Study Title:

A retrospective, real-world multicenter study of **DO**starlimab in patients with **R**ecurrent or **A**dvanced DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) endometrial cancer (DORA Study)

Sponsor:	Grupo Español de Investigación en Cáncer de Ovario (GEICO)
Principal Investigators:	Dr. Alejandro Gallego Martínez (Clinical study) Dr. Marta Mendiola Sabio (Translational study)
Sponsor Study Number:	GEICO 120-R & GEICO 120-T
Study Drug Name:	Dostarlimab
Clinical Phase:	Retrospective observational study
Number of Subjects:	Around 100-110
Date of Original Study:	13 June 2022
Date of Current Study:	13 June 2022
Version:	1.0

The study will be conducted as described herein and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor

Title: A retrospective, real-world multicenter study of **DO**starlimab in patients with **R**ecurrent or **A**dvanced DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) endometrial cancer (DORA Study)

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This observational plan was subjected to critical review and has been approved by the Sponsor. The information contained herein is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

_____ _____

Sponsor Signature **Date**

INVESTIGATOR SIGNATURE PAGE

Declaration of the Investigator

Title: A retrospective, real-world multicenter study of **DO**starlimab in patients with **R**ecurrent or **A**dvanced DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) endometrial cancer (DORA Study)

Date of Original Study:	13 June 2022
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Version:	1.0

I have read this study in its entirety, including all appendices. By signing this study, I agree to conduct the study in accordance with the plan described herein, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB). I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study and will receive all instructions necessary to perform the study as described herein.

Investigator

_____ _____

Investigator Signature **Date**

_____ _____

Investigator Signature **Date**

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LIST OF ABBREVIATIONS AND DEFINITIONS

Table 1: List of Abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse event
AEMPS	Spanish Agency for Medicinal Products and Medical Devices
AESI	Adverse event of special interest
AUC	Area under the curve
CA-125	Cancer antigen 125
CBC	Complete blood count
CL	Oral clearance
CT	Computed tomography
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DOR	Duration of response
EAP	Expanded Access Program
EC	Endometrial Cancer
ECOG	Eastern Cooperative Oncology Group
EDMA	Electronic Data Management System
EOT	End of treatment
FIGO	International Federation of Gynecology and Obstetrics
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GCP	Good clinical practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
irAEI	immune-related adverse events of interest
IRB	Institutional review board
IB	Investigator's Brochure
ICF	Informed Consent Form
IgG4	Immunoglobulin G4
LLN	Lower limit of normal
mAb	Monoclonal antibody
MMR	Mismatch repair system
dMMR	Mismatch repair deficient
pMMR	Mismatch repair proficient

Abbreviation	Definition
MSI	Microsatellite instability
MSI-H	High microsatellite instability
MSI-L	Low microsatellite instability
MSS	Microsatellite stable
NCI	National Cancer Institute
NIH	National Institutes of Health
NGS	Next generation sequencing
NSMP	non-specific molecular profile
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD1	Programmed cell death-1
PD-L1/2	Programmed death-ligand ½
PFS	Progression-free survival
PK	Pharmacokinetics
PIS	Patient Information Sheet
POLE	DNA polymerase epsilon
PR	Partial response
PRO	Patient reported outcomes
PS	Performance status
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TCGA	The Cancer Genome Atlas
TEAE	Treatment-emergent adverse events
ULN	Upper limit of normal

1. SUMMARY

1.1. Study Design

1.1.1. Primary Clinical Objective

- To assess the antitumor activity of dostarlimab in patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer, in terms of objective response rate (ORR) and duration of response (DOR) based on investigators' assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

1.1.2. Secondary Clinical Objectives

- To assess the effectiveness of dostarlimab in terms of investigator-assessed progression-free survival (PFS) and overall survival (OS).
- To analyze the PFS rate at 6, 12, 18 and 24 months.
- To assess the disease control rate (DCR) based on investigators' assessment using RECIST 1.1.
- To evaluate duration of treatment with dostarlimab.
- To describe the time to response to dostarlimab.
- To evaluate the safety and tolerability of dostarlimab in patients with dMMR/MSI-H endometrial advanced cancer, including immune-related adverse events of interest (irAEI).
- To evaluate Neutrophil-to-lymphocyte ratio as a potential predictive biomarker for treatment with dostarlimab.

1.1.3. Translational Objectives

- To compare centralized immunohistochemistry (IHC) re-testing with local testing.
- To compare centralized IHC re-testing results with two PCR-based techniques (Promega® and Idylla®) and with possible MMR gene alterations (genetic and epigenetic).
- To analyze the overall response rate and progression-free survival of the dMMR/MSI population selected by each biomarker technique: IHC, Polymerase chain reaction (PCR) Promega®, PCR Idylla®, or gene alteration (next generation sequencing (NGS)/hypermetilation).

1.1.4. Population

The study population consists of adult female patients with diagnosis of dMMR/MSI-H recurrent or advanced endometrial cancer with progression to a previous platinum regimen, who were treated within the Spanish dostarlimab Expanded Access Program (EAP).

