Adverse event assessment in research studies involving patients with gynecologic malignancies: integrating the patient and clinician perspective

Ainhoa Madariaga Urrutia

UAB
Universitat Autònoma de Barcelona

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Directed by Stephanie Lheureux MD, PhD

& Ana Oaknin Benzaquen MD, PhD

Tutored by David Valcarcel Ferreiras MD, PhD

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ABBREVIATIONS

AE: Adverse event

AEMPS: Spanish Agency for Medicines and Medical Devices

AI: Artificial intelligence

ATR: ataxia telangiectasia and Rad3-related protein

AML: Acute myeloid leukemia

aOR: Adjusted Odds Ratio

ASCO: American Society of Clinical Oncology

AUC: Area under the curve

BRCA1/2: breast cancer susceptibility genes 1/2

CBR: Clinical benefit rate

CCNE1: Cyclin E1

CHK1: checkpoint kinase 1

CONSORT: Consolidated Standards of Reporting Trials

CRO: Contract research organization

CT: Computerised Tomography

CTCAE: Common Terminology Criteria for Adverse Events

DDR: DNA damage response

DLT: Dose limiting toxicity

EA: Efecto adverso

ECOG: Eastern Cooperative Oncology Group Performance Status scale

EMA: European Medicine Agency

EORTC: European Organisation for Research and Treatment of Cancer

ESMO: European Society of Medical Oncology

FACT-G: Functional Assessment of Chronic Illness Therapy measurement system general questionnaire

GCIG: Gynecologic Cancer InterGroup

GEICO: Spanish Group of Gynecologic Cancers

HADS: Hospital Anxiety and Depression Scale

HGSOC: High grade serous ovarian cancer

HPV: human papillomavirus

HRd: Homologous recombination deficiency

HR-QoL: Health related Quality of Life

ICH: International Conference on Harmonisation

ICI: Immune checkpoint inhibitors

irAEs: Immune related AEs

ISOQOL: International Society of Quality of Life

MBO: Malignant bowel obstruction

MBOT: My bowels on track

MDS: Myelodysplastic syndromes

MMR: Mismatch repair

MMRd: Mismatch repair deficient

MOST: Measure of Ovarian cancer Symptoms and Treatment

NCI: National Cancer Institute

NSMP: No specific molecular profile

OR: Odds Ratio

p53abn: p53 abnormal

PARP: Poly (ADP-ribose) polymerase

PD-1: Programmed cell death protein-1

PD-L1: Programmed death-ligand 1

PPV: Positive predictive value

PMMBO: Princess Margaret Malignant Bowel Obstruction scoring

PRO: Patient reported outcomes

PRO-CTCAE: Patient reported outcomes Common Terminology Criteria for Adverse Events

QoL: Quality of life

RN: Resource nurse

SEOM: Spanish Society of Medical Oncology

EORTC QLQ OV28: Ovarian cancer quality of life module of the European Organisation for Research and Treatment of Cancer

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ABSTRACT

Adverse event (AE) assessment in gynecologic oncology clinical trials is essential for understanding treatment tolerability and safety. This dissertation investigates AE reporting, clinical outcomes, patient-reported outcomes (PROs), and novel monitoring approaches in gynecologic oncology research studies. The thesis includes a compendium of four published articles and results from an additional unpublished research study.

The assessment of treatment emergent AEs in clinical trials utilizing the Common Terminology Criteria for Adverse Events (CTCAE) is performed by clinicians. The thesis explored AE reporting patterns across gynecologic oncology systemic therapy trials at an institutional level, revealing factors influencing on high-grade related AE occurrence, such as therapy type and patient age. Safety assessment utilizing CTCAE in early phase studies in paramount to assess treatment feasibility. The dissertation includes results of a phase II trial assessing niraparib with or without dostarlimab in recurrent endometrial carcinoma, showing treatment feasibility with no new safety signals.

A complementary consideration in AE assessment is the incorporation of the patient's perspective on toxicity reporting. The thesis includes results from a randomized phase II trial assessing Wee1 inhibition in ovarian cancer that analyzed the patient self-reporting of tolerability utilizing the patient reported outcomes CTCAE (PRO-CTCAE). The study revealed nuanced treatment-related symptomatic AEs, including fatigue and difficulty swallowing, potentially related to wee1 inhibition. Patients experience and perspective is also paramount when addressing non-treatment related research procedures, such as research biopsies. A prospective survey highlighted acceptance and willingness for future procedures in patients with gynecologic malignancies, with attention to psychosocial factors influencing patient experience and consent. Lastly, digital health may have a role in improving patient safety and outcomes of patients with cancer. The thesis includes results of an electronic PRO monitoring smartphone application for patients with gynecologic cancers at risk of malignant bowel obstruction, demonstrating feasibility and potential clinical utility.

In conclusion, the comprehensive research presented in the thesis contributes to enhancing AE assessment, understanding treatment outcomes, incorporating patient perspectives, and implementing innovative monitoring approaches in gynecologic oncology research studies.

RESUMEN

La evaluación de los efectos adverso (EAs) en los ensayos clínicos de oncología ginecológica es esencial para comprender la tolerabilidad y la seguridad de los tratamientos. Esta tesis investiga la notificación de EAs por los clínicos, resultados notificados por los pacientes y nuevos enfoques de monitorización continua de síntomas en estudios de investigación de oncología ginecológica. La tesis incluye un compendio de cuatro estudios de investigación publicados y resultados de un estudio no publicado.

Los clínicos a evaluación de los EAs emergentes del tratamiento en los ensayos clínicos utilizando los CTCAE. La tesis explora los patrones de notificación de EAs en ensayos de terapia sistémica a nivel institucional, revelando factores que influyen en la aparición de EAs relacionados de alto grado en ensayos de tumores ginecológicos, como el tipo de terapia y la edad de la paciente. La evaluación de la seguridad realizada por los clínicos en los ensayos clínicos tempranos es primordial para valorar la viabilidad de nuevos tratamientos. La tesis incluye resultados de un ensayo clínico fase II que evalúo el tratamiento de niraparib con o sin dostarlimab en carcinoma de endometrio recurrente. El estudio no mostró nuevos perfiles de seguridad diferentes a los reportados en otro tipo de tumores.

Una importante consideración en la evaluación de EAs es la incorporación de la perspectiva del paciente en la notificación de toxicidad. La tesis incluye resultados de un ensayo clínico fase II aleatorizado en el que se evaluó la inhibición de Wee1 en el cáncer de ovario platino resistente o refractario. En este estudio la tolerabilidad reportada por pacientes se analizó mediante los CTCAE reportados por paciente. El estudio revela longitudinalmente los matices en EAs sintomáticos potencialmente relacionados con los inhibidores de Wee1, incluyendo fatiga y disfagia, y las perspectivas de los pacientes en cuanto a tolerabilidad. La experiencia y la perspectiva de los pacientes también deben incorporarse a los procedimientos de investigación no relacionados con el tratamiento, como las biopsias de investigación. La tesis reporta resultados de un estudio prospectivo que recoge la experiencia de los pacientes con tumores ginecológicos con las biopsias de investigación. Los resultados destacan la aceptación y la disposición para futuros procedimientos, con atención a los factores psicosociales que influyen

en la experiencia y el consentimiento a futuras biopsias. Por último, la salud digital puede tener un papel en la mejora de la seguridad de pacientes con tumores ginecológicos. La tesis reporta los resultados de una aplicación de móvil para monitorización electrónica de pacientes con cánceres ginecológicos en riesgo de obstrucción intestinal maligna, demostrando su viabilidad y potencial utilidad clínica.

En conclusión, la investigación exhaustiva presentada en la tesis contribuye a mejorar la evaluación de EAs y aporta una mejor comprensión de los resultados y toxicidad asociada a nuevos tratamientos, incorporando las perspectivas de las pacientes y los clínicos.

1- INTRODUCTION

1.1. Gynecologic malignancies and drug development

Gynecologic cancers refer to any tumour that originates in the female reproductive system, including the ovaries/fallopian tubes, uterus, cervix, vagina, and vulva. Collectively gynecologic cancers are among the most prevalent cancers in women worldwide (Figure 1).[1]

Cervical cancer is the leading cause of gynecologic cancer death around the world, being high-risk human papilloma virus (HPV) subtypes the principal cause of the disease.[2] Advances in screening and vaccination programs have significantly decrease its incidence, mainly in high-income countries.[2] Yet, in patients with metastatic or recurrent disease, outcomes remain poor. Recently, contemporary therapeutic advances with the incorporation of antiangiogenics, immune check-point inhibitors and antibody drug conjugates have shown improvements in overall survival.[3]

Ovarian cancer is the second most common cause of gynecologic cancer death worldwide.[1] Risk factors include germline mutations in breast cancer susceptibility genes (*BRCA1/2*), Lynch syndrome, nulliparity, infertility, endometriosis, obesity and older age.[4,5] The treatment landscape of advanced ovarian carcinoma often includes debulking surgery with the aim of no residual disease, platinum-based chemotherapy, and maintenance treatment strategies with poly (ADP-ribose) polymerase (PARP) inhibitors, and/or antiangiogenics.[5] Recurrent disease is associated with a high mortality from this malignancy, with median overall survival of approximately 12-months in the platinum resistant setting.[6]

Endometrial cancer is the leading cause of gynaecological cancer in high income countries, being one of the few tumours with a rising incidence.[7] Risk factors for the development of this tumour include obesity, nulliparity and Lynch syndrome, among others.[7,8] Most endometrial cancers are diagnosed at early stage with a good prognosis after surgery.[8] Advances in the understanding of the molecular classification and the biological heterogeneity of the different endometrial cancer subtypes have paved the way to personalized treatment strategies both in early and advanced stages.[8,9] Contemporary therapeutic developments in the advanced or recurrent setting include

incorporation of immune-checkpoint inhibitors and targeted therapies, often tailored by the molecular classification of the disease.[9]

Vulvar and vaginal cancers are considered rare tumours.[10,11] The presence of HPV infection is one of the risk factors to develop these tumours. Treatment landscape of these tumours may include surgery, radiation, and chemotherapy. [10,11] The thesis will not focus on these pathologies given that clinical research is scarce.

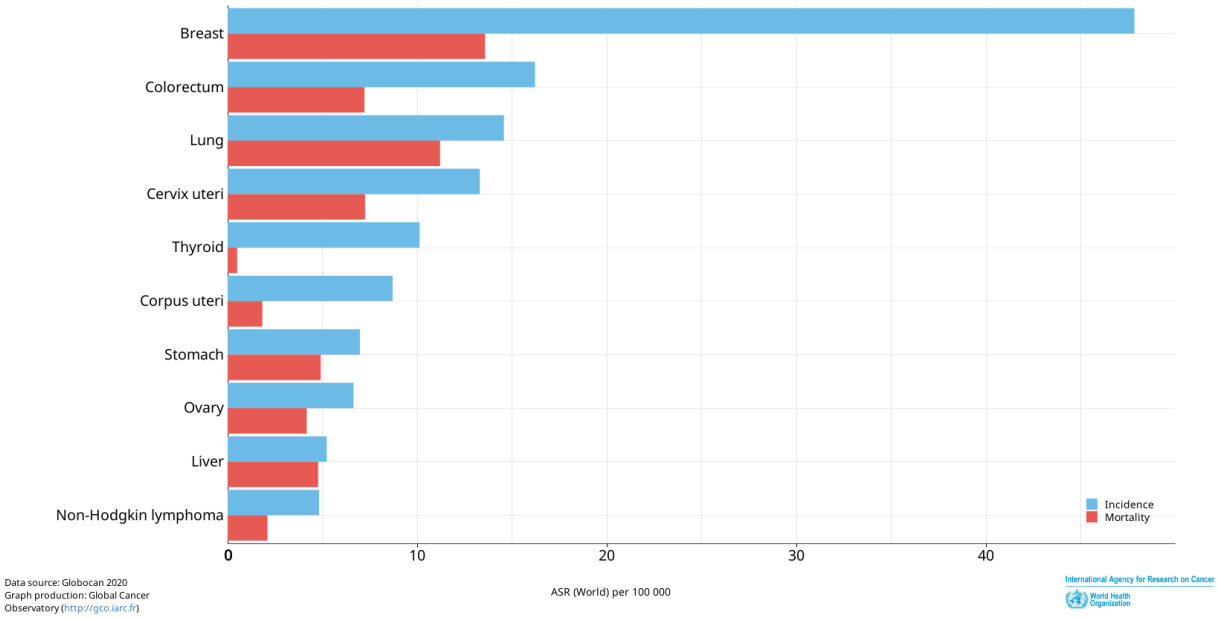

Figure 1. Estimated age-standardized incidence and mortality rates in 2020 in females in the world, excluding non-melanoma skin cancer.[1]

As previously described, each type of gynecologic cancer has distinct biology, histology subtypes, risk factors, and treatment approaches.[2,5,8] Globally, the advances in understanding the molecular and genetic basis of these tumours have led to novel therapeutics and personalized treatment approaches. The goal of drug development in this context is to identify and create effective medications that can target specific molecular and genetic pathways involved in the development and progression of gynecologic malignancies.

Clinical trials assessing cutting-edge therapeutics including targeted therapy, immunotherapy, antibody-drug conjugates, and antiangiogenics, among others, have yield access to treatment strategies that have positively impacted in patients' outcomes.[12] A systematic overview of the

European Medicine Agency (EMA) oncology drugs from 2015 to 2020 showed 11 new drug approvals in the gynecologic oncology landscape, mainly driven by DNA damage repair agents for ovarian carcinoma (see section 2.1.1).[13] More recently, immune check-point inhibitors have been granted approval both in endometrial and cervical carcinoma (see section 2.1.2).[3,9] While contemporary therapies and combinations emerge, challenges on patient monitoring, optimal adverse event (AE) assessment, reporting and management need to be accounted to ensure patient safety and to maintain their quality of life (QoL). Multidisciplinary collaborations remain one of the pillars to address patients needs in this setting, when these therapeutics are often administered continuously for months or years.

