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METHOD

DOMENICA: dostarlimab versus chemotherapy alone in first-line MMR-deficient advanced endometrial cancer patients

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ABSTRACT

Immunotherapy (IO) in endometrial cancer (EC) is the standard of care in the second line setting in combination with an anti-angiogenic agent. Randomized clinical trials have reported results supporting the addition of IO to chemotherapy (paclitaxel plus carboplatin) in the first-line setting in advanced EC patients in the global population, with high efficacy in mismatch repair deficient (MMRd) patients. These trials were not designed to answer this de-escalation question in the MMRd population, who benefit greatly from IO.

The international, randomized phase III, DOMENICA trial compares first-line dostarlimab versus chemotherapy alone (with planned cross-over) for advanced MMRd EC. Our primary endpoint will be progression-free survival. The key secondary endpoints will be overall survival, safety and quality of life [NCT05201547].

PLAIN LANGUAGE SUMMARY

Endometrial cancer (EC) is divided into four biological sub-groups. One of them is defined by mismatch repair deficiency (MMRd). MMRd in cancer is associated with microsatellite instability and a high mutation rate, leading to the creation of numerous neo-antigens and a strong immune environment. Immunotherapy (IO) is associated with numerous successes for MMRd patients, such as in colorectal cancer. IO for EC is now the standard of care in the second-line setting in association with a tyrosine-kinase inhibitor after the result of the KEYNOTE-775 study. Four randomized studies have been conducted among advanced EC patients testing IO and chemotherapy in the first line (regardless of MMR status): RUBY with dostarlimab, NRG-GY -018 with pembrolizumab, AtTEnd with atezolizumab and DUO-E with durvalumab reporting positive result particularly in MMRd population. However, for MMRd patients, the benefit of adding chemotherapy to immunotherapy and the associated toxicity is not clear. Even more so when we take into account the characteristics of EC patients, often elderly with comorbidities (e.g.obesity, diabetes, etc)

The ongoing phase 3 multicentric randomized DOMENICA trial will address the question of de-escalation by comparing carboplatin-paclitaxel to dostarlimab alone in the first-line setting in advanced MMRd EC. A cross-over to dostarlimab is planned in the chemotherapy group. Our primary endpoint will be progression-free survival. The key secondary endpoint will be overall survival. Other secondary endpoints will be safety and quality of life. Translational studies will be performed to explore immune biomarkers and the geriatric population.

Registration number on ClinicalTrial.gov is [NCT05201547].

TWEETABLE ABSTRACT

Immunotherapy is particularly efficient in deficient MMR cancer patients with advanced/metastatic endometrial cancer. Recent trials showed a benefit of the association of immunotherapy with chemotherapy in a first-line setting. However, chemotherapy remains toxic (especially as “real-world” patients are often frail), and could be avoided for MMRd patients. The international phase III randomized DOMENICA trial has been designed to evaluate Dostarlimab vs chemotherapy alone for first-line advanced MMRd EC.

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Mismatch repair deficient; endometrial cancer; advanced/metastatic; immunotherapy; dostarlimab; de-escalation; progression-free survival; treatment-related biomarkers

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Article highlights

Study rationale
- Advanced endometrial cancer (EC) patients are often frail, older and comorbid
- Mismatch repair deficiency/high microsatellite instability (MMRd/MSI-H) EC subgroups are expected to be strong responders to immunotherapy treatment
- Immunotherapy is already a standard of care in the second line in association with an antiangiogenic agent
- Immunotherapy is now a standard of care in the first line in combination with chemotherapy
- The combination of chemotherapy to immunotherapy adds toxicity, and it remains unknown whether it is required for MMRd/MSI-H patients.

Study objective
- Evaluate the efficacy and safety of dostarlimab alone versus carboplatin-paclitaxel in patients with MMRd/MSI-H relapse or advanced/metastatic endometrial cancer in first-line.

DOMENICA study
- A phase 3, open-label, randomized, multicentre study
- Stratification will be performed according to prior adjuvant chemotherapy, prior pelvic radiotherapy, and disease status: newly diagnosed versus relapse.

Endpoint
- Our primary endpoint will be progression-free survival (PFS) according to a blinded independent central review
- Overall Survival will be a key secondary endpoint.
- Safety, Quality of life and PFS 2 are other secondary endpoints
- DOMENICA includes translational studies in the search for immune biomarkers and the efficacy of treatment based on geriatric assessment.