1.1.5. Treatment Under Observation

In this study, the treatment under observation is dostarlimab administered on day 1 of each treatment cycle until disease progression, unacceptable toxicity or patient/doctor's decision. The recommended dose for dostarlimab is 4 cycles of 500 mg every 3 weeks followed by 1000 mg every 6 weeks for all subsequent cycles.

1.1.6. Operational Milestones

Table 2: Table of Study Milestones

Number of Patients	Around 100-110
Enrollment Rate (patients/month)	Around 35
Number of Sites	50-60
Country	Spain
Study Duration	3 months (recruitment)
FPI (date)	December 2022
LPLV (date)	March 2023
Publications and/or Other Reports	September 2023 (Clinical Study) September 2024 (Translational Study)

2. BACKGROUND AND SIGNIFICANCE

2.1. Introduction to endometrial cancer

In Europe, endometrial cancer (EC) is the most common gynecological tumor and the fourth among cancer in women (1). There has been an increase in recent years in the incidence of EC, likely associated with the aging of the population and the increase in obesity. The incidence of EC may continue growing in the following decades (2). In 2018, an estimated 382,069 new cases and 89,929 deaths were attributed to this cancer type worldwide (3). Mortality from EC has not been modified in recent years, in large part driven by high grade carcinomas that are more likely to present at an advanced stage and to ultimately recur.

EC are classified into various histological subtypes, which differ in frequency, clinical presentation, prognosis and associated risk factors. Most ECs are adenocarcinomas, and the most common of these is the endometrioid subtype (75% to 80% of diagnosed cases). The majority of patients are diagnosed with early-stage disease (Stage I or II) and have favorable outcomes (5-year overall survival of approximately 75-90%), whereas advanced stages and non-endometrioid histologies, such as serous, clear cell, undifferentiated and carcinosarcoma, in any stage, are known to be associated with a worse prognosis.

2.2. Metastatic endometrial cancer treatment

For distant dissemination of EC that is not susceptible to radical treatment, systemic therapy should be considered. However, patients who recur or present with more advanced disease have a low probability of response rates to conventional treatment and clinical outcomes are poor.

For most patients with metastatic EC chemotherapy will be the preferred treatment, with the combination of carboplatin and paclitaxel as the standard first-line regimen. The phase III GOG 209 trial demonstrated that this regimen was not inferior to the TAP scheme (paclitaxel, adriamycin, and cisplatin) in terms of efficacy and had a more favorable toxicity profile. The median PFS and overall survival (OS) with carboplatin and paclitaxel were 13 and 37 months, respectively (4). There have not been randomized clinical trials comparing chemotherapy with hormone therapy as first-line treatments.

There is no chemotherapy regimen approved in second line. Only limited data are available for some drugs derived from small single-arm studies, showing a poor clinical activity, with objective response rates (ORRs) of approximately 7% to 14%, and median overall survival (OS) of 6 to 11 month. Even for the agents with a higher ORR (13.5%), the reported median OS remained at <1 year (Table 1) (5).

Table 1. Summary of efficacy data of different drugs assessed after prior platinum-containing regimen in endometrial cancer

Agent	Endpoint	Summary of Results	Reference
Liposomal doxorubicin	ORR	N=45 ORR=9.5% Median DOR=2.7 months Median OS=9.2 months	GOG 129-H
Oxaliplatin	ORR	N=52 ORR=13.5% Median DOR=10 months (range: 4.1 to 50.3 months)	GOG 129-K
Docetaxel	ORR	N=26 ORR=7.7% Median OS=6.4 months	GOG 129-N
Topotecan	ORR	N=28 ORR=9% Median DOR=4.5 months (N=2 responses) Median OS=N/A	GOG 129-J
Bevacizumab	ORR	N=52 ORR=13.5% Median DOR=6 months Median OS=10.6 months	GOG 229-E

DOR=duration of response; N=number of patients; N/A=not applicable; NR=not reached; ORR=objective response rate; OS=overall survival. Of note: none of these therapies are approved for treatment of endometrial cancer.

In addition to chemotherapy, some patients with EC may benefit from hormone therapy, mainly those with low-grade tumors and positive hormone receptors. Various hormonal drugs (progestins, selective estrogen receptor modulators, gonadotropin-releasing hormone analogs, and aromatase inhibitors) have been evaluated in phase II and retrospective studies, demonstrating modest activity, with a highly variable ORR (5%–56%) and short PFS (median 2–9 months) (6,7). A recent randomized phase II trial showed that the ORR and PFS associated with letrozole were significantly increased with the addition of palbociclib (8). Hormone therapy can be used in the second- line setting, but also in highly selected patients in the first-

line setting (those with low-grade EC with positive hormone receptors, low tumor burden, and slow growth).

