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DOMENICA: Randomized phase III trial in MMR deficient endometrial cancer patients comparing chemotherapy alone versus dostarlimab in a first-line advanced/metastatic setting

Submission date	**Recruitment status**	[X] Prospectively registered
02/06/2023	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/01/2024	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
28/08/2026	Cancer	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

The DOMENICA study aims to evaluate the effectiveness of dostarlimab, as a new treatment for advanced/metastatic endometrial cancer by significantly reducing the chance of relapse. Dostarlimab is a type of immunotherapy (doesn't target the tumour directly, but has an impact on the immune system to be able to attack and destroy the cancer cells). When the immune system detects a foreign body (virus, bacteria, etc), it produces antibodies which are proteins that combat infections. They can attach to other molecules or cells of your body, and work by helping your immune system to fight the cancer.

The current standard treatment for this cancer is chemotherapy alone (paclitaxel and carboplatin). Despite chemotherapy, the cancer can progress in some patients.

Who can participate?

The study will be carried out among 142 patients with advanced or metastatic endometrial cancer, in more than 60 healthcare facilities in 7 countries (France, Belgium, Spain, Italy, Germany, Canada and United Kingdom) over an 8 year period.

What does the study involve?

In order to evaluate the efficacy of dostarlimab, it is necessary to compare this treatment to the standard treatment. In order to be able to make comparisons, it is necessary that the distribution between the 2 groups is randomly selected by a computer (this is called randomization). There will be the same number of patients in each treatment group therefore patients have 1 possibility out of 2 to receive dostarlimab.

The duration of participation in this research study for each patient is around 5 years. Participation will be divided into 5 periods:

• Collection of a tumour sample (standard of care, not an extra procedure),

• Ensuring the criteria for inclusion is met,
• Allocation of treatment,
• Treatment period,
• Follow up period.
Participants will have the right to withdraw at any point and treatment will not be compromised.

If successful this study could help patients get quicker access to the therapeutic innovation, especially immunotherapy.

What are the possible benefits and risks of participating?
Benefits:
We hope that dostarlimab is more efficient than chemotherapy, and significantly reduces the rate of relapse of advanced or metastatic endometrial cancer. If successful this study could help patients get quicker access to the therapeutic innovation, especially immunotherapy. If you participate in this study, you will have access to immunotherapy much sooner than you otherwise would. However, you may not benefit from participating in this study. Your condition may remain the same, improve or worsen. Your participation will not limit the access to the standard treatments, in case of benefit or progression after the treatments dispensed in this study.
By participating in this research, you will be helping scientists and clinicians better understand the disease and improve future treatment options. The information from this study will also hopefully help future endometrial cancer patients.

Risks:
Current information continues to support an acceptable benefit-risk profile for Dostarlimab when used with the precautions, dosing & safety monitoring outlined in the Protocol and routine pharmacovigilance practices. The study treatment may be responsible for side effects of which all of them may not have been identified even though the drugs proposed in this study have all been marketed in many countries worldwide for several years. Most of them are variable from one patient to another and can be mild, moderate or sometimes severe. Some may go away as soon as study treatment(s) is stopped. In some cases, they can be serious, long-lasting or may never resolve (irreversible). Where possible medicines will be prescribed to help attenuate side effects reported. In addition, by combining several drugs, side effects may be more frequent and /or more intense than when taking only one of these drugs. A list of ongoing medication, dietary supplement or phytotherapy will be captured prior to trial entry to ensure the risk of potential interactions is minimised.

Safety of study treatments will be assessed at each visit by the study doctor. Additional treatments may be prescribed to control side effects. If they are significant, the doctor may change the treatment doses or stop study treatment(s)* for a given time or permanently. Side effects may occur based on the experience from other patients who have been treated with dostarlimab. They are listed in the Protocol and Patient Information Sheet according to their frequency regardless of their severity including very common (> 10 %), common (1-10 %), uncommon (0.1-1%) and rare but serious. If experienced patients will be prompted to contact there Doctor immediately.

CT & MRI scans may involve venous perfusion of a contrast agent. As with any product, there is a risk of an allergic reaction to that product.

Needle pricking during injection of the contrast agent, during treatment administration or blood sampling can cause pain, swelling, bruise, irritation or redness.

During the electrocardiogram, may experience itching or bruising on the skin where the patches were placed.