Key inclusion/exclusion
- ≥18 years of age
- Histologically confirmed advanced-stage FIGO Stage IIIA to C2 or Stage IV disease or first recurrent endometrial cancer without curative treatment available.
- MMRd/MSI-H tumor is mandatory for inclusion with central confirmation before inclusion.
- Patients need to be able to receive chemotherapies or checkpoint inhibitor treatments

Procedure
- 260 patients (130 per arm) will be randomized 1:1
- 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 withdraw or completion of 2 years of treatment
- Arm B: carboplatin AUC 5 or 6 plus paclitaxel 175 mg/m^2, every 3 weeks, 6 cycles.
- A cross-over to dostarlimab is planned at the first progression

1. Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed countries with an increasing incidence (over 200,000 new cases yearly). Most of the cases are diagnosed at an early stage. However, 15–20% of the women have an advanced stage at diagnosis or will develop a recurrence. For this sub-group, the 5-year overall survival (OS) rate ranges from 30–40% for para-aortic lymph node invasion (stage IIIC2) to 15–20% for stage IV [1]. Historically, EC were classified according to clinicopathological and molecular features, grade, endometrioid or other histology (serous, clear-cell), expression of estrogen and progesterone receptors, deletions of *KRAS*, *PTEN*, or deficiency in mismatch repair, *TP53* mutations and *HER2/NEU* overexpression [2]. More recently, the Cancer Genome Atlas Network identified four molecular types of endometrial carcinoma according to their mutational profile, which profoundly changed EC care [3–5]. Group 1 (7%) with somatic inactivating mutations in POLE exonuclease and very high mutation rates (hypermutated), is associated with a good prognosis. Group 2 (28%) includes endometrial adenocarcinoma with high microsatellite instability (MSI-H) due to mismatch repair deficient proteins (MMRd), frequently with MLH-1 promoter hypermethylation and high mutation rates. Group 3 (39%) included endometrial adenocarcinoma with low copy number alterations. Group 4 (26%; serous-like or copy-number high) showed a low mutation rate, but frequent TP53 mutations with the worst prognosis [3,5,6].

1.1. Background and rationale

The backbone of treatment for first-line advanced EC is still chemotherapy with a platinum-based combination with taxanes, whatever the histology and the molecular profile. According to the studies, response rates vary between 40% and 50%, and median progression-free survival (PFS) is between 8 to 12 months [7]. EC patients are a particularly frail group of patients linked to the age of diagnosis (>70% over 70 years old) and many associated comorbidities (i.e., obesity, diabetes and high blood pressure). Moreover, chemotherapy is often not well tolerated and can induce long-term toxicities (with a high rate of neurotoxicities) [8].

The molecular classification with its strong predictive value should be incorporated in the risk stratification of these patients with already practice changes in early EC [3,9]. MMRd/MSI-H tumors represent 15 to 20 % of EC in advanced disease, and new strategies other than chemotherapy, such as immunotherapy, have been recently explored [10]. Preclinical data suggested that MMRd/MSI-H tumors would be more resistant to cisplatin and carboplatin because a functional MMR/MSI system is required for the detection of damaged DNA created by these two drugs [11].

MMR guarantees genomic integrity and stability and avoids insertions and deletions of abnormal DNA at microsatellites. Patients with MMRd/MSI-H have active tumor microenvironments expressing high numbers of neo-antigens and an elevated amount of tumor infiltrating lymphocytes (TILs), which can be recognized by the patient's immune system and are good candidates for immune checkpoint inhibitors (IO). Pembrolizumab, a programmed cell death-1 (PD-1) inhibitor, was the first agent to be evaluated in this situation, demonstrating high efficacy in different MMRd/MSI-H cancers [12].

Pembrolizumab received "tumor-agnostic" accelerated approval by the FDA in May 2017 for the treatment of patients with unresectable or metastatic MMRd/MSI-H solid tumors (including endometrial cancer) [13,14]. Phase-1 clinical trials (KEYNOTE-028, 158–164) demonstrated the antitumor activity of pembrolizumab in heavily pretreated advanced EC, including complete and durable responses [15].

Notably, in the KEYNOTE-164 and 177 studies, pembrolizumab was more effective than chemotherapy in MMRd/MSI-H advanced colorectal cancer and is now used in routine clinical practice [16–18].

In the EC-relapsed setting, after chemotherapy, different studies reported the efficacy of IO either as monotherapy for MMRd/MSI-H EC or in combination with an anti-angiogenic tyrosine kinase inhibitor for the global population. The phase I-II Garnet study investigated dostarlimab (anti-PD-1 Inhibitor) in women with recurrent or advanced EC in the second line or later setting

[19]. The first result showed good activity for the two groups. Higher responses were associated with MMRd/MSI-H status with an impressive objective response rate (ORR) of 43.5% (95%CI 34.0–53.4%) with 11 complete responses and a median duration of response not yet reached. The safety analysis was reassuring with most treatment-related AEs (TRAEs) being grade 1 or 2 (fatigue, diarrhea, and nausea) and manageable. Only 5% discontinued dostarlimab because of TRAEs [19]. The KEYNOTE-146 result testing the combination of pembrolizumab and lenvatinib in relapsed EC after platinum-containing therapy was confirmed in KEYNOTE-775, comparing the combination against investigator-choice chemotherapy. There was a statistically significant improvement in OS (HR 0.62, 95% CI 0.51–0.75, $p < 0.0001$), PFS (HR 0.56, 95% CI 0.47–0.66, $p < 0.0001$) and ORR (31.9% versus 14.7%) compared with standard of care [20,21]. The benefit was particularly high amongst MMRd/MSI-H patients however, this combination had a high toxicity rate, with grade 3 or higher adverse events occurring in 88.9% of the patients receiving lenvatinib plus pembrolizumab versus 72.7% of those receiving chemotherapy [21].