2.3. Mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer

EC classification has changed from the Tumor Cancer Genome Atlas (TCGA) and ProMisE studies, resulting in a molecular classification with prognosis and therapeutic implications (9,10). Four subtypes were defined with the following molecular features: mutations in *DNA polymerase epsilon* (POLE), (representing 9-10% of total); MMRd (20-30%); p53 wild-type or non-specific molecular profile (NSMP) (43-50%); and p53 abnormal (12-27%).

dMMR defects can occur somatically or germline due to mutations or hypermethylation of their promoters. There are two commonly accepted approaches for the identification of dMMR. The first one is based on the expression of MLH1, PMS2, MSH2 and MSH6 proteins by IHC. Conserved expression or loss of one or more proteins classify patients in MMR proficient (pMMR) and dMMR. The other approach is based on PCR amplification of repetitive regions known as microsatellites within the genome. Amplified microsatellite loci by PCR establish high microsatellite instability (MSI-H) when two or more markers show instability, low MSI (MSI-L) when only one marker is altered, or stable, when none of the markers show instability (microsatellite stable, MSS). Different microsatellite panels have been developed. Promega® 1.2 is a commercial kit based in the Bethesda panel (5 markers commonly studied), but there are other commercially available based on the expression of different markers, as the Idylla® MSI system analyzed the expression of 7 markers. There are other approaches based on discrete panel by PCR, but also commercial solutions based on NGS.

Tumors with dMMR/MSI-H are associated to a high tumor mutational load, to a large number of neoantigens and to tumor-infiltrating lymphocytes, characteristics that confer a higher probability to respond to immune checkpoint inhibitors.

In the last 5 years, immunotherapy is undergoing an important development in EC. The first evidence of clinical activity of an immunotherapy in EC was obtained in a phase II trial published in 2015. The efficacy of the anti-programmed cell death 1 (anti-PD-1) monoclonal antibody pembrolizumab was studied in three cohorts of patients with metastatic solid tumors: dMMR colorectal cancer, pMMR colorectal cancer, and dMMR non-colorectal cancer. The ORR and progression-free survival (PFS) at 20 weeks for the dMMR non-colorectal cancer cohort (which included 2 EC patients) was 71% and 67%, respectively (11). These results confirmed the role of MMR status as a predictive biomarker to immunotherapy, and pembrolizumab was the first treatment approved by United States Food and Drug Administration (FDA) for dMMR tumors that had progressed to a previous line of treatment, regardless of the type of neoplasm. Other anti-PD-1 and anti-PD-L1 antibodies, like avelumab

or durvalumab, have achieved ORR ranging from 27% to 58% in highly pretreated patients with dMMR EC (12,13).

2.4. Background of Dostarlimab

2.4.1. Mechanism of Action and Development

Dostarlimab (formerly referred to as TSR-042) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds with high affinity and specificity to the immune checkpoint receptor, programmed cell death-1 (PD-1). PD-1 is expressed on the surface of activated T-cells, forming part of a complex system of receptors and ligands that are involved in controlling T-cell activation. Binding of PD-1 to its ligands (PD-L1, PD-L2) reduces T-cell activity in the peripheral tissues during an inflammatory response, limiting lytic ability (14,15). PD-L1 and PD-L2 are commonly upregulated on many tumor types in response to multiple proinflammatory molecules. Their binding to PD-1 on T-cells contributes to T-cell exhaustion, protecting tumor cells from immunologic surveillance and promoting immune suppression; blockade of this pathway with a PD-1 inhibitor can therefore enhance anti-tumor effector function, resulting in decreased tumor growth (16,17).

Dostarlimab was generated using a proprietary platform that employs affinity maturation to select highly specific antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab was confirmed in a mixed lymphocyte reaction assay, demonstrating enhanced Interleukin-2 (IL-2) production upon the addition of dostarlimab. Dostarlimab has an acceptable safety profile based on toxicology studies in monkeys and in nonclinical experiments. Based on published clinical experience with antibodies of the same drug class and the nonclinical data for dostarlimab, the safety and activity profile of dostarlimab is in line with the expectations for this class of agent.

2.4.2. Clinical Experience

The efficacy and safety of dostarlimab were investigated in GARNET (Study 4010-01-001), a multicenter, non-randomized, multiple parallel cohort, open label study conducted in patients with advanced solid tumors.

The recruitment began in March 2016 and the trial was conducted in 2 parts. Part 1 was a dose–escalation study to evaluate weight-based doses of dostarlimab. Part 2A evaluated the safety of non weight-based fixed doses of dostarlimab, while part 2B enrolled patients into several expansion cohorts based on tumor type and MMR status (regarding EC, cohort A1 included patients with dMMR tumors, and cohort A2 included patients with pMMR tumors) to assess the antitumor activity and safety of dostarlimab.

Part 1 employed a modified 3 + 3 design to evaluate ascending weight-based doses of intravenous infusion. Part 2A assessed the safety and tolerability of two fixed doses of

dostarlimab. No dose-limiting toxicities were observed, and the recommended therapeutic dose was deter- mined to be 500 mg every 3 weeks for the first 4 cycles followed by 1000 mg every 6 weeks for all subsequent cycles, based on the efficacy, safety, receptor occupancy (fully occupied at all dose levels), and pharmacokinetics analysis. This dosing schedule was selected for part 2B.