The effects of the study products on an unborn child or newborn are not known therefore participants are not allowed to participate in this research if pregnant or plan to be, this will be considered by the Principal Investigator at each site prior to consent of a potential participant.

Prior to consent the Principal Investigator(s) at each site will ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study, including any information on the mandatory and optional tumor biopsies. Participants will also be informed of there rights to discontinue from the study and/or study treatment at any time. Likewise participants may be discontinued from study treatment by the Principal Investigator at any time. Reasons for discontinuing study treatment prematurely include adverse events, clinical progression, PD according to RECIST v.1.1 (criteria per Investigator assessment), risk (as judged by the Investigator, Sponsor, or both), severe noncompliance with the protocol, pregnancy & lost to follow-up.

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. Circumstances that may warrant termination or suspension include, but are not limited to:
• Determination of unexpected, significant, or unacceptable risk to participants
• Demonstration of efficacy that would warrant stopping
• Insufficient compliance to protocol requirements
• Data that are not sufficiently complete and/or evaluable

Where is the study run from?
ARCAGY-GINECO (France)

When is the study starting and how long is it expected to run for?
May 2023 to December 2029

Who is funding the study?
ARCAGY-GINECO (France)

Who is the main contact?
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Contact information

Type(s)
Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05201547

Clinical Trials Information System (CTIS)
2021-002124-21

Integrated Research Application System (IRAS)
1006901

Central Portfolio Management System (CPMS)
60707

Protocol serial number
GINECO-EN105b/ENGOT-en13

Study information

Scientific Title
DOMENICA (GINECO-EN105b/ENGOT-en13 study): Randomized phase III trial in MMR deficient endometrial cancer patients comparing chemotherapy alone versus dostarlimab in first-line advanced/metastatic setting

Acronym
DOMENICA

Study objectives
The DOMENICA study aims to evaluate the effectiveness of dostarlimab, as a new treatment for advanced/metastatic endometrial cancer by significantly reducing the chance of relapse.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 19/11/2023, East Midlands - Nottingham 2 Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8169, (0)207 104 8278, (0) 208 104 8051; nottingham2.rec@hra.nhs.uk), ref: 23/EM/0142

Primary study design
Interventional

Study design
Phase III randomized open-label cross-over trial

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Endometrial cancer

Interventions
Patients will be randomized 1:1 to receive either 4 cycles of dostarlimab every 3 weeks followed by dostarlimab every 6 weeks as maintenance up to 2 years* or 6 cycles of carboplatin-paclitaxel:
• Arm A: Dostarlimab 500 mg, every 3 weeks, 4 cycles and then 1000 mg every 6 weeks until progression, unacceptable toxicity, patient/investigator decision to withdrawal or completion of 2 years of treatment
• Arm B: Carboplatin AUC 5 or 6 plus Paclitaxel 175 mg/m2, every 3 weeks, 6 cycles.
A cross over to dostarlimab is permitted at progression.

*Treatment ends after 2 years, progression of disease, toxicity, withdrawal of consent, Investigator’s decision, or death, whichever occurs first. Continued treatment with dostarlimab

beyond 2 years may be considered for patient in Complete Response and if the investigator considers that the patient may benefit from a longer duration of treatment, only after discussion with the sponsor and its agreement.

Within 1 week, prior to C1D1, authorised UK investigators or a delegated member of the research team at the site, will register and randomise patients, who have given their informed consent, using the Interactive Voice/Web Response System (IVRS/IWRS). Randomization will be as a result of the local and centralised MMRd/MSI-H status; the block for central analysis will be sent the one of two French laboratories (Caen or Cochin) allocated via the IVRS/IWRS system. Sites will be provided with login details to the IVRS/IWRS system once authorised. A unique enrolment number will be assigned to potential patients once registered in the system. Courier labels for both laboratories (3x Caen, 3x Cochin) will be provided in the sample kits provided to sites.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Dostarlimab, carboplatin, paclitaxel

Primary outcome(s)
Progression-free survival (PFS), defined as the time from the date of randomization to the earliest date of assessment of PD or death by any cause in the absence of PD, whichever occurs first. Tumour response will be evaluated using RECIST v.1.1 based on Investigator assessment. The primary analysis population will be the intention-to-treat (ITT) population.