1.1.1 DNA damage repair therapeutics in gynecologic malignancies

DNA damage repair therapeutics are drugs that target the DNA damage response (DDR) pathway.[14] DDR is a complex network of cellular processes that detect and repair DNA damage caused by endogenous and exogenous factors such as radiation, chemicals, and oxidative stress.[14] The DDR pathway is essential to maintain the genomic stability and prevent mutation accumulation. Drugs targeting DDR inhibitors are promising in the gynecologic oncology landscape, given that they are able to selectively target cancer cells with defects in DNA repair pathways, that could lead to synthetic lethality.[14]

Alterations in DNA repair pathways are common in certain gynecologic cancers. High grade serous ovarian cancers (HGSOC), the most common histologic subtype of ovarian carcinoma, have ubiquitously alterations in DNA repair pathways (acquired and/or inherited).[4] Alterations in *BRCA1* (mutations in 12%, DNA hypermethylation in 11%) and *BRCA2* (mutations in 11%) and other homologous recombination DNA repair alterations are common, with approximately half of HGSOC cases exhibiting homologous recombination deficiency (HRd).[4] In addition, the presence of alterations in *TP53* are nearly universal. This gene is also known as the "guardian" of the genome, and is involved in DNA repair, cell cycle, and apoptosis of irreparable DNA damage.[4] Other gynecologic malignancies, such as serous endometrial carcinoma, have intrinsic genomic characteristics and disrupted cell cycle regulation.[15] Serous endometrial carcinomas have

frequent *TP53* mutations (> 90%) and cell cycle dysregulations due to alterations in cyclin E1 (*CCNE1;* 26%), among others.[15]

The most widely studied DDR agents are PARP inhibitors.[5] The standard treatment of advanced ovarian cancer consisted on surgical debulking and platinum-taxane combination therapy, with or without the addition of a continuation-maintenance of bevacizumab (antiangiogenic).[4] More recently, PARP inhibitors have been approved as a switch-maintenance strategy, which involves the start of the PARP inhibitor after response to platinum-based chemotherapy. Three PARP inhibitors hold approvals in different settings as maintenance: olaparib (in monotherapy or in combination with bevacizumab), niraparib and rucaparib (both in monotherapy).[5] In general, the use of PARP inhibitor have shown prolonged disease-free or progression-free survival, although the magnitude of benefit varies widely among subgroups (higher in *BRCA1/2* mutation carriers and HRd tumours).[5]

The front-line PARP inhibitor maintenance study designs incorporated a treatment duration of two or three years, which could be prolonged in the case of persistent disease.[5] As a result, many patients are being treated with PARP inhibitors for prolonged periods of time, which warrants an optimal management of AEs to ensure that patients QoL is maintained.[16] Some of the PARP inhibitor emergent AEs are class effects, meaning that all the drugs of the PARP inhibitor family are associated with these specific AEs. These include fatigue, nausea and hematological toxicity.[16] In addition, there are specific drug-to-drug differences, including non-class effect AEs, and differences in frequency of class-effect toxicities that are important to recognize at the time of counselling patients. Other rare but potentially fatal AEs have been reported, such as secondary malignancies. Myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) have been related to PARP inhibitor treatment, with an estimated incidence of ~1%.[16] A meta-analysis that included 28 randomized controlled trials demonstrated a significant increase in the risk of MDS/AML in those treated with PARP inhibitors compared with placebo (OR 2.63 [95% CI 1.13-6.14], p=0.026).[16]

Other DDR targeting agents that are currently under investigation include Wee1 inhibitors, ataxia telangiectasia and Rad3-related protein (ATR) inhibitors, checkpoint kinase 1 (CHK1) inhibitors,

among others.[15,17,18] These drugs have shown promising results in preclinical studies and early phase clinical trials in ovarian cancer.

Endometrial cancer clinical trials are assessing the role of PARP inhibition maintenance in the frontline setting in combination immune checkpoint inhibitors (ICI).[19] Other DDR agents, such as Wee1 inhibitors have shown a signal of activity in the recurrent setting.[15]

1.1.2 Immune check-point inhibition in gynecologic malignancies

Immune checkpoint inhibitors have emerged as a novel therapeutic paradigm in the treatment of cervical and endometrial carcinomas, both in the front-line and recurrent settings.[3] ICIs work by removing inhibitory signals of T-cell activation, and enabling tumour-reactive T cells to overcome regulatory mechanisms and increase the antitumor response.[20]

Endometrial carcinoma is a biologically diverse disease that is divided into four distinct prognostic categories: *POLE* mutated, mismatch repair deficient (MMRd), p53 abnormal (p53abn) and no specific molecular profile (NSMP).[21] Among these, MMRd and *POLE* have been described as biomarkers of response to ICI. In the recurrent setting, results from the early phase KEYNOTE-158 (NCT02628067) and GARNET (NCT02715284) trials assessing programmed cell death protein-1 (PD-1) inhibitors pembrolizumab and dostarlimab, respectively, demonstrated the strong activity of ICI monotherapy in patients with advanced or recurrent MMRd endometrial cancer, following progression to front-line treatment.[22,23] Yet, ICI monotherapy showed modest results in mistmach repair (MMR) proficient tumours.[22] In the setting of absence of MMRd, additional combinations may be required to enhance anti-tumour immune response. The KEYNOTE-775 (NCT03517449) trial, a phase III randomized study assessing the role of pembrolizumab and lenvatinib (tyrosine kinase inhibitor) vs single agent chemotherapy, led to an improvement of progression-free and overall survival favoring the immunotherapy combination arm, which was irrespective of MMR status.[24] The therapeutic advances with ICI are moving forward to the front-line therapy setting. The NRG-GY018 (NCT03914612) and RUBY (NCT03981796) phase III randomized trials assessed the role of PD-1 inhibitor pembrolizumab and dostarlimab, respectively, in combination with chemotherapy followed by a maintenance.[25,26] The studies demonstrated improved outcomes with the addition of PD-1 inhibitor, which were more

substantial in the MMRd subgroup.[25,26] The addition of PARP inhibition as a maintenance strategy along with the ICI has been explored in randomized phase III trials.[19]

The development of ICI in cervical cancer has a strong biological rationale, as it is a virally driven tumor, with high lymphocyte infiltration, and programmed death-ligand 1 (PD-L1) expression.[3] Treatment with ICI has transformed the treatment landscape of cervical cancer, both in the post-platinum and front-line settings. Two pivotal phase III trials in the frontline persistent, recurrent, or metastatic cervical cancer setting, KEYNOTE-826 (NCT03635567) and BEATcc (NCT03556839), demonstrated significant overall survival improvements with pembrolizumab and atezolizumab throughout maintenance, respectively.[27,28] In the post front-line platinum setting, the EMPOWER-Cervical 1 (NCT03257267) clinical trial demonstrated that cemiplimab yield to a significant improvement in overall and progression-free survival, compared to single agent chemotherapy.[29]

These novel therapeutic advances are associated with AEs that need careful recognition and management in clinical practice. Disinhibition of T-cell function by ICIs can lead to inflammatory side effects and immune related AEs (irAEs).[30] Toxicity can affect nearly any organ system, and multiple presentations of rare but severe irAEs have been reported, highlighting the importance of careful monitoring and multidisciplinary collaboration.[30] The incidence of irAEs can vary according to the drug and setting, and it is estimated to be 65% in anti-PD-1/PD-L1 monotherapy studies, being these mostly low grade events.[30] In addition, treatment combinations with additional agents may increase the AE frequency and severity. As an example, the KEYNOTE-775 trial (NCT03517449) assessing pembrolizumab and lenvatinib in recurrent endometrial carcinoma, reported grade ≥3 AEs in 88.9% of participants.[24] In contrast, the KEYNOTE-158 clinical trial (NCT02628067) assessing pembrolizumab monotherapy in MMRd endometrial carcinoma, reported 14.6% of grade ≥3 AEs.[31] Similarly, in the GARNET phase I clinical trial (NCT02715284) assessing dostarlimab monotherapy in endometrial cancer, grade ≥3 treatment related AEs occurred in 17.6% and 20.5% of patients with MMRd and MMR proficient tumours, respectively.[22]

1.2 Adverse event assessment and reporting in oncology clinical trials: stakeholders

Patient safety is of paramount importance and reporting accurate, objective AEs on clinical trials is critical. Variations on AE reporting may occur according to the phase of the trial.[32] Phase I trials typically evaluate the drug's safety and optimal dosing in a small number of patients. The AE reporting in phase I trials includes acute toxicity monitoring and early emergent toxicity signs. In contrast, phase III trials include a larger population of patients that is usually more representative of the target population of the new intervention.[33] AE reporting in phase III trials includes capturing treatment-related and treatment-emergent AEs, serious AEs, and long-term safety. Phase III trials usually provide more information on rare AEs, and toxicity that occurs after treatment discontinuation, including secondary malignancies.

In Spain, the Royal Decree 1090/2015 regulates clinical trials with medical products.[34] The regulation requires that all suspected unexpected serious AEs are reported to the Spanish Agency for Medicines and Medical Devices (AEMPS) and the relevant Ethics Committee for investigation.[34] Other stakeholders involved in the process of clinical trial AE reporting include investigators, institutions, sponsors, contract research organizations (CROs), and data safety monitoring boards.[35] Investigators are responsible for reporting AEs to the sponsor and Ethics Committee, while sponsors are responsible for reporting AEs to regulatory authorities.[35] CROs are responsible for managing the clinical trial on behalf of the sponsor, while data safety monitoring boards are responsible for monitoring the safety of the trial.[35]

Institutions provide the overarching framework, policies, and reporting systems of AEs in clinical trials.[36] Regulatory documents, study protocols, and standard operating procedures of the institution are needed to allow clinicians the optimal way of identifying, documenting, and reporting AEs. The International Conference on Harmonisation (ICH) E6 guideline, titled "Good Clinical Practice" provides a guidance on safety reporting.[36] Institutions maintain clinical trial AE reporting systems and databases to collect, track and manage the information. Data may be stored in electronic data capture systems from the clinical trials, global institutional trial databases, and health information systems (several may apply). Certain institutions collect AEs from different clinical trials in local datasets, allowing for global analysis of results, trends in AE

occurrence and severity to improve patient safety. As an example, the US National Cancer Institute (NCI) database includes AEs from all phase 1 trials conducted by the NCI investigators since 1995, allowing a coordinated analyses of reports.[37]

There is an increased interest in leveraging novel technology in pharmacovigilance and safety monitoring to improve drug safety monitoring. Automated AE detection and predictive analytics in electronic health records and AE databases using artificial intelligence (AI) algorithms are increasingly being explored.[38] Novel technologies in this setting, including smartphone health applications and wearable devices, have also been used to detect and predict toxicity patterns in oncology.[39-41] Studies assessing these technology innovations in the gynecologic oncology landscape are scarce.

1.3 Adverse event assessment and reporting in gynecologic oncology clinical trials: clinicians' role

Adverse event reporting by clinicians has been standardized with the use of Common Terminology Criteria for Adverse Events (CTCAE), which provides a framework to objectively measure and document toxicities.[42] Safety reporting in clinical trials usually reports the percentage of patients who experience an AEs by grade at least once over the course of their treatment in the clinical trial. The CTCAE grading includes laboratory based AEs (for example neutropenia, elevated transaminases) that are reported according to the laboratory tests, clinical measurement based toxicities (for example hypertension), and symptomatic toxicities, such as fatigue, pain and nausea.[43] The CTCAE have been updated several times, being the most recent version 5.0 (published in 2017).[42]

Limitations have been described to the traditional CTCAE maximum grade approach, including:

1) Complexity of CTCAE reporting system across versions: The CTCAE expanded from 9 categories and 49 AEs in version 1.0 to 947 AEs organized in 28 different categories in version 5.0.[42,44] These updates have been made to enhance the utility and relevance of CTCAE in the context of an expanding scope of clinical trials, as new AEs may be identified or existing ones may be better characterized. In addition, the new versions of CTCAE

include rare or less common AEs, which also provides a more comprehensive framework. As an example, in the field of gynecologic oncology drug development, the incorporation of certain antibody drug conjugates with ocular toxicity have challenged the comprehensiveness of CTCAE version 5.0 to measure ocular AEs for decision making.[45] In some instances toxicity assessment and grading using additional non-CTCAE assessments needs to be considered to improve accuracy.

2) Subjectivity of CTCAE assessment: Fairchild and colleagues assessed the inter-rater reliability of CTCAE version 5.0 measures through a multi-reviewer toxicity identification.[46] In the study, two reviewers independently evaluated 100 clinical notes from patients with weekly assessments while they were receiving radiation therapy, and discrepancies were evaluated by a third reviewer. Disagreements in symptom identification was detected in 93% of the notes, with significant discrepancies in inter-rated reliability. Another study by Atkinson and colleagues performed a retrospective reliability analysis on the AE assessment utilizing CTCAE by two clinicians in 393 patients with cancer (36% gynecologic malignancies).[43] The levels of agreement were moderate, with significant differences detected in the grading of the AEs. A two-point grading discordance was detected in 18% of cases for constipation, 15% for vomiting, and > 5% of the time for nausea, dyspnea, and fatigue. These discrepancies are concerning, given that these differences in grading may result in meaningful treatment dose reductions, discontinuations and dose determinations in clinical trial and usual care practice.
3) Absence of time parameters at the time of disclosing the results: AE duration, toxicity load over time and impact of low-grade long-lasting AEs is often missing in the drug labels and main clinical trial AE table publications. The contemporary therapeutic landscape in gynecologic oncology is constantly evolving and novel agents with diverse toxicities are being incorporated into clinical practice. Many of these new therapeutics are administered for a long-term, rather than a pre-stablished number of cycles. The different toxicity profile of these treatments may include a later onset of AEs, sometimes outside of the dose-limiting toxicity period, low-grade but long-term symptomatic AEs and toxicities emerging at the time of subsequent therapies, including secondary malignancies. These warrant the

incorporation of longitudinal time-related assessment of AEs and a longer safety assessment period.[47-49] Several approached have been used to overcome these limitations, such as assessment of "AE load" and the "toxicity over time" analysis that include assessment of the area under the curve (AUC), repeated measures models that describe the changes in AEs over each time period, and time-to-event analyses.[50,51]

Other factors that may influence in the AE profile in oncology include specific disease characteristics, such as type of cancer, tumour location, individual patient factors including presence of certain genetic mutations and/or polymorphisms and frailty syndrome, among others. Patients with advanced gynecologic cancers may be at increased risk for certain toxicities because of the extent of peritoneal disease, presence of pelvic masses, and type of prior therapies (surgery, radiation, chemotherapy, antiangiogenics, others).[37,52-54] As an example, the PI3K inhibitor BKM120 stablished an acceptable safety profile at its maximum tolerated dose in a phase 1 trial. A subsequent phase II trial in advanced or recurrent endometrial carcinoma was prematurely discontinued due to toxicity.[55] The safety profile of BKM120 differed according to clinical trial phase, primary tumour site and even according to histology. Another relevant example is cervical cancer, where rates of fistulisation are higher in studies involving antiangiogenics and tyrosine kinase inhibitors.[56] In this setting, a retrospective analysis of the NCI phase 1 database assessed AE reporting in 4,269 patients diagnosed with cancer.[37] The study divided the subjects in three main categories: females with gynecologic cancers (n= 685), females with non-gynecologic cancers (n=1,698) and males with cancer (n=1,886). Results showed that baseline AE characterization was similar across all subgroups. Yet, the mean number of AEs and drug related AEs reported was higher for women with gynecologic cancers, compared to women or men with other cancers in early phase trials.[37]

1.4 Adverse event assessment in gynecologic oncology clinical trials: patients' perspective

An important and often unrecorded aspect of AE reporting has been the patients' perspective, which can include a direct qualitative and quantitative self-assessment of toxicity. The patient reported outcomes (PRO) are defined as any report of the status of a patient's health condition coming directly from the patient, without interpretation of the patient's response by a clinician

or anyone else.[57] Patient reported outcome is a broad concept that in the setting of oncology may encompass: 1) QoL measures and Health related QoL (HR-QoL), 2) Symptom assessments, 3) Functional status (patient's ability to perform daily activities and functions), 4) Psychosocial distress, 5) Treatment satisfaction and adherence, 6) Survivorship and late adverse effects.

The assessment of PRO measures, which also encompass HR-QoL, is an important determinant of treatment benefit that can provide a detailed understanding of the risks and benefits of a therapeutic strategy. The HR-QoL measures provide the patients' general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.[57] Currently, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 generic questionnaire and the Functional Assessment of Chronic Illness Therapy measurement system general questionnaire (FACT-G) are the most widely used HR-QoL measures.[58,59] These can be supplemented by disease specific modules or other modules of relevance depending on the trial.

