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ENGOT-EN20/GOG-3083/XPORT-EC-042 – A phase III, randomized, placebo-controlled, double-blind, multicenter trial of selinexor in maintenance therapy after systemic therapy for patients with p53 wild-type, advanced, or recurrent endometrial carcinoma: rationale, methods, and trial design

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ABSTRACT

Background Patients with advanced/recurrent endometrial cancer have a poor prognosis and limited treatment options. Biomarkers such as tumor protein 53 (*TP53*) in endometrial cancer can integrate novel strategies for improved and individualized treatment that could impact patient outcomes. In an exploratory analysis of the phase III ENGOT-EN5/GOG-3055/SIENDO study of selinexor maintenance monotherapy 80 mg in advanced/recurrent endometrial cancer, a pre-specified subgroup of patients with *TP53* wild type (wt) endometrial cancer showed preliminary activity at long-term follow-up with a generally manageable safety profile (median progression-free survival 27.4 months vs 5.2 months placebo, HR=0.41).

Primary Objective To evaluate the efficacy of selinexor compared with placebo as maintenance therapy in patients with advanced or recurrent *TP53*wt endometrial cancer.

Study Hypothesis Selinexor administered at 60 mg weekly as maintenance therapy will show manageable safety and maintain efficacy in patients with *TP53*wt advanced/recurrent endometrial cancer after systemic therapy versus placebo.

Trial Design This is a prospective, multicenter, double-blind, placebo-controlled, randomized phase III study designed to evaluate the efficacy and safety of selinexor as a maintenance therapy in patients with advanced or recurrent *TP53*wt endometrial cancer.

Major Inclusion/Exclusion Criteria Eligible patients must have histologically confirmed endometrial cancer, *TP53*wt confirmed by next-generation sequencing, completed at least 12 weeks of platinum-based therapy with or without immunotherapy, with confirmed partial response or complete response, and primary Stage IV disease or at first relapse.

Primary Endpoint The primary endpoint is investigator-assessed progression-free survival per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the intent-to-treat population.

Sample Size A total of 220 patients will be enrolled.

Estimated Dates for Completing Accrual and Presenting Results Accrual is expected to be completed in 2024 with presentation of results in 2025.

Trial Registration NCT05611931

INTRODUCTION

Endometrial cancer is the sixth most commonly diagnosed cancer in women globally with alarming increases in incidence across all age groups in middle- to high-income countries.[1] For patients with advanced/recurrent endometrial cancer, current treatment options include surgery, systemic, hormonal, or targeted therapies, as well as radiation, with a combination of the chemotherapy drugs carboplatin and paclitaxel as standard front-line treatment.

Molecular characterization has become an instrumental part of informed treatment decisions in patients with endometrial cancer given their prognostic and, in some cases, predictive, value.[1] In combination with histopathological classification, biomarker-driven treatments can lead to improved patient management and clinical outcomes. Access to full molecular profiling is uncommon and the use in routine clinics is scant. While The Cancer Genome Atlas (TCGA) classifications were developed from a genome-wide analysis,[2] the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) was derived from data integrating features of molecular

and histological subtypes. The following four risk categories have emerged from ProMisE: (1) polymerase epsilon exonuclease domain mutated (*POLE EDM*); (2) mismatch repair deficient (dMMR); (3) tumor protein 53 abnormal (*TP53*abn), and (4) *TP53* wild type (wt).[3] According to the TCGA molecular categories, *TP53*wt endometrial cancer is often also characterized as NSMP (no specific molecular profile), encompassing endometrial cancer that does not exhibit features of the *POLE*, dMMR, or *TP53*abn molecular subgroups and therefore does not have a surrogate marker. This combination of assessments by immunohistochemical expression for mismatch repair proteins together with sequencing for *POLE* mutations allows subgroups to be defined in order to allocate risk, inform prognosis, and potentially identify novel treatment strategies.