Key secondary outcome(s)
1. Quality of Life Questionnaires (QoL) will be assessed on EORTC QLQ-C30, EORTC QLQCIP20, EORTC QLQ-EN24 and EUROQOL EQ-5D completion. The targeted dimension will be the Global QoL/Health Status dimension of the QLQ-C30 at 18 weeks
2. Overall Response Rate (ORR) is defined as the proportion of patients with the best overall response (BOR) of CR or PR. Patients who have no postbaseline evaluable tumour assessments will be considered non-responders. Overall Response Rate (ORR) will be calculated based on ITT population, using Investigator’s tumor assessment.
3. Duration of Response (DOR) is defined as the time from first documentation of CR or PR until the time of first documentation of subsequent PD per RECIST v.1.1 based on Investigator assessment or death by any cause in the absence of PD per RECIST v.1.1, whichever occurs first.
4. Overall Survival (OS) is defined as the time from the date of inclusion until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. The analyses for Overall Survival will be based on ITT population, according to the treatment group subjects are randomized to at baseline. The distribution of OS will be compared between the two treatment groups.
5. Time to first and second Subsequent Treatment or death is defined as the time from the date of randomization to date of the first and second subsequent anticancer therapy or death.
6. Safety and tolerability will be assessed for all the patients in terms of :
6.1. AEs, deaths, laboratory data, vital signs and ECG. AE will be described according to MedDRA

terms and graded according to CTCAE version 5.0 by investigators.
6.2. Self-report symptoms and adverse events by patients using PRO CTC-AE (Self-reported PRO) of cancer treatments

Completion date
31/12/2029

Eligibility

Key inclusion criteria
1. Female patient is at least 18 years of age
2. Patient has signed the Informed Consent (ICF) and is able to comply with protocol requirements
3. Patient with histologically proven endometrial adenocarcinoma with recurrent or advanced disease
4. Patient with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
5. Patient must have primary Stage IIIC2 or Stage IV disease or first recurrent endometrial cancer without curative treatment by radiation therapy or surgery alone or in combination, and meet at least one of the following situations:
5.1. Patient has primary Stage IIIC2 (with nodes involvement from the outset, not allowing a curative radiotherapy, or with remaining measurable lumbo-aortic nodes after lumbo-aortic dissection, which cannot be treated by curative radiotherapy) or Stage IV disease
5.2. Patient has first recurrent disease and is chemotherapy naïve for this 1st recurrence or metastatic setting
5.3. Patient may have received prior neo-adjuvant/adjuvant systemic chemotherapy or locoregional concomitant radio-chemotherapy for the primary cancer and had a recurrence ≥ 6 months after completing treatment (first recurrence only)
6. All histologic subtypes of endometrial adenocarcinoma could be included if MMRd/MSI-H
7. MMRd/MSI-H tumor (defined in routine local IHC), is mandatory for inclusion. In case of ambiguous result of IHC (lack of positive internal control, heterogeneous loss of MMR protein expression), the MMRd/MSI-H status will be assessed by PCR/NGS
8. Availability of 1 block for MMR/MSI status centralized confirmation for IHC or PCR/ NGS, and additional block(s) for Translational Research
9. Patient with measurable disease according RECIST 1.1 criteria
10. Patient could have been previously treated with hormone therapy, for the metastatic /advanced disease
11. Patient may have received pelvic and lombo-aortic external beam +/- vaginal brachytherapy
12. Patient has adequate organ function, defined as follows:
12.1. Absolute neutrophil count ≥ 1,500 cells/µL
12.2. Platelets ≥ 100,000 cells/µL
12.3. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
12.4. Serum creatinine ≤ 1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault equation for patients with creatinine levels > 1.5× institutional ULN
12.5. Total bilirubin ≤ 1.5× ULN (≤ 2.0 x ULN in patients with known Gilbert’s syndrome) or direct bilirubin ≤ 1× ULN
12.6. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5× ULN unless liver metastases are present, in which case they must be ≤ 5× ULN
12.7. International normalized ratio or prothrombin time (PT) ≤1.5× ULN and activated partial thromboplastin time ≤1.5× ULN.Patients receiving anticoagulant therapy must have a PT or

partial thromboplastin within the therapeutic range of intended use of anticoagulants
13. Patient must have a negative serum pregnancy test within 72 hours of the first dose of study medication, unless they are of nonchildbearing potential. Nonchildbearing potential is defined as follows:
13.1. Patient is ≥ 45 years of age and has not had menses for > 1 year
13.2. A follicle-stimulating hormone value in the postmenopausal range upon screening evaluation if amenorrhoeic for < 2 years without a hysterectomy and oophorectomy
13.3. Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation:
13.3.1. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound, MRI, or CT scan
13.3.2. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise, the patient must fulfil the criteria in Inclusion Criterion 14
13.3.3. Information must be captured appropriately within the site's source documents
14. Patient of childbearing potential must agree to use a highly effective method of contraception (protocol section 18.9) with their partners starting from time of consent through 150 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient (Information must be captured appropriately within the site's source documents)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
Female