In expansion A1 cohort of part 2B eligible patients had recurrent or advanced dMMR/MSI-H EC, with measurable disease that had progressed after a platinum-containing chemotherapy regimen (administered in the adjuvant setting or for the advanced disease) and were to have received no more than 2 lines of therapy for advanced or recurrent disease. The primary objective of the A1 cohort analysis was to evaluate the antitumor activity of dostarlimab by assessing the ORR by blinded independent central review (BICR) using RECIST v1.1, and DOR.

The secondary endpoints included the following: 1) DCR, defined as the proportion of patients with an objective response or stable disease lasting 12 weeks or longer, based on BICR using RECIST 1.1 criteria; 2) immune- related ORR (irORR) and immune-related DOR (irDOR) based on the investigator assessment using immune-related RECIST (irRECIST); 3) PFS, based on BICR using RECIST 1.1; 4) immune- related PFS, based on the investigator assessment using irRECIST; and 5) OS.

A total of 104 patients with MMRd EC were enrolled and treated with dostarlimab. The first interim efficacy analysis (data cut-off: July 2019) was performed on only 71 patients who had at least 1 measurable lesion and a minimum follow-up of 6 months. Baseline characteristics of these patients were: median age 64 years and Eastern Cooperative Oncology Group (ECOG) PS 0 (35%) or 1 (65%). A total of 65.3% were FIGO (International Federation of Gynecology and Obstetrics) Stage IV at the most recent assessment, and 69.7% had a histologic diagnosis of endometrioid carcinoma Type 1. The most common disease grade at diagnosis was Grade 2 (40.3%). Only half of the patients had received prior treatment for metastatic disease, and the median PFS from the last platinum regimen was 6.4 months (range, 1.6–79.6).

With a median follow-up of 11.2 months, 30 patients achieved an objective response (ORR 42.3%; 95% CI 30.6%– 54.6%): 9 patients (12.7%) had a complete response, and 21 (29.6%) had a partial response. All patients with a confirmed complete response remained in response as of the data cutoff date. The ORR was observed independently of histologic subtype and previous lines of therapy, although the subgroup analyses were not powered and should be interpreted with caution. Although the median DOR was not reached, it was estimated that 96.4% of the patients would have a sustained response at 6 months and 76.8% at 12 months. The DCR was 57.7% (95% CI 45.4%–69.4%), and the median PFS was 8.1 months (95% CI 3.0–18.0). The median OS was also not reached, with an estimated 76.9% of patients alive at 12 months (18).

The second interim analysis (data cut off: March 2020), with a median follow-up of 16.3 months, was performed on 103 patients, showing an ORR of 44.7% (95% CI 34.9%–54.8%) and a DCR of 57.3% (95% CI 47.2%–67%). 89.1% of patients had a response ongoing, and the median DOR was not reached yet. The estimated probabilities of remaining in response at 6, 12 and 18 months were 97.8%, 90.6%, and 79.2%, respectively (19).

A subanalysis by the number of prior lines of this cohort has been presented. Patients with only 1 prior line (n = 66) achieved an ORR of 50% (95% CI 37.4–62.6), while patients with 2 or more prior lines (n = 39) achieved an ORR of 35.9% (95% CI 21.2–52.8). 70% of the patients with 1 prior line and 67% of the patients with 2 or more prior lines remained in response at the data cutoff date (19).

At 2022 American Society of Clinical Oncology (ASCO) meeting the latest update from the third prespecified interim analysis was presented (Data cutoff date: November 1, 2021). A total of 151 patients (143 in the efficacy-evaluable population) with dMMR EC were enrolled and treated with dostarlimab in A1 cohort.

With a median follow-up of 27.6 months, 45.5% of patients achieved an objective response (95% CI 37.1%– 54.0%): 16.1% had a complete response and 29.4% had a partial response. 83.1% had an ongoing response at the data cut-off. Although the median DOR was not reached, it was estimated that 96.8% of the patients would have a sustained response at 6 months, 93.3% at 12 months and 83.7% at 24 months. The DCR was 60.1% (95% CI 51.6%–68.2%) and the median PFS was 6.0 months (95% CI 4.1–18.0). The estimated PFS was 46.4% at 12 months and 40.1% at 24 months. The median OS was also not reached, with an estimated 73.3% of patients alive at 12 months and 60.5% at 24 months (20).

Description of selected adverse reactions

Of the 104 patients included in the safety analysis of the A1 cohort, 65.4% had a treatment-related adverse event (TRAE), most of which were mild (grade 1 or 2). The most frequent TRAEs were asthenia, diarrhea, fatigue, and nausea. The incidence of grade 3–4 TRAEs was 11.5%; 10 patients (9.6%) experienced at least 1 grade 3–4 TRAE, with colitis the most frequent event (2 [1.9%]). Only two patients (1.9%) had to discontinue the study because of a TRAE (transaminase increase). Immune-related TRAEs were reported in 23.1% of the patients, with diarrhea (5.8%) and hypothyroidism (5.8%) the most frequent; only 6.7% of these TRAEs were grade 3–4. No deaths due to treatment-related AEs were reported (18).