Tumor protein 53 (*TP53*) is a well-recognized, prognostic, genetic biomarker for endometrial cancer, with tumors with mutations in *TP53* resulting in poor outcomes.[1] Approximately 25% of patients with endometrial cancer have mutations in *TP53* at diagnosis and approximately 50% of advanced/recurrent endometrial cancer tumors are *TP53*wt, of which 40–55% are also mismatch repair proficient (pMMR) or microsatellite stable (MSS).[4–6] *POLE*, *TP53*wt, and pMMR subgroups are found in approximately 36% of advanced or recurrent endometrial cancer.[7] Patients with *TP53*wt tumors have a paucity of options and limited evidence of beneficial treatment that leaves a notable unmet need. In addition, patients with advanced/recurrent endometrial cancer who need second-line treatment commonly develop chemoresistance, have poor response to treatment, and experience substantial toxicity.[8]

Selinexor is an investigational oral exportin 1 (XPO1) inhibitor that prevents the XPO1-mediated export of several tumor suppressor proteins (TSPs), including wt p53 (Figure 1). Aberrant XPO1-mediated nuclear export of p53 is a mechanism by which cancer cells can inhibit regulatory and functional activities of *TP53*, which is a tumor suppressor gene. Overexpression of XPO1 is associated with a poor endometrial cancer prognosis and 57% of endometrial cancer tumors have a high expression of XPO1.[9] Selinexor is currently approved for use in relapsed/refractory multiple myeloma and has received accelerated approval for relapsed/refractory diffuse large B cell lymphoma.[10] Inhibition of XPO1 leads to nuclear accumulation of p53 across various cancer types, including endometrial cancer, as observed in cell lines and patient samples.[9] While there are several mechanisms by which selinexor induces cancer cell death, the primary mechanism in endometrial cancer is presumed to be through the nuclear retention and reactivation of *TP53*. Promising single-agent activity of selinexor was observed in gynecological malignancies, including endometrial cancer, in the phase II SIGN study.[11] In the primary analysis of the ENGOT-EN5/GOG-3055/SIENDO study of selinexor maintenance therapy after first-line chemotherapy for advanced/recurrent endometrial cancer,

