purpose of this trial is to determine if chemotherapy (carboplatin/paclitaxel) plus Nintedanib (BIBF 1120) can improve progression free survival compared to chemotherapy (carboplatin/paclitaxel) plus placebo in patients with advanced or recurrent cervical cancer.

Secondary Outcome Measures:
- Safety and toxicity [Time Frame: 5 years after LPI] [Designated as safety issue: Yes]
  Secondary objectives: To evaluate the safety and toxicity reported for the combination regimen
- Overall survival [Time Frame: 5 years after LPI] [Designated as safety issue: No]
  To evaluate the response rate according to RECIST 1.1
- Patient health status [Time Frame: 5 years after LPI] [Designated as safety issue: No]
  To explore the effect of Nintedanib on patient reported health status as measured by EORTC-QOL-Cx 24 and EORTCQLQ-C30 questionnaires
- Overall survival [Time Frame: 5 years after LPI] [Designated as safety issue: No]
  To evaluate the overall survival

Estimated Enrollment: 120
Study Start Date: March 2014
Estimated Study Completion Date: July 2020
Estimated Primary Completion Date: May 2017 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Comparator:</td>
<td>Drug: Nintedanib</td>
</tr>
<tr>
<td>Experimental arm</td>
<td>Subjects will receive 6 cycles of 3-weekly carboplatin (AUC 5) + paclitaxel (175 mg/m2) and Nintedanib 200 mg BID followed by Nintedanib maintenance until progression or for a total maximum duration of 120 weeks. Other Name: Vargatef</td>
</tr>
<tr>
<td>Nintedanib/vargatef</td>
<td></td>
</tr>
<tr>
<td>Placebo Comparator:</td>
<td>Drug: Placebo</td>
</tr>
<tr>
<td>Comparator arm</td>
<td>Subjects will receive 6 cycles of 3-weekly carboplatin (AUC 5) + paclitaxel (175 mg/m2) and placebo 200 mg BID followed by placebo maintenance until progression or for a total maximum duration of 120 weeks.</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Eligibility

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

Criteria

Inclusion Criteria:
- Female subjects more than 18 years of age
- Histologically or cytologically confirmed advanced ([FIGO] stage IVB), or recurrent/persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix will be eligible.
- No prior chemotherapy for recurrent cervical cancer.
- Prior concomitant cisplatinum chemotherapy during radiotherapy is allowed (except if recurrence is within 6 months after the end of the platinum containing chemotherapy).
- Cases primarily treated with neoadjuvant chemotherapy before radical local surgery are eligible at the time of first recurrence. (except if recurrence is within 6 months after the end of the platinum containing chemotherapy).
- Cases primarily treated with neoadjuvant chemotherapy before radical local surgery followed by adjuvant radiochemotherapy are eligible at the time of first recurrence (except if recurrence is within 6 months after the end of the platinum containing chemotherapy).
- Cases primarily treated with neoadjuvant chemotherapy before radical local surgery followed by adjuvant radiotherapy are eligible at the time of first recurrence (except if recurrence is within 6 months after the end of the platinum containing chemotherapy).
- Life expectancy at least 3 months.
- ECOG Performance status score of 0 or 1
At least one measurable lesion according to RECIST 1.1 criteria
Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP guidelines and to the local legislation