Based on the encouraging data among heavily pretreated EC patients, different studies have evaluated the benefits of immunotherapy in the first line. Four randomized studies have been conducted in advanced EC patients in the first-line setting, regardless of MMR status (ENGOTen6/NSGO/RUBY [NCT03981796] with dostarlimab, NRG-GY-018 KEYNOTE-868 [NCT03914612] with pembrolizumab, DUO-E/GO G-3041/ENGOT-EN10 with durvalumab [NCT04269200], ENGOT-en7 /MaNGO/AtTEnd with atezolizumab [NCT03603184]); all compared chemotherapy to chemotherapy plus check-point inhibitors (with no single agent IO arm, particularly among the subgroup of MMR deficient patients). The trials have all shown that the addition of IO to standard first-line chemotherapy resulted in significantly longer PFS and a signal of OS gain (results are still insufficiently mature), notably among MMRd/MSI-H see Table 1 [22–25]. The addition of IO to chemotherapy increased the high-grade toxicity by 10%. In the Ruby trial, the incidences of adverse events were 70.5% vs. 59.8% in the chemotherapy alone arm and serious adverse events were 37.8% vs. 27.6%. However, the majority of these toxicities are associated with chemotherapy; for instance, over 40% of patients reported peripheral neuropathy [23]. The safety profile was similar in NRG-GY -018 KEYNOTE-868, and the AtTEnd trial [22,25]. The combination of IO and chemotherapy is now the new standard of care, already routinely used in clinical practice.

Finally, the ENGOT-en9/LEAP001 study recently evaluated the combination of pembrolizumab and lenvatinib to chemotherapy regardless of MMR/MSI status, in first-line setting [26,27]. Statistical significance criteria for OS and PFS in pMMR patients were not met. Even if the results had been in favor of the non-chemotherapy arm, the poor toxicity profile of this combination strategy would likely limit its practicability in the "real world" setting. Furthermore, it is not clear whether MMRd patients benefit from the addition of antiangiogenic agents to immunotherapy [27].

These recent studies have all demonstrated the high efficacy of IO in the first-line advanced/metastatic EC setting, particularly among MMRd/MSI-H EC. However, these recent studies didn't answer the de-escalation question with the use of IO alone to avoid chemotherapy, in the MMRd EC patients, as it has already been demonstrated in MMRd colorectal cancer(CRC) patients. However, not all dMMR tumors are the same, and dMMR status alone is not sufficient to predict tumor immunogenicity [28]. For example, dMMR was associated with an increased density of tumor-infiltrating CD3 + and CD8 + T-cells in CRCs and ECs, but the increases were substantially greater in CRCs. Additionally, IFNγ pathway activity was strongly upregulated by dMMR/MSI in CRC, but

Table 1. Results of principal randomized trials in first line with immunotherapy in advanced endometrial cancer.

Trial	NCT	Population	randomization	PFS	OS	Reference
NRG-GY018	NCT03914612	All Comers (n = 816) 225 dMMR	Pembrolizumab or placebo along with combination therapy with paclitaxel plus carboplatin	dMMR cohort not reached (95% CI 30,7-NR) months for pembrolizumab vs 8,3 (95% CI,6.5–12.3) months for placebo; pMMR cohort 13.1 (95% CI, 9.1–19.8) vs 8.5 (95% CI, 8.0–10.7) months	Not mature but pMMR 27.96 (95% CI, 21.42-NR) for Pembrolizumab vs 27.37 (95% CI, 19.52-NR) months in the placebo arm. dMMR NR in either arm	[22]
RUBY/ENGOT-EN6 /GOG3031/ NSGO	NCT03981796	All comers (n = 494) 118 dMMR	Dostarlimab or placebo along with combination therapy with paclitaxel plus carboplatin	At 24 month dMMR 61,4%(95% CI 46.3–73.4) for dorstarlimab vs 15,7% (95% CI 7,2–27) for placebo; pMMR 28,4 (95% CI 21,2–36,0) vs (95% CI 12,8–25,7)	24 months OS 71.3%(95% CI, 64.5 to 77.1) for dostarlimab vs 56.0%(95% CI, 48.9 to 62.5) with placebo	[23]
DUO-E/GOG-3041/ENGOT-EN10	NCT04269200	All comers (n = 718) 143 dMMR	Durvalumab plus Carboplatin-Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib	All comers 15,1(95% CI 12,6–20,7) months for Durvalumab + Olaparib arm vs 10,2(95% CI 9,7–14,7)monthsvfor durvalumab arm vs 9,6 (95% CI 9,0–9,9) for control arm	OS was 18.7 months (1.1–33.4) for durvalumab + olaparib arm; 18.4 months (2.1–33.0) for durvalumab arm and 18.6 months (0.5–32.9) for the control arm	[24]
ENGOT-en7 /MaNGO/ AtTEnd	NCT03603184	All comers (n = 551) 125 dMMR	Atezolizumab or placebo along with combination therapy with paclitaxel plus carboplatin	At 28·3 months All comers 10·1 (95% CI 9·5–12·3) months for atezolizumab vs 8·9 (8·1–9·6) months for placebo; dMMR cohort NE (95% CI 12·4-NE) vs 6·9 months (6·3–10·1)	Median OS 38·7 (95%CI 30·6-NE) months for atezolizumab vs 30·2 (25·0–37·2) months for placebo group (HR 0·82, 95% CI 0·63–1·07; log-rank p = 0·048)	[25]