Data on patient-reported outcomes were available for 66 of the 104 patients who were administered 1 or more doses of dostarlimab. These outcomes showed that dostarlimab was, generally, well tolerated, and key disease-related symptoms, such as pain and fatigue, improved while on the treatment. Several AEs, such as nausea, vomiting, constipation, and diarrhea, remained relatively stable compared with baseline over the course of the treatment.

At the latest interim analysis presented at ASCO 2022 meeting, 17.6% of patients had TRAE grade 3 or higher and in 8.5% led to discontinue the treatment.

The toxicity reported for cohort F of the GARNET trial was similar to the dMMR EC cohort. 68.8% of the patients experienced a TRAE, and 8.3% experienced at least 1 grade 3 or higher TRAE. Only two patients (1.8%) discontinued dostarlimab due to a TRAE, and no deaths were attributed to the drug (21).

3. STUDY RATIONALE

There is a paucity of real-world data of patients with EC treated with dostarlimab, something that has an especial interest considering the limited evidence available with dostarlimab (only a phase I open-label study).

Moreover, there are only some discrete published studies comparing different dMMR/MSI-H approaches in EC and there are almost not data assessing their correlation to ORR of immunotherapy. To our knowledge only one phase II trial with avelumab made a comparison of dMMR/MSI-H tested by IHC, PCR or NGS, but only 15 patients were assessed in the dMMR cohort.

In January 2021, GlaxoSmithKline opened an EAP in Spain to make dostarlimab available to eligible women with recurrent or advanced dMMR/MSI-H endometrial cancer, a clear unmet medical need for these endometrial cancer patients.

EAPs allow patients with a serious or life-threatening disease or condition who are not otherwise eligible to participate in a clinical trial and have no other comparable or satisfactory therapeutic options to access drugs, with demonstrated benefit in clinical trials, that are pending approval.

This study seeks to evaluate the efficacy and tolerability of dostarlimab in recurrent or advanced dMMR/MSI-H endometrial cancer patients treated in a real world setting within the Spanish EAP. In addition, the translational study aims to assess the efficacy according to the biomarker technique used (IHC, PCR Promega®, PCR Idylla®, or gene alteration by NGS/hypermetilation).

4. STUDY DESIGN

4.1. Overview

This is a multicenter, retrospective, observational (non-interventional) study, in patients treated in a real-world setting within the Spanish dostarlimab EAP. The study is planned to be conducted in the Medical Oncology departments at 50-60 Spanish GEICO-associated hospitals. Its multicenter nature aims to improve the representativeness of the study population in Spain. The study would include approximately 110 patients with dMMR/MSI-H recurrent or advanced EC, that have progressed on or following prior treatment with a platinum-containing regimen, treated within the dostarlimab EAP, available in Spain from January 2021 to September 2022. The total number of participating centers and patients will be confirmed once the EAP is closed.

Patient's medical records will be screened by local clinical staff to assess for eligibility according to selection criteria. The study comprises a single study visit, in which the patient will give her informed consent to participate (when the patient is alive) and the physician will extract the study data from the patient's medical charts.

Alive patients who fulfill inclusion criteria and meet no exclusion criteria will be informed by a member of their care team about the purpose of the study, as well as about potential risks and benefits of study participation. The written informed consent form (ICF) should be signed prior to study initiation in alive patients in order to access their medical records. Deceased patients will be still included but their relatives will not be contacted. In these instances, data will be collected by members of the direct care team, unless there is a prior express order from the patient to preserve confidentiality. All eligible deceased and consenting living patients at the participating centers will be included. Data will be directly retrieved from hospital medical records and reported in the electronic Case Report Form (eCRF).

4.2. Study Objectives

4.2.1. Primary Clinical Objective

- To assess the antitumor activity of dostarlimab in patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer, in terms of objective response rate (ORR) and duration of response (DOR) based on investigators' assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

4.2.2. Secondary Clinical Objectives

- To assess the effectiveness of dostarlimab in terms of investigator-assessed progression-free survival (PFS) and overall survival (OS).
- To analyze the PFS rate at 6, 12, 18 and 24 months.

- To assess the disease control rate (DCR) based on investigators' assessment using RECIST 1.1.
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- To evaluate Neutrophil-to-lymphocyte ratio as a potential predictive biomarker for treatment with dostarlimab.

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- To compare centralized immunohistochemistry (IHC) re-testing with local testing.
- To compare centralized IHC re-testing results with two PCR-based techniques (Promega® and Idylla®) and with possible MMR gene alterations (genetic and epigenetic).
- To analyze the overall response rate and progression-free survival of the dMMR/MSI population selected by each biomarker technique: IHC, Polymerase chain reaction (PCR) Promega®, PCR Idylla®, or gene alteration (next generation sequencing (NGS)/hypermetilation).

4.3. Study Population

The study population consists of adult female patients with diagnosis of dMMR/MSI-H recurrent or advanced endometrial cancer with recurrent disease to a previous platinum, treated within the Spanish dostarlimab EAP.

4.4. Treatment Under Observation

In this study, the treatment under observation is dostarlimab administered on day 1 of each treatment cycle until disease progression, unacceptable toxicity or patient/doctor's decision. The recommended dose for dostarlimab is 4 cycles of 500 mg every 3 weeks followed by 1000 mg every 6 weeks for all subsequent cycles.

