RAINBO: Refining Adjuvant treatment IN endometrial cancer Based On molecular features, MMRd-GREEN trial

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This study has been transitioned to CTIS with ID 2023-503267-42-00 check the CTIS register for the current data. Primary:• 3 year recurrence free survival (RFS), in patients with MMRd HREC Secondary:• RFS (median and at 5 years)• OS (median, 3yr,...

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

Summary

ID

NL-OMON54178

Source
ToetsingOnline

Brief title
RAINBO MMRd-GREEN

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
Endometrial cancer inclusive carcinosarcoma of the endometrium

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Astra Zeneca,KWF grant;Astra Zeneca medicatie en unrestricted grant

Intervention

Keyword: durvalumab, Endometrial Cancer, MMRd, radiotherapy

Outcome measures

Primary outcome

3 year recurrence free survival (RFS) in patients with MMRd EC.

RFS is defined as time from randomization until date of any recurrence (local

or distant) or date of death due to any cause.

Secondary outcome

- Investigator assessed 5 yr RFS

- OS (median, 3yr, 5yr)

- Vaginal RFS, pelvic RFS, distant metastasis free-survival (median,

3-year, 5-year)

- Disease-specific survival (median, 3-year, 5-year)

- HRQoL (EORTC QLQC30 and EORTC QLQEN24)

- Safety & tolerability, grade 3-5 according to NCI-CTC version 5.0.

- Exploratory TR, including PD-L1 testing using SP263 assay and TIP algorithm

(>1% and 5%) on biopsy or resections of EC samples

Study description

Background summary

The incidence of endometrial cancer (EC) is rising due to increased population obesity and aging.
Adjuvant treatment after surgery is based on risk factors such stage and histological type. The Cancer Genome Atlas defined four molecularly distinct subclasses providing a basis for personalized treatment. We and others have developed key data on the clinical relevance of the molecular classification

and surrogate marker-based techniques which enable detection of molecular markers in routine clinical diagnostic pathology.
The TransPORTEC consortium evaluated the benefit of adjuvant chemoradiotherapy vs radiotherapy according to the four molecular subgroups on tumor tissues from patients enrolled in the randomized PORTEC-3 trial: p53-mutant (p53abn), POLE ultra-mutated (POLEmut), mismatch-repair deficient (MMRd), or with no specific molecular profile (NSMP). PORTEC-3 results showed clear differences between the molecular groups, both in prognosis and efficacy of adjuvant chemotherapy added to radiotherapy. Patients with p53abn-HREC (23% of cases) significantly benefited from chemoradiotherapy (5-year recurrence-free survival (RFS) 59 vs 36%) and NSMP-HREC (32%) had 5-year RFS 80 vs 68% (non significant) with chemoradiotherapy. In contrast, POLEmut-HREC (12%) had 97-100% survival in both trial arms. For MMRd-EC (33% of cases), 5-year RFS was not improved by adjuvant chemoradiotherapy compared to radiotherapy alone (68% vs 76%). However, advanced MMRd cancers are known to be particularly sensitive for inhibition of programmed cell death-1/ligand-1 (aPD-1/aPD-L1) therapy. These results strongly suggest that molecular factors should direct adjuvant treatment in HREC.
We hypothesize that durvalumab, a checkpoint inhibitor (aPD-L1) that binds with high affinity and specificity to the immune checkpoint receptor PD-L1, will increase survival outcomes of MMRd-HREC. The efficacy and safety of checkpoint inhibitors were recently confirmed in MMRd solid tumors by the FDA and in patients with advanced EC at progression after platinum-containing chemotherapy. Sensitivity of MMRd-EC to PD-L1 inhibition may be increased when given after radiotherapy.

Study objective

This study has been transitioned to CTIS with ID 2023-503267-42-00 check the CTIS register for the current data.

Primary:
• 3 year recurrence free survival (RFS), in patients with MMRd HREC

Secondary:
• RFS (median and at 5 years)
• OS (median, 3yr, 5yr)
• Vaginal RFS, pelvic RFS, distant metastasis free-survival (median, 3-year, 5-year)
• Disease-specific survival (median, 3-year, 5-year)
• HRQoL
• Safety & tolerability (NCI-CTC grade 3-5)
• Exploratory translational research (TR), including PD-L1 testing using SP263 assay and TIP algorithm (>1% and 5%) on biopsy or resections of EC samples.