The regulatory agencies are currently requiring accurate, well defined, and validated methods to capture patients' perspective and symptomatic AEs by incorporating PROs in clinical trials.[60] In the gynecologic oncology setting, the Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup (GCIG) provided guidance on optimal reporting of PRO endpoints in epithelial ovarian cancer trials (Table 1).[61] The consensus indicated the need to standardize the choice of PRO instruments based on the study objective, needs and setting (different for first line vs recurrent, treatment vs maintenance), and highlighted this as an area that could improve consistency and cross-study comparability.[61] The consensus recommended that guidelines should endorse the International Society of Quality of Life (ISOQOL) and Consolidated Standards of Reporting Trials (CONSORT) PRO guidelines on the inclusion and reporting of PRO endpoints. One of the areas of improvement identified in the consensus was the incorporation of PRO measures as primary or co-primary endpoints in clinical trials and adequately powering the trial to assess its results, specially when progression free survival was the primary endpoint.[61] These recommendations should also apply for studies involving other gynecologic malignancies.

Context	-Patient population: What are the aims and objectives of the treatment? -Are we measuring what patients consider important?

	-Will the results impact on regulatory approval and clinical care?
Hypothesis	-What is the PRO hypothesis? -Will PROs support the primary objective? -What are the most important PRO endpoints?
Methods	-Have we selected the right instrument? -Have we defined criteria for what constitutes a clinical important difference? -Do we have a pre-defined PRO endpoint? -Is the study adequately powered for the PRO/QoL endpoint? -Do we have a statistical plan in place? -Do we have a strategy to reduce missing data (specific monitoring plan)? -How will we deal with missing data in the analysis?

Table 1. Gynecologic Cancer InterGroup (GCIG) checklist for patient reported outcomes integration in phase III clinical trials, based on the International Society of Quality of Life (ISOQOL) checklist.

An effort from the GCIG group to harmonize and measure relevant PROs in ovarian cancer is the generation of "Measure of Ovarian Symptoms and Treatment" (MOST) surveys.[53] These PRO measures assess the symptom burden and impact of chemotherapy in recurrent ovarian cancer, symptoms during surveillance, and relevant symptomatic changes over-time.

In gynecologic oncology studies PROs have been mainly incorporated as secondary endpoints.[62] A systematic review assessed QoL reporting standards and measured the adherence to the Fifth Ovarian Cancer Consensus Conference in ovarian cancer systemic therapy phase III clinical trials.[62] The study identified 35 clinical trials that included 24,664 patients, and showed that there was an increased use of PROs from 2% (1980s) to 62% (from 2010 onwards). Only one of the studies included QoL as a primary endpoint. Moreover, minimally important differences and missing data was not included in most studies.[62]

In terms of specific symptom assessment, the patient reported outcomes CTCAE (PRO-CTCAE) is a validated PRO measure that evaluates symptomatic toxicity in oncology clinical trials. It includes a 124-item library, representing 78 symptomatic toxicities from the CTCAE.[63,64] Each item can be scored depending on frequency, severity and/or interference of the symptom. The choice of PRO-

CTCAE items usually depend on the toxicity profile of the drug or intervention that is being assessed. The PRO-CTCAE provide an unbiased assessment of the anticipated AE profile of the therapies and is applicable for oncologic clinical trials where an improved description of symptomatic treatment toxicity is required for a better understanding of the tolerability of the drug.[64,65] The PRO-CTCAE data analyses enable patient self-assessment and allow for monitoring toxicities over time based on reported treatment related AEs, including low-grade but burdensome AEs.

A prospective observational study compared patient- and clinician-reported symptomatic utilizing PRO-CTCAE and CTCAE measures in phase I clinical trials at Princess Margaret Cancer Centre. Patients were surveyed with the complete PRO-CTCAE library at baseline, and at mid-cycle one and two, and the clinicians completed the CTCAE measures as usual.[32] The study included 243 evaluable patients (gynecologic malignancies 8.6%), and demonstrated that the overall patient–clinician agreement for individual symptomatic AEs ranged from poor (κ = 0.00-0.19) to moderate (κ = 0.40-0.59). [32] These discordances were driven by lack of clinician reporting. Specifically, sexual health, bodily emissions, and cognition were under-reported by clinicians. This study suggests potential clinician under-reporting in phase I clinical trials and highlights the importance of incorporating the patient's perspective for a better overview of treatment tolerability.

Incorporation and proper assessment of PROs is critical in patients receiving both clinical trial and standard of care management. Basch and colleagues performed a randomized phase III trial assessing the role of electronic monitoring of PROs compared to usual care (no PROs), in patients undergoing routine cancer treatment.[66] The study included 766 patients, and revealed that median overall survival was 31.2 months (95% CI, 24.5-39.6) in the PRO group compared to 26 months (95% CI, 22.1-30.9) in the usual care group (p=0.03). This study highlights the importance of performing and assessing PRO results in real time to improve patients' outcomes. A systematic review from our group reported that proactive assessment of PROs only occurred in <1% of prospective studies performing PROs for ovarian cancer, leaving room for improvement.[67]

A clinical scenario that requires close monitoring in patients with advanced gynecologic malignancies pertains to malignant bowel obstruction (MBO). The MBO is considered a severe complication in advanced cancer and occurs in approximately 50% of patients with advanced ovarian cancer.[68] Presence of active MBO is synonym of high symptom burden, and is an exclusion criterion for participation in most research studies assessing new systemic therapy in gynecologic malignancies.[68] In Princess Margaret Cancer Centre (tertiary cancer centre in Toronto, Canada), a pilot program performed an integrated outpatient model of care with a proactive nurse-led phone call-based monitoring system to patients with gynecologic cancers with or at risk of MBO.[69] A retrospective analysis revealed that compared to historical controls, there was a significantly shorter cumulative hospital length of stay within the first 60 days of MBO diagnosis for patients enrolled in the pro-active management MBO program, compared with the historical data (13 vs 22 days, respectively; p= 0.006).[69] Median overall survival for patients managed in the MBO program was also significantly longer compared with the historical control (243 vs 99 days, respectively; p= 0.002). The implementation of customized electronic symptom monitoring approaches in patients with or at risk of MBO has not been explored.

1.5 Adverse event assessment in gynecologic oncology clinical trials: other research procedures and measures

Patients diagnosed with cancer undergo procedures during their care which may include research biopsies, repeated bloodwork, and radiological imaging. The distress caused by these procedures can be more intangible to measure than treatment emergent AEs, and tend to be under reported.[70] One of the areas detected to cause more symptoms and phycological distress are the tumour biopsies.[70] Repeated tumour biopsies continue to be required in early phase clinical trials for molecular profiling and biomarkers assessment, despite the advances in the liquid biopsy field.[71] The impact of these procedures on the patients' QoL is not well studied.

Another relevant measure in patients undergoing oncologic therapy is the time-toxicity, which is defined as time spent in coordinating care, visits to a health care facility (including travel and wait times), assessments in the emergency department due to treatment AEs, hospitalization, and follow-up procedures.[72,73] This concept is particularly relevant in patients undergoing palliative

systemic therapy, with an expected short survival gain with the additional systemic therapy or clinical trial.[72] There is no standardization for measuring time-toxicity in clinical trials. One of the proposed approaches has been to measure the time costs as any day with physical health care system contact.[74] This includes outpatient visits (bloodwork, computerised tomography [CT] scans, biopsies, among others), emergency department visits, and overnight stays in a health care facility.[74] A proof-of-concept retrospective analysis was performed in a phase III randomized clinical trial comparing weekly cetuximab infusions and supportive care alone in recurrent colorectal cancer. The trial showed a modest overall survival improvement favouring the cetuximab arm.[74] The subsequent time-toxicity assessment revealed that home days were similar across arms, supporting the initial survival advantage results. To date, this concept has not been explored in the gynecologic oncology landscape.

2- HYPOTHESES

The primary hypothesis of the thesis is that a better understanding of AE occurrence, duration and reporting will improve outcomes and well-being of patients with gynecologic malignancies.

The secondary hypothesis are:

i) A coordinated electronic AE assessment across gynecologic oncology institutional clinical trials is feasible and can detect factors associated with higher likelihood of AE occurrence.

ii) Utilization of PRO-CTCAE is a feasible and accurate way to characterize symptomatic AEs in early phase clinical trials in gynecologic oncology.

iii) Research biopsies have a negative impact on the patient's well-being, including psychologic distress.

iv) Incorporation of patient monitoring technologies will allow early detection and intervention on disease or treatment emergent AEs.

3- OBJECTIVES

The primary objective of the thesis is to globally evaluate AE assessment and reporting in gynecologic oncology research studies.

The secondary objectives of the thesis dissertation are:

i) Describe the clinician reported adverse event assessment in gynecologic oncology clinical trials.
ii) Assess the patient self-reporting of adverse event frequency, severity and/or interference in a randomized phase II trial assessing gemcitabine in combination with adavosertib or placebo in platinum resistant ovarian cancer, utilizing the PRO-CTCAE measurement system.
iii) Describe the patient reported outcomes and experience related to research biopsies performed in patients with gynecologic cancers.
iv) Assess the feasibility of remote electronic symptom monitoring in patients with gynecologic cancers.

4- COMPENDIUM OF PUBLICATIONS

The thesis includes the results of four published articles and a methodologic consideration for unpublished results.

4.1 High grade adverse event reporting and enrolment in gynecologic oncology clinical trials

Madariaga A, Cole H, Pittman T, Grant RC, Dhani NC, Liu A, Bowering V, Sellman S, Oza AM, Lheureux S. High grade adverse event reporting and enrolment in gynecologic oncology clinical trials. Gynecol Oncol. 2024 Feb 10;185:1-7. doi: 10.1016/j.ygyno.2024.02.003

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4.2 Clinical outcome and biomarker assessments of a multi-centre phase II trial assessing niraparib with or without dostarlimab in recurrent endometrial carcinoma

Madariaga A, Garg S, Tchrakian N, Dhani NC, Jimenez W, Welch S, MacKay H, Ethier JL, Gilbert L, Li X, Rodriguez A, Chan L, Bowering V, Clarke B, Zhang T, King I, Downs G, Stockley T, Wang L, Udagani S, Oza AM, Lheureux S. Clinical outcome and biomarker assessments of a multi-centre phase II trial assessing niraparib with or without dostarlimab in recurrent endometrial carcinoma. Nat Commun. 2023 Mar 15;14(1):1452. doi: 10.1038/s41467-023-37084-w

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Clinical outcome and biomarker assessments of a multi-centre phase II trial assessing niraparib with or without dostarlimab in recurrent endometrial carcinoma

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Ainhoa Madariaga[1,2,3,4], Swati Garg[1], Nairi Tchrakian[2,5], Neesha C. Dhani[1,2], Waldo Jimenez[6], Stephen Welch[7], Helen MacKay[8], Josee-Lyne Ethier[9], Lucy Gilbert[10], Xuan Li[11], Angela Rodriguez[1], Lucy Chan[1], Valerie Bowering[1], Blaise Clarke[2,5], Tong Zhang[12,13], Ian King[12,13], Gregory Downs[12,13], Tracy Stockley[12,13], Lisa Wang[2,11], Smitha Udagani[1], Amit M. Oza[1,2] & Stephanie Lheureux[1,2]

This multi-centre, non-randomized, open-label, phase II trial (NCT03016338), assessed niraparib monotherapy (cohort 1, C1), or niraparib and dostarlimab (cohort 2, C2) in patients with recurrent serous or endometrioid endometrial carcinoma. The primary endpoint was clinical benefit rate (CBR), with ≥5/22 overall considered of interest. Secondary outcomes were safety, objective response rate (ORR), duration of response, progression free survival and overall survival. Translational research was an exploratory outcome. Potential biomarkers were evaluated in archival tissue by immunohistochemistry and next generation sequencing panel. In C1, 25 patients were enrolled, and CBR was 20% (95% CI: 9–39) with median clinical benefit duration of 5.3 months. The ORR was 4% (95% CI: 0–20). In C2, 22 patients were enrolled, and the CBR was 31.8% (95% CI: 16–53) with median clinical benefit duration of 6.8 months. The ORR was 14% (95% CI: 3–35). No new safety signals were detected. No significant association was detected between clinical benefit and IHC markers (PTEN, p53, MMR, PD-L1), or molecular profiling (*PTEN*, *TP53*, homologous recombination repair genes). In conclusion, niraparib monotherapy did not meet the efficacy threshold. Niraparib in combination with dostarlimab showed modest activity.

Endometrial carcinoma (EC) is the gynaecologic malignancy with highest incidence and remains the fourth most common cancer diagnosis in North American women[1]. The incidence of EC is rising, mainly driven by the more aggressive non-endometrioid histologies[1,2]. Treatment options in recurrent EC are limited, and response rates to single agent chemotherapy are poor. Recent therapeutic breakthroughs have included the incorporation of immune-checkpoint inhibitors (ICI) in monotherapy in mismatch repair deficient (MMRd) patients, and in combination with targeted therapy as a non-biomarker selected strategy[3].

A single-arm phase I trial assessing treatment with the PD-1 inhibitor dostarlimab (NCT02715284) demonstrated an objective response rate (ORR) of 42.3% (95% confidence interval [CI] 31–55%) in 104 women with MMRd recurrent or advanced EC previously treated with

A full list of affiliations appears at the end of the paper. e-mail: stephanie.lheureux@uhn.ca

platinum[4]. Another cohort of the same study included 142 patients with mismatch repair proficient (MMRp) tumours, showing an ORR of 13.4% (95% CI 9.3–20.1)[5]. Single agent ICI have shown modest activity in MMRp recurrent EC[6,7], and combination strategies may be needed to enhance the immune response and improve treatment outcomes.

A randomized phase III trial (NCT03517449) compared pembrolizumab and lenvatinib to single agent chemotherapy in patients with EC previously treated with platinum[8]. The study showed an increase in progression free survival (PFS; 7.2 vs 3.8 months; HR 0.56 [95% CI 0.47–0.66]) and overall survival (OS; 18.3 vs 11.4 months; HR = 0.62 [95% CI: 0.51–0.75]), favouring the pembrolizumab and lenvatinib arm[8]. Yet, the combination was associated with 89% grade ≥3 adverse events, that may require proactive medical management and patient monitoring. Cabozantinib as a single agent has shown a signal of activity in recurrent endometrioid (ORR 14%, PFS 4.8 months) and serous (ORR 12% and PFS 4.0 months) EC in a phase II trial[9], which may be enhanced when administered in combination with nivolumab (ORR 25%; PFS 5.3 months)[10].

Other potential combination therapies with ICI in EC include DNA damaging agents. Preclinical studies have shown synergy between combining a PARP inhibitor and ICI[11,12]. Combination of these agents may enhance the immunogenic cell death, alter the tumour microenvironment and/or stimulate neoantigen production, activating an antitumour immune response[12]. In terms of subgroups of patients that may benefit from DNA damaging agents, several potential biomarkers have been proposed. Endometrioid EC often show alterations in *PTEN* (up to 78%)[13]. Loss of PTEN function can cause defects in repair of DNA double-strand breaks by homologous recombination, and in preclinical studies PTEN loss has been described as a possible biomarker of response to PARP inhibitors[14,15]. In non-endometrioid histologies, homologous recombination deficiency (HRd), a biomarker of response to PARPi in ovarian cancer, has been associated with some tumours harbouring *TP53* mutations[16].

