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The PENDOR study: establishment of a panel of patient-derived tumor organoids from endometrial cancer to assess efficacy of PARP inhibitors

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Abstract

Background Combination of chemotherapy and immunotherapy is the current standard of care for advanced endometrial cancer. However, survival outcome remains poor, highlighting the urgent need for new treatments and reliable tools to identify patients who will benefit from them. Patient-Derived Tumor Organoids (PDTO) are three-dimensional structures established from patient tumors, and are closely mimicking the features of the tumor of origin. Moreover, more and more evidences show that PTDOs hold promises as predictive tools for the response to treatment of patients.

Method The PENDOR study is a monocentric observational study designed to assess the feasibility of generating and testing PDTOs derived from endometrial cancer for evaluating treatment sensitivity. PDTOS will be established from surgical specimens not required for anatomopathological diagnosis. Tumor cells will be dissociated, embedded in extracellular matrix, and cultured in a medium supplemented with growth factors and signaling pathways inhibitors. Molecular and histological analyses will be conducted to validate the resemblance of PDTO to the original tumor. Response of PDTO to conventional chemotherapy and PARP inhibitors will be evaluated and compared to clinical

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response and to the results of an academic HRD test Genomic Instability Scar (GIScar), respectively, to assess their predictive value.

Discussion This pilot study aims to validate the feasibility to develop PDTOs from endometrial cancer from patients who will undergo surgical resection. We aim to provide a proof of concept regarding the predictive value of these models for their potential application into routine clinical practice as part of precision medicine. This approach could therefore facilitate the identification of patients who could benefit from PARP inhibitors.

Trial registration This clinical trial (N°ID-RCB: 2024-A01206-41) has been validated by local research ethic committee on July 16th 2024 and registered at ClinicalTrials.gov with the identifier NCT06603506 on September 6th 2024, version 1.

Keywords Endometrial cancer, Patient-derived tumor organoids, Predictive functional assays, Homologous recombination deficiency, PARP inhibitors

Background

Endometrial cancer and treatment modalities

Endometrial cancer (EC) ranks at the seventh most common cancer among women globally and is the second most frequent gynecological malignancy, with 420 000 new cases and nearly 100,000 deaths reported in 2022 [1]. Most EC are diagnosed at an early stage, when the disease is confined to the uterus, often due to postmenopausal bleeding, which facilitates prompt detection. Despite available treatments, the 5-year overall survival for metastatic/advanced EC remains below 20%.

EC has traditionally been divided into two histological subtypes: type I endometriod tumors and type II non endometrioid tumors, such as serous carcinomas. The latter is associated with a worse prognosis, and patients with this subtype may benefit from chemotherapy for smaller tumors compared to those with type I tumors.

In the past decade, The Cancer Genome Atlas (TCGA) [2] analysed 373 endometrial carcinomas and offered key molecular insights that have refined tumor classification and improved adjuvant treatment strategies. ECs are now categorized into four molecular subgroups: POLE ultramutated (POLEmut), microsatellite instability (MSI) hypermutated, *TP53* mutated, NSMP (Non-Specific Molecular Profile) group. This classification has led to better-targeted post-surgical adjuvant treatments for aggressive tumors. The POLEmut group, for instance, has an extremely low risk of recurrence and does not require adjuvant therapy. Conversely, the copy-number low and copy-number high groups, which include most serous and serous-like endometrioid tumors, have a poorer prognosis, with the majority of tumors harboring TP53 mutations and significant transcriptional dysregulation, particularly related to the cell cycle, suggesting that these patients might benefit from adjuvant chemotherapy.

For early-stage EC, treatment typically involves surgery, potentially followed by radiotherapy and chemotherapy depending on poor prognostic factors [3] such as TCGA molecular subgroup, histologicalgroup, tumor grade, extent of the tumor, and the presence of vascular emboli. In cases of advanced or metastatic EC, treatment consists of chemotherapy (platinum-based or paclitaxel), immunotherapy (e.g. pembrolizumab, dorstalimab), anti-angiogenic agents (e.g. lenvatinib) and occasionally hormone therapy, depending on the expression of hormone receptors. Immunotherapy has shown promising results in patients with MSI tumors [4] but prognosis for most patients with advanced or metastatic EC remains poor. Therefore, it is crucial to develop new effective therapeutic alternatives and associated predictive tools (biomarkers, functional assays) to identify patients likely to benefit from these strategies.

