Neo-adjuvant Pembrolizumab in dMMR/ POLE-EDM uterine cancer patients: a feasibility study

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

Summary

ID

NL-OMON49601

Source
ToetsingOnline

Brief title
PAM

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
endometrial cancer, uterine cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KRF-subsidie,Merck Sharp & Dohme (MSD)

Intervention

Keyword: deficient mismatch repair (dMMR), DNA polymerase epsilon exonuclase domain mutation (POLE-EDM), PD-1 checkpoint inhibition, Uterine cancer

Outcome measures

Primary outcome

The primary objective is to assess pathological response will be determined on

tumor tissue collected during standard of care hysterectomy. Which is planned

approximately 3 weeks after the second cycle of pembrolizumab..

Secondary outcome

The secundary endpoint is to assess the radiograpic response is measured by MRI

using RECIST 1.1 criteria. Baseline MRI will be scheduled before start therapy.

The follow-up MRI scan is scheduled as close to the hysterectomy as possible

(approximatly 3 weeks after the second cycle of pembroluzimab.)

Study description

Background summary

Uterine cancer (UC) is the most common gynecological malignancy in the Western world. Standard treatment comprises surgery with or without chemo/radiotherapy. Despite an overall favorable prognosis, many women relapse and succumb to the disease. In addition, patients experience a reduction in quality of life as a result of the hysterectomy. This is particularly true for younger women and especially for women of childbearing age. A significant improvement for UC patients could therefore be achieved by therapies that i) spare the uterus and ii) reduce risk of relapse. Herein, we believe a strong case can be made for the use of checkpoint inhibition.

Approximately 30% of all uterine cancers are characterized by a high mutational load which are results of MisMatch Repair deficiency (dMMR) or mutations in the exonuclease (proofreading) domain of DNA polymerase epsilon (POLE-EDM). DMMR and POLE-EDM occur in 20% and 12% of all uterine cancers (UCs), respectively. Both tumors types are characterized by a high number of

mutation-associated neo-antigens (MANAs) and are therefore prime targets for immunotherapy. In line with this, objective tumor response rates to immune checkpoint blockade (ICB) in recurrent dMMR endometrial cancer were 53%, with 20% complete responses. ICB in POLE-EDM has only been reported in case studies, but has so far been promising. In addition two recent studies show that neo-adjuvant administration of ICB is effective and safe as described in *nature and extent of the burden and risks* later in this section.

If these numbers translate well to the primary setting, ICB could have a place as neo-adjuvant therapy in primary dMMR/POLE-EDM UC. ICB as a neo-adjuvant therapy can potentially reduce relapse rates especially in dMMR UC, replace adjuvant therapy with chemo/radiotherapy and thereby reduce toxicity and may even be used as a uterus-sparing intervention in woman of childbearing potential.
However, an essential question that first needs to be addressed is whether ICB as neo-adjuvant treatment is feasible in primary dMMR/POLE-EDM UC.

Study objective

We aim to establish proof-of-concept for use of pembrolizumab as novel neo-adjuvant therapy in dMMR and POLE-EDM UC. When ICB proves to be feasible as defined in the primary endpoint (see 2.1), we will follow-up with larger studies to determine clinical efficacy, such as postponing standard-of-care surgery or randomized studies to standard-of-care.

Study design

We propose a window-of-opportunity study of pembrolizumab in 20 primary dMMR UC and primary POLE-EDM UC patients. Pembrolizumab (anti-PD1) will be administered in two cycles of 3 weeks between diagnosis and standard-of-care hysterectomy. Tumor responses to pembrolizumab will be assessed 3 weeks after the second cycle of pembrolizumab by MRI. In case of progressive or stable disease the hysterectomy will take place (standard-of care).

Peripheral blood and tumor samples will be used to evaluate immune responses.

Intervention

Pembrolizumab, 200mg IV Q3W for a total of 2 administrations per patient integrated into standard-of-care protocol prior to surgery.

Study burden and risks

Neo-adjuvant administration of ICB has already been performed in at least three published clinical trials using similar dosing scheme as proposed here; in melanoma, early-stage colon cancer and resectable non-small-cell-lung cancer. A

randomized phase IB trial in 20 melanoma patients compared 4 courses adjuvant ICB treatment with 2 courses neoadjuvant and 2 courses adjuvant ICB treatment. The neo-adjuvant treatment was feasible, all patients underwent surgery at the preplanned time point and no surgery-related adverse events were attributed to the prior immunotherapy. Furthermore, the trial demonstrated possible superiority of neo-adjuvant therapy and high clinical activity, 6 out of 9 evaluable patients achieving near complete (<10% viable tumor cells) or complete pathological responses. A subsequent phase II randomized trial comparing different neo-adjuvant dosage regimes resulted in a complete pathological response in 17/30 patients (57%) in the best performing study-arm.

Neo-adjuvant administration of ICB in early-stage colon cancer resulted in major pathologic response in all 7 dMMR colon tumors, including 4 complete responses. In lung cancer, neo-adjuvant ICB induced a major pathological response in 9 out of 20 (45%) of the resected tumors, of which three complete responses in the primary tumor. Importantly, no treatment-related surgical delays occurred in either studies and adverse events are highly consistent with those reported across clinical trials for anti-PD1 ICB.
We expect grade 1-2 adverse events in 2-4 of our 20 patients with no treatment-related surgical delays. Nevertheless, ~3% of patients treated with pembrolizumab are at risk of developing thyroiditis or colitis. Theoretically, this may result in postponement of surgery for 1-3 weeks. Nevertheless, we expect that after management using corticosteroids, surgical intervention can still be successfully achieved in these women. Based on available literature, postponing the surgery for this time-period will not negatively affect survival.
Based on the response rates to ICB in recurrent dMMR UC women included in the trial can potentially benefit from the ICB prior to standard-of-care therapy.
We expect that risk of recurrence will be reduced in responding participants.

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

- Female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed primary diagnosis of dMMR/POLE-EDM uterine cancer who are intended to be treated with hysterectomy will be enrolled in this study.
- A female participant is eligible to participate if she is not pregnant, not breastfeeding, is not a woman of childbearing potential (WOCBP) or agrees to follow the contraceptive guidance in section 5.2 during the treatment period and at least until standard-of-care hysterectomy.
- The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

Exclusion criteria

- A woman who has a positive urine pregnancy test within 72 hours prior to allocation.
- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor
- Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to allocation.
- Has received prior radiotherapy within 2 weeks of start of study treatment.
- Has received a live vaccine within 30 days prior to the first dose of study drug.
- Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid

therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
- Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
- Has known active CNS metastases and/or carcinomatous meningitis.
- Has severe hypersensitivity (>=Grade 3) to pembrolizumab and/or any of its excipients.
- Has active autoimmune disease that has required systemic treatment in the past 2 years
- Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- Has an active infection requiring systemic therapy.
- Has a known history of Human Immunodeficiency Virus (HIV).
- Hepatitis B of C
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject*s participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding, or expecting to conceive within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-12-2020

Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	pembrolizumab
Generic name:	KEYTRUDA
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-12-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-01-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2018-001816-31-NL
CCMO	NL67996.042.19

Study results

Date completed:	01-07-2023
Actual enrolment:	10