CI :confidence interval, PFS : Progression free survival, OS : Overall survival; dMMR mismatch repair-deficient; NR:Not reached; NE: not estimable.

downregulated in EC [29]. The phase III randomized DOMENICA trial will evaluate IO monotherapy in a first-line setting in advanced MMRd/MSI-H EC. The objective is to compare the benefit of dostarlimab in advanced endometrial MMRd/MSI-H cancer versus chemotherapy (carboplatin plus paclitaxel regimen). A systematic cross-over is organized at the first progression.

Our study is particularly important in the strategy of treatments for elderly and/or comorbid patients who often cannot tolerate chemotherapy. Moreover, moving to IO alone, instead of chemotherapy or the combination for this specific population, who are highly responsive to IO, could contribute to being part of the new standard of care for MMRd/MSI-H advanced EC patients, with major practice changes.

1.2. Objectives

All the objectives and endpoints of the study are detailed in Table 2. Our primary endpoint will be the PFS and OS will be our key secondary endpoint. Other secondary endpoints will be safety and tolerability, quality of life (QoL), overall response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS 2). Exploratory analyses will include the quantification of efficacy according to biomarkers of interest and geriatric assessment for patients ≥70 years old.

2. Study methods

2.1. Trial design see **Figure 1**

DOMENICA is an ENGOT international Phase III, open-label, randomized, multicentre study to evaluate the efficacy and safety of dostarlimab versus carboplatin-paclitaxel in patients with MMR deficient/MSI High relapse or advanced/metastatic endometrial cancer. A total of 400 patients should be screened, and 260 patients (130 per arm) will be randomized in the trial. Randomization will be stratified according to prior adjuvant chemotherapy (yes or no), prior pelvic radiotherapy (yes or no) and disease status (newly diagnosed advanced/metastatic disease versus relapse).

Patients will be randomized 1:1 to receive either treatment:

- 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 withdraw or completion of 2 years of treatment.
- Arm B: carboplatin AUC 5 or 6 plus paclitaxel 175 mg/m2, every 3 weeks, 6 cycles. The cross-over to receive Dostarlimab is planned at the time of first progression.

2.2. Sample size estimation

The ongoing DOMINICA trial will enroll 260 patients from around 130 centers. The sample size calculation for this

Table 2. Study objectives and associated endpoints.

Primary Objective	Primary endpoint
Progression Free Survival	Defined as the time from the date of randomization until the first documented disease progression based on RECIST 1.1 assessed by BICR, or death due to any cause, whichever occurs first. Patients alive and free of progression at the cutoff date will be censored at the last tumor assessment date
Secondary Objectives	**Secondary endpoints**
Overall Survival	Measured as the time from the date of randomization to the date of death due to any cause. Patients alive at the cutoff date will be censored at the last date they are known to be alive
Progression Free Survival 2	Defined by the time from initial randomization to the second objective disease progression (i.e., after the first subsequent therapy) as assessed by the investigator or death due to any cause, whoever occurs first. Patients alive and free of second progression (including patients without any progression), will be censored at the last disease assessment date
Quality of life	Determined by EORTC QLQ-C30, EORTC QLQ-CIP20,EORTC QLQ-EN24 and EUROQOL EQ-5D Defined as the Global Health Status score from the EORTC QLQ-C30 at 18 weeks
Best Objective Response Rate	Defined as the proportion of patients with confirmed complete or partial response as per RECIST 1.1
Disease Control Rate	Defined as the proportion of participants who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks; per RECIST 1.1.
Duration of Response Rate	Measured from the time of initial response until documented tumor progression.
Safety and tolerability	Assessed by CTCAE v5.0 (by investigators) Assessed by NCI PRO-CTCAE (by patients)
Time to first and second Subsequent Treatment	Defined as the time from the date of randomization to date of respectively the first and second subsequent anticancer therapy or death.
PFS, DoR as per investigator assessment	Same endpoint as defined above but assessed by investigator
Efficacy of second systemic therapies	Objective response rate of first subsequent systemic therapy
To describe the pharmacokinetics of dostarlimab	Serum concentrations and PK parameters (C-EOI and C trough) for dostarlimab
To determine the immunogenicity of dostarlimab	Incidence of ADA against dostarlimab
Exploratory Objectives	**Exploratory endpoints**
Efficacy (efficacy and response)	Efficacy, safety and PROs according to geriatric assessment (GVS, ADL, IADL, HADS questionnaires) for patients ≥70 year-old).
Analyses of efficacy (PFS and response)	Biomarkers of interest based on IHC, NGS or immune signature will be explored.
Centralized MMR/MSI	Comparison between local and central MMRd/MSI-H status by IHC and NGS.

