A PHASE II STUDY OF TAILORED ADJUVANT THERAPY IN POLE-MUTATED AND p53-WILDTYPE/NSMP EARLY STAGE ENDOMETRIAL CANCER (RAINBO BLUE & TAPER)
SUBSTUDY A: RAINBO POLEmut-BLUE: Refining Adjuvant treatment IN endometrial cancer Based On molecular features (RAINBO) TransPORTEC platform trials

Published: 26-10-2023
Last updated: 21-12-2024

In the RAINBO POLEmut-BLUE trial, omission of adjuvant therapy will be investigated in very low risk disease and de-escalation of treatment (observation or radiotherapy, but not chemoradiation) in low risk disease.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON55931

Source
ToetsingOnline

Brief title
RAINBO POLEmut-BLUE trial

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
cancer of the womb, malignancy of the uterus

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: subsidie aan KWF aangevraagd - beslissing volgt dec 2023

Intervention

Keyword: adjuvant treatment, deescalation, endometrial cancer, POLE mutant

Outcome measures

Primary outcome

3-year pelvic recurrence

Secondary outcome

5-year pelvic recurrence, 3- and 5-year RFS, decisional conflict, and fear of recurrence. 3- and 5-year vaginal recurrence-free survival, distant recurrence-free survival, endometrial cancer-specific survival, overall survival, treatment-related toxicity (using the Common Terminology Criteria for Adverse Events (CTCAE) version 5) and health-related quality of life (using the common and endometrial cancer European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires C30 and EN24).

Study description

Background summary

POLEmut endometrial cancer is the least common molecular class of endometrial cancer (~10%), and excellent patient outcomes are consistently demonstrated with this tumor feature, regardless of adjuvant therapy. POLEmut endometrial cancer is characterized by
a high tumor mutational burden and has one of the 11 pathogenic mutations in the exonuclease domain of the POLE gene.(Leon et al. J Pathol 2020) Endometrial cancer with non-pathogenic POLE mutations has been shown to have significantly more disease-related
events and is often associated with mismatch-repair deficiency.(McAlpine et al. 2021, Cancer) A meta-analysis of 294 patients with pathogenic POLE mutations showed that 4.1% had disease recurrence or progression and only 1.0% died due to their
disease.(McAlpine et al. 2021, Cancer) There was no apparent benefit in clinical outcomes from receiving adjuvant therapy.(McAlpine et al. 2021, Cancer) An in vitro study showed that pathogenic POLE mutations did not increase sensitivity to radiotherapy or chemotherapeutics.(van Gool et al. 2015 CCR) Women with high-risk POLEmut endometrial cancer included in PORTEC-3 had excellent outcomes regardless of the addition of chemotherapy (5-year RFS 100% vs 97%, p=0.64).(Leon et al. JCO 2020) A recent Danish population-based study confirmed that the prognosis of women with POLEmut endometrial cancer is excellent even in the absence of adjuvant treatment.(Leon et al. Gyn Onc 2023) These data support a phase II clinical trial on treatment de-escalation for POLEmut endometrial cancer.

Study objective

In the RAINBO POLEmut-BLUE trial, omission of adjuvant therapy will be investigated in very low risk disease and de-escalation of treatment (observation or radiotherapy, but not chemoradiation) in low risk disease.

Study design

The POLEmut-BLUE trial is a prospective phase II clinical that will recruit 120 patients with select stage I-II POLEmut endometrial cancer in the main *very low risk* study cohort. A 3-year pelvic recurrence rate of 1% (upper 95% CI 2.4%) is assumed. If the upper 95% CI is <5%, it will be concluded that no adjuvant therapy has an acceptable low risk of pelvic recurrence (one-sided α=0.05). Patients will be recruited over 36 months with 36 months of additional follow-up. In addition, patients with *low risk* POLEmut endometrial cancer will be accrued into an exploratory cohort (approximately 25 patients) for descriptive analysis.

Study burden and risks

Given the experience of previous studies with tumors with a POLE mutation, it is expected that patients will benefit from de-escalation of adjuvant treatment. This is not entirely certain. There is an extremely small chance that the cancer will come back locally due to the omission of additional treatment. This risk is estimated at 2-3%. Risks of up to 5% are considered acceptable. The study will be terminated if the risk is 5% or more.
The expectation is that the chance of survival will be the same for all women, and that the chance that the disease will not recur is very high. For the few women whose disease recurs locally (in the pelvis), external and internal radiation can still be given. For the very small group of women whose cancer has returned elsewhere in the body, further treatment depends very much on the situation.
The risk classification of this study is estimated to be moderate.

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

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- Patients must have had surgery consisting of hysterectomy (total abdominal, laparoscopic or robotic-assisted) and bilateral salpingo-oophorectomy. Lymph node dissection can be performed as per institutional standards (sentinel or full lymphadenectomy). There must be no macroscopic residual disease after surgery.
- Patients must have histologically confirmed Stage I to III endometrial carcinoma which can be endometrioid, serous, clear cell, un/dedifferentiated, carcinosarcoma or mixed.
- Patients* Eastern Cooperative Group (ECOG) performance status must be 0, 1, or 2
- Patients* age must be >= 18 years.
- Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate. A similar process must be followed for sites outside of Canada as per their respective cooperative group*s procedures.
- Patient is able (i.e. sufficiently fluent) and willing to complete the patient reported outcomes (PRO) questionnaires in either English, French or a validated language. The baseline assessment must be completed within required timelines, prior to enrollment. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.
- Patients must be accessible for treatment and follow-up. Patients enrolled on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits placed on patients being considered for this trial. The patient*s city of residence may be required to verify their geographical proximity. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients enrolled on this trial will be available for complete documentation of the treatment, adverse events, and follow-up. Patients must agree to return to their primary care facility for any adverse events which may occur through the course of the trial.
- Protocol treatment is to begin within 10 weeks of hysterectomy/bilateral salpingo-oophorectomy.

Exclusion criteria

- Prior Neoadjuvant chemotherapy for current endometrial cancer diagnosis.
- prior pelvic radiation.

- Patients with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for >= 5 years.
- Clinical evidence of distant metastasis as determined by pre-surgical or post-surgical imaging (CT scan of chest, abdomen and pelvis or whole-body PET-CT scan) (see the radiology timeline outlined in Section 5).

Study design

Design

Study phase:	2
Study type:	Observational non invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-11-2023
Enrollment:	35
Type:	Actual

Ethics review

Approved WMO

Date:	26-10-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-12-2023

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-11-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
ClinicalTrials.gov	NCT05640999
CCMO	NL84566.058.23