PARP inhibitors (PARPi)

Poly(ADP-ribose) polymerase (PARP) is a family of enzymes involved in the repair of single strand breaks by the base excision repair (BER) mechanism. When PARP is inhibited, the single strand breaks will remain unrepaired and may evolve toward double strand breaks, usually repaired by Homologous Recombination (HR) pathway. Cells harboring HR alterations (e.g. invalidating mutations in *BRCA1* and *BRCA2* genes) are not able to repair double strand breaks, thus letting them accumulate and leading to synthetic lethality [5]. Therefore, HR deficient (HRD) tumors are vulnerable to the increase in DNA double strand breaks generated by PARP inhibitors. PARPi are currently indicated for several cancers, including prostate [6], ovarian [7], breast [8], pancreatic [9] cancers. Currently, HRD status is determined by next-generation sequencing (NGS) of a gene panel that evolves with scientific advances and using companion diagnostic tests such as Myriad Genetic MyChoice (MGMC) or the GIScar test [10] developed by our team for ovarian cancers [11]. However, not all HRD tumors are sensitive to PARPi, and efficacy has been demonstrated even in tumor with homologous recombination proficiency (HRP), such as in platinum-sensitive relapsing ovarian cancer or in combination with new-generation hormone therapy in prostate cancer [12]. This suggests that current HRD tests may not fully capture all homologous

recombination deficiencies, underscoring the need for improved tests to optimize the selection for PARPi therapy.

Targeting this DNA repair pathways appears to be highly promising in EC, particularly for a molecular subgroup (group 4 of the TCGA molecular classification [2]) that includes high-grade tumors with mutations in the *TP53* gene involved in DNA repair. Several clinical trials have thus evaluated the use of PARPi in EC. The French UTOLA trial (NCT03745950) is actually investigating maintenance therapy with olaparib in advanced EC following platinum-based chemotherapy. Initials results revealed that *TP53* mutations were associated with a complete response rate of 39%, compared to 22% and 9% in dMMR (deficient MisMatch Repair) and NSMP patients respectively [13]. In the LST (Large scale transition) high subgroup, Olaparib extended median progression-free survival (PFS) to 5.4 months with Olaparib versus 3.6 months with Placebo (HR = 0.59; $p = 0.021$). The phase 3 RUBY trial [14] demonstrated that combining Dorstarlimab with chemotherapy, followed by Niraparib, significantly improved PFS in advanced or recurrent EC [15]. Concurrently, the DUO-E trial [16] reported significantly improved PFS benefits with Durvalumab and Olaparib in first-line therapy. The international RAINBO umbrella program (NCT05255653), will further investigate adjuvant therapies based of EC molecular profiles through four phase 3 trials.

These trials underscore the growing interest in PARPi for EC. While PARPi has shown efficacy in advanced EC patients, not all of them will benefit from this treatment and information of efficacy of PARPi in early stage EC are lacking. Moreover, research tends to suggest that advanced EC patients may benefit from PARPi if tumors are harboring *TP53* mutated or high LST but further refinement is needed to better identify these patients.

Therefore, it is crucial to implement companion diagnostic tests to detect HRD status, such as genomic scar-based signature and to go one step further by directly using predictive functional assay.

Functional precision medicine based on Patient-Derived Tumor Organoids

Functional precision medicine is a strategy whereby alive tumor cells from patients are directly exposed to drugs to provide immediately personalized information to guide therapy. Improved feasibility of generating tumor models recapitulating the patient tumor and able to integrate all the determinants of the response to PARPi, such as Patient-Derived Tumor Organoids (PDTO), has made these models accessible for personalized treatment. PDTO are often generated by embedding cells from tumor tissue into an extracellular matrix and by culturing them in a medium supplemented with growth factors and inhibitors of some signaling pathways. PDTO offer several advantages, including rapid amplification from a small sample of tumor. They are able to retain molecular characteristics of the original tumor, and most of all, more and more studies indicate that PDTO could recapitulate clinical response of patients with different types of cancers (e.g. colorectal, ovarian, head and neck cancers…) [17]. There is limited data in the literature on the use of PDTO from EC [18–23], and none have investigated their ability to predict response to conventional chemotherapy and PARPi, despite a high success rate of establishment (close to 100%).

