Randomised controlled study comparing AEZS-108 with doxorubicin as second line therapy for locally advanced, recurrent or metastatic endometrial cancer

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1. Overall survival (primary efficacy endpoint)2a. Efficacy: progression-free survival (PFS), overall response rate (ORR = CR + PR), and a clincal benefit rate (CBR) will be evaluated as CR + PR + SD for at least 3 months.2b. Safety: adverse events...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cervix disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON40258

Source
ToetsingOnline

Brief title
AEZS-108 and doxorubicin in patients with endometrial cancer

Condition

- Cervix disorders (excl infections and inflammations)

Synonym
cancer of the inner lining of the uterus, endometriumcancer

Research involving
Human

Sponsors and support

Primary sponsor: Aeterna Zentaris

Source(s) of monetary or material Support: studie gefinancierd door de sponsor Aeterna Zentaris

Intervention

Keyword: cancer, doxorubicin, endometrial

Outcome measures

Primary outcome

The primary efficacy variable will be overall survival (OS)

The primary analysis of the primary efficacy variable will be based on the ITT population. The final OS analysis, which is event-based, will be conducted after approximately 384 randomized patients have died. In the primary analysis, a log-rank test with an overall two-sided Type I error rate of 0.05 after taking the interim analyses into account will be used to compare OS between the two treatment arms via a SAS lifetest procedure. Kaplan-Meier estimates will be used to calculate median OS and the 95% confidence interval of the median OS. The proportion of patients alive at six and 12 months (from randomization date) and the 95% confidence intervals for these estimated proportions, if appropriate, will be presented.

Secondary outcome

Approximately 384 events of deaths will be required to achieve 80 % power to detect a treatment difference at the two-sided 0.05 significance level. It is expected that approximately 500 patients will be enrolled during an estimated 24-month recruitment period and will then be followed for 12 months to observe a total of approximately 384 death events. In the sample size calculation, it

is assumed that the median OS is 12 months for AEZS-108 and 9 months for

doxorubicin. The sample size calculation has taken two planned interim looks

into account, the first being a futility analysis only.

Study description

Background summary

AEZS-108 is an experimental drug
. AEZS-108 is composed of two parts: one part is doxorubicin (an approved chemotherapy drug) and the other part is a kind of hormone that helps doxorubicin to stick and to enter tumors with docking sites for this hormone (so called LHRH receptors). The first research studies with AEZS-108 in humans were completed in 2006. In 2010, other studies in Europe were completed in women with endometrial and ovarian cancers. There are ongoing studies in patients with prostate cancer, bladder cancer, and breast cancer.

Study objective

1. Overall survival (primary efficacy endpoint)
2a. Efficacy: progression-free survival (PFS), overall response rate (ORR = CR + PR), and a clincal benefit rate (CBR) will be evaluated as CR + PR + SD for at least 3 months.
2b. Safety: adverse events, clinical laboratory, ECG and LVEF
2c. Quality of Life: EORTC QLQ30 + QLQ-EN24 questionnaires.
3. Pharmacokinetic and electrocardiographic parameters of the PK sub-study

Study design

Open-label, randomized, active-controlled, two-arm Phase III study to compare the efficacy and safety of AEZS-108 and doxorubicin. The study will include about 500 patients with endometrial cancer resistant to platinum and taxane-based chemotherapy

Intervention

Patients will be centrally randomized in a 1:1 ratio to receive treatment with either AEZS 108 (Arm A) or doxorubicin (Arm B).
During ongoing treatment, response will be evaluated every 3 cycles; earlier reassess-ments should be scheduled to verify a response (at least 4 weeks after first observation of the response) or in case of suspected progression.
Patients, who have gone off-treatment for reasons other than progression, will

be reassessed every 12 weeks until progression. All patients will be followed-up for survival.
On a regular basis, at intervals no longer than 6 months, results from safety analyses will be submitted to an independent Data and Safety Monitoring Board (DSMB) that will advise the Sponsor of potentially critical findings.
The final analysis will be performed after about 384 deaths have been observed.
There will be two planned interim analyses; the first will be for futility only, the second will be for safety and efficacy.
Based on the availability of the assay for LHRH receptor expression in tumor specimens, subgroup analyses stratified for extent of LHRH receptor expression will assess the predictive value of the LHRH receptor assay.

Study burden and risks

No standard of care or approved drugs are available for patients with endometrial cancer failing on or after first line chemotherapy for advanced/recurrent disease if this comprised platinum/taxane-based combination chemotherapy. In prior studies, it has been shown that, patients with endometrial and ovarian cancer who failed after or were resistant to platinum/taxane-based chemotherapy, including combinations, still responded to AEZS 108.
Although the investigational drug AEZS-108 is a targeted drug that is expected to enter cells bearing preferentially LHRH receptors, the study is being conducted in patients who will not be selected for expression of this specific target. Ultimately, a patient whose tumor cells do not express LHRH receptors could have a higher uptake of doxorubicin if it was administered as free doxorubicin, not coupled to the LHRH analog. In the Phase II study of AEZS-108, 92.8% of the endometrial cancer specimens analyzed during prescreening had been classified as receptor positive, so that only about 7% of the patients who might have entered the study if the receptor assay had been omitted. No correlation of the degree of receptor expression and the tumor response was noted in this earlier study. Accordingly, even patients with tumors classified as LHRH receptor negative * with the former assay - could have a chance to benefit from treatment with AEZS-108. Ultimately, since doxorubicin is being gradually released during and after the infusion of AEZS-108, a patient with an LHRH receptor negative tumor has the chance to benefit from the uptake of hydrolytically released doxorubicin by the tumor