ADA: antidrug antibodies; ADL: activities of daily living; BICR: Blinded independent central review; C-EOI: Concentration at the end of infusion, CTCAE: Common Terminology Criteria for Adverse Events; CR: Complete response, DoR: Duration of Response Rate; EORTC: European Organisation for Research and Treatment of Cancer ; GVS: geriatric vulnerability score; HADS: Hospital Anxiety and Depression Scale; IADL: instrumental activities of daily living; IHC: Immunohistochemistry; MMRd: Mismatch Repair deficiency,MSI-H: Microsatellite instability Hight; NGS: Next Generation Sequencing; PFS: Progression Free Survival; PK: Pharmacokinetics; PR: Partial Response, PRO; Patient Reported Outcome; QoL:Quality of life; RECIST: Response Evaluation Criteria In Solid Tumours; SD: Stable disease.

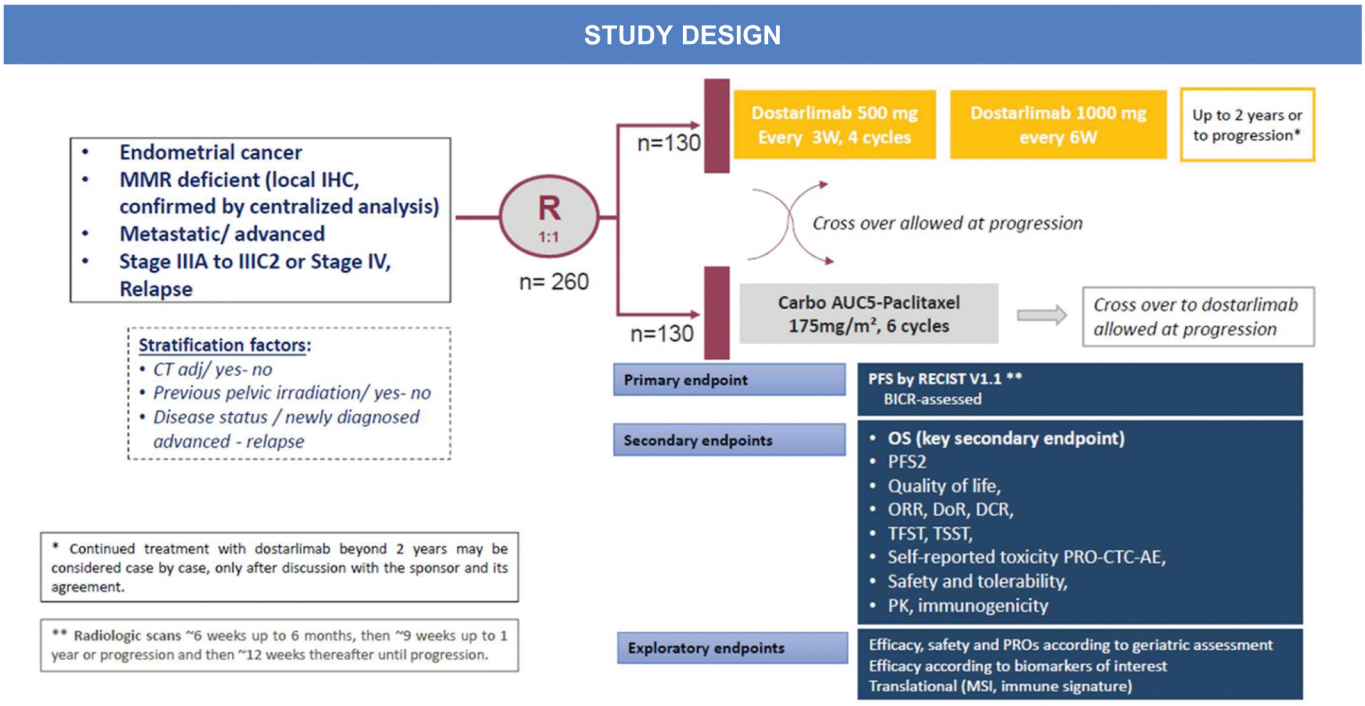

Figure 1. Study design.

MMRd: mismatch repair deficient, MSI: Microsatellite instability; IHC: Immuno Histochemistry; PFS: Progression Free Survival; ORR: Best Objective Response Rate; DoR: Duration of Response Rate; DCR: Disease control rate; TFST: Time to first Subsequent Treatment; TSST: time to second subsequent therapy, PK: pharmacokinetics.

Flow Chart Arm B supplementary data 2.

study is driven by the primary efficacy endpoint of PFS, as assessed by Blinded Independent Central Review (BICR) using RECIST v.1.1. The log-rank test stratified on stratification factors at randomization will be used.

The median PFS in the standard chemotherapy arm is expected to be close to 10 months [7]. We powered the trial to detect a hazard ratio of 0.61, translating into a median PFS in the dostarlimab arm of 16.3 months under the proportional hazards assumption and an exponential distribution of the time to progression or death. To achieve an 87.5% power with a 5% (two-sided) type I error rate and a balanced (1:1) randomization, one would have to observe a total of 161 events (progressions or deaths).