Our study aims to generate PDTOs from surgical specimens obtained from patients with localized EC. We will assess their response to chemotherapy, immunotherapy and PARPi to evaluate their predictive potential.

Method/design

The PENDOR study is a single-centre non-interventional study conducted to investigate the feasibility of generating and testing PDTO from EC to assess their sensitivity to treatments (Fig. 1). The PENDOR study and this manuscript have been written in accordance with standard protocol items, namely recommendations for interventional trials (SPIRIT). The method and design of this study are based on the ORGAVADS [24], TRIPLEX [25] and OVAREX [26] studies previously published by our team.

HRD (Homologous Recombination Deficiency) HRP (Homologous Recombination Proficency) LP WGS (Low Pass Whole Genome Sequencing) NGS (Next Generation Sequencing) PARPi (PARP inhibitor) PBMC (Peripheral Blood Mononuclear Cells) PDTO (Patient-Derived Tumor Organoid) iPDTO (immunocompetent PDTO) STR (Short Tandem Repeat) TILS (Tumor Infiltrating Lymphocytes) (Figure created with Biorender.com).

Study objectives and endpoints

The main objective of the study is to assess the feasibility of developing PDTO from EC that can be used for predictive functional assays.

The secondary objectives are: *i*) to assess the feasibility of ex vivo functional assays for evaluation of sensitivity to treatments (chemotherapy, PARPi and immunotherapy); *ii*) to investigate the predictive value of EC PDTO response to conventional chemotherapy and PARPi; *iii*) to assess the HRD status using GIScar test; *iv*) to identify molecular signatures common to PDTO and tumor samples; *v*) to investigate the relationship between molecular signatures and response to treatment.

Study population

Eligibility criteria are described in Table 1. The PENDOR study focuses on patients with early stage endometrial