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

1. Woman * 18 years of age
2. Histologically confirmed endometrial adenocarcinoma of any subtype
a) Endometrioid carcinoma
i. variant with squamous differentiations
ii. Villoglandular variant
iii. Secretory variant
iv. Ciliated cell variant
b) Mucinous adenocarcinoma
c) Serous adenocarcinoma
d) Clear cell adenocarcinoma
e) Mixed cell adenocarcinoma
f) Squamous cell carcinoma
g) Transitional cell carcinoma
h) Small cell carcinoma
i) Undifferentiated carcinoma;3. Advanced (FIGO stage III or IV), recurrent or metastatic disease.;4. Measurable or non-measurable disease that has progressed since last treatment.;5. Patients with advanced, recurrent or metastatic endometrial cancer who have received one chemotherapeutic regiment with platinum and taxane (either as adjuvant or as first line treatment) and who have progressed.;6. Availability of fresh or archival FFPE tumor

specimens for analysis of LHRH receptor expression.

Exclusion criteria

1. Eastern Cooperative Oncology Group (ECOG) performance status > 2
2. Inadequate hematologic, hepatic or renal function
- thromobocyte count: < 100 x 109/L;
- absolute neutrophil count (ANC): < 1.5 x 109/L;
- hemoglobin: < 5.6 mmol/L (< 9 g/dL);
- ASAT, ALAT, AP: > 2.5 times upper limit of normal range (ULN) (> 5x ULN if clearly related to liver metastases)
- creatinine, bilirubin: > 1.5x ULN
3. Red blood cell transfusion within 2 weeks prior to anticipated start of study treatment.
4. History of myocardial infarction, acute inflammatory heart disease,unstable angina, or uncontrolled arrhythmia within the past 6 months.
5. Impaired cardiac function defined as left ventricular ejection fraction (LVEF) < 50 % (or below the study site*s lower limit of normal) as measured by MUGA or ECHO.
6. Concomitant use of prohibited therapy (as specified in Section 6.3.2).
7. Chemo-, immune- or hormonetherapy within 5 elimination half life times or 4 weeks prior to randomization, whichever is the shorter. Radiotherapy (including pre- or post- operative brachytherapy) within 4 weeks prior to randomization.
8. Previous anthracycline-based chemotherapy (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone and valrubicin) in any formulation.
9. Anticipated ongoing concomitant anticancer therapy during the study.
10. History of serious co-morbidity or uncontrolled illness that would preclude study therapy, such as active tuberculosis or any other active infection.
11. Brain metastasis, leptomeningeal disease.
12. Pregnant or lactating female or female of child-bearing potential not employing adequate contraception. Women of childbearing potential must agree to employ adequate contraception until 6 months after the last dose of study drug, defined as
- complete abstinence (Note: acceptable only as *true abstinence*, i.e. when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence, (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).;
- any intrauterine device (IUD) with published data showing that the lowest expected failure rate is < 1 % per year; or
- any other methods with published data showing that the lowest expected failure rate is less than 1 % per year.
13. Subjects with known hypersensitivity to peptide drugs, including LHRH agonists.
Lack of suitability for the trial:
22. Malignancies arising from the uterine Cervix.
23. Uterine sarcomas or mixed epithelial and mesenchymal tumors including carcinosarcoma, adenosarcoma, or carcinofibroma.
14. Receipt of 2 or more prior cytotoxic chemotherapy regimens for advanced, recurrent, or

metastatic endometrial cancer.
15. Prior treatment with AEZS-108.
16. Use of LHRH agonist or antagonist treatment within 6 months prior to randomization.
17. Malignancy within last 5 years except non-melanoma skin cancer.
18. Any concomitant disease or condition which would interfere with the subjects* proper completion of the protocol assignment.
19. Concomitant or recent treatment with other investigational drug (within 4 weeks or 5 elimination half life times prior to anticipated start of study treatment).
Administrative reasons:
20. Lack of availability for willingness to give informed consent.
21. Anticipated non-availability for study visits/procedures.

Study design

Design

Study phase:	3
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):	05-05-2014
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	doxorubicin HCl
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Doxorubicine HCl Oncotrade
Generic name:	doxorubicin HCl
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog geen naam bekend
Generic name:	Zoptarelin doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	DOXORUBICINE HYDROCHLORIDE 2 MG/ML PCH
Generic name:	doxorubicine HCl
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog geen naam bekend
Generic name:	Zoptarelin doxorubicine

Ethics review

Approved WMO Date:	15-08-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2016
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	EUCTR2012-005546-38-NL
ClinicalTrials.gov	NCT01767155
CCMO	NL45515.018.13