Study design

International, multicenter, randomized, phase 3 trial in patients with mismatch- repair deficient, high risk endometrial cancer (MMRd HREC; no POLEmut; all histology including carcinosarcoma), Stage IB/II with substantial LVSI or stage IIIA-C, which randomly assigns (1:1) patients to adjuvant durvalumab in combination with and following radiotherapy versus adjuvant radiotherapy alone .

Intervention

Adjuvant durvalumab 1500 mg or placebo i.v. once every 4 weeks for in total 1 year (13x) in combination with and following adjuvant radiotherapy up to one year, after surgery with curative intent.

Study burden and risks

The patient risks will be the known side effects of durvalumab. Additional extra blood test before durvalumab will be done and patients will be asked to fill out quality of life questionairres.
Weighed against the possible advantage of having a clinical benefit, the risk-benefit analysis according to the investigators is positive. In addition, the patients with stage III EC will not have cytotoxic chemotherapy which is not expected to be effective in the MMRd subgroup, and thus have a better toxicity profile and health related quality of life
The benefit of participating in this study might be that the adjuvant therapy can have an improved therapeutic effect. All patients contribute to our knowledge and understanding how to further develop new strategies for anti-cancer therapies.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion criteria for the RAINBO program:
• Histologically confirmed diagnosis of EC of the following histologic subtypes: endometrioid endometrial carcinoma, serous endometrial carcinoma, uterine clear cell carcinoma, dedifferentiated and undifferentiated endometrial carcinoma, uterine carcinosarcoma, and mixed endometrial carcinomas of the aforementioned histotypes.
• Full molecular classification performed following the diagnostic algorithm described in WHO 2020 (5th Edition, IARC, Lyon, 2020, adapted from Vermij et al. 2020)
• TLH-BSO or TAH-BSO with or without lymphadenectomy and/or full surgical staging, without macroscopic residual disease after surgery
• No distant metastases as determined by pre-surgical or post-surgical imaging (CT/MRI scan of chest, abdomen and pelvis or PET-CT scan)
• Age > 18 years
• Expected start of adjuvant treatment (if applicable) within 10 weeks after surgery
• Patients must be accessible for treatment and follow-up
• Written informed consent for participation in one of the RAINBO trials, permission for the contribution of a tissue block for translation research and permission for the use and sharing of data for the overarching research project according to the local Ethics Committee requirements.

Inclusion criteria specific for MMRD-Green trial:
• Written informed consent
• WHO Performance score 0-1
• Histologically confirmed Stage III EC or stage IB/II EC with substantial LVSI
• Molecular classification: MMRd EC
• No prior pelvic radiotherapy

• Body weight > 30 kg
• Adequate systemic organ function:
o Creatinine clearance (> 40 cc/min): Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.
o Adequate bone marrow function : hemoglobin >9.0 g/dl, Absolute neutrophil count (ANC) >=1.0 x 109/l, platelet count >=75 x 109/l.
o Adequate liver function:
• bilirubin <=1.5 x institutional upper limit of normal (ULN). <apply to patients with confirmed Gilbert*s syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.>>
• ALT (SGPT) and/or AST (SGOT) <=2.5 x ULN

Exclusion criteria

Exclusion criteria for RAINBO program
• History of another primary malignancy, except for non-melanoma skin cancer, in the past 5 years
• Prior pelvic irradiation

Exclusion criteria specific for MMRd-GREEN trial:
• Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP.
• History of allogenic organ transplantation.
• Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
• Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.
• Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
• Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab with the exceptions of :
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
- Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan

premedication).
• History of active primary immunodeficiency
• Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome. The following are exceptions to this criterion:
- Patients with vitiligo or alopecia
- Patients with hypothyroidism (e.g., following Hashimoto syndrome)stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
• Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immuno-deficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
• Known allergy for durvalumab.
• Medical or psychological condition which in the opinion of the investigator would not permit the patient to complete the study or sign meaningful informed consent.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	30-08-2022
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imfinzi
Generic name:	Durvalumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-08-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-01-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO
Date: 24-11-2022

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 05-02-2023

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 20-02-2023

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 30-03-2023

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 06-04-2023

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
EU-CTR	CTIS2023-503267-42-00
EudraCT	EUCTR2021-000518-40-NL
CCMO	NL77847.058.21