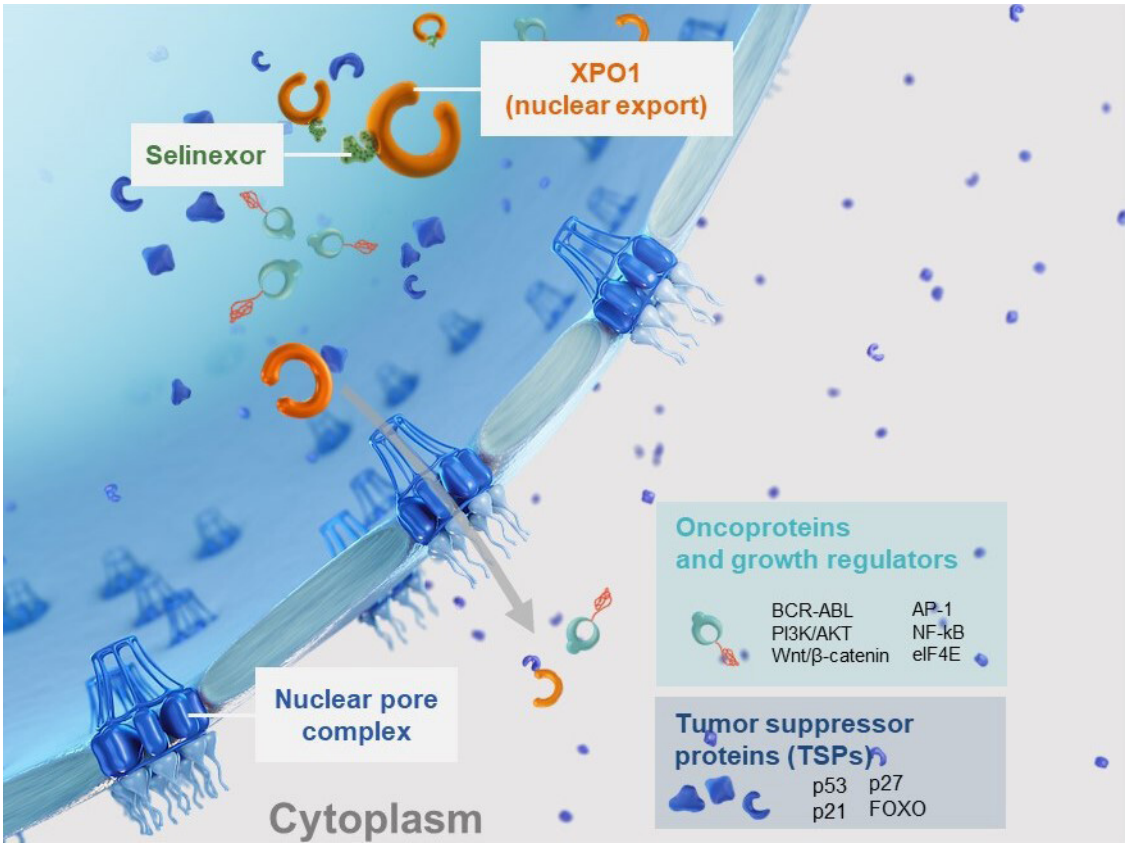

Figure 1 Selinexor mechanism of action. Selinexor is an oral exportin 1 (XPO1) inhibitor. XPO1 inhibition by selinexor results in the retention/reactivation of tumor suppressor proteins such as p53. The retention of wild type p53 and other tumor suppressor protein leads to the selective killing of cancer cells while largely sparing normal cells. Export of mRNA is prevented, which inhibits oncoprotein translation. Inhibition of mRNA export of select oncogenes decreases subsequent translation and synthesis of oncoproteins, while simultaneously targeting several oncogenic pathways involved in cancer development, maintenance, and progression.

the improvements in median progression-free survival for the intent-to-treat population were not clinically meaningful.[5] In the long-term follow-up of the pre-specified *TP53*wt subgroup as of September 1, 2023, there were progression-free survival improvements in patients receiving selinexor maintenance therapy (80 mg oral once-weekly) compared with placebo (27.4 months vs 5.2 months, HR=0.41; median follow-up of 28.9 months). Further analysis suggests benefit is regardless of microsatellite stability status.[12] An increase in progression-free survival was observed particularly in the *TP53*wt/pMMR (MSS) subgroup with selinexor maintenance therapy (not reached) compared with 4.9 months with placebo, HR: 0.32, median follow-up of 31.6 months). The *TP53*wt/dMMR (MSI-H) subgroup reached a median progression-free survival of 13.1 months with selinexor versus 3.7 months with placebo (HR=0.45).[12] The safety profile for selinexor in the *TP53*wt subgroup was generally manageable with nausea, vomiting, and diarrhea as the most common adverse events.[12] The complete safety profile of the ENGOT-EN5/GOG-3055/SIENDO study where patients received 80 mg selinexor dose has been published.[5] The ENGOT-EN5/GOG-3055/SIENDO study showed that *TP53*wt and *TP53*wt/pMMR status may represent a robust predictive biomarker for selinexor efficacy in endometrial cancer, in addition to its role as an important prognostic marker.[12] Based on the efficacy and safety of selinexor monotherapy from existing data, the ENGOT-EN20/GOG-3083/XPORT-EC-042 study will evaluate the safety and efficacy of once-weekly selinexor (60 mg) versus placebo to prolong progression-free survival in patients with *TP53*wt endometrial cancer, especially in patients with *TP53*wt/pMMR (MSS) tumors.[5]

METHODS

Trial Design

ENGOT-EN20/GOG-3083/XPORT-EC-042 (NCT05611931) is a prospective, multicenter, double-blind, placebo-controlled, randomized phase III study designed to evaluate the efficacy and safety of selinexor as a maintenance therapy in patients with *TP53*wt advanced or recurrent endometrial cancer, who have achieved a partial response or complete response per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 after completing at least 12 weeks of platinum-based therapy (Figure 2). For this study, the primary objective is to evaluate the efficacy of selinexor compared with placebo as maintenance therapy in patients with advanced or recurrent *TP53*wt endometrial cancer.

A total of 220 patients will be enrolled globally across approximately 140 sites in the United States, Europe, Israel, Australia, and Canada. Eligible patients will be randomized 1:1 to maintenance therapy with either 60 mg oral once-weekly selinexor or placebo administered in 28-day cycles on Days 1, 8, 15, and 22. Exposure/response modeling from the ENGOT-EN5/GOG-3055/SIENDO study observed pharmacokinetic analyses predicts that a 60 mg dose would provide a manageable safety profile while maintaining efficacy. The following stratification factors will be applied: primary Stage IV versus recurrent disease at the time of platinum-based therapy, along with disease status after chemotherapy (partial response vs complete response). Treatment will be continued until documented disease progression per RECIST v1.1, unacceptable adverse events, withdrawal of consent, or other reasons requiring treatment discontinuation. A blinded independent central review will be formed to review disease assessment data and independently assess disease response and time of progressive disease.