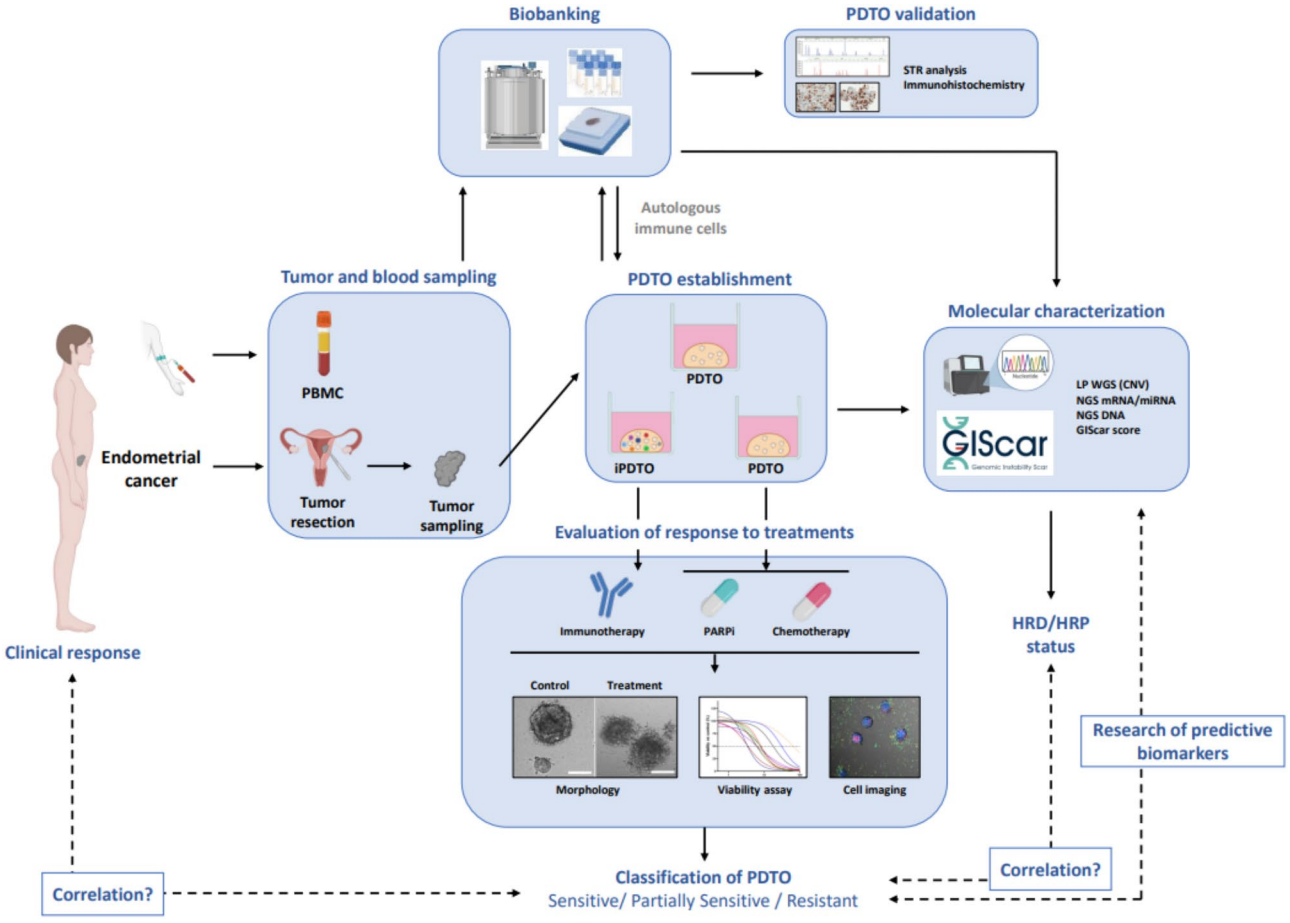

Fig. 1 PENDOR study design

Table 1 PENDOR study criteria

Inclusion criteria	Non-inclusion criteria
Patient over 18 years of age	History of any other clinically active malignancy in the last 6 months prior to inclusion
Patient with histologically proven endometrial cancer	
Localized EC FIGO I-IVA eligible for surgical treatment	
High grade EC: high grade endometrioid subtype, non-endometrioid subtype, mutation TP53	Persons deprived of liberty or under guardianship (including curatorship)
Patient affiliated to the French social security system	
Patient informed having signed the consent to participate	

cancer (I-IVA) who undergo surgical treatment at Comprehensive Cancer Center François Baclesse.

Study assessment

This clinical trial (N°ID-RCB: 2024-A01206-41) has received ethical approval from the Comité de Protection des Personnes Ouest II on September April 5th, 2024. Following the screening of patients according to criteria, a proposal for enrollment will be given by the clinicians who will inform all patients prior to enrollment in the study. During the preoperative consultation, patients will sign a consent form for the use of their biological samples for research purposes. An identification number will be assigned to each patient to be used throughout the study. The enrollment period in the study is planned over one year.

Medical data collection

In order to correlate the biological data obtained from the initial tumor or serum, the response to ex vivo treatments and, where applicable, the response observed in the clinic, the study will include the collection of patients' medical data (Table 2).

Table 2 Medical data collected in the PENDOR study

Age
Disease history (diagnosis, management, TNM, etc.), POLE, P53, MMR, RH, HRD status
History of other cancers
Surgical procedure, tumor size, healthy/invaded margins, presence of capsular rupture, presence of perineural sheathing, presence of vascular emboli
Nature and duration of other treatments: chemo/immunotherapy (molecules, administration regimens, complete or incomplete treatment, toxicities), radiotherapy
Response to treatment: disease-free survival, progression-free survival, overall survival
Recurrence (type, date, location)
Survival

Collection of tumor and blood samples

Tumor

During therapeutic management, surgical excision of the endometrial tumor will be performed and the surgical specimen will be sent for anatomopathological analysis. In agreement with the pathologists of the Comprehensive Cancer Centre François Baclesse, excess of tumor that is not required for anatomopathological diagnosis (surgical waste) will be used for this study.

Blood

Blood sampling will be performed before surgery with a specific blood draw for this study. Blood will be collected in two 5 ml dry tubes and seven 5 ml EDTA tubes and transported to the laboratories to be processed for serum and peripheral blood mononuclear cells (PBMC) isolation, respectively.

Biological sample processing

Serum preparation

Serum will be isolated by a two-step centrifugation (2500 g for 10 min at room temperature), and aliquoted (about 5 tubes of 300 µL) before storage at − 80 °C in the Biological Resource Center 'Tumorotheque de Caen Basse-Normandie' (TCBN) (NF-S 96900 quality management, AFNOR No. 2016: 72860.5).

