A Randomised Phase II Study of Nintedanib (BIBF1120) Compared to Chemotherapy in Patients with Recurrent Clear Cell Carcinoma of the Ovary or Endometrium

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The objectives are to assess the efficacy, safety and effect on quality of life of Nintedanib compared to chemotherapy in women with relapsed, advanced or metastatic clear cell cancer of the ovary of endometrium.

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

Summary

ID

NL-OMON47688

Source
ToetsingOnline

Brief title
NiCCC Trial

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
clear cell endometrial cancer, clear cell ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research and Treatment of Cancer
Source(s) of monetary or material Support: Boehringer Ingelheim,Scottish Gynaecological Cancer Trials group (SGCTG);en KWF Kankerbestrijding

Intervention

Keyword: clear cell endometrial cancer, clear cell ovarian cancer, nintedanib

Outcome measures

Primary outcome

The primary endpoint is progression free survival (PFS).

The study is designed to detect an improvement in median PFS from 3 months with standard chemotherapy to 5 months with Nintedanib with 90 power, 20% 1-sided level of statitical significance for clear cell ovarian cancer. Up to 30 clear cell endometrial cancer patients will be randomized, but there is no specific power calculation for these patients as this disease is extremely rare, even more so than clear cell ovarian cancer, and it was not considered feasible to conduct more than an exploratory study.

Secondary outcome

Secondary endpoints are overall survival, response rates, disease control rate, toxicity and quality of life.

Study description

Background summary

The prognosis for women with recurrent clear cell carcinoma of the ovary or endometrium is poor and the benefit gained from current chemotherapy regimens is limited, with response rates of less than 10%. Any benefit is at the expense of the toxicity of chemotherapy. Antiangiogenic therapy such as nintedanib

offers the potential to control tumour progression, and is a strategy that has shown considerable clinical benefit in clear cell carcinomas of the kidney.

Study objective

The objectives are to assess the efficacy, safety and effect on quality of life of Nintedanib compared to chemotherapy in women with relapsed, advanced or metastatic clear cell cancer of the ovary of endometrium.

Study design

The study is a multi-center randomized open label phase II study. Up to 120 eligible patients (90 with ovarian clear cell cancer and up to 30 with endometrial clear cell cancer) will be randomized between chemotherapy and the oral anti-angiogenic tyrosine kinase inhibitor Nintedanib 200 mg twice daily.

Intervention

The standard chemotherapy of physician*s choice consists of 3 options for ovarian- and 2 options for endometrial clear cell cancer patients. Patients on the standard arm will receive up to a maximum of 6 cycles of chemotherapy. Patients on the experimental arm will receive oral Nintedanib continuously, provided they continue to meet the eligibility criteria, until progression, unacceptable toxicity, withdrawal of consent or the investigator decides it is not in the best interest of the patient to continue. Apart from standard evaluations of toxicity and response, regular QoL questionnaires will be administered. Patients will be followed-up after end of treatment for QoL, survival status and progression (if that was not the reason for ending treatment) until withdrawal of consent.

Study burden and risks

The well known side effects of standard chemotherapy are not expected to be any different for patients within this study than outside it. Side effects of nintedanib include fatigue, nausea, vomiting, stomach ache, diarrhea, anorexia and liver function test deterioration.Nintedanib toxicity is generally considered to be milder than conventional cystatics toxicity,
There are no extra visits associated with participation in the study, although

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients will be eligible for the study if the following criteria are met:
1. Progressive or recurrent ovarian peritoneal or fallopian tube clear cell carcinoma, or progressive or recurrent endometrial clear cell carcinoma. The primary diagnosis must be histologically confirmed and central pathological review of the presenting tumour or biopsy of relapsed disease must find at least 50% clear cell carcinoma with no serous differentiation. Progressive disease as defined by RECIST 1.1
2. Failure after >=1 prior platinum containing regimen which may have been given in the adjuvant setting. For patients with ovarian clear cell carcinoma, progression must have occurred within 6 calendar months of their last platinum dose.
3. ECOG Performance status of <=2
4. Life expectancy of >3 months
5. Adequate hepatic, bone marrow coagulation and renal function
a. Hepatic function: total bilirubin< ULN; ALT and AST < 2.5 x ULN

b. Coagulation parameters: INR <2 x ULN and prothrombin time and activated partial thromboplastin time < 1.5 x ULN in the absence of therapeutic anticoagulation
c. Absolute neutrophil count (ANC) >=1.5 x 109/L
d. Platelets >= 100 x 109L
e. Haemoglobin >= 9.0 g/dL
f. Proteinuria < grade 2 (CTCAE version 4)
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g. Glomerular Filtration Rate >=40ml/min. (calculated using the Wright, Cockroft & Gault equation or measured by EDTA clearance)
6. Female and > 18 years of age
7. Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP guidelines and local legislation.
8. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other study procedures.