Defining the molecular vulnerabilities of recurrent EC may guide treatment strategy. Blood based biomarkers have shown the potential of capturing multiclonal heterogeneity over time in certain tumour sites. To our knowledge, the potential of ctDNA to monitor the tumour evolution and as a biomarker for treatment selection has not yet been described in EC.

In this work we assess whether the PARP inhibition approach with niraparib, or the combination of niraparib and dostarlimab, provides clinical benefit in patients with recurrent EC. Exploratory analyses include immunohistochemistry (IHC), genomic and ctDNA-based biomarker analysis, and association between a ctDNA-based genomic panel with tissue profiling[17].

Results

Forty-seven patients with recurrent EC were treated between November 2017 and January 2021 (data cut-off) in six Canadian centres (Fig. 1). Two patients in cohort 1 (C1), assessing niraparib, started therapy but were not evaluated for treatment efficacy due to development of malignant bowel obstruction on day 2 of therapy ($n = 1$) and withdrawal of consent during the first cycle ($n = 1$). At data cut-off two patients in cohort 2 (C2), assessing niraparib and dostarlimab, continued treatment. The baseline demographic characteristics of patients are shown in Table 1.

Cohort 1: niraparib monotherapy

Twenty-five patients were enrolled (Fig 1). Median age was 69 years, and 64% of patients had serous EC, being 76% of tumours platinum resistant (Table 1). The median prior lines of therapies was two (range 1–4), including chemotherapy (all patients), hormonal therapy (4 patients), and targeted therapy (2 patients).

Median number of cycles of niraparib was three (1–8). The clinical benefit rate (CBR) was 20% (5/25; 95% CI: 9–39), with a median clinical benefit duration of 5.3 months (range 1.8–7.2). The ORR was 4% (1/25; 95% confidence interval [CI] 0–20), with one patient with serous EC experiencing a partial response (Fig. 1). Considering the platinum free interval (cut-off of 6 months), the ORR was 16.7% (1/6) and 0% in platinum sensitive and resistant disease, respectively. The median PFS was 2.5 months (95% CI 1.8–3.7), and median OS was 12.5 months (95% CI 6.6–19.3) (Supplementary Fig. 1).

Adverse events that were considered to be related to therapy were mostly grade 1–2. Related grade ≥3 adverse events (AEs) occurring in ≥ 10% of patients were anaemia (24%), fatigue (16%) and thrombocytopenia (16%). Any AE occurring in ≥15% of patients is shown on Table 2. There were no grade 5 adverse events. Discontinuations due to AEs occurred in four patients (16%), and reason for discontinuation were fatigue ($n = 2$), bowel obstruction ($n = 1$) and other not specified ($n = 1$). Dose reductions of niraparib occurred in 36% of patients (8/25; one patient had three AEs as cause of dose reduction), due to haematologic toxicity ($n = 6$), followed by fatigue ($n = 2$) and/or gastrointestinal AEs ($n = 2$).

Cohort 2: niraparib and dostarlimab

Twenty-two patients were enrolled in C2 (Fig 1). Median age was 64 years, 46% had a serous histology and 68% had a platinum-resistant

Table 1 | Baseline patient characteristics

		C1 – Niraparib ($n = 25$)	C2 – Niraparib + Dostarlimab ($n = 22$)
Age	Median (range)	69 (53–80)	64.5 (38–80)
ECOG status	0	5 (20%)	2 (9%)
	1	19 (76%)	18 (82%)
	2	1 (4%)	2 (9%)
Histology	Serous	15 (60%)	9 (41%)
	Endometrioid grade 1	3 (12%)	3 (14%)
	Endometrioid grade 2	3 (12%)	2 (9%)
	Endometrioid grade 3	3 (12%)	7 (32%)
	Mixed serous and endometrioid	1 (4%)	1 (5%)
Molecular characteristics	MMR deficient	4 (16%)	3 (14%)
	p53 abnormal or overexpressed	15 (60%)	12 (55%)
	POLE mutant	0	1 (5%)
Prior Regimens	1	8 (32%)	6 (27%)
	2	9 (36%)	6 (27%)
	3	2 (8%)	5 (23%)
	4	6 (24%)	3 (14%)
	5	0	1 (5%)
	6	0	1 (5%)
Number of prior regimens	Median (range)	2 (1–4)	2 (1–6)
Prior Therapy[a]	Systemic platinum chemotherapy	25 (100%)	22 (100%)
	Radiation	18 (72%)	19 (86%)
	Surgery	21 (84%)	22 (100%)
Platinum sensitivity[b]	Platinum Resistant	19 (76%)	15 (68%)
	Platinum Sensitive	6 (24%)	7 (32%)

[a]None of the patients received prior immune-checkpoint inhibitor therapy.
[b]Platinum sensitivity was defined as per the definition utilized in ovarian cancer, based on platinum free interval time. Platinum sensitive: disease relapse occurs >6 months from last dose of platinum chemotherapy; Platinum resistant: Disease relapse occurs <6 months from last dose of platinum chemotherapy.

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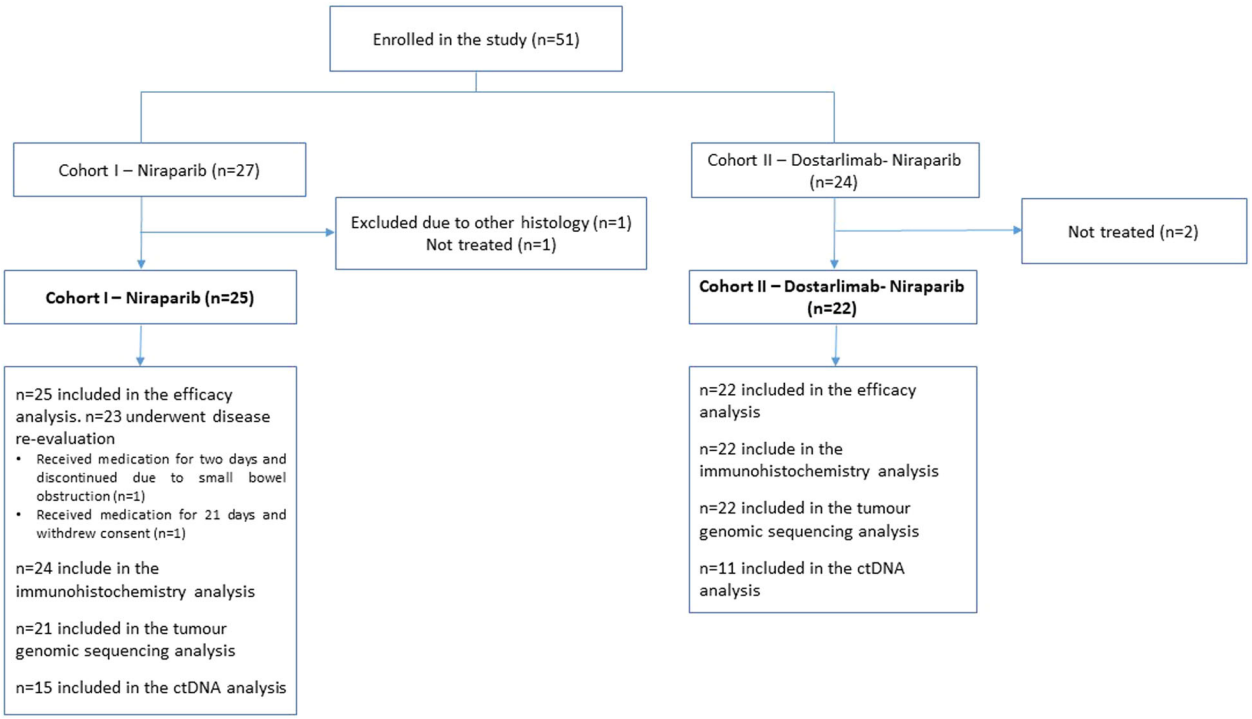

Fig. 1 | CONSORT flow diagram of patients enrolled in the study. Results are shown per cohort, including the number of patients evaluated for efficacy and translational studies.

Table 2 | Adverse events occurring in ≥15% of patients in any treatment group

	C1 – Niraparib (*n* = 25)		C2- Niraparib + Dostarlimab (*n* = 22)	
AE detail	**Grade ≥ 3**	**Total**	**Grade ≥ 3**	**Total**
Nausea	0 (0%)	14 (56%)	1 (5%)	13 (59%)
Fatigue	5 (20%)	15 (60%)	1 (5%)	11 (50%)
Dyspnoea	0 (0%)	11 (44%)	2 (9%)	13 (59%)
Anaemia	7 (28%)	12 (48%)	6 (27%)	9 (41%)
Constipation	0 (0%)	11 (44%)	0 (0%)	5 (23%)
Dizziness	0 (0%)	6 (24%)	0 (0%)	9 (41%)
Vomiting	0 (0%)	8 (32%)	0 (0%)	8 (36%)
Creatinine increased	0 (0%)	6 (24%)	0 (0%)	7 (32%)
Anorexia	0 (0%)	7 (28%)	0 (0%)	5 (23%)
Cough	0 (0%)	4 (16%)	0 (0%)	7 (32%)
Palpitations	0 (0%)	4 (16%)	0 (0%)	7 (32%)
Platelet count decrease	4 (16%)	5 (20%)	2 (9%)	6 (27%)
Diarrhoea	0 (0%)	4 (16%)	0 (0%)	5 (23%)
Abdominal pain	1 (4%)	5 (20%)	0 (0%)	4 (18%)
Insomnia	0 (0%)	5 (20%)	0 (0%)	4 (18%)
Gastroesophageal reflux	0 (0%)	2 (8%)	0 (0%)	6 (27%)
Headache	0 (0%)	6 (24%)	0 (0%)	2 (9%)
Hypertension	2 (8%)	6 (24%)	1 (5%)	2 (9%)
Neutrophil count decreased	1 (4%)	3 (12%)	3 (14%)	4 (18%)
Hyponatremia	2 (8%)	6 (24%)	0 (0%)	1 (5%)
Back pain	0 (0%)	5 (20%)	0 (0%)	2 (9%)
Bloating	0 (0%)	1 (4%)	0 (0%)	5 (23%)
White blood cell decreased	0 (0%)	4 (16%)	1 (5%)	2 (9%)
Myalgia	0 (0%)	0 (0%)	1 (5%)	5 (23%)
Hypomagnesemia	0 (0%)	4 (16%)	0 (0%)	1 (5%)

Data are represented in *n* (%). The order of the adverse events follows the total frequency in both cohorts. Generalized muscle weakness and general muscle weakness have been merged.

tumour. The median prior lines of therapies was two (range 1–6), including chemotherapy (all patients), hormonal therapy (4 patients) and targeted therapy (2 patients). Three patients had MMR deficient (MMRd) tumours (14%).

Median number of cycles was three (range 1–20). The CBR was 31.8% (7/22; 95% CI 16–53) and median clinical benefit duration was 6.8 months (95% CI 3.7–9.5). The ORR was 14% (3/22; 95% CI 3–35), with three patients experiencing a partial response (Fig. 2). Out of the three responders, one had a MMRd tumour, and one harboured a somatic *POLE* mutation. Taking into account the platinum free interval, the ORR was 14.3% (1/7) and 13.3% (2/15) in platinum sensitive and resistant disease, respectively. The ORR was 33.3% (1/3) in MMRd and 10.5% (2/19) in MMRp patients. The median PFS was 2.4 months (95% CI: 1.6–3.7), and median OS was not reached (95% CI: 5.7—not reached).

Adverse events that were considered related to therapy were mostly grade 1–2. Related grade ≥3 AEs occurring in ≥ 10% of women were anaemia (27%) and neutropenia (14%). One patient experienced an AE of special interest, grade 3 myasthenia gravis. Any AE occurring in ≥15% of women is shown on Table 2. There were no grade 5 adverse events. Discontinuation due to AEs occurred in one patient (4.5%); reason for discontinuation was myasthenia gravis ($n = 1$). Dose reductions of niraparib occurred in 45% of patients (10/22), due to haematological AEs ($n = 5$), fatigue ($n = 2$), diarrhea ($n = 1$), palpitations ($n = 1$), hypertension ($n = 1$).

Correlative studies

Correlative analyses were performed on archival tissue. Forty-six patients had sufficient tissue available and were included in the immunohistochemistry analysis (24/25 from C1 and all from C2), and forty-three in the molecular analysis (21/25 from C1 and all from C2; Fig. 1).

An overview of the immunohistochemistry and genomic findings per cohort and histology are listed in supplementary table 1. PD-L1 positivity (1% combined positive score [CPS] cut-off) was seen in 40% and 64% of samples in C1 and C2, respectively. MMR deficiency was detected in 16% and 14% of samples in C1 and C2, respectively.

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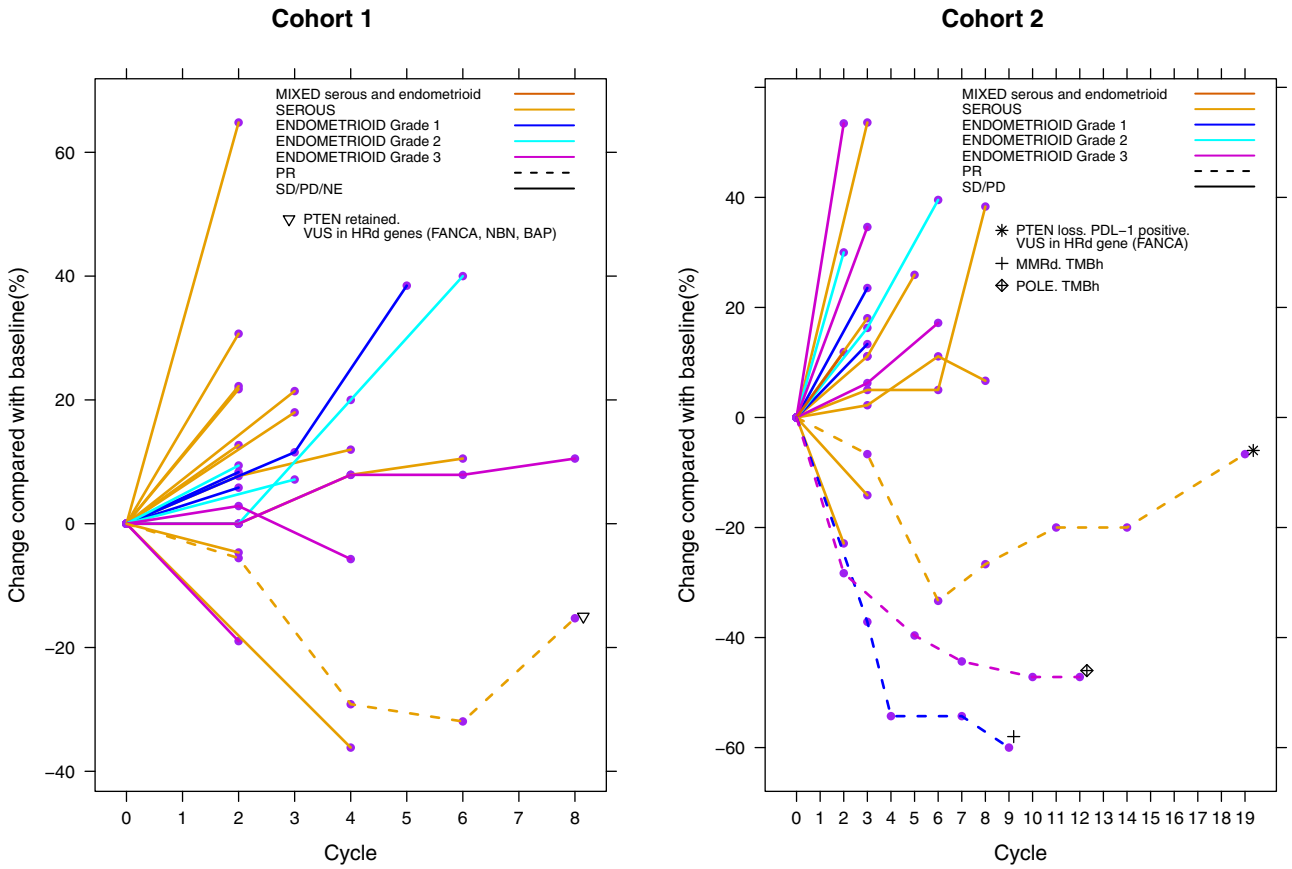

Fig. 2 | Spider plot showing the best response as per RECIST 1.1 criteria and duration of response as per histological subtype. Cohort 1 with niraparib monotherapy ($n = 23$), and Cohort 2 with niraparib and dostarlimab ($n = 22$).