Participants

Select eligibility criteria are the following: patients 18 years of age or older, histologically confirmed endometrial cancer, *TP53*wt confirmed by next-generation sequencing, completion of at least 12 weeks of platinum-based therapy with or without immunotherapy, and confirmed partial response or complete response at primary Stage IV disease or at first relapse. Patients cannot have uterine sarcomas, previous treatment with an XPO1 inhibitor, and cannot have received concurrent systemic anti-cancer therapy including investigational agents ≤3 weeks prior to Cycle 1 Day 1. Table 1 contains a complete list of inclusion and exclusion criteria.

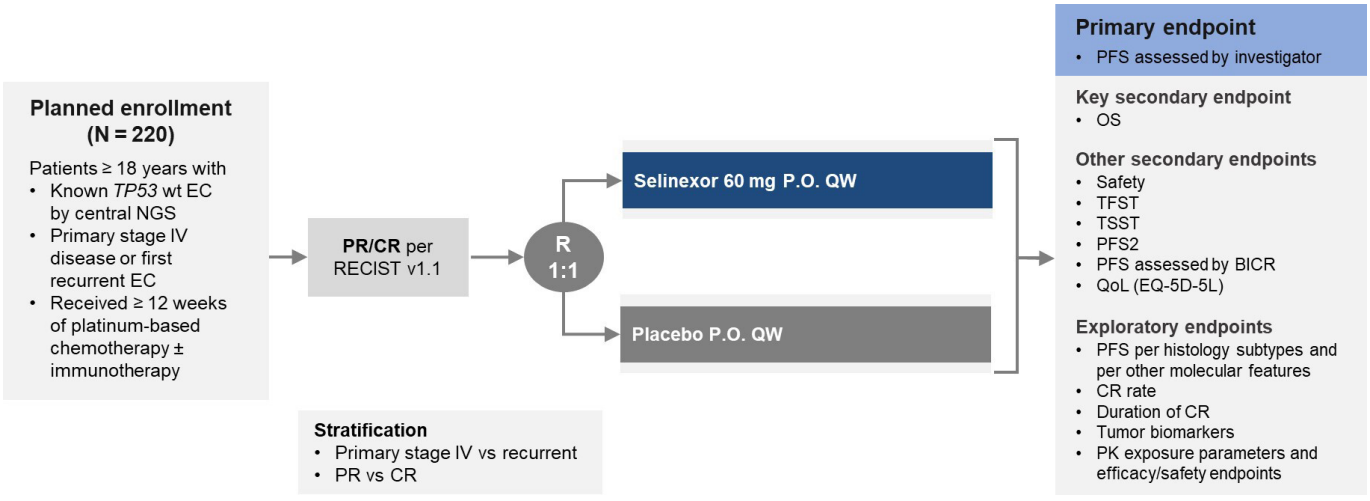

Figure 2 Trial design. BICR, blinded independent central review; CR, complete response; EC, endometrial cancer; EQ-5D-5L, Quality of Life Questionnaire EuroQol-5 Dimensions-5 Levels; NGS, next-generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival after consecutive treatment; PK, pharmacokinetics; P.O., per oral; PR, partial response; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to tirst subsequent therapy; TSST, time to second subsequent therapy; QoL, quality of life; QW, once-weekly.[14]