Exclusion criteria

Patients will be excluded from the study in the following circumstances:
1. Prior treatment with Nintedanib or other angiogenesis inhibitor/VEGF targeted therapy, except for prior treatment with bevacizumab which is permitted.
2. Treatment within 28 days prior to randomisation with any investigational drug, radiotherapy, immunotherapy, chemotherapy, hormonal therapy or biological therapy. Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases in extremities, provided that the radiotherapy does not affect target lesions, and the reason for the radiotherapy does not reflect progressive disease.
3. Previous treatment with the chemotherapy regimen selected as the control arm by the investigator. (Prior therapy with paclitaxel given on a three weekly regimen is permitted for patients receiving weekly Paclitaxel. Prior treatment with weekly paclitaxel is permitted where this has been used as part of first line therapy and it is greater than 6 months since the last dose of weekly paclitaxel. Prior weekly paclitaxel for relapsed disease is not permitted).
4. Other malignancy diagnosed within 5 years of enrolment except for:

a. Non-melanomatous skin cancer (if adequately treated)
b. Cervical carcinoma in situ (if adequately treated)
c. Carcinoma in situ of the breast (if adequately treated)
d. For patients with ovarian clear cell cancer, prior or synchronous endometrial cancer (if adequately treated), provided all of the following criteria are met:
• Disease stage FIGO Stage 1a (tumour invades less than one half of myometrium)
• Grade 1 or 2
5. Patients with any other severe concurrent disease, which may increase the risk associated with study participation or study drug administration and, in the judgement of the investigator, would make the patient inappropriate for entry into this study, including significant neurologic, psychiatric, infectious, hepatic, renal, or gastrointestinal diseases or laboratory abnormality.
6. Symptoms or signs of gastrointestinal obstruction requiring parenteral nutrition or hydration or any other gastro-intestinal disorders or abnormalities, including difficulty swallowing, that would interfere with drug absorption.
7. Serious infections in particular if requiring systemic

antibiotic (antimicrobial, antifungal) or antiviral therapy, including known hepatitis B and/or C infection and HIVinfection.
8. Symptomatic CNS metastasis or leptomeningeal carcinomatosis
9. Known, uncontrolled hypersensitivity to the investigational drugs or their excipients.
10.Hypersensitivity to Nintedanib, peanut or soya, or to any of the excipients of Nintedanib.
11.Significant cardiovascular diseases, including uncontrolled hypertension, clinically relevant cardiac arrhythmia, unstable angina or myocardial infarction within 6 months prior to randomisation, congestive heart failure > NYHA III, severe peripheral vascular disease or clinically significant pericardial effusion.
12.History of major thromboembolic event, such as pulmonary embolism or proximal deep vein thrombosis, unless on stable therapeutic anticoagulation
13. Known inherited predisposition to bleeding or thrombosis.
14.History of a cerebral vascular accident, transient ischemic attack or subarachnoid haemorrhage within the past 6 months.
15.History of clinically significant haemorrhage in the past 6 months

16.Major injuries or surgery within the past 28 days prior to start of study treatmentor planned surgery during the ontreatment study period.
17. Pregnancy or breastfeeding. Patients with preserved reproductive capacity must have a negative pregnancy test (β-HCG test in urine or serum) prior to commencing study treatment.
18. Patients with preserved reproductive capacity, unwilling to use a medically acceptable method of contraception (see section 5.7) for the duration of the trial and for 6 months afterwards.
19.Radiographic evidence of cavitating or necrotic tumours with invasion of adjacent major blood vessels.
20.Any psychological, familial, sociological or geographical consideration potentially hampering compliance with the study protocol and follow up schedule; those considerations should be discussed with the patient before registration in the trial.
21. Patients who have already received maximal lifetime dose of anthracycline or have experienced cardiac toxicity from an anthracycline should not receive doxorubicin or PLD.

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:	Completed
Start date (anticipated):	14-08-2017
Enrollment:	10

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caelyx
Generic name:	Pegylated Liposomal Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	carboplatin
Generic name:	carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Hycamtin
Generic name:	topotecan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vargatef
Generic name:	nintedanib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	11-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-002109-73-NL

Register	ID
ISRCTN	ISRCTN50772895
CCMO	NL58671.018.16

Study results

Date completed: 23-07-2020

Results posted: 14-01-2022

First publication
16-09-2021