PTEN loss by IHC was present in 32% and 50% of samples in C1 and C2, respectively. Based on the molecular profiling results, 33.3% (9.5% serous and 24% endometrioid) of C1, whereas 41% (35.5% endometrioid and 4.5% mixed serous and endometrioid) of cases of C2 harboured *PTEN* alterations by next generation sequencing (NGS). The presence of PTEN alterations by IHC had a sensitivity of 80% and a specificity of 75% in predicting a *PTEN* oncogenic mutation.

Abnormal p53 by IHC was seen in 56% and 55% of patients in C1 and C2, respectively. Alterations in *TP53* by NGS were detected in 76% (57% serous, 14% endometrioid and 5% mixed) of patients in C1, and 54.5% (41% serous, 9% endometrioid and 4.5% mixed) in C2. All tumours that were p53 abnormal on IHC testing also had a *TP53* genomic alteration.

Oncogenic alterations in homologous recombination repair (HRR) genes were seen in 38% and 45.4% of patients in C1 and C2, respectively, with *BRCA1/2* oncogenic variants detected in 9% in C2 and none in C1. No *BRCA1/2* reversion variants were detected. An oncogenic *POLE* variant was present in one patient in C2. No *CCNE1* amplifications were detected. Oncogenic alterations in the *PI3K* pathway genes (namely *PIK3CA, PIK3R1, PIK3R2, ATK1, AKT2* and *MTOR*) were detected in 62% and 50% of patients in C1 and C2, respectively (Fig. 3). A tumour mutation burden (TMB) score of >20% was considered high. The TMB-high cases were distributed in C1 and C2 at 19% and 23% respectively, and half of them were MMRd tumours (Fig 3).

No significant association was detected between clinical benefit and IHC markers (PTEN, p53, MMR, PDL-1), or NGS (*PTEN*, *TP53*, HRR genes, TMB-high) in C1 and C2. Similarly, none of the biomarkers had a statistically significant association with longer PFS. In C2, the median PFS was 3.6 months (95% CI 1.6-not reached) in those with PTEN loss vs 1.8 months (95% CI 0.5–3.6) in PTEN retained ($p = 0.07$). The median PFS in TMB-high was 7.4 months (95% CI 1.1-not reached) vs not high TMB 1.8 months (95% CI 1.6–3.6; $p = 0.06$).

We tested the feasibility of assessing HRR in the baseline ctDNA samples from EC using a custom NGS panel. Baseline blood sample for ctDNA analysis was available in 26 patients (C1 $n = 15$, C2 $n = 11$) and 24 of them had a matching tumour sample. Median time from tumour to blood sample collection was 2.4 years (range 0.32–8.3). Variants in the ctDNA panel were detected in 92% (24/26) of patients (Fig. 4). The detection of oncogenic *TP53, PTEN* or HRR gene variants between tumour and ctDNA was significantly associated ($p < 0.01$). Interestingly, additional variants were detected in 25% (6/24) of patients that were undetected in previous tumour testing (Fig. 4); however, 21% (5/24) of them were VUS (Supplementary Table 2). There was no association between presence of HRR oncogenic variants in the ctDNA and clinical benefit or PFS.

In four patients who had a long response to treatment (PFS > 6 months), ctDNA was collected at a second time point. The two patients from C1 (NEC11—grade 3 endometrioid carcinoma and NEC16—serous EC; Figs. 3 and 4) had ctDNA collected at the time of progression. In NEC-011, no variants were detected in both ctDNA samples (Supplementary Table 2). In patient NEC16 an *ATR* VUS (c.6793G>A; p.Val2265Ile) was detected with increasing variant allele frequency in samples collected prior to start of treatment and upon progression (VAF 1.4% vs 3.4%). There were other variants detected in HRR genes in both the samples for this patient (Supplementary Table 3), corresponding to likely germline variants as observed at VAF close to 50%. The two patients from C2 (NEC44—MMRd grade 1 endometrioid and NEC45—grade 3 endometrioid with a *POLE* variant; Figs. 3 and 4) had a second time point of ctDNA collected while on maintained response to therapy. In both cases, the variants that were seen below VAF of 20% seen in pre-treatment samples were not detected in the ctDNA sample collected while the

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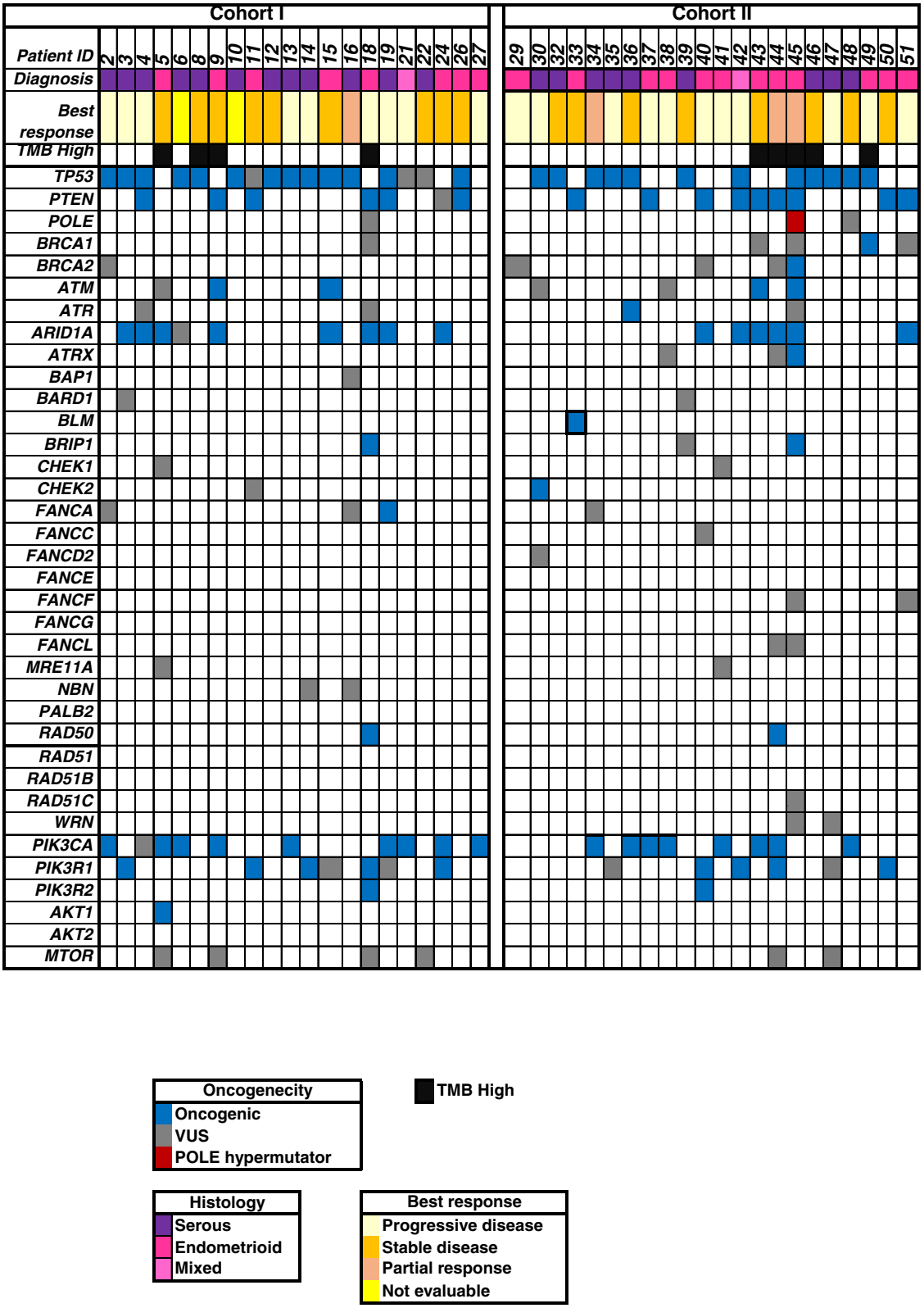

Fig. 3 | Oncoprint representing distribution of oncogenic and variants of uncertain significance (VUS) from archival tumour tissue. Cohort 1 with niraparib monotherapy ($n = 21$). Cohort 2 with niraparib and dostarlimab ($n = 22$).

patients were still responding to treatment. The only variants seen in the samples collected at response to therapy were the likely germline variants as observed at VAF close to 50% (Supplementary Table 3). No reversion *BRCA1/2* variants were detected in ctDNA samples.

Discussion

In this pilot phase II trial, patients with recurrent EC were enrolled in two consecutive cohorts. In C1, niraparib as a single agent did not meet the pre-specified efficacy criteria. The CBR and ORR observed in C2 with the combination of niraparib and dostarlimab were aligned with

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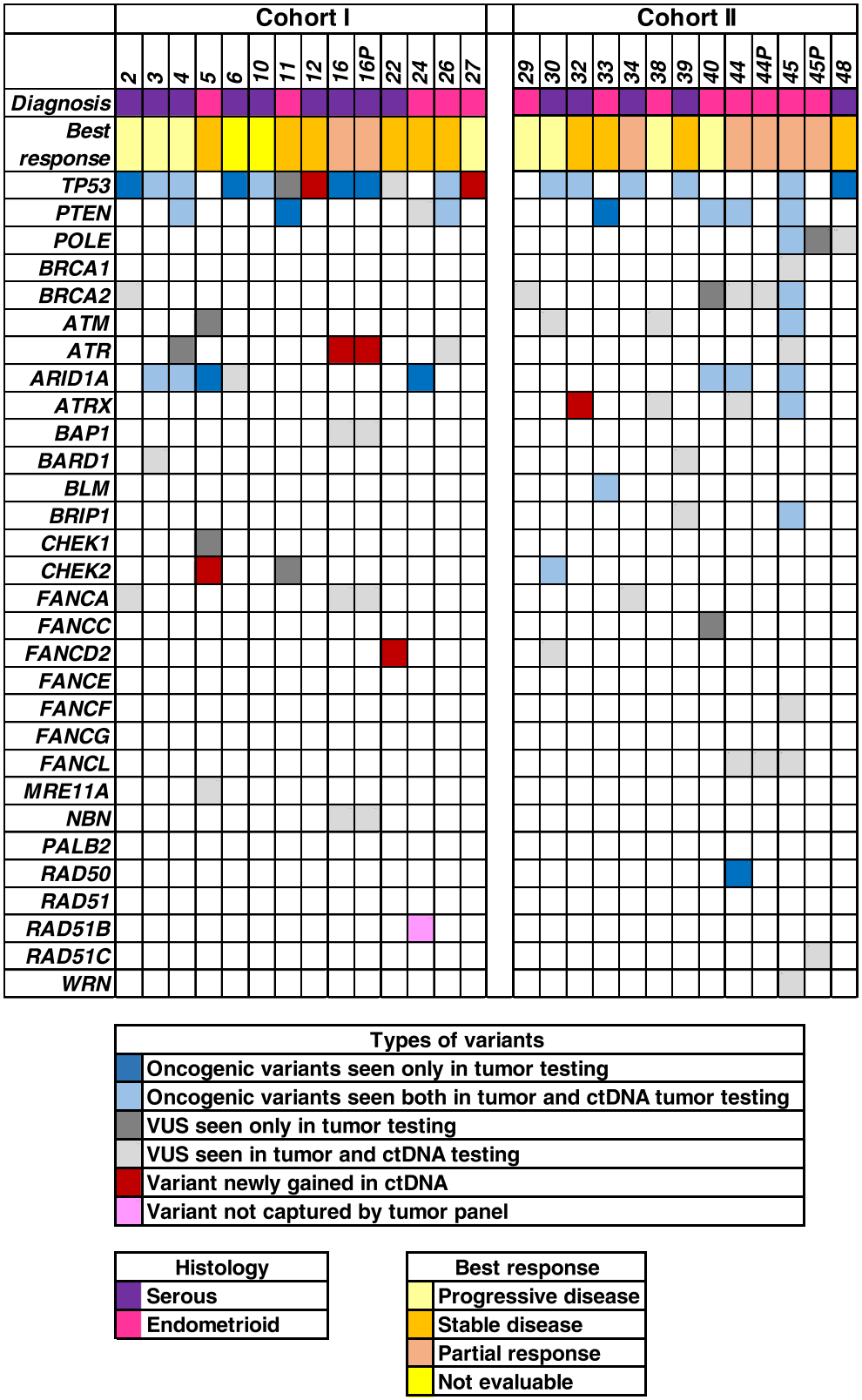

Fig. 4 | Oncoprint representing distribution of oncogenic and variants of uncertain significance (VUS) in ctDNA at baseline. Cohort 1 includes patient identifications listed as NEC-2–27 ($n = 13$), and Cohort 2 includes patient identifications listed as NEC-29–48 ($n = 11$). p: second sample.

other studies that assessed the role of ICI monotherapy in non molecularly selected EC, suggesting no synergistic activity as per the data in this study[5]. One of the limitations of the study is its heterogeneous population, in terms of histological, molecular characteristics and platinum sensitivity. In this study, a predominantly platinum-resistant population was included[18]. While platinum sensitivity is a known biomarker of response to PARP inhibition in ovarian carcinoma[18], its role in EC is not established and the platinum free interval is not clearly defined to guide treatment strategy in clinic. In the trial, only one partial response was observed in the niraparib monotherapy

cohort (C1), corresponding to a patient with platinum sensitive disease, while no response was observed in the platinum resistant. In the combination cohort (C2), partial response was observed in two patients with platinum-resistant disease and biomarkers of response to ICI (MMRd or POLE mutation, both with TMB-high), and one patient with platinum sensitive disease with no clear biomarkers of response to ICI. While numbers are too small to draw any conclusions, given the relation between PARPi and platinum sensitivity[18,19], assessing the role of PARP inhibition earlier in the EC diagnosis or prior to platinum resistance may be interesting.