Assuming a uniform 36-month accrual period for a total duration of 60 months (24 months of follow-up for the last included patients) and a uniform risk of lost-to-follow-up of 3% per month, 260 patients (130 per arm) will be randomized in the trial. The primary analysis will take place when 161 events (progressions or deaths) (62% data maturity), have been observed in the trial. With an expected screen-failure rate of 35%, including 4% of MMR-proficient tumors after centralized review, a total of 400 patients should be screened.

2.3. Eligibility criteria

The key eligibility criteria are listed in Table 3. In summary, eligible patients include those ≥18 years of age with histologically confirmed advanced-stage FIGO Stage IIIA to C2 without curative intent stage IVA-B disease or first recurrent endometrial cancer without curative treatment available [30]. MMRd/MSI-H tumor is mandatory for inclusion with a central confirmation before randomization. Patients need to be able and suitable to receive either chemotherapy or checkpoint inhibitor treatment.

2.4. Planned study timeline

DOMENICA is an event-driven trial. The expected timeline is as follows: the first patient was recruited on the 15th of April 2022 with an expected end of enrollment in mid-2025. If the accrual proceeds as expected, the last maintenance treatment will be terminated in mid-2027. The last visit of the last subject with cross-over will be in mid-2029. Finally, we are expecting the definitive end of the study in the last semester of 2029 defined as the last visit of the last patient.

As of March 2025, 60 centers across nine countries had already randomized over 90% of the required patient population.

2.5. Study procedure (see supplementary flowcharts 1 and 2)

The patient journey is divided into the following phases: screening period, randomization, treatment in Arm A or B, maintenance treatment if Arm A, and follow-up visits. Patients can crossover at the time of first progression.

The informed consent form should be signed before any screening assessment. The following screening procedures should be performed within 28 days before randomization:

- Inclusion/exclusion criteria review (reason and justification of some inclusion/non-inclusion criteria should be collected in the case report form [CRF])

Table 3. Eligibility criteria of DOMENICA.

Inclusion Criteria	Exclusion Criteria
1. Female patient is at least 18 years of age	1. Patient has received neoadjuvant/adjuvant systemic chemotherapy for primary Stage III or IV disease and has had a recurrence or PD within 6 months of completing this 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 signed the Informed Consent ICF and is able to comply with protocol requirements.	2. Patient has had > 1 recurrence of endometrial cancer, treated with chemotherapy. Surgery of the recurrence is allowed.
3. Patient with histologically proven endometrial adenocarcinoma with recurrent or advanced disease.	3. Patient previously treated with systemic chemotherapy for non-curable advanced disease or metastatic disease.
4. Patient with an ECOG performance status score of 0 or 1.	4. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
5. Patient must have primary Stage IIIA to C2 or Stage IV disease or first recurrent endometrial cancer (see International Federation of Gynecology and Obstetrics staging FIGO Staging 18.1) without curative treatment by radiation therapy or surgery alone or in combination, and meet at least one of the following situations: a) Patient has primary Stage IIIA-IIIC1 with not amenable curative intent surgery or radiation b) Patient has primary Stage IIIC2 (with nodes involvement from the outset, not allowing a curative radiotherapy, or with remaining lumbo-aortic nodes after lumbo-aortic dissection, which cannot be treated by curative radiotherapy) or Stage IV disease. c) Patient has recurrent disease and is chemotherapy naïve for recurrence or advanced/metastatic setting. d) Patient may have received prior irradiation for advanced endometrial cancer with or without radiosensitizing chemotherapy if >2 weeks before the start of the study	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 evaluable disease (measurable and not measurable disease) according RECIST 1.1 criteria	6. Patient with contraindication to chemotherapy or checkpoint inhibitor treatments
7. Patient may have received prior neo-adjuvant/adjuvant systemic chemotherapy or loco-regional concomitant radio-chemotherapy for the primary cancer and had a recurrence ≥6 months after completing treatment (first recurrence only).	7. Patient has a concomitant malignancy, or patient 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. All histologic subtypes of endometrial adenocarcinoma could be included if MMRd/MSI-H	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 least4 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 with MMRd/MSI-H status (first diagnosed by routine local IHC performed either on primitive tumor tissue or on relapse/metastatic tumor sample) is mandatory for inclusion. A central confirmation will be done before inclusion; in case of ambiguous result of central IHC (lack of positive internal control, heterogeneous loss of MMR protein expression), the MSI-H status will be assessed by PCR/NGS.	9. Patient has a known history of human immunodeficiency virus (HIV; HIV 1 or 2 antibodies).
10. Availability of 1 block for MMR status centralized confirmation for IHC or NGS/PCR	10. Patient has known active viral infection of hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid qualitative detection).
11. Patient could have been previously treated with hormone therapy, for the metastatic/advanced disease	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 may have received pelvic and lombo-aortic external beam ± vaginal brachytherapy	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 adequate organ function, defined as follows: a) Absolute neutrophil count ≥ 1,500 cells/μL b) Platelets ≥ 100,000 cells/μL c) Hemoglobin ≥9 g/dL or ≥5.6 mmol/L d) Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault equation for patients with creatinine levels > 1.5 × institutional ULN e) Total bilirubin ≤ 1.5 × ULN (≤2.0 × ULN in patients with known Gilbert's syndrome) or direct bilirubin ≤ 1 × ULN f) AST and ALT ≤ 2.5 × ULN unless liver metastases are present, in which case they must be ≤ 5 × ULN g) International normalized ratio or 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 has not recovered (i.e., to Grade ≤ 1 or to baseline) from cytotoxic therapy-induced 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 must have a negative serum pregnancy test within 72 hours prior to the first dose of study medication, unless they are of nonchildbearing potential.	14. Patient has not recovered adequately from AEs or complications from any major surgery prior to starting therapy

(*Continued*)

Table 3. (Continued).