Table 1 Patient eligibility criteria

Inclusion criteria	Exclusion criteria
1. At least 18 years of age at the time of signing informed consent. 2. Histologically confirmed endometrial cancer including: endometrioid, serous, undifferentiated, and carcinosarcoma. 3. *TP53*wt assessed by NGS, evaluated by a central vendor. 4. Completed at least 12 weeks of platinum-based therapy with or without immunotherapy (not including adjuvant or neoadjuvant therapy for Stage I-III disease) and achieved confirmed partial or complete response by imaging, according to RECIST version 1.1. The patients should have received treatment for: 1. Primary Stage IV disease OR first relapse. Must be able to initiate study drug 3 to 8 weeks after completion of their final dose of chemotherapy. Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. 5. Patients must have adequate bone marrow function and organ function within 2 weeks of C1D1 before starting study drug. 6. In the opinion of the Investigator, the patient must: 1. Have a life expectancy of at least 12 weeks, and 2. Be fit to receive investigational therapy. 7. Pre-menopausal females of childbearing potential must have a negative pregnancy test (serumβ-human chorionic gonadotropin test) prior to the first dose of study drug at each cycle. Female patients of childbearing potential must agree to use highly effective methods of contraception throughout the study and for 90 days following the last dose of study drug. 8. Written informed consent signed in accordance with federal, local, and institutional guidelines prior to the first screening procedure.	1. Has any uterine sarcomas (carcinosarcomas – not excluded), clear cell or small cell carcinoma with neuroendocrine differentiation. 2. Received a blood or platelet transfusion during the 2 weeks prior to C1D1. Patients' hemoglobin must be assessed within 2 weeks of screening and at least 1 week post-transfusion. 3. Concurrent systemic steroid therapy higher than physiologic dose (>10 mg/day of prednisone or equivalent). Systemic steroid therapy as pre-medication for taxane is allowed. 4. Insufficient time since or not recovered from procedures or anti-cancer therapy. 5. Having ongoing clinically significant anti-cancer therapy-related toxicities CTCAE Grade >1, with the exception of alopecia. In specific cases, patients whose toxicity has stabilized or with Grade 2 non-hematologic toxicities can be allowed following documented approval by the Sponsor's Medical Monitor. 6. Palliative radiotherapy within 14 days of the intended C1D1. Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases, provided that the radiotherapy does not involve target lesions, and the reason for the radiotherapy does not reflect evidence of disease progression. 7. Any gastrointestinal dysfunctions that could interfere with the absorption of selinexor. 8. Patients unable to tolerate two forms of anti-emetics prior to each dose for at least two cycles will not be eligible for the trial. 9. Active, ongoing, or uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week of screening. 10. Serious psychiatric or medical condition that could interfere with participation in the study or in the opinion of the Investigator would make study involvement unreasonably hazardous. 11. Previous treatment with an XPO1 inhibitor. 12. Stable disease or PD on the post-chemotherapy scan or clinical evidence of progression prior to randomization. 13. Patients who received any systemic anti-cancer therapy including investigational agents ≤3 weeks (or ≤5 half-lives of the drug (whichever is shorter)) prior to C1D1. 14. Major injuries or surgery within 14 days prior to C1D1 and/or planned major surgery during the on-treatment study period. 15. Other malignant disease with disease-free ≤3 years except: curatively treated carcinoma in situ of the cervix, basal cell carcinoma of the skin, or ductal carcinoma in situ of the breast. 16. History of allergic reactions attributed to compounds of similar chemical or biologic composition to selinexor, or other agents used in the study. 17. Active brain metastases. 18. Females who are pregnant or lactating. 19. Any other life-threatening illness, active medical condition, organ system dysfunction, or serious active psychiatric issue which, in the Investigator's opinion, could compromise the patient's safety or the patient's ability to remain compliant with study procedures.

C1D1, Cycle 1 Day 1; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NGS, next-generation sequencing; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; *TP53* wt, tumor protein 53 wild type; XPO1, exportin 1.

Primary Endpoints

The primary endpoint is investigator-assessed progression-free survival per RECIST v1.1 in the intent-to-treat population. The key secondary endpoint is overall survival. Other secondary endpoints include safety and tolerability, time to first subsequent therapy, time to second subsequent therapy, time from randomization until the second progression event, progression-free survival assessed by blinded independent central review, and health-related quality-of-life (HR-QoL) outcomes. Exploratory endpoints include progression-free survival per histology and molecular features, complete response rate for patients who entered as partial response, duration of complete response, tumor biomarkers, and pharmacokinetics.

During pre-screening, patients will be required to provide tumor biopsies (fresh or archival) for mandatory central molecular characterization/next-generation sequencing validated testing. If all other

eligibilities are met, patients known to have *TP53*wt endometrial cancer will be enrolled. Tumor response will be evaluated according to RECIST v1.1 by the investigator and independently by a blinded independent central review.

Adverse events will be graded by the Investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grading Scale v.5.0. This includes clinically significant findings in vital signs, physical examinations, laboratory, and investigation results, including hematology and serum biochemistry.

HR-QoL outcomes will be measured by the Quality-of-Life Questionnaire EuroQol-5 Dimensions-5 Levels (EQ-5D-5L).

Sample Size

To observe up to 120 progression-free survival events (ie, progression or death due to any cause), a total of up to 220 patients will be enrolled and randomized, which provides 90% power to detect a hazard ratio (HR) with a two-sided alpha of 0.05. To compare progression-free survival of selinexor versus placebo, a two-sided stratified log-rank test adjusting for stratification factors will be performed (primary Stage IV vs recurrent disease at the time of platinum-based therapy and disease status after chemotherapy (partial response vs complete response). When approximately 36 progression-free survival events are reached throughout both treatment arms, an interim analysis (futility of progression-free survival) will be performed.