4.5. Participant Selection

- Patients must meet all the following EAP inclusion criteria and none of the exclusion criteria to be eligible.
- Participants must have received dostarlimab (at least 1 cycle) within the Spanish EAP.

5. COLLECTED DATA AND OUTCOME MEASURES

5.1. Demographics

- Age (at dostarlimab treatment initiation within EAP)

5.2. Medical History

- Non-oncological history
- Other cancers

5.3. Endometrial Cancer History

- Initial diagnosis date
- Tumor histology (and degree of tumor differentiation for endometrioid subtype)
- Disease stage
- Recurrent or initial metastatic disease
- MMR (IHC / MSI-H / MMR genetic study/ MLH1 hypermetilation)

5.4. Endometrial Cancer Previous Treatments

- Previous surgeries
- Previous drugs (types and number of previous treatments)
- Previous radiotherapy

5.5. Baseline (pre-dostarlimab)

- ECOG
- Existence of measurable disease
- CA 125

5.6. Dostarlimab Treatment

- Start date (first dose)
- Number of cycles
- Last dose
- Number of interruptions
- End of treatment date
- End of treatment reason (toxicity, doctor's decision, patient's decision, progression or other)

5.7. Disease progression after dostarlimab

- Progression date
- Progression type

5.8. Best Response Assessment

- Radiological best overall response

- Radiological best overall response assessment date
- Number of dostarlimab cycles previous to first and best radiological response
- CA125 best overall response
- CA125 best overall response assessment date

5.9. Dostarlimab -Related Adverse Events

- Event term according to Common Terminology Criteria for Adverse Events (CTCAE) criteria
- Time from dostarlimab initiation
- Event duration
- Grade
- Action taken with dostarlimab
- Outcome

5.10. Death

- Date of death
- Cause of death

5.11. Survival Status

- Last follow-up date
- Status

5.12. Subsequent Therapies for Endometrial Cancer

- Subsequent drugs

6. SAMPLE SIZE

The study will include between 100-110 patients in total (retrospective in all cases) recruited in 50-60 sites.

The population will include all patients who received dostarlimab at least during one cycle as part of the EAP in GEICO-associated hospitals. The sample size will be based on the number of patients treated in the EAP of Spain.

There will be no formal calculation of the sample size. Most patients included in the Spanish EAP will be analyzed.

7. STANDARD OF CARE

In this retrospective observational study, patients will not be exposed to clinical interventions different from those belonging to the standard of care. There are no study-specific procedures other than the normal activities that patients would undergo if they were not participating in the study. Accessible/reachable patients will be interviewed during routine care visits and principal investigators at each site will offer them the possibility of participating in the study. This will involve reading and signing the ICF.

8. DATA COLLECTION PROCESS

8.1. Patient Information and Consent

All patients participating in the study (accessible, alive patients who can be interviewed in the hospital) will receive a Patient Information Sheet (PIS) describing, in simple language, the goals, scope, procedures and relevant implications of the study. The PIS will integrate an ICF to be signed by the patient, which is indispensable for study participation (for accessible patients). Written informed consent must be given by each accessible/reachable patient before study initiation (prior to registration of the patient in the eCRF). The PIS/ICF will include the consent of patients for the collection and analysis of their clinical data.

Data of inaccessible/unreachable patients (dead, lost, etc.) could still be used according to the permissions of ethics committees and Spanish law, regarding the use of data in retrospective studies.

8.2. Clinical Data Entry

Participating local sites (GEICO-associated hospitals with expertise in gynecological cancer management) will enter clinical data of patients in the study eCRF in order to create a multicenter database. The specific data items to be entered in the eCRF are described in an eCRF specification provided as a separate document.

It is expected that data collection for the study will take place on an ongoing basis since the first site is activated and until around 100-110 subjects have been accrued, depending on timelines of regulatory and committees' authorizations.

Considering the retrospective nature of the study, no data will be recorded prospectively. For alive patients, no data generated after the date of ICF signature will be collected.

8.3. Data Sources

Considering the retrospective nature of this study, the source of information will be the patient´s medical chart. Other potential sources of data are pharmacy records, databases or electronic prescribing systems. The data to be extracted in this study which are available in the patient´s medical charts will be recorded in the eCRFs. Only data obtained before study initiation (the date of the first ethics committee approval) will be extracted from the patient´s medical chart in order to ensure they are retrospective in nature. Data unavailable in patients' medical charts will be mentioned in the eCRFs as "not available". The degree of detail and completeness of data extracted for this study will depend on their availability according to local clinical practice. The investigator participating in this study will revise patient´s medical chart to confirm eligibility of the patient. Once it is confirmed that all selection criteria are meet and informed consent is given, the investigator will proceed to extract the study data available

(previously registered) in patient's medical charts and completing the eCRF. Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the informed consent form signed by the subject, unless permitted or required by law. Confidentiality standards will be maintained by coding each patient enrolled in this study through assignment of a unique subject identification number.