PARP inhibitor maintenance therapy has changed the treatment landscape of high-grade serous ovarian carcinoma (HGSOC)[19]. The cancer genome atlas described that HGSOC and serous EC, have pathologic and molecular similarities[13]. Response to PARP inhibition in HGSOC has been determined by molecular subgroups with the presence of *BRCA1/2* mutations suggested best activity, followed by HRd, and at a lesser extent in the non-HRd subgroup[19]. The association between the presence of *BRCA1/2* mutations and response to PARP inhibition in EC is unclear, although anecdotal single patient responses have been reported[20,21]. A profiling study (NGS600 testing) showed that the frequency of alterations in HRR related genes was high in EC, compared to other cancer types, accounting for 34.4%[22]. The most frequently altered genes were *ARID1A* (27%), *ATM* (4.61%), *ATRX* (3.13%) and *BRCA2* (3.05%)[22]. Results according to histological subtype were not reported. De Jonge et al. assessed the functional HRd in EC using a RAD51 assay[16]. The study showed that 24% of all EC were HRd, which was only restricted to non-endometrioid histologies (46% of non-endometrioid carcinomas classified as HRd)[16]. In the current study, oncogenic alterations in HRR genes were detected in 24% of serous and 60% of endometrioid carcinomas, respectively (Supplementary Table 1). Amongst these alterations, oncogenic variants in *ARID1A* contributed largely. Therefore, data were reassessed after removal of *ARID1A* from the HRR gene list. Following exclusion of *ARID1A* oncogenic variants, oncogenic HRR gene variants were detected in 14.3% (3/21) of serous and 38% (8/21) of endometrioid carcinomas. No association was detected in this study between HRR gene status and clinical benefit with or without oncogenic *ARID1A* alterations. The role of alterations in HRR genes as a biomarker of response is not established in EC.

The optimal way of defining and evaluating HRd, both genotypically and phenotypically, is not well established. In HGSOC, companion diagnostics can identify patients with a 'genomic scar' that reflects an underlying genomic instability or HRd phenotype, which is considered a biomarker of response to PARP inhibition[23]. However, the HRd phenotype is dynamic over time and with treatment pressure, not reflecting potential acquired resistance mechanisms[23]. The definition of HRd genotype, beyond *BRCA1/2* variant, as biomarker of response to PARP inhibition is under investigation. Small studies have suggested the role of *RAD51C* variants and promoter methylation as a biomarker of better outcomes with PARP inhibition in HGSOC[23–25]. However, studies assessing the predictive role of non-*BRCA* HRR mutations have been inadequately powered to draw conclusions, and HRR gene selection is not well established. In the current study, the HRd phenotype through companion diagnostics was not measured, given that the study population was platinum resistant enriched and archival tissue was employed, which would have limited the interpretations of the 'genomic scarring' results. The HRR gene selection was performed based on previously defined most frequent HRR mutations across multiple tumours[22].

PTEN variant is the most common molecular-genetic event in endometrioid EC, and is rarely seen in serous subtype[13]. PTEN IHC is not widely used in routine clinical practice, in part owing to ill-defined staining interpretation criteria[26]. Although there is good agreement between PTEN IHC and *PTEN* loss of function mutation, it is not considered a surrogate[27]. In this study, a complementary interpretation algorithm has been implemented[27], whereby PTEN status is designated abnormal if detected by IHC, NGS, or both. Based on preclinical data in EC cell lines, we anticipated that tumours with alterations in PTEN, would be more likely to respond to PARP inhibition[14,15]. PTEN protein has an important role in maintaining the genomic integrity, as it upregulates the RAD51 expression levels[14,15]. It has also been proposed that PTEN loss may mediate resistance to ICI through activation of the PI3K pathway[28]. In the trial we detected PTEN loss in 29%, 45% and 60% of serous, low and high-grade endometrioid carcinomas, respectively. No association with clinical benefit were detected according to PTEN status (genomic, protein loss, or combination) in C1 or C2. There were differences in PFS in patients according to PTEN status by IHC (PTEN lost median 3.6 months [95% CI 1.6-not reached] vs PTEN retained 1.8 months [95% CI 0.5–3.6]; $p = 0.07$) in C2, which did not reach statistical significance.

The selection of patients for anti-PD-1/PD-L1 therapy may be guided by PD-L1 IHC assays. Scoring cut-offs vary according to tumour type and individual ICI agents. In EC, several studies have reported PD-L1 expression in tumour cells and tumour-associated inflammatory cells[28]. In an exploratory analysis of a phase II trial assessing durvalumab in recurrent EC, the presence of tumour-associated immune cells correlated better with outcomes than PD-L1 staining of tumour cells and immune cells[29]. In our study, no association with clinical outcomes was detected according to PD-L1 CPS status. Another biomarker that has been proposed to predict response to ICI includes the TMB[30]. Treatment with pembrolizumab as monotherapy was granted approval from the Food and Drug Administration for solid tumours with ≥10 mutations per megabase that had progressed to prior line of therapy[30]. The cut-off used to define TMB-high in this study was the top 20% mutation load within EC patients assessed, following the approach described in Samstein et al.[31]. In C2 numbers were too small to establish an association between TMB-high and response (PFS in TMB-high 7.4 months [95% CI 1.1-not reached] vs not high TMB 1.8 months [95% CI 1.6–3.6]; $p = 0.06$).

The combination of ICI and the PARP inhibitor talazoparib showed an ORR of 11.4% in a small phase II trial in MMRp recurrent EC[32]. Other combinations that have been assessed with both PARP inhibition and ICI include antiangiogenics. In this setting, a randomized phase III trial assessing pembrolizumab and lenvatinib has demonstrated improved PFS and OS in advanced EC following prior therapy, when compared to single agent chemotherapy[8]. The combination of antiangiogenics with PARP inhibition has also been assessed in a phase II trial (NCT03660826)[33]. In this three-arm randomized trial, PFS was 3.8 months for cediranib alone, 2 months for olaparib and 5.5 months for olaparib and cediranib combination[33]. However, the between-arm differences were not statistically significant. The role of triplet therapy with antiangiogenics, immune-checkpoint therapy and PARP inhibition has not yet been reported. A phase I/II study showed promising activity of the PARP inhibitor olaparib in combination with metronomic cyclophosphamide and metformin in recurrent or metastatic EC[34]. In fact, metformin may have a synergistic activity with PARP inhibition, via direct (insulin-independent) and indirect effects, through the PIK3CA-AKT-mTOR pathway[35]. Targeting the cell cycle modulation and replication stress has also a special interest in EC, particularly in the serous subtype[3]. In this setting, a small non-randomized phase II study assessing Wee1 inhibition in monotherapy with adavosertib in serous EC, showed promising clinical activity, with an ORR of 29.4% and 6-month PFS of 47.1%[3,36].

Circulating tumour DNA (ctDNA) is increasingly becoming important for disease monitoring as the tumour evolves, and potentially guiding which patients may experience a benefit from treatment. In ovarian cancer presence of *BRCA* reversion mutations in ctDNA, is a known marker of absence of benefit from the PARP inhibitor[17]. Disease evolution overtime also plays a critical role in EC, as newly acquired MMRd has been described in the recurrent setting[37]. One study

suggests that ctDNA might be used as a tool for early detection and monitoring disease recurrence in EC[38]. In this study, we aimed to test the feasibility and clinical utility of monitoring HRR gene status in the ctDNA samples of EC and guiding response towards niraparib using a targeted sequencing customized panel. Even though the median time from archival sample retrieval to ctDNA sample was 2.4 years, the results indicated a high degree of concordance in the detection of oncogenic *TP53*, *PTEN* and HRR gene variants between tumour and ctDNA. Further evaluation of the peripheral blood PBMCs would help exclude contribution from mutations arising from age related clonal hematopoiesis[39]. There was no significant association between HRR gene status in ctDNA and clinical outcome, However, our results indicate that ctDNA analysis may be feasible for biomarker selection in clinical trials (i.e. oncogenic *ARID1A* detected in 20% of blood samples), as suggested by the significant association of archival tumour mutations and ctDNA.

The role of PARP inhibition and ICI is currently being assessed earlier in the therapeutic armamentarium of EC, with several ongoing studies assessing these agents along with chemotherapy in the front-line setting, prior to the development of resistance to platinum. Ongoing studies include chemotherapy with maintenance PARP inhibition (CAN-STAMP NCT04159155, RAINBO), ICI (NCT03981796, NCT03914612,NCT04269200,NCT03603184), and both strategies (NCT03981796, NCT04269200). It will be important to determine the therapeutic selection at each time point, including the role of early administration of PARP inhibition and/or ICI therapy, and potential biomarker selection.

Methods

A multi-centre, open-label, two-stage, phase II study assessed niraparib monotherapy or in combination with dostarlimab in recurrent EC (NCT03016338). The study initially enrolled patients with recurrent EC to the niraparib monotherapy cohort (cohort 1—C1). Once C1 was completed, a sequential second cohort assessed niraparib in combination with dostarlimab (cohort 2—C2). Cross-over between cohorts was not permitted. The trial complied with all relevant ethical regulators. The protocol was approved by the Ontario Cancer, McGill University, Alberta Health Research Ethics Board, and Health Canada. All patients provided written informed consent. The study design and conduct complied with all relevant regulations regarding the use of human study participants and was conducted in accordance with the criteria set by the Declaration of Helsinki. There was no compensation for study participants. Enrollment occurred between the 17 November 2017 and 29 January 2019 in Cohort 1, and 2 October 2019 and 8 October 2020 in Cohort 2.

Patients with recurrent serous or endometrioid EC were enrolled. There was no limit on prior lines of therapy, and prior platinum-based chemotherapy was required with no limitation on timing. Previous treatment with a PARP inhibitor, or other targeted therapy directed against the homologous recombination pathway was not allowed. Enrolled patients had an Eastern Cooperative Group (ECOG) performance status of ≤2. Within 7 days of the proposed start of treatment, patients had adequate organ and marrow function (protocol in supplementary note 1). In cohort 2, prior ICI was not allowed, and participants receiving corticosteroids were eligible if the dose was stable for at least four weeks prior to initiating protocol therapy. Refer to protocol for full eligility criteria (Supplementary note 1). Mandatory archival tissue was requested for molecular profiling and blood samples were collected for ctDNA at baseline for patients (correlative studies performed as part of NCT03420118, NCT03702309 and NCT02906943 studies).

In the first cohort patients received niraparib 200 or 300 mg orally once daily, based on baseline body weight and platelet count, in a four-week cycle. In the second cohort niraparib (same dose and schedule) was given with dostarlimab 500 mg intravenously every three weeks for four cycles, followed by 1,000 mg every six weeks thereafter.

The primary endpoint of the trial was clinical benefit rate (CBR) in the intention-to-treat population, which includes complete or partial response, or stable disease ≥16 weeks. Secondary endpoints included ORR, PFS, OS, and safety and tolerability assessment. Response assessment was performed per RECIST (Response Evaluation Criteria in Solid Tumours) v1.1 every eight weeks. All patients who initiated treatment were evaluable for safety and toxicity from first treatment dose. Adverse event (AE) grading was per the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Exploratory objectives included assessment of PTEN, MMR status and PD-L1 by IHC as a predictor of response to therapy, as well as the role of genes involved in the HRR pathway, *CCNE1* amplifications and alterations in *PTEN* by NGS as biomarkers of outcome.

Correlative studies

Formalin fixed, paraffin-embedded (FFPE) sections of archival tumour tissue were used. Haematoxylin & eosin (H&E) and immunohistochemistry (IHC) stains were examined (Supplementary Fig. 2). The stains were performed on 4µm whole sections of FFPE tissue, which were processed using standard techniques. A single H&E stain was undertaken to assess routine histological features. The IHC panel comprised PD-L1, p53, PTEN, and mismatch repair (MMR) proteins MLH1, PMS2, MSH2 and MSH6. IHC staining was undertaken according to the manufacturer's instructions using the following antibodies: PD-L1 (Agilent Technologies, clone 22C3 pharmDx, 1:100), p53 (Leica, clone D0-7, 1:1000), PTEN (Cell Signaling, clone 138G6, 1:50), MLH1 (DAKO, clone ESOS, pre-dilute), PMS2 (BD Pharmigen, clone 556415, 1:200), MSH2 (BD Pharmigen, clone 556349, 1:500) and MSH6 (Abcam, clone ab92471, 1:150).

The H&E- and IHC-stained slides were assessed by a gynaecology expert pathologist blinded to clinical data. A second pathologist examined equivocal cases to reach consensus. PD-L1 expression was defined as complete or partial membrane staining in tumour cells (TC) and membranous and/or cytoplasmic staining in immune cells (IC) – namely, lymphocytes and macrophages. We determined the percentage of positive TCs and ICs in combination, using the combined positive score (CPS). CPS was derived by dividing the total number of PD-L1 positive cells (TCs and ICs) by the number of viable TCs and multiplying by 100. The cut-off value for positive PD-L1 staining was set at 1%. Normal tonsil was used as positive control. For p53, strong positive nuclear expression in >80% of TCs (overexpression pattern) and complete loss of expression in TCs with a positive non-tumour internal control (null pattern) were considered mutation-type. Wild-type (normal) expression was defined as heterogeneous weak to moderate staining. PTEN was scored as either retained (staining of similar intensity seen in TCs relative to non-tumour internal control) or complete absence (negative PTEN staining in TCs with retained expression in non-tumour internal control). MMR protein status was considered deficient (MMRd) when the tumour showed complete loss of nuclear expression in any MMR protein (MLH1, PMS2, MSH2, MSH6). Stromal cells, inflammatory cells and non-tumour epithelial cells served as internal control for MMR, similar to p53 and PTEN.

Tumour genomic profiling was conducted as part of two correlative studies (NCT03420118, NCT02906943). A multigene targeted panel spanning exonic regions of 555 cancer-related genes (UHN Hi5 Panel) at the College of American Pathologists/Clinical Laboratory Improvement Amendment (CAP/CLIA)-accredited Advanced Molecular Diagnostics Laboratory (AMDL) at Princess Margaret Cancer Centre[40]. Besides, *TP53, PTEN* we reviewed mutations in HRR pathway, *ARID1A, ATM, ATR, BAP1, BARD1, BLM, BRIP1, CHEK1/2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, POLE, RAD50, RAD51, RAD51B*, and *WRN*[20]. In addition, we reviewed mutations in genes involved in the PI3Kinase pathway- mainly, *PIK3CA, PIK3R1, PIK3R2, MTOR* and *AKT1/2*. For *CCNE1*

amplifications, copy number variants were examined in NGS data using two callers-CNVkit (version 0.7.11) and Contra (version 2.0.8)[41]. A fold change of ≥2.5 observed by both pipeline callers was considered a *CCNE1* amplification. Tumour mutational burden (TMB) was calculated as mutations per megabase, counting variants in coding regions with a depth greater than 50, and a variant allele frequency greater than 8%, while excluding driver mutations (COSMIC), technical artifacts, and variants with minor allele frequency greater than 0.001 in the gnomAD database. TMB-high was defined as falling within the top 20% mutation burden of all historic endometrial cancers.

The ctDNA analysis was performed as part of LIBERATE (NCT03702309) study. Extraction of ctDNA was performed from baseline plasma samples and analyzed using a custom designed panel. Exonic coding regions and ±20 bp of the intron for the following genes (*ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, CCNE1, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, MRE11A, NBN, PALB2, POLE, PTEN, RAD50, RAD51, RAD51B, RAD51C, RAD51D, TP53* and *WRN*) were examined using SureSelect Target Enrichment hybrid capture followed by paired-end sequencing (Illumina, California, USA). Variant calls are generated using the UHN AMDL custom bioinformatics pipeline with alignment to genome build GRCh37/hg19, and variants assessed using Alissa Interpret (Agilent, California, USA). The reportable range was 1–100% variant allele frequency, and test sensitivity >94% for detection of substitutions and small insertions/ deletions (≤25 bp).

