A Phase 3 Randomized, Open-label, Active-comparator Controlled Clinical Study of Pembrolizumab versus Platinum Doublet Chemotherapy in Participants With Mismatch Repair Deficient (dMMR) Advanced or Recurrent Endometrial Carcinoma in the First-line Setting (KEYNOTE-C93/GOG-3064/ENGOT-en15)

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This study has been transitioned to CTIS with ID 2023-506361-56-00 check the CTIS register for the current data. This study is designed to assess the efficacy and safety of pembrolizumab monotherapy compared with SoC platinum doublet chemotherapy...

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

Summary

ID

NL-OMON53504

Source
ToetsingOnline

Brief title
MK3475-C93

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
endometrial carcinoma, uterus cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme

Intervention

Keyword: endometrial carcinoma, immune therapy, pembrolizumab, platinum-based chemotherapy

Outcome measures

Primary outcome

1. PFS: The time from randomization to the first documented disease progression

or death due to any cause, whichever occurs first.

2. OS: The time from randomization to death due to any cause.

Secondary outcome

1. OR: Confirmed CR or PR.

2. ORR: The percentage of participants who have a best response of either

confirmed CR or PR.

3. DC: Confirmed CR or PR or stable disease for at least 24 weeks.

4. DCR: The percentage of participants who have achieved confirmed CR or PR or

have demonstrated stable disease for at least 24 weeks.

5. DOR: The time from first documented evidence of confirmed CR or PR until the

first documented date of disease progression or death due to any cause,

whichever occurs first.

6. Progression-free survival (PFS).

7. PFS2: The time from randomization to subsequent disease progression after initiation of a new anticancer therapy as assessed by investigator according to the local standard of clinical practice, or death due to any cause, whichever occurs first.

8. Adverse events (AEs). Study intervention discontinuation due to AEs.

9. Change from baseline of the Global Health Score (GHS)/ Quality of Life (QoL) scale of the EORTC QLQC30

Study description

Background summary

Carcinoma of the uterine body is often referred to as EC because the vast majority of cases (~92%) occur in the endometrium (inner wall of the uterus). A majority of EC cases are identified at an early stage with a 5-year survival rate of 94.9% for localized EC. However, despite early detection, approximately 13% of all ECs recur. Women diagnosed with non-specific (ie, regardless of MMR/MSI status) advanced or recurrent EC have a poor prognosis, with a 5-year survival rate of 17% when treated with chemotherapy.
Standard of care is platinum-based chemotherapy with Q3W carboplatin/paclitaxel (TC). This is the most frequently used regimen based on efficacy and hasa lower toxicity compared to cisplatin/doxorubicin/paclitaxel (TAC).
Approximately 24% of EC is MSI-H/dMMR. Previous research indicated worst OS and RFS are associated with the dMMR-subtype compared to other subgroups, with the exeption of p53. In addition, adjuvant chemotherapy combined with radiotherapy did not result in a significant therapeutic advantage in this subgroup.
The efficacy of pembrolizumab used in treatment of advanced solid malignancies is well determined and there are enough indications that pembrolizumab leads to significantly longer PFS in MSI-H/dMMR cancertypes (KEYNOTE-158 and KEYNOTE-177). In addition, pembrolizumab is generally tolerated well and has an acceptable clinical safety profile (fewer AEs). Therefore, this treatment might be of added value in the unmet treatment need for this indication.

Study objective

This study has been transitioned to CTIS with ID 2023-506361-56-00 check the CTIS register for the current data.

This study is designed to assess the efficacy and safety of pembrolizumab monotherapy compared with SoC platinum doublet chemotherapy for first-line treatment of participants with dMMR advanced or recurrent EC. The primary objectives are to compare pembrolizumab to chemotherapy with respect to PFS and OS. Hypothesis: pembrolizumab is superior to chemotherapy on both area's.

Secondary objectives are comparing both treatment groups on:
1. ORR
2. DCR
3. DOR
4. PFS-PFS2
5. Safety & tolerability
6. Quality of life & functioning

Study design

This is a randomized, unblinded open-label controlled, multicenter, phase 3-study of pembrolizumab (MK-3475) in participants with dMMR advanced or recurrent EC in the First-line setting.

Subjects will be randomized in 1 of the 2 treatment groups :
Group 1: 18 cycles of pembrolizumab (Q6W) mono-therapy.
Group 2: 6 cycles of chemotherapy (Carboplatin/paclitaxel or cisplatin/docetaxel in case if intolerance) (Q3W).

Cross-over for group 2 is allowed, where subjects might be eligible for 18 cycles of pembrolizumab. Subjects in group 1 or cross-over may be eligible for second course treatment of 9 cycles (~1 year) of pembrolizumab.