Inclusion Criteria	Exclusion Criteria
15. Patient of childbearing potential must agree to use a highly effective method of contraception	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, nonmalignant systemic disease, or active infection requiring systemic therapy. Specific examples include, but are not limited to, active, noninfectious 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: a)Systemic corticosteroids (at dose higher than 10 mg/day equivalent prednisone); if systemic corticoid use at higher dose than 10 mg/day, corticoid must be stopped at least 7 days before study treatment start b) Interferons c) Interleukins d) Live vaccine 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. 20. Patients who had an allogenic tissue/solid organ transplant

AE: Adverse Event;,AST: Aspartate aminotransferase; ALT: alanine aminotransferase; CTCAE:Common Terminology Criteria for Adverse Events; CR: Complete response; ECOG: Eastern Cooperative Oncology Group;EORTC: European Organisation for Research and Treatment of Cancer; ICF: Informed Consent ICF:IHC: Immunohistochemistry; MMRd: Mismatch Repair deficiency,MSI-H:Microsatellite Instability Hight; NGS: Next Generation Sequencing; PFS: Progression Free Survival; PT: prothrombin time; RECIST : Response Evaluation Criteria In Solid Tumours; SD: Stable disease; ULN; upper limit of normal.

- Demographics details
- Clinical assessments, including medical/surgical/cancer history and prior treatment for endometrial cancer, including FIGO stage
- Physical examination of body weight, height, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status
- Laboratory assessments
- Electrocardiogram (ECG)
- Tumor assessment: thoraco-abdomino-pelvic CT scan, and in case of pelvic disease suspicion, pelvic magnetic resonance imaging (MRI)
- Concomitant medications:
- Collection of tumor tissue (1 block) for MMR/MSI testing for local and centralized analysis.

Randomization must be performed within 1 week prior to C1D1. All screening procedures are to be performed, and patient eligibility is to be confirmed before randomization. Local MMRd/MSI-H status needs to be confirmed by the central laboratory. The interactive Voice/Web Response System centralized randomization center will be contacted for allocation of randomized study treatment. Block randomization (block of unequal size) with permutation is implemented. Randomization is stratified on: prior adjuvant chemotherapy, prior pelvic radiotherapy, and newly diagnosed cancer versus relapse for a total of 8 strata.

During treatment, patients will have a physical examination, complete laboratory evaluation at each cycle and adverse event collection (see supplementary flowcharts 1 and 2). They will also respond to QoL questionnaires and self-reported toxicity PRO-CTC-AE through a specific website. An additional oncogeriatric questionnaire (ADL, IADL, HADS), will be filled out at C1D1 if the patient is ≥70 years.

From C5D1, every 6 weeks up to 24 months (± 3 days), the patient will have a physical examination, laboratory evaluation, QoL questionnaire, and self-reported toxicity PRO-CTC-AE adverse event collection. From W52, every 12 weeks, the patient will have a physical examination and self-reported toxicity PRO-CTC-AE until the first subsequent therapy.

Tumor assessments, with CT-scan of the thorax, abdomen and pelvis, are to be performed every 6 weeks (± 7 days) for the first 6 months, then every 9 weeks up to week 52 or objective disease progression, whichever occurs first. From W52 up to 3 years or the second objective disease progression or initiation of subsequent anticancer therapy, tumor assessments are to be performed every 12 weeks (± 7 days). This assessment will be the same between the two arms. Positron emission tomography/CT may be used according to RECIST v.1.1 guidelines, but the same imaging technique must be used in a patient throughout the study, from the baseline to the end of the study.

An end-of-treatment visit will be performed within 30 days of the last chemotherapy or dostarlimab administration or objective disease progression, whichever occurs first. Assessments are to be performed within 30 days of the last treatment injection.

- Physical examination, vital signs, ECOG performance status
- Hematology
- Serum biochemistry

- Pregnancy test
- CA125
- Thyroid panel
- Quality of life questionnaires, through a specific website designed for handled devices
- Self-reported toxicity PRO-CTC-AE, through a specific website designed for handled devices
- Adverse events and concomitant medication collection,
- Tumor assessments

Blood samples for pharmacokinetic and immunoglobulin dosage will be collected at C1D1 pre-infusion and the end of infusion. Prior to the administration of cycle 2 (C2D1), cycle 4 (C4D1), cycle 5 (C5D1), cycle 9 (C9D1) then at the end of treatment.