Statistics and trial design

The trial was designed as a multicenter, non-randomized, open-label, phase II study. A Simon two-stage design was employed, with the null hypothesis that CBR, $p \leq 0.10$ versus the alternative that $p \geq 0.35$ and setting alpha = beta = 0.10. In C1 stage I, the accrual of 10 patients was planned. If at least one clinical benefit instance was observed at the end of stage I, the study would proceed to stage II with 12 additional patients to be accrued (total 22 evaluable patients). If at least five instances of clinical benefit were observed among the 22 patients, this agent would be considered worthy of further investigation. If the CBR does not reach the pre-defined level (positive ≥5/22 overall) after stage II in C1, PTEN analysis will be performed, and the study may be considered to expand to PTEN-loss subgroup. After the enrollment in C1 (niraparib alone) is completed, new patients were registered in C2 with the combination of niraparib and dostarlimab. In C2, the same criteria (≥1/10 CBR to proceed to stage II, and positive study ≥5/22 CBR overall) was used.

Patient demographics, clinical features and response details were described using summary statistics, such as medians, ranges, frequencies and proportions. Progression free survival and OS analyses were conducted using the Kaplan-Meier method by cohort.

Medians and confidence intervals were reported to assess PFS and OS. Treatment related toxicity was evaluated using frequencies and proportions of adverse events based on severities and attributions. The clinical benefit rate and 95% CI for each cohort were estimated to evaluate the efficacy of treatment. Association between clinical benefit and biomarkers was evaluated using Chi-squared test or Fisher exact test. Association between biomarkers and survival outcomes was evaluated using Cox proportional hazards models. Individual patient's changes in tumour response over time were displayed using spider plots.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The individual, de-identified genomic data are deposited in the European Genome-Phenome Archive (EGA) database at https://ega-archive.org/studies/EGAS00001007013. The data are available under restricted access, access can be obtained by contacting the corresponding author (stephanie.lheureux@uhnresearch.ca). Source data for Fig. 2, Supplementary Table 1 and Supplementary Fig. 1 are provided as a Source Data file. The study protocol, including the statistical analysis plan has been uploaded as Supplementary Note 1 in the Supplementary Information file. The remaining data are available within the Article, Supplementary Information or Source Data File. Additional de-identified clinical data will be made available upon request by contacting the corresponding author. Source data are provided with this paper.

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Author contributions

A.M.: conceptualization, methodology, data curation, formal analysis, writing – original draft, writing – review & editing. S.G.: conceptualization, methodology, data curation, formal analysis, writing – original draft, writing – review & editing. N.T.: methodology, formal analysis, writing – review & editing. N.C.D.: resources, supervision, writing – review & editing. W.J.: resources, writing – review & editing. S.A.W.: resources, writing – review & editing. H.M.: resources, writing – review & editing. J.L.E.: resources, writing – review & editing. L.G.: resources, writing – review & editing. X.L.: methodology, data curation, formal analysis, writing – review & editing. A.R.: resources, data curation, writing – review & editing. L.C.: resources, writing – review & editing. V.B.: resources, supervision, writing – review & editing. B.C.: resources, methodology, supervision, writing – review & editing. T.Z.: methodology, formal analysis, writing – review & editing. I.K.: methodology, formal analysis, writing – review & editing. G.D.: methodology, formal analysis, writing – review & editing. T.S.: resources, methodology, formal analysis, writing – review & editing. L.W.: methodology, data curation, formal analysis, writing – review & editing. S.U.: resources, supervision, writing – review & editing. A.M.O.: conceptualization, resources, supervision, writing – review & editing. S.L.: conceptualization, methodology, data curation, resources, supervision, writing – review & editing.

Competing interests

A.M. received honoraria from AstraZeneca, Clovis, GSK and PharmaMar. N.C.D. declared honoraria from AstraZeneca and Merck. W.J. received honoraria from AstraZeneca and GSK. S.W. declared honoraria from GSK, Merck, AstraZeneca. H.M. is on the advisory board for AstraZeneca, Merck, Essai and GSK. J.L.E. reported speaker fees and advisory board participation for AstraZeneca, GSK and Merck. L.G. declared consulting advisory board fees from AstraZeneca, Alkermes, Merck, Eisai, Eisai-Merck, GSK. She also declared institutional grants from Astra Zeneca, Pfizer, Merck Sharp & Dohme, Kayopharm, Alkermes, ImmunoGen Inc, Roche, Mersana, Esperas, Novocure GmbH, Oncoquest Pharmaceuticals, K-Group Beta Inc. V.B. received honoraria from AstraZeneca and had an uncompensated advisory role in AstraZeneca and GSK. T.S. received honoraria from GSK, AstraZeneca, and Merck. AMO declared uncompensated consulting or advisory role in AstraZeneca and GSK. He has uncompensated relationships with AstraZeneca and Clovis and research funding from AstraZeneca, GSK and Clovis. S.L. declared consulting fees from AstraZeneca, GSK, Merck, Eisai, Novocure, Novartis, Shattuck laboratories. Stephanie Lheureux is principal investigator or co-investigator of different clinical trials with agents from AstraZeneca, Merck, Roche, GSK, Regeneron, Repare Therapeutics, Clovis. The remaining authors declare no other competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Stephanie Lheureux.

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[1]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [2]University of Toronto, Toronto, ON, Canada. [3]Autonomous University of Barcelona, Barcelona, Spain. [4]Department of Medical Oncology, 12 de Octubre University Hospital, Madrid, Spain. [5]Department of Pathology and Laboratory Medicine, University Health Network, Toronto, ON, Canada. [6]Division of Gynecologic Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada. [7]Division of Medical Oncology and Hematology, London Health Sciences Center, London Regional Cancer Program, London, ON, Canada. [8]Division of Medical Oncology and Hematology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada. [9]Division of Medical Oncology and Hematology, Kingston Health Sciences Cancer Centre, Kingston, ON, Canada. [10]Division of Gynecologic Oncology, McGill University Health Centre, Royal Victoria Hospital, Montréal, QC, Canada. [11]Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [12]Division of Clinical Laboratory Genetics, Laboratory Medicine Program, University Health Network, Toronto, ON, Canada. [13]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada.
✉e-mail: stephanie.lheureux@uhn.ca

4.3 Patient self-reporting of tolerability using PRO-CTCAE in a randomized double-blind, placebo-controlled phase II trial comparing gemcitabine in combination with adavosertib or placebo in patients with platinum resistant or refractory epithelial ovarian carcinoma

Madariaga A, Mitchell SA, Pittman T, Wang L, Bowering V, Kavak N, Quintos J, Chang K, Ramsahai J, Karakasis K, Welch SA, Dhani NC, Lheureux S, Oza AM. Patient self-reporting of tolerability using PRO-CTCAE in a randomized double-blind, placebo-controlled phase II trial comparing gemcitabine in combination with adavosertib or placebo in patients with platinum resistant or refractory epithelial ovarian carcinoma. Gynecol Oncol. 2022 Nov;167(2):226-233. doi: 10.1016/j.ygyno.2022.08.006

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4.4 Research biopsies in patients with gynecologic cancers: patient-reported outcomes, perceptions, and preferences

Madariaga A, Bhat G, Wilson MK, Li X, Cyriac S, Bowering V, Hunt W, Gutierrez D, Bonilla L, Kasherman L, McMullen M, Wang L, Ghai S, Dhani NC, Oza AM, Lheureux S. Research biopsies in patients with gynecologic cancers: patient-reported outcomes, perceptions, and preferences. Am J Obstet Gynecol. 2021 Dec;225(6):658.e1-658.e9. doi: 10.1016/j.ajog.2021.06.071.

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4.5 Methodological Clarifications

The thesis includes results of unpublished work that addresses a secondary objective of the dissertation that requires methodological clarification. This work aims to assess feasibility of electronic monitoring systems in patients with gynecologic malignancies.

A smartphone application was designed for patients with gynecologic malignancies with an active or at risk of MBO. The study was approved by Research Ethics Board, as a sub-analysis of the Risk Stratified Multidisciplinary Ambulatory Management of Malignant Bowel Obstruction in Gynecological Cancers program (MAMBO, NCT03260647), and by the institutional Quality Improvement Committee (ID:22-0512). All participants agreed to an end user license agreement through the smartphone application that was collected along with informed consent.

Participants

Eligible patients had a histologically and/or cytologically confirmed gynecological cancer, including ovarian, fallopian tube, primary peritoneal, endometrial, or cervical cancer. Patients were deemed to be at risk of developing or have a clinical diagnosis of MBO, defined using the International Conference on MBO and Clinical Protocol Committee standardized criteria: clinical evidence of bowel obstruction (history, physical, radiological examination), and bowel obstruction beyond the ligament of Treitz.[75] Patients that did not speak English, but had support from a family member to perform the questionnaires were eligible to participate.

Candidate participants were identified in the outpatient gynecologic oncology clinic based on the clinical criteria for MBO risk (Princess Margaret Malignant Bowel Obstruction [PMMBO] criteria).[69] The PMMBO criteria were determined by assessing the patients disease characteristics and symptoms (Table 2) and applied at a risk colour coding system (Table 3) that tailors proactive assessments according to patient needs.

Clinical Criteria for MBO Risk	
Disease Factors	**Signs and Symptoms**
Previous history of MBO	No bowel movement in ≥ 2 days
Ovarian cancer	Nausea and vomiting
≥ 3 lines of chemotherapy treatment	Not passing gas
Presence of ascites	Abdominal pain
Presence of pelvic mass and/or retroperitoneal metastases	Unable to tolerate any oral intake (including fluids)

Table 2. Princess Margaret MBO (PMMBO) clinical criteria for MBO risk. MBO: Malignant bowel obstruction.

Red	Orange	Yellow	Green	Blue
-MBO diagnosis -Inpatient management -Inpatient unit clerk emails RN team about admissions & discharge -Outpatient RN books proactive call upon discharge home →Transition to orange management	-MBO diagnosis -Outpatient management -RN to provide educational materials on MBO -RN proactive call timeline: Week 1-4 weekly, based on RN assessment -If patients bowels remain active at 4 weeks →Transition to yellow management	-No MBO but at risk -Patient has ≥2 signs & symptoms of MBO -Patient has ≥3 disease factors -RN to provide educational materials on MBO -RN proactive call timeline: Week 1-4 biweekly based on RN assessment -If bowels remain active at 4 weeks →Transition to green management	-No MBO -Patient may have ≥1 signs & symptoms of MBO -Patients may have ≥3 disease factors -Patient can self-manage -Patient calls nursing triage line for symptom management of MBO →Discharged from MBO program	-No further systemic therapy options -Supported by Palliative Care Team →Discharged from MBO program

Table 3. Princess Margaret MBO (PMMBO) risk-based triage system. PMMBO Risk colour coding system. MBO: Malignant bowel obstruction. RN: resource nurse.

Smartphone application and electronic PRO questionnaires

A smartphone application called ¨My Bowels on Track¨ (MBOT) was developed by Princess Margaret Cancer Centre in conjunction with Vivify (Vivify Health®). The application included electronic PRO questionnaires, customized education resources and a secure messaging system (Figure 2). The educational material was based on existing institutional and external MBO educational materials, including dietary recommendations, Bristol stool scale, general laxative information, educational videos and clinic contact information.[68,76,77] A secure messaging tool to

contact the healthcare team was also provided within the application. The application and questionnaires were reviewed by a patient partner.

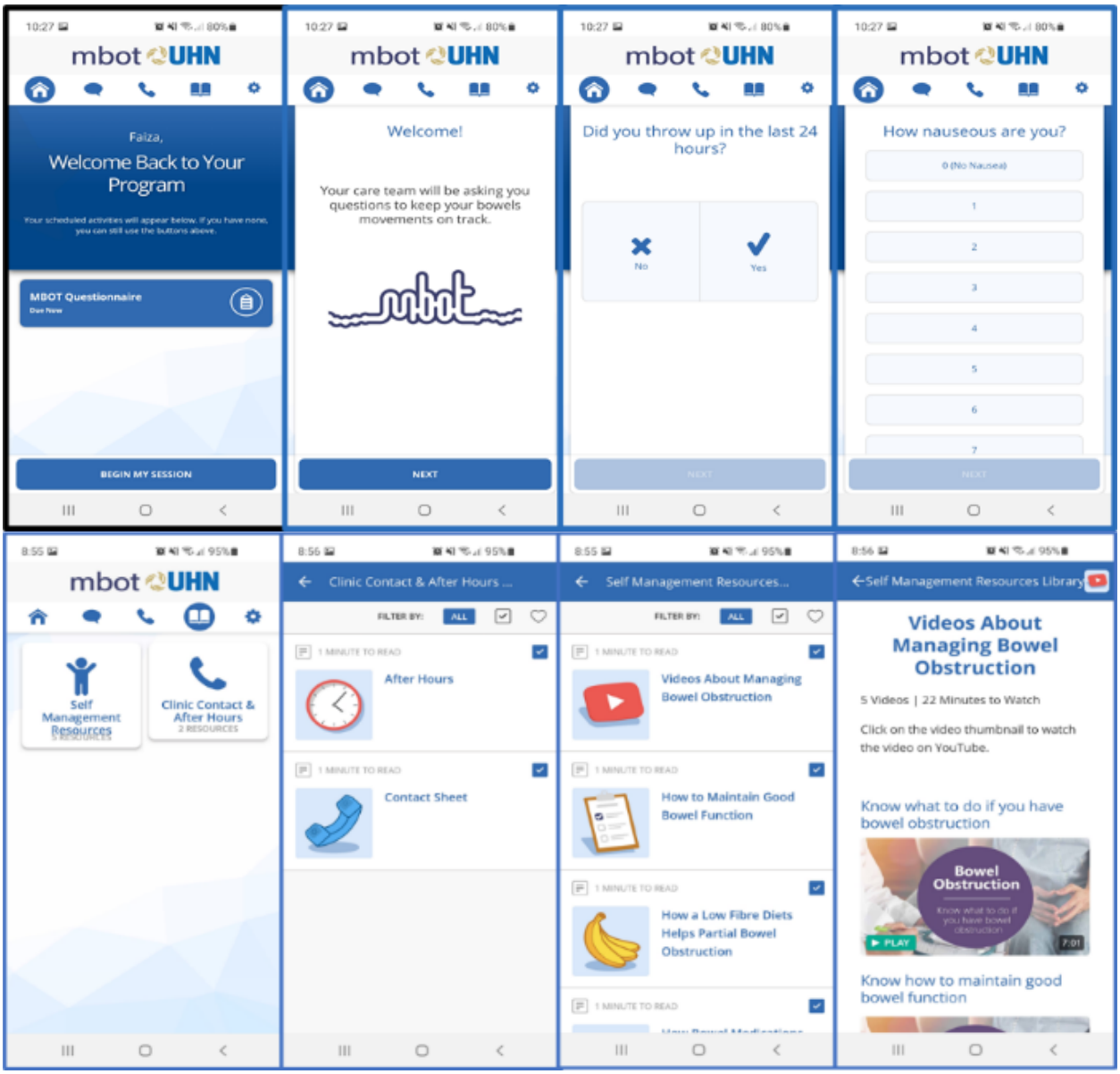

Figure 2. My Bowels on Track (MBOT) application. Patient application including welcome page and examples of questionnaires, and the patient application resource library, including self management resources (educational videos, dietary recommendations, information regarding laxatives, among others), and contact information.