Isolation of peripheral blood mononuclear cells (PBMC)

PBMC will be isolated from human peripheral blood by density gradient centrifugation using Ficoll-Paque in Leucosep tubes. Then, cells will be resuspended in culture media, and counted. PBMC will be resuspended in freezing solution (10% DMSO, 90% non-inactivated FBS), aliquoted (about 5 cryovials, 4.10^6 cells / cryovial), and frozen with gradually decreasing temperatures (1 °C/min) to − 80 °C before long-term storage at -150 °C in the Biological Resource Center 'TCBN'.

Tumor samples

Tumor specimen will be cut into 1–3 mm^3 pieces. Depending on the quantity of tumor, different procedures will be carried out in the following order of priority: (1) one random piece will be processed for the isolation of viable cells and PDTO establishment; (2) two random pieces will be snap frozen and stored at − 80 °C for molecular analyses; (3) One random piece will be fixed in paraformaldehyde for parafin embedding and subsequent histopathological analysis and immunohistochemistry; (4) the remainder will be cryopreserved in freezing solution (10% DMSO, 90% non-inactivated FBS) for future isolation of viable cells. All tumor samples will be stored in the Biological Resource Center 'TCBN'.

Etablishment and culture of PDTO

Tumor samples will be mechanically and/or enzymatically dissociated to obtain single cells or small cell clusters. Cells will then be embedded in extracellular matrix BME-2 (Bio-Techne) and cultured in PDTO medium [Advanced DMEM (Gibco) supplemented with 100 UI/mL of penicillin and streptomycin (Gibco), 1% GlutaMAX (Gibco), 1X B27 (Gibco), 1X N2 (Gibco) 10 mM Nicotinamide (Sigma-Aldrich), 1.25 mM N-Acetyl-L-Cysteine (Sigma-Aldrich), 50 µg/mL Primocin (InvivoGen), 5 µM Y27632 (Interchim), 1ng/mL FGF-10 (PeproTech), 500 nM A-83–01 (PeproTech), 50 ng/mL EGF (PeproTech), 2 ng/ml FGF-basic (PeproTech), 1 µM SB202190 (PeproTech), 10mM HEPES (Gibco), 10nM b-Estradiol (Gibco), 10% Noggin- conditioned media (L-WRN, ATCC), 100 ng/mL Noggin (Preprotech) and 10% RSPO1-conditionned media (Cultrex HA-R-Spondin-1-Fc 293T, AmsBio).

Culture medium will be changed twice a week and PDTO passaged every 2–4 weeks in order to expand them. Once they will reach 150–200 µm in diameter, PDTO will be dissociated using TrypLE Express (Gibco) (at 37 °C for 5–15 min). PDTO lines will be considered as established as PDTO line after cell expansion over 5 successive passages and the ability to grow in culture after thawing. For each established PDTO line, samples will be flashfrozen for DNA/RNA/protein analyses and embedded in paraffin for histopathological analysis. Dissociated cells of PDTO will be cryopreserved in Recovery cell culture freezing medium (Fisher Scientific) and stored at -150 °C in the Biological Resource Center 'TCBN' for future use.

Generation of autologous T cells

PDTO specific autologous T cells will be induced according to a modifed version of the protocol described in Dijkstra et al. [27]. Briefly, PBMC will be activated with the corresponding PDTO lysate and specifc T cells clones will be isolated based on their expression of CD154 and

CD137 markers using fow cytometry sorting. Once isolated and their purity controlled, specifc T cells will be amplifed using a stimulation matrix and then cryopreserved. A quality control will be performed before cryopreservation by flow cytometry to check for reactivity against PDTO using CD107a expression and cytokines production after antigen re-stimulation.

Evaluation of the response of PDTO to treatments

Response to PARPi and chemotherapy

The evaluation of the response to treatments will be performed when PDTO have reached a diameter of 100 µm. PDTO will be collected, resuspended in 2% BME-2 in PDTO treatment medium (PDTO culture medium lacking N-Acetylcysteine, Y-27632 and primocin) and then platted in white and clear bottom 96-well plates previously coated with a 1:1 volume mix of PDTO treatment medium with extracellular matrix. For evaluation of the response to chemotherapy or PARP inhibitors, drugs will be prepared in 2% extracellular matrix/PDTO treatment medium and added 1 h after PDTO have been seeded. At the end of the treatment, PDTO response will be assessed using CellTiter-Glo 3D cell viability assay (Promega) according to the manufacturer's instruction and luminescence will be measured using GloMax Discover GM3000 (Promega) with the associated software. Results will be normalized to the control condition. IC50 and Area Under the Curve (AUC) will be calculated using GraphPad software.