8.4. Limitations of the Research Method

This is a retrospective study designed to extract information already obtained in an EAP clinical practice of the participating sites that is registered in patients´ medical chart. The main limitation of this study therefore arises from the obvious limitations of a retrospective chart review that uses existing medical data recorded for reasons other than research, including incomplete or unrecorded documentation. The validity of study results will therefore be limited by the information available and the presence of missing data.

Nevertheless, it is expected that most data to be collected in this study will be available as they are routinely registered in the medical charts of the target population.

So, the information obtained in this study regarding safety data must be considered with caution given that these came from a retrospective review of medical charts where it is likely that information on adverse events may has been under recorded in comparison with a prospective and controlled clinical trial setting. In addition, safety results must be interpreted within the context of the current safety management systems in the participating hospitals.

9. STATISTICAL ANALYSIS

Statistical analyses and study reports will be developed by the Coordinating Investigator of the study in collaboration with the biostatisticians of the study Contract Research Organization (CRO). The World Programming System (WPS) platform (a SAS language software) will be used for these analyses.

All variables will be summarized separately. Depending on the type of the variable, the following statistics will be reported:

- Continuous variables: number of subjects (n), number of missings, mean, standard deviation (STD), median, standard error (SE, if needed), 25th and 75th percentiles, minimum, and maximum.
- Categorical variables: frequencies and percentages (calculated over the number of non-missing values).

In general, minimum and maximum are going to be reported using the same number of decimal places as collected in the raw data. Mean, STD, median, 25th and 75th percentiles will be reported with one additional decimal place.

Time to event data will be listed and summarized at every specified timepoint using the number patients at risk, number of patients censored, number of patients with the event, Kaplan Meier estimate (%), and the 95% confidence interval. In addition, 25th, 50% and 75th percentiles from Kaplan-Meier curves will be used.

Progression-free survival is defined as the time from the date of the first administration of dostarlimab and the occurrence of disease progression or death, whichever occurs earlier.

Overall survival is defined as the time between the start of treatment and death. Patients alive at the last follow-up will be censored for the analysis of OS.

Both PFS and OS will be analyzed using the Kaplan-Meier method. The responses (valid only for patients who have started dostarlimab with measurable disease) will be assessed following the RECIST 1.1 criteria and reported in percentages.

Further details on statistical analyses will be specified in the Statistical Analysis Plan (SAP).

10. ADVERSE EVENT REPORTING

In non-interventional studies, the sponsor and investigator obligations for the reporting of suspected adverse reactions are specified in the Spanish Royal Decree 957/2020, of 3 November, which contains the guidelines for post-authorization observational studies with medicinal products for human use, in accordance with the Guideline on Good Pharmacovigilance Practices, Module VIII-Post-Authorization Safety Studies.

However, considering the retrospective nature of this study, expedited reporting of suspected adverse reactions will not be required. All AEs extracted from the data source for the study as specified in the protocol will be summarized as part of the final study report publication.

Reportable events, time for reporting and definitions are included in sections 8.3 and appendix 14.1 of the EAP (EAP for Dostarlimab in adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen) protocol.

11. BIOLOGICAL SAMPLE COLLECTION AND SHIPMENTS

Formalin-fixed paraffin-embedded (FFPE) blocks will be sent to the central laboratory, which will prepare the biological material according to the analytical needs of the study.

The central laboratory is:

Dr. Marta Mendiola
Laboratorio de Anatomía y Oncología Traslacional
Edificio IdiPAZ, planta 2
Paseo de la Castellana 261
28046 Madrid, Spain

Archival FFPE block (from biopsy/surgery) will be used for:

1. IHC purposes for the evaluation of expression of MLH1, PMS2, MSH2 and MSH6 proteins

2. DNA extraction for

    a) microsatellite instability evaluation based on PCR techniques (Promega and Idylla)

    b) Mutation testing (*MLH1, PMS2, MSH2 and MSH6* genes) and hypermethlyation evaluation (*MLH1* gene)

All tumor and blood samples will be shipped from local sites to the central laboratory via courier service coordinated by the study CRO.

To arrange shipments, please contact:

Sofpromed Investigación Clínica, SLU
Tel: +34 648 414 261
E-mail: ensayos@sofpromed.com

12. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

12.1. Ethics Review

The final study plan, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any patient into the study.

The Sponsor (or appointed agent) is responsible for informing the IRB or IEC of any amendment to the study plan in accordance with local requirements. The study plan must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Sponsor (or appointed agent) is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

Progress reports will be provided to the IRB or IEC according to local regulations and guidelines.

12.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization and Good Clinical Practice standards as well as any applicable regulatory requirements.

This may include an inspection by Sponsor representatives/designees, and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/Sponsor representatives/designees and must allow direct access to source documents to the Regulatory Authority/Sponsor representatives/ designees. The investigator must allocate time (investigator and study staff) to discuss findings and relevant issues with the regulatory authority/Sponsor representatives.

Since this is an observational study, it is exempt from the compulsory subscription of insurance.