2.6. Crossover

Patients who progress based on RECIST 1.1 are allowed to cross over to dostarlimab or to the chemotherapy arm, after discussion with the sponsor. The schedule of the treatment will be according to that of the GARNET study i.e., arm A schedule includes 4 doses of dostarlimab 500 mg once every 3 weeks and then 1000 mg once every 6 weeks until the second objective progression. Arm B schedule includes 6 cycles of carboplatin (AUC5 or AUC6 according to local practice) and paclitaxel (175 mg/m2) until the second progression is objectively documented.

Once a patient has crossed over, scan evaluations follow the frequency of Q12W (±7 days) from W52 up to 3 years or second objective disease progression or initiation of subsequent therapy

2.7. Safety

Adverse events (AE) will be collected from the time of signature of informed consent, throughout the treatment period and up to and including the 90-day follow-up period. All ongoing and any new AEs identified during the 90 calendar days follow-up period after the last dose of study medication must be followed to resolution. For each episode of an adverse event, the highest attained grade should be reported according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [31].

2.8. Statistics

PFS is defined as the time from the date of randomization to the earliest date of assessment of PD or death by any cause. Tumor response is evaluated using RECIST v.1.1 based on BICR assessment for patients with evaluable disease (measurable and non-measurable disease) at study entry. The PFS will be estimated using the Kaplan–Meier method. The median PFS along with 95% confidence intervals (Greenwood formulae) will be presented by treatment group. The stratified Cox regression will be used to estimate the HR of PFS along with its 95% confidence interval, after checking the proportional hazard (PH) assumption using the Therneau test against a linear or log-linear alternative. The primary efficacy analysis will be the comparison of the distribution of PFS between the 2 treatment groups using a stratified two-sided log-rank test at the 5% level.

To evaluate the robustness of the treatment effect on the PFS endpoint, sensitivity analyses will be performed with different sets of censoring rules. Sensitivity analysis 1: the same as the primary analysis except that PFS is censored at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. Sensitivity analysis 2: PFS is censored at the last tumor assessment prior to the discontinuation of treatment or initiation of new anticancer therapy if they occur before PD is documented. Sensitivity analysis 3: the same as the primary analysis on the per-protocol population.

Overall survival, one of the key secondary outcomes, will be based on the ITT population and analyzed hierarchically if a statistically significant difference in PFS is detected (gatekeeper strategy). Therefore, a 5% type I error rate will be available for the analysis. The hazard ratio of death and its 95% confidence interval will be estimated from a Cox model stratified on the stratification factors used at randomization after examination of the proportional hazards assumption (Therneau test). Results will be presented by treatment group. The cutoff date for the inferential statistical analysis (i.e., tests) will be done at 60 months post-randomization of the first patient or after a 50% data maturity (i.e., 130 events) whichever comes first.

3. Translational research project

For translational research, blood samples will be collected for biomarker analysis during the screening period, at different treatment times and at progressive disease. A collection of fixed primary tumor samples will be sent to the central biobank after randomization and at progressive disease (if feasible).

Biomarkers to be explored will include NGS MMR/MSI, P53 and POLE; PD1/L1 expression, tumor mutational burden (TMB), composition of circulating immune cells, expression of immune proteins, and immune signatures.

One of the objectives of the translational work will be to identify potential predictive markers of early resistance to dostarlimab in circulating tumor DNA (ctDNA), which can be detected in endometrial cancer by NGS and correlated to tumor burden and recurrences [32,33]. It may also be a robust predictive marker of IO efficacy [34]. DOMENICA represents a unique opportunity to define the unique and distinctive immune tumor micro-environment (iTME) of responders versus non-responders to dostarlimab as described in previous studies [35,36]. A third translational project will focus on the impact of humoral immunity (B lymphocyte) and tertiary lymphoid structures (TLS) due to their potential involvement in response to IO [37,38]. Other translational research dedicated to the prognostic biomarkers is anticipated and will be developed.

Finally, efficacy, safety and PRO analyses will be compared between populations of patients under 70-year-old and older. Further in-depth analyses based on geriatric assessments will be conducted.

4. Ethics of research

This study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and

regulations of the country in which the research is conducted, whichever affords greater protection to the individual. The study will fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (November 2006) ICH Tripartite Guideline (January 1997), or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Regulation (536/2014).

ARCAGY GINECO has realized a declaration of conformity to a reference methodology (MR001), to the French Data Protection Committee (Commission Nationale de l'Informatique et des Libertés, CNIL) (declaration number: 2214267 v 0, dated 20 November 2017). The study was approved by the French "Committee for the Protection of Persons" Ouest VI (protocol version 3.0, date of approval 16/05/2023). Informed consent will be obtained from all subjects involved in the study

5. Conclusion

The DOMENICA trial is a de-escalation study aiming to demonstrate the superiority of dostarlimab monotherapy over chemotherapy as a first-line treatment for patients with MMRd/MSI-H advanced endometrial cancer. This represents a specific subgroup with a high anticipated benefit and an improved safety profile compared to the current standard of care of IO combined with chemotherapy. The findings will be particularly significant for frail, elderly, or comorbid patients, as they highlight the potential to omit chemotherapy and its associated toxicities.

Author contributions

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Reference annotations: authors should highlight 6–8 references that are of particular significance to the subject under discussion as (•) of interest or (••) of considerable interest, and provide a brief (1–2 line) synopsis.

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