Response to immunotherapy

Once produced and checked for antigen specifcity, PDTO specific T cells will be cocultured with PDTO to produce iPDTO for the evaluation of response to immunotherapy. The viability of each cell type (T cells and tumor cells) will be followed using real time microscopy (Incucyte S3, Sartorius and Celldiscoverer 7, Zeiss) thanks to fluorescent labelling prior to the coculture and the addition of a viability dye (e.g. propidium iodide) in the culture media. Image segmentation and quantification will be employed at regular time point all along the coculture to precisely evaluate a serie of parameters (e.g. PDTO size, shape, number and propidium iodide intensity). A condition containing an MHC-I blocking antibody will be added to control for antigen specific killing. The treatment response of the iPDTO will be finally compared to the clinical response (Progression Free Survival/Disease Free Survival/Overall Survivall) of the patient from whom they are derived in order to validate the predictive value of this model for EC.

Evaluation of PDTO model relevance and identification of potential predictive biomarkers

Transcriptomic analysis

RNA analysis will be performed according to the protocol described by Perréard et al. [24]. Briefly, total RNA will be extracted using the Nucleospin RNA kit (Macherey Nagel, Hoerdt) and libraries will be made with the QuantSeq 3'RNA Library Kit. Once produced, the final library will be purified and deposed on High sensitivity DNA chip to be controlled on Agilent bioanalyzer 2100 and sequenced on NovaSeq 6000 (Illumina). Elimination of poor-quality regions and poly(A) of reads will be done through the use of the fastp program. Read alignments will be performed using the program STAR with the human genome reference (GRCh38) and the Ensembl reference gene annotations. Reads counts will be obtained using FeatureCount and statistical analysis will be realized with the R/bioconductor package DESeq2.

Copy number variation (CNV) analysis by low-pass whole genome sequencing (WGS).

WGS will be performed using Illumina DNA PCR Free prep kit, starting with 500ng of DNA. Data will be analyzed with HMMcopy, and and ichorCNA and further analyzed with R/Bioconductor packages.

Transcriptome and CNV analyses

Analysis of intr-reproducibility and differences between original tumors and PDTO will be assessed by principal component analysis and unsupervised hierarchical clustering as described in Perréard et al. [24]

The molecular signatures will be identified using the NMF method (Non-negative Matrix Factorization) combining tumor samples et associated PDTO. Then, the enrichment of top-genes from previously detected signatures will enable potential connections with responses to be identified.

HR status

The status of homologous recombination will be tested using the GIScar genomic instability score developed by Leman et al. [10] GISCAR was developed through targeted sequencing of a 127-gene panel to determine HRD status. GIScar is a valuable diagnostic tool, reliably detecting HRD and predicting sensitivity to olaparib for ovarian cancer and it will be optimized for EC.

Statistical consideration

Sample size determination

According to the literature [18, 23] and preliminary data, the rate of tumor samples with PDTO established and available for treatment testing is around 100%. In order to estimate the rate of ex vivo tumor samples usable for ex vivo models with a 95% confidence interval of 30% width,

and assuming this rate to be around 90%, it is necessary to collect 16 tumor samples. We therefore plan to include 16 patients in this pilot study.

Statistical analyses

General considerations: Qualitative variables will be described using the frequencies and percentages, while quantitative variables will be described using the mean (+/- standard deviation) or the median and when data are not normally distributed. The statistical significance threshold is set at 5% for each statistical analysis and confidence interval.

To meet the main objective, the rate of ex vivo tumor samples thant can be used for predictive tests of response to treatment will be estimated with its 95% confidence interval. To identify factors favoring a successful technique a descriptive analysis of the size of the sample and culture conditions will be carried out according relation to the success or failure of PDTO establishment.

The response to treatment observed ex vivo will be correlated with the clinical response by calculating the disagreement rate, as well as the kappa concordance coefficient. The predictive nature of the ex vivo response on clinical response will be assessed using a sensitivity and specificity analysis.