Intervention

Group 1:
- Pembrolizumab 400mg; Q6W; IV-infusion; 18 cycles

Group 2:
- Carboplatin AUC (area under the concentration-time curve;) 5 of 6; Q3W; IV-infusion; 6 cycles

OR
- Cisplatin 75mg/m2; Q3W; IV-infusion; 6 cycles
- Paclitaxel 175 mg/m2; Q3W; IV-infusion; 6 cycles

OR
- Docetaxel 75mg/m2; Q3W;IV-infusion; 6 cycles

(In case of intolerance carboplatin can be replaced by cisplatine, and paclitaxel can be replaced by docetaxel)

Study burden and risks

For this study, patients will be exposed to invasive procedures such as biopsy, blood collection, IV infusions, CT-MRI or bone scans, physical exams, possible confrontational questionnaires about quality of life, and patients will be asked to visit the hospital regularly. Patients will receive immune therapy or chemotherapy in six-week or three-week cycles. It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Pembrolizumab has been administered in a large number of oncology patients (different indications) with a known safety profile. It has been approved for treatment of different types of cancer. Overall, pembrolizumab is well tolerated and has demonstrated clinical anti tumor activity and efficacy in different types of cancer.

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.Has a histologically confirmed diagnosis of inoperable Stage III/IV persistent or recurrent EC or carcinosarcoma (mixed Mullerian tumor) that is centrally confirmed as dMMR. 2.Has radiographically evaluable disease, either measurable or nonmeasurable per RECIST 1.1, as assessed by the investigator. Prior Therapy 3.Has received no prior systemic therapy for EC except as noted below: * May have received 1 prior line of systemic platinum-based adjuvant and/or neoadjuvant chemotherapy in the setting of curative-intent resection if the recurrence occurred =6 months after the last dose of chemotherapy. * May have received prior radiation with or without radiosensitizing chemotherapy if >2 weeks before the start of study intervention * May have received prior hormonal therapy for treatment of EC, provided that it was discontinued =1 week prior to randomization 4.Is female, at least 18 years of age at the time of providing the informed consent (either Authorization for Release of Tumor Tissue or main study consent). 5.Has ECOG performance status of 0 or 1 within 7 days before randomization. 6.A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: -Is not a WOCBP OR -Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows: - Pembrolizumab (120 days after last dose) - Chemotherapy (180 days after last dose) The investigator should evaluate the potential for contraceptive method failure in relationship to the first dose of study intervention. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within 24 hours for urine or 72 hours for serum before the first dose of study intervention. If a urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention must adhere to protocol. Abstains from breastfeeding during the study intervention period and for at least 120 days after the last dose of pembrolizumab, 30 days after the last dose of cytotoxic chemotherapy agents

(paclitaxel, docetaxel, carboplatin, cisplatin), or as per local regulations. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed. 7.The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR. 8.Provides an archival tumor tissue sample or newly obtained (core, incisional, or excisional) biopsy of a tumor lesion not previously irradiated for verification of dMMR status and histology. 9.If HBsAg positive is eligible if they have received HBV antiviral therapy for at least 4 weeks and has undetectable HBV viral load prior to randomization. Hepatitis B screening tests are not required unless: -Known history of HBV infection -As mandated by local health authority. Refer to the protocol for country-specific requirements. 10.With history of HCV infection is eligible if HCV viral load is undetectable at screening. Hepatitis C screening tests are not required unless: -Known history of HCV infection -As mandated by local health authority Refer to the protocol for country-specific requirements. 11.Has adequate organ function. Specimens must be collected within 7 days before randomization.

Exclusion criteria

1.Has uterine mesenchymal tumor such as an endometrial stromal sarcoma, leiomyosarcoma, or other types of pure sarcomas. Adenosarcomas are also not allowed. Neuroendocrine tumors are also not allowed.
2.Has EC of any histology that is pMMR.
3.Is a candidate for curative-intent surgery or curative-intent radiotherapy.
4.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 coinhibitory T-cell receptor.
5.5.Has received prior systemic anticancer therapy including investigational agents for advanced or metastatic EC.
6.Has had a major operation and has not recovered adequately from the procedure and/or any complications from the operation before starting study intervention.
7.Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.
8.Is currently participating in or has participated in a study of an investigational agent for EC; or has participated in a study of an investigational agent for non-EC within 4 weeks before the first dose of study intervention; or has used an investigational device within 4 weeks before the first dose of study intervention.

9.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 the first dose of study intervention.
10.Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
11.Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, for at least 4 weeks by repeat imaging, clinically stable and without requirement of steroid treatment for at least 14 days before the first dose of study intervention.
12.Has a known intolerance to any study intervention and/or any of its excipients.
13.Has an active autoimmune disease that has required systemic treatment in past 2 years.
14.Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
15.Has an active infection, requiring systemic therapy.
16.Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.Refer to the protocol for country-specific requirements.
17. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
18.Has had an allogenic tissue/solid organ transplant.Refer to the protocol for country-specific requirements.

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:	Recruiting
Start date (anticipated):	27-09-2022
Enrollment:	24
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	22-03-2022
Application type:	First submission

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2023-506361-56-00
EudraCT	EUCTR2021-003185-12-NL
ClinicalTrials.gov	NCT05173987
CCMO	NL80391.028.22