Exclusion Criteria:
- Prior chemotherapy except platin-based concomitant chemotherapy during radiotherapy
- Prior chemotherapy for advanced (FIGO stage IVB) or recurrent disease except as mentioned in point 3.1.3.
- Prior treatment with nintedanib or any other VEGFR inhibitor.
- Known hypersensitivity to the trial drugs or to their excipients.
- Brain or leptomeningeal metastases.
- Centrally located tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels.
- Tumor infiltrating the mucosa of the bowel or bladder, or known fistulas between the tumor and the gastrointestinal or urinary tract.
- Treatment with other investigational drugs or treatment in another clinical trial within the past 4 weeks before start of therapy or concomitantly with the trial.
- Therapeutic anticoagulation or anti-platelet therapy is not allowed, unless the patient is on stable anti-coagulation
- Major injuries within the past 10 days prior to start of study treatment with incomplete wound healing and/or planned surgery during the on-treatment study period.
- History of clinically significant haemorrhagic or thromboembolic event in the past 6 months.
- Known inherited predisposition to bleeding or thrombosis.
- Significant cardiovascular diseases (i.e. uncontrolled hypertension, unstable angina within the past 6 months, history of infarction within the past 6 months prior to start of study treatment, congestive heart failure > NYHA II, serious cardiac arrhythmia, pericardial effusion).
- History of a cerebral vascular accident, transient ischemic attack or subarachnoid hemorrhage within the past 6 months.
- Abnormal renal, liver or bone marrow function defined as:
  - Proteinuria CTCAE grade 2 or greater
  - Creatinin > 2 ULN or GFR < 30 ml/min
  - Hepatic function: total bilirubin outside of normal limits; ALT or AST > 1.5 ULN in pts without liver metastasis. For Pts with liver metastases: total bilirubin outside of normal limits, ALT or AST > 2.5 ULN
  - Coagulation parameters: International normalised ratio (INR) > 2, prothrombin time (PT) and partial thromboplastin time (PTT) > 50% of deviation of institutional ULN
  - Absolute neutrophil count (ANC) < 1500/µl, platelets < 100000/µl, haemoglobin < 9.0 g/dl
- Other malignancies within the past 3 years or other malignancy with recurrence in the past 3 years or with high risk of recurrence in the first year. In exception to this rule, the following malignancies may be included: non-melanomatous skin cancer (if adequately treated), any premalignant (e.g. in situ) carcinoma, or basocellular carcinoma.
- Active serious infections in particular if requiring systemic antibiotic or antimicrobial therapy.
- Active or chronic hepatitis C and/or B infection or known HIV infection.
- Gastrointestinal disorders or abnormalities that would interfere with absorption of the study drug.
- Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study.
- Patients of child-bearing potential who are sexually active and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner or sexual abstinence for participating females) during the trial and for at least three months after end of active therapy.
- Pregnancy or breast feeding, female patients must have a negative pregnancy test (β-HCG test in urine or serum) prior to commencing study treatment, if applicable.
- Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule.
- Active alcohol or drug abuse.

Contacts and Locations
Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02009579

Contacts
Contact: Ignace Vergote, MD  +32(0)16 344207  bgog@engot.eu

Locations
Belgium
CHU Saint-Pierre  Active, not recruiting
Bruxelles, Belgium
Institut Jules Bordet  
Bruxelles, Belgium  
Recruiting

Grand Hopital de Charleroi  
Charleroi, Belgium  
Active, not recruiting

UZ Antwerpen  
Edegem, Belgium  
Active, not recruiting

AZ Groeninge  
Kortrijk, Belgium  
Recruiting

UZ Leuven  
Leuven, Belgium, 3000  
Principal Investigator: Ignace Vergote, MD  
Recruiting

CHR Citadelle  
Liege, Belgium  
Recruiting

CHU de Liège  
Liege, Belgium, 4000  
Contact: Christine Gennigens, MD  
Recruiting

Clinique et maternite St. Elisabeth  
Namur, Belgium  
Recruiting

Cliniques Universitaires mont godinne  
Yvoir, Belgium  
Active, not recruiting

Spain

Hospital Provincial Reina Sofia  
Córdoba, Spain, 14004  
Contact: Maria Jesús Rubio, MD  
Recruiting

H. Ramón y Cajal  
Madrid, Spain, 28034  
Contact: Eva Maria Guerra, MD  
Recruiting

Hospital Clinico San Carlos  
Madrid, Spain, 28040  
Contact: Antonio Casado, MD  
Recruiting

Hospital Universitario Morales Meseguer  
Murcia, Spain, 30008  
Contact: Helena Garcia, MD  
Not yet recruiting

Hospital Son Llatzer  
Palma Mallorca, Spain, 07198  
Contact: Isabel Bover, MD  
Recruiting

Sponsors and Collaborators

Belgian Gynaecological Oncology Group
Grupo Español de Investigación en Cáncer de Ovario
Mario Negri Gynecologic Oncology group (MANGO)
Multicenter Italian Trials in Ovarian Cancer (MITO)
Institute of Cancer Research, United Kingdom
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO)

More Information

Additional Information:

BGOG website

ENGOT website

History of Changes

Other Study ID Numbers: BGOG-cx1/ENGOT-cx1

Study First Received: October 24, 2013

Last Updated: March 31, 2016

Health Authority: Belgium: Federal Agency for Medicines and Health Products, FAMHP  
Spain: Agencia Española de Medicamentos y Productos Sanitarios

Keywords provided by Belgian Gynaecological Oncology Group:

Uterine Cervical Cancer
Paclitaxel
Carboplatin
Nintedanib

Additional relevant MeSH terms:
Uterine Cervical Neoplasms
Genital Diseases, Female
Genital Neoplasms, Female
Neoplasms
Neoplasms by Site
Urogenital Neoplasms
Uterine Cervical Diseases
Uterine Diseases
Uterine Neoplasms
Albumin-Bound Paclitaxel

ClinicalTrials.gov processed this record on June 12, 2016