Randomization and Blinding

Randomization will occur in a double-blind fashion in a 1:1 ratio of 60 mg selinexor or placebo maintenance therapy. Patients will be stratified according to the following two factors: (1) primary Stage IV versus recurrent disease at the time of platinum-based therapy and (2) disease status after chemotherapy (partial response vs complete response). Patient treatment assignments will be blinded to all staff including blinded administration during blinded study period.

Statistical Analysis

The primary endpoint of progression-free survival is defined as the time from randomization until progressive disease or death due to any cause or whichever occurs first. To compare progression-free survival and secondary time to event endpoints between treatment groups, a two-sided stratified log-rank test adjusted for stratification factors will be used. A stratified Cox proportional hazards model will be used to estimate the hazard ratio and corresponding two-sided 95% confidence intervals. The Kaplan–Meier method will be used to plot the progression-free survival and secondary time to event endpoints by treatment group. Raw scores for HR-QoL measures for both multi- and single-item measures will be linearly transformed to a score ranging from 0 to 100.

DISCUSSION

Standard treatments for patients with advanced or recurrent endometrial cancer have limited disease control especially in those who relapse after first-line therapy.[1 8] Maintenance therapy following first-line systemic chemotherapy could potentially prolong intervals between treatments with fewer disease symptoms and treatment-related toxicities, therefore providing the added benefit of improved quality of life. The lack of effective treatment has resulted in an interest in using molecular classification as not only a prognostic marker in endometrial cancer, but also as a means to direct therapy, placing an emphasis on biomarker-driven targeted therapy to maximize therapeutic strategies.[1] For endometrial cancer, this could lead to an individualized treatment approach using selinexor specifically for tumors that are *TP53*wt and *TP53*wt/pMMR (MSS).

The overall frequency of *TP53*wt tumors in endometrial cancer and lack of specific therapy highlights this unmet need. While immune checkpoint inhibitors such as dostarlimab have shown significant benefit compared with placebo in patients with dMMR (MSI-H) endometrial cancer, less evidence of benefit was seen in patients with pMMR (MSS) endometrial cancer.[13] Relatedly, in February 2023, the US Food and Drug Administration (FDA) approved dostarlimab concomitantly with chemotherapy and as maintenance therapy for patients with dMMR advanced or recurrent endometrial cancer. This emphasizes the further need to consider molecular profiles to develop agents for tumors with classifications such as *TP53*wt/pMMR (MSS). The ENGOT-EN5/GOG-3055/SIENDO study suggests that selinexor maintenance therapy may provide survival benefit in *TP53*wt endometrial cancer tumors, including those that are *TP53*wt/pMMR. Building on these data, the ENGOT-EN20/GOG-3083/XPORT-EC-042 will further investigate the potential role for a *TP53*wt-directed approach in strategically selecting the most suitable maintenance therapy for patients with advanced/recurrent endometrial cancer.

This phase III trial offers a potential option for an oral-only maintenance therapy to delay the next recurrence of disease (or in rare cases to prevent recurrence), allowing patients to have a longer disease-free period thereby improving quality of life. Based on the exploratory analysis in the ENGOT-EN5/GOG-3055/SIENDO study, there appears to be benefit of selinexor treatment for patients with pMMR (MSS) and *TP53*wt endometrial cancer.[5] The data from this trial will provide important information about the safety, efficacy, and quality of life of selinexor as a maintenance strategy for patients with *TP53*wt endometrial cancer that may ultimately lead to the use of *TP53* as marker for clinical decision-making.

In summary, the ENGOT-EN20/GOG-3083/XPORT-EC-042 trial may influence current practice by providing clinicians with an option of a convenient and safe oral maintenance therapy for patients with advanced/recurrent *TP53*wt endometrial cancer. ENGOT-EN20/GOG-3083/XPORT-EC-042 is actively enrolling patients with *TP53*wt advanced/recurrent endometrial cancer.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and will be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements, as applicable. This study will be conducted in collaboration with the European Network of Gynaecological Oncological Trial groups (ENGOT) and the Belgium and Luxembourg Gynaecological Oncology Group (BGOG) and the Gynecologic Oncology Group-Foundation (GOG-F) according to the ENGOT-GOG model C. Participants will give informed consent to participate in the study before taking part.

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