12.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

13. DISCONTINUATION FROM STUDY

All patients included in the study have the right to withdraw from the study at any time by withdrawing their consent, without having to give an explanation for this decision and without any influence on their clinical follow-up.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study Approval and Amendments

The study and all the possible amendments will be approved by Ethics Committee before starting any data collection procedure.

14.2. Investigator Responsibilities

Data collection, cleaning, patient's safety surveillance and compliance to study plan will be investigator's responsibilities.

14.3. Data Collection and Quality Assurance

The Sponsor must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (if applicable), and documentation of IRB/EC and governmental approval (if necessary). The Sponsor shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

14.4. Subject Confidentiality and Data Protection

Confidentiality standards should be maintained by coding each patient enrolled in the study through assignment of a unique patient identification number so that patient names are not included in datasets that are transmitted. The Sponsor undertakes in terms of obtaining, processing, preserving, communicating and transferring its data in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR), Spanish Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights. The investigator will inform the patients that the data obtained in this study will be stored and analyzed by computer according to the international regulations on handling computerized data

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, marketing authorization holder monitors, representatives, and collaborators, and the EC for each study site, as appropriate.

14.5. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the study plan, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.6. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a minimum period of 2 years and for as long as required per regulatory authorities after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

15. PUBLICATION POLICY

The final publication of the study results will be written by the coordinating investigators based on the final analysis performed. An abstract and a manuscript will be written.

The draft manuscript will be reviewed by the coordinating investigators, other co-authors and representatives from the funding entity. After revision the manuscript will be sent to a major, high-impact scientific journal.

All manuscripts will include an appropriate acknowledgement section, mentioning all investigators who have contributed to the study, as well as supporting parties.

All publications (papers, abstracts, or presentations) including data from the study will be submitted for review to all co-authors and the funding entity representatives prior to submission.

In addition, the study may be registered in the *clinicaltrials.gov* database of the National Institute of Health of the United States of America. Provide a plan for publications including expected number of publications and timeline.

16. LIST OF REFERENCES

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APPENDIX 1. PERFORMANCE STATUS

ECOG PS	KARNOFSKY PS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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APPENDIX 2. RADIOLOGICAL RESPONSE CRITERIA

Response will be assessed by RECIST v.1.1 criteria using investigator's review.

https://project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf

APPENDIX 3. DOSTARLIMAB EAP INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

To be considered eligible to participate in this program, all of the following requirements must be met:

1. At least 18 years of age, able to understand the program procedures and agree to participate by providing written informed consent.
2. Histologically diagnosed endometrial cancer (note: all histologies are permitted except endometrial sarcoma [including carcinosarcoma]).
3. Patient has evidence of tumor DNA damage repair dysfunction (dMMR/MSI-H) via locally available, validated methodology.
4. Patient has progressed on or after platinum containing chemotherapy (and has received no more than 2 lines of anti-cancer therapy for recurrent or advanced (Stage ≥ IIIB) disease (first or second line)); prior treatment with hormone therapies is acceptable and does not count towards the number of lines of therapy.
5. ECOG performance status of ≤ 2.
6. Adequate organ and bone marrow function, as defined below:
    a. Absolute neutrophil count (ANC) ≥ 1,500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL
    d. Adequate liver and renal function:
        - Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5 × institutional ULN.
        - Total bilirubin ≤ 1.5 × ULN AND direct bilirubin ≤ 1 × ULN.
        - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN unless liver metastases are present, in which case they must be ≤ 5 × ULN.
7. Cannot be satisfactorily treated with available alternative treatments.
8. Not eligible for a clinical trial with dostarlimab within the indication of the EAP (where access to the clinical trial site is possible).

9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and if one of the following conditions applies:

    - Is a woman of non-childbearing potential (WONCBP)

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failurerate of < 1 % per year), preferably with low user dependency, during treatment and for at least 4 months after treatment. The treating physician should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first doseof dostarlimab.

    A WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours before the first dose of dostarlimab.

    The treating physician is responsible for review of medical history, menstrual history, andrecent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Exclusion Criteria

Patients will not be eligible for treatment with dostarlimab under this protocol if any of the following criteria apply:

1. Has received prior therapy with an anti-programmed death-1 (anti-PD-1), anti-PD-1-ligand-1 (anti-PD-L1), or anti-PD-1 ligand-2 (anti-PD-L2) agent.
2. Is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring antibiotic, antifungal or antiviral treatment.
3. Has undergone major surgery 3 weeks prior to initiating dostarlimab (and not recovered from surgical effects).
4. Has malignancies other than endometrial cancer (except for any other malignancy for which the patient is not being actively treated).
5. Has a history of interstitial lung disease.
6. Has an active autoimmune disease that required systemic treatment in the past 2 years (i.e., use of disease-modifying agents, corticosteroids, or immunosuppressive drugs); hormone replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

7. Has experienced ≥ Grade 3 immune related AE with prior immunotherapy, except for non-clinically significant laboratory abnormalities.
8. Has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., hepatitis C virus [HCV] ribonucleic acid [qualitative] is detected).
9. Has received a live vaccine within 14 days of 1st dose of dostarlimab.
10. Has a known hypersensitivity to dostarlimab components or excipients.