Total final enrolment
264

Key exclusion criteria
1. Patient has received neoadjuvant/adjuvant systemic chemotherapy for primary Stage IIIc2 or IV disease and has had a recurrence or PD within 6 months of completing chemotherapy treatment prior to entering the study. Note: Low-dose cisplatin given as a radiation sensitizer or hormonal therapies do not exclude patients from study participation.
2. Patient has had >1 recurrence of endometrial cancer, treated with chemotherapy (surgery of the recurrence is allowed)
3. Patient previously treated with chemotherapy for non-curable advanced disease or metastatic disease
4. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent
5. Patient has received prior anticancer therapy (chemotherapy, targeted therapies, hormonal

therapy, radiotherapy) within 21 days or <5 times the half-life of the most recent therapy prior to Study Day 1, whichever is shorter. Note: Palliative radiation therapy to a small field ≥1 week prior to Day 1 of study treatment may be allowed.
6. Patient with contraindication to chemotherapy or checkpoint inhibitor treatments
7. Patient has a concomitant malignancy, or has a prior non-endometrial invasive malignancy who has been disease-free for < 3 years or who received any active treatment in the last 3 years for that malignancy (Non-melanoma skin cancer is allowed)
8. Patient has known uncontrolled central nervous system metastases, carcinomatosis meningitis, or both
Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of disease progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not been using steroids for at least 7 days prior to study treatment. Carcinomatous meningitis precludes a patient from study participation regardless of clinical stability.
9. Patient has a known history of human immunodeficiency virus (HIV; HIV1 or HIV2 antibodies)
10. Patient has known active hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative] is detected)
11. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy is not considered a form of systemic therapy (e.g., thyroid hormone or insulin)
12. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of systemic immunosuppressive therapy within 7 days prior to the first dose of study treatment
13. Patient has not recovered (i.e., to Grade ≤ 1 or to baseline) from cytotoxic therapy-induced adverse events (AEs). Note: Patients with Grade ≤2 neuropathy, Grade ≤2 alopecia, or Grade ≤2 fatigue are an exception to this criterion and may qualify for the study.
14. Patient has not recovered adequately from AEs or complications from any major surgery prior to starting therapy
15. Patient has a known hypersensitivity to carboplatin, paclitaxel, or dostarlimab components or excipients
16. Patient is currently participating and receiving study treatment or has participated in a study of an investigational agent and received study treatment or used an investigational device within 4 weeks of the first dose of treatment
17. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring systemic therapy. Specific examples include, but are not limited to, active, non-infectious pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent)
18. Use of any of the following immunomodulatory agents within 30 days prior to the first dose of study drug:
18.1. Systemic corticosteroids (at dose higher than 10 mg/day equivalent prednisone); if systemic corticoid use at higher dose, corticoid must be stopped at least 7 days before study treatment start
18.2. Interferons
18.3. Interleukins
18.4. Live vaccine
Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza

vaccines for injection are generally killed virus vaccines and are allowed as other killed vaccines, if done at least 2 weeks prior the first dose of study drug; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
19. Patient is pregnant or breastfeeding or is expecting to conceive children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study treatment, or lactating woman

Date of first enrolment
01/03/2024

Date of final enrolment
30/06/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Belgium

Canada

France

Germany

Italy

Spain

Study participating centre
Velindre Cancer Centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Arcagy Gineco

ROR
https://ror.org/03mzxvt76

Funder(s)

Funder type
Research organisation

Funder Name

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and analysed during the trial are/will be available upon request directly from the sponsor ARCAGY-GINECO, domenica@arcagy.org

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3.3	12/09/2024	05/11/2024	No	Yes
Participant information sheet	version 4.0	06/05/2024	28/08/2026	No	Yes