Data management

Medical data management will be performed by the Data Processing Centre (DPC) of the Northwest Canceropole (Centre de Traitement des Données du Cancéropôle Nord-Ouest, Services Unit PLATON, Comprehensive Cancer Center François Baclesse) in charge of data management, supported by the French National Cancer Institute (INCa). The data collection will be done using an eCRF (electronic Case Report Form) and in accordance with the study protocol. After checking accuracy and completeness of the recorded data, the eCRFs will be signed by the investigator and archived by the data management center.

Discussion

There is a growing interest in PARPi for EC. Clinical trials suggest their efficacy in patient subgroups, and it is necessary to develop a companion test, such as 3D functional assay [28], that will more precisely identify the patients who will benefit from this treatment. PDTOs serve as preclinical models that closely recapitulate the morphological and genetic features of the tumors from which they originate. Numerous studies suggested that the response to treatments of PDTOs is correlated with clinical response of cancer patients [17], but the predictive potential of EC-derived PDTO has not been investigated so far. Furthermore, no study has evaluated the efficacy of PARPi in PDTOs derived from endometrial tumors.

In this pilot study, we aim to establish PDTO lines from localized EC of patients who will undergo surgical treatment. Our objective is to demonstrate the feasibility of generating PDTO from EC tissues and assessing the efficacy of treatments, including both conventional therapies such as platinum-based chemotherapy, immunotherapyy, and innovative approaches such as PARPi. Response of PDTO will be compared to the clinical response of patients to chemotherapy and to the results of companion diagnostic test GIScar. This will help to determine if PDTO could potentially serve as potent indicators of treatment response in EC patients. In the meantime, the establishment of the panel of PDTO lines from EC could be used to test new therapeutic strategies and identify associated predictive biomarkers.

If this pilot study is successful, a larger scale study will be designed to investigate the predictive value of functional assay based on PDTO from EC in clinically relevant time frames, to determine if PDTO could be used for guiding clinical decision making, especially for PARPi indication.

Abbreviations

AUC	Area under the curve
BER	Base excision repair
BRCA	Breast cancer gene
CNV	Copy number variation
dMMR	Deficient DNA mismatch repair
EC	Endometrial cancer
eCRF	Electronic case report form
FBS	Fetal bovine serum
GIScar	Genomic instability scar
HRD	Homologous recombination deficiency
HRP	Homologous recombination proficiency
LP WGS	Low pass whole genome sequencing
NGS	New genomic sequencing
PARPi	PARP inhibitor
PBMC	Peripheral blood mononuclear cells
PDTO	Patient-derived tumor Organoid
iPDTO	Immunocompetent PDTO
TILs	Tumor infiltrating lymphocytes
LST	Large scale transition
MGMC	Myriad genetic MyChoice
MSI	MicroSatellite instable
MSS	MicroSatellite stable
NGS	New genomic sequencing
NMF	Non-negative matrix factorization
NMSP	No molecular specific profile
PARPi	Poly(ADP-ribose) polymerase inhibitor
PBMC	Peripheral blood mononuclear cells
PDTO	Patient derived tumor organoid
ROC	Receiver operating characteristic
STR	Short tandem repeat
TCGA	The cancer genome Atlas
WGS	Whole genome sequencing

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Author contributions

GLG, FChe, RF, JD, LBW and FJ wrote the manuscript. GLG, FChe, FChr, RF, JD, AL, LP, LBW and FJ devised the study concept and design. FChr was responsible for overseeing the statistical section. AL, CS, GD, LL, BC, SB, LT, BD, VH, NR, LG, SMF, JFLB, ED, RR, CJ, CBF, MF, RL, LP and LC contributed to the study protocol, read and approved the final manuscript. Each author has been sufficiently involved in the work to take public responsibility for appropriate portions of the content. Figures and illustrations were designed and created by GLG and LBW. Funding was obtained by GLG.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study has received ethical approval from the « West II » ethical commitee (IDRCB: 2024-A01206-41) on July 16th, 2024. This committee is independent and not related with any affiliation of the authors. Any subsequent will of modification of the protocol would be submitted for approval from the committee. The clinical trial has been registered registered at ClinicalTrials.gov with the identifier NCT06603506 on September 19th, 2024. The study will be explained to the patients by the surgeons or the medical oncologists and an informed consent form will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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