This study served as the pilot evaluation of the electronic PRO module of the application. Nurses helped participants download the application by providing an educational video with step-by-step instructions.

Patient reported outcome measures

The MBO electronic PROs were based on previously published nurse-led phone-based MBO monitoring questionnaires.[69,76] These were designed as per health literacy grade 5-6 level. Symptom domains that were assessed included: abdominal bloating, pain, nausea, vomiting, bowel function (constipation, diarrhea, stool consistency) passing gas, oral intake (in case of no parenteral nutrition) and medication use (Annex 10.3). Three types of questionnaires were developed and were assigned by the specialized oncology nurses at enrollment: i) general population with or at risk of MBO, ii) participants with an ostomy, iii) participants on parenteral nutrition.

The surveys were completed at baseline, weekly or bi-weekly, according to patient criteria (Table 3). Additional surveys could be scheduled based on nursing assessment. The frequency of the questionnaires was established according to PMMBO risk-based triage system, based on patient needs (disease characteristics, symptom burden, autonomy for self-management; table 2). During design and testing, it was estimated that each survey with up to 13 questions would take approximately three minutes to complete.

Push notification reminders were sent for survey completion (main questionnaire), and if the patient did not respond a second reminder was sent at 24 hours (reminder questionnaire). If this was not responded an alert was generated in the nursing dashboard to connect with the patient either through secure messaging or a phone call to assess the scenario and ensure patient safety.

Scoring and alert algorithm

According to the responses of questionnaires an alert system was generated in the nursing dashboard (Annex 10.4). Based on the answers to the questionnaire, an alerting system (yellow or red alerts indicating moderate or high concern, respectively) was created to flag the patients with high symptom burden. Participants were contacted by nurses following clinical (red/yellow) and non-compliance (unanswered questionnaire) alerts. Initial self management recommendations were provided to the patient when an alert was generated (Annex 10.5). Patients with no alerts on the electronic PRO survey were not contacted by the nurses. The

program ended when patients were considered to be able to self-manage or were transferred to hospice care.

Nurses underwent training regarding the application and the dashboard. When alerts were generated, nurses would receive them on their dashboard and respond accordingly. Based on the patients' symptoms nurses would either call, use the text messaging or video call feature to assess the patient and document into the patient's medical record.

Other measures

Staff satisfaction was assessed by a survey nine months after deployment of MBOT. The questionnaire (Annex 10.6) was submitted by email, and consisted of 14 questions regarding general experience, perception, safety, satisfaction, necessity, and additional feedback about the MBOT program.

Sample size calculation and statistical analysis

The primary objective of the study was to assess patients' adherence and completion of surveys during the first two months on the program. A completion of 70% of the questionnaires by each patient was considered an adherent patient, given that patients with, or at risk of MBO are frail; thus, diminishing the options to complete all questionnaires. To assess feasibility of the electronic monitoring system, 40 patients at risk or who have developed MBO are required. This sample size produces a two-sided 95% confidence interval with a width equal to 0.30 using the Exact method.

Descriptive statistics were used. Questionnaire completion rate (adherence) at 2 months were calculated for all patients as a rate and the Exact 95% confidence interval was reported. Generalized linear model was used to test the trend in pain over time while the generalized estimation equation approach was applied to estimate the positive predictive value (PPV). The intra-patient correlation was accounted for in both models.

The PPV of the yellow and red alerts to trigger actions were performed by calculating the true positive alarms that trigger nurse phone calls and actions (e.g., hospital visit, dietary

recommendation, laxatives) over the total alarms. Alert PPV was assessed with a generalized estimation equation with the delta confidence interval reported.

5- GLOBAL SUMMARY OF RESULTS

The AE assessment and reporting in gynecologic oncology studies is complex and many factors need to be accounted. Ideally the clinician reported AEs and patient tolerability overview should be evaluated to address the true toxicity impact of new treatment strategies in gynecologic malignancies. Real-time AE assessment and novel technology advances can provide improvements in symptom detection, potentially improving patient safety.

5.1 Clinician and institutional reporting of adverse events in gynecologic oncology research studies

The thesis dissertation evaluated data recorded in the Princess Margaret Clinical Trial AE database from January 2016 to December 2018. The database included safety outcomes from 3,440 participants nested in systemic therapy clinical trials. Within the gynecologic oncology trials, the database included 317 unique patients (359 nested on trials, with 37 patients participating in ≥1 trial) in 42 systemic therapy trials. Recording of the AEs in real-time by clinical trial nurses with subsequent medical doctor sign-off was feasible at an institutional level. In gynecologic oncology studies, 17,175 related AEs were reported, and 7.4% were considered high grade (CTCAE grade ≥3).

Factors associated with high grade related AEs were assessed. On multivariate analysis, after adjusting to potential confounding factors, no odds differences of related grade ≥3 related AEs were detected according to study phase. Patients participating in immunotherapy clinical trials had lower odds of related grade ≥3 AEs than patients on targeted or other therapy (adjusted OR [aOR] 0.43; 95% CI 0.24-0.75). There was greater odds of related grade ≥3 AEs in clinical trials assessing combination vs single therapeutic studies (aOR 2.26, 95% CI 1.34-3.80). Patients aged ≥ 65 (aOR 1.77; 95% CI 1.08-2.89) had greater odds of related grade ≥3 AEs than patients aged 50 to 65 years. There was no significant difference in high grade AE reporting in patients with ECOG 0 compared to those with ECOG 1 or 2. When compared to other disease sites, the odds of having a grade 3 or higher related AE reported in gynecology clinical trials was no different.

The Princess Margaret AE database analysis provided data on feasibility of global clinical trial AE recording at an institutional level. In addition, the study was able to detect factors influencing the odds of related grade ≥3 AE reporting in gynecologic trials included type of therapy and age.

The clinician AE assessment at individual trial level is paramount to provide an overview of the safety of new treatment strategies in gynecologic malignancies. The AE assessment in early phase gynecologic oncology trials provide the initial signs of feasibility of novel therapeutics. An investigator-initiated, multi-centre, non-randomized, open-label, phase II trial (NEC, NCT03016338), assessed niraparib monotherapy (cohort 1), or niraparib and dostarlimab (cohort 2) in patients with recurrent serous or endometrioid endometrial carcinoma. The primary endpoint of the trial was the clinical benefit rate (CBR), with ≥5/22 (22.7%) overall considered of interest. Safety assessed by clinicians utilizing CTCAE version 4.0 was a secondary outcome. In cohort 1, 25 patients were enrolled, and CBR was 20% (95% CI: 9–39). In cohort 2, 22 patients were enrolled, and the CBR was 31.8% (95% CI: 16–53). Safety findings were similar to what is reported in the literature in other disease sites for these drugs. In the niraparib monotherapy cohort, related grade ≥3 AEs occurring in ≥10% of participants were anemia (24%), fatigue (16%) and thrombocytopenia (16%), while in the combination cohort, these were anaemia (27%) and neutropenia (14%). Discontinuations due to AEs occurred in four patients in C1 (16% of participants), reasons included fatigue (n=2), malignant bowel obstruction (n=1, not related to therapy), and other not specified (n=1). In C2 one patient discontinued therapy (4.5%) due to an AE of special interest, grade 3 myasthenia gravis related to dostarlimab. The study did not report any grade 5 AEs.

5.2 Incorporation of the patient's perspective in gynecologic oncology research studies

The PRO-CTCAE tool allows patient self-reporting of treatment tolerability in clinical trials, by assessing the frequency, severity, and/or interference of selected symptomatic AEs. An investigator-initiated phase II randomized clinical trial assessed gemcitabine and adavosertib (arm A) vs gemcitabine and placebo (arm B) in platinum resistant or refractory ovarian cancer (PHL-093, NCT02151292). The study demonstrated improved progression-free and overall survival, favouring the adavosertib arm. The PRO-CTCAE measures were assessed in two centres to characterize the symptomatic AEs, and results from 55 patients were evaluable. The analysis

showed high completion rate of surveys. Any grade abdominal pain, bloating, anxiety, fatigue, and nausea were high in both treatment arms, occurring in >70% of patients. The most frequent high score (3–4) symptomatic AEs occurring in >30% of patients were abdominal pain, anxiety, bloating and fatigue. Between arm comparisons revealed that the high score (grade ≥3) symptomatic diarrhea was more frequent in gemcitabine/adavosertib (arm A 25% vs arm B 0%, p=0.03). Longitudinal assessment of patient self-reported tolerability showed greater difficulty swallowing (arm A 35.7% vs arm B 5.3%, p = 0.02) and fatigue severity (arm A 71.43% vs arm B 42.1%; p=0.04) in patients receiving gemcitabine/adavosertib, compared to gemcitabine/placebo. The patient free-text analysis revealed potential findings of oral toxicity in the gemcitabine and adavosertib arm.

The thesis shows that the utilization and analysis of PRO-CTCAE tools in an early phase trial involving heavily pre-treated patients with ovarian cancer is feasible. Results allow the assessment of complementary and objective assessment of drug tolerability from a patient's perspective.

5.3 Impact of research procedures in gynecologic oncology

Clinical trials in oncology involve research procedures, including complementary blood work, radiological imaging, and biopsies. A prospective study offered surveys before and after a research biopsy was performed to patients with gynecologic malignancies. Results from 91 patients with ovarian or endometrial cancer were evaluable. During the biopsy procedure, pain and physical discomfort was experienced in 60.3% and 61.8% of patients, respectively. Embarrassment and loss of dignity were experienced by 13.2% and 11.8% of patients, respectively. The mean Hospital Anxiety and Depression Scale (HADS) score was in the normal range before and after biopsy, with a significant decline in the total score after the biopsy (pre-biopsy, 5.3 [standard deviation, 4.7] vs post-biopsy, 3.7 [standard deviation, 4.5]; p= 0.005).

Most patients reported they would consent to a future biopsy (84%). There was a negative impact on patients' willingness for future biopsies based on experienced embarrassed (odds ratio [OR] 0.03, p=0.004) or loss of dignity (OR 0.05, p= 0.01) during the biopsy. Those who experienced flu-like symptoms (OR 0.2, p= 0.018) or felt feverish (OR 0.2, p= 0.035) one-week after biopsy, were

also less likely to undergo a sequential biopsy. Similarly, patients with higher HADS scores before (OR 0.83, p= 0.008) and after the biopsy (OR 0.8, p= 0.003) were less likely to consent for a second biopsy. The presence of pain in the biopsy site did not correlate with patients' willingness to undergo a serial biopsy.

The research biopsy study presented in the thesis revealed that research biopsies were generally well accepted, and most patients were willing to undergo serial biopsies if necessary. Addressing the potentially modifiable psychosocial aspects of the procedure may improve the experience with research biopsies in patients with gynecologic cancers.

5.4 Novel technological advances in symptom monitoring in gynecologic oncology

The digital health allows monitoring of patient disease related symptom and treatment emergent AE outside of clinic days. The smartphone application "My Bowels on Track" (MBOT) was designed for patients with gynecologic cancers that were diagnosed with MBO and for those considered at high risk of developing it. Between August 2021 and September 2022, 40 patients enrolled in the MBOT program and used the application at least once. Median duration of the program was 55 days (range 8-121), and 13 patients were on the program for more than two months.

Median age of participants was 64.5 years (range 29-79). The most frequent primary tumour was ovarian (72.5%), followed by endometrial (17.5%), cervical (7.5%), and granulosa cell carcinoma (2.5%). Median number of prior therapy lines was 3 (range 1-9). Among participants, 23 (57.5%) had a platinum resistant disease. Median time from initial cancer diagnosis to enrollment in the program was 1,176 days (inter-quartile range 763-2,617). At enrollment, 37 (92.5%) patients were undergoing systemic therapy (chemotherapy [24], targeted therapy [5], clinical trial [4], hormonal therapy [3], immunotherapy and targeted therapy [1]). One patient was receiving best supportive care and two were on surveillance. Prior to enrollment in the program, 12 (30%) patients had one or more episodes of active MBO.

The total MBO survey responses were 199. Patients completing ≥70% of scheduled surveys were considered as adherent patients. The two-month adherence to the program was 65% (95% CI 50-80%). The overall adherence to the program was 60% (95% CI 43-75%). The use of the secure

messaging feature of the app to communicate with the nurses was very high (39 [97.5%] patients).

The program detected 65 symptom-related alerts (Figure 3), out of which 75% were yellow/moderate, and 25% were red/serious. At some point during their time in the program 60% (24/40) of patients had one or more symptom alert, and 27.5% (11/40) of patients reported one or more red/serious symptom alert.

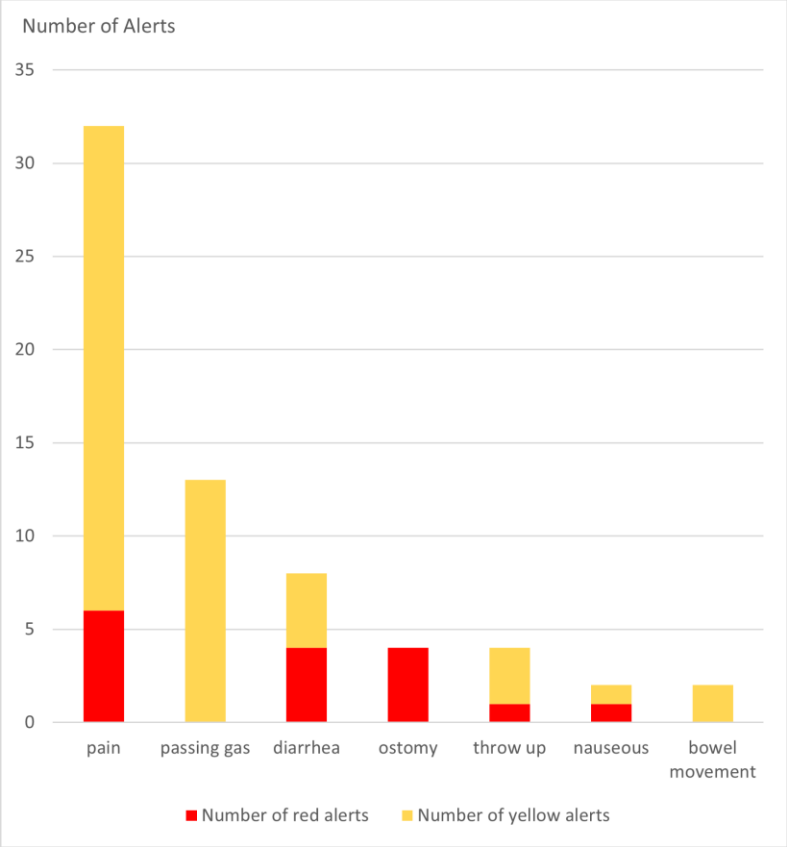

Figure 3. Number of alerts per patient. Yellow denotes alerts of moderate severity, while red denotes severe alerts. The ostomy corresponds to increased output through the ostomy bag.

The number of alerts per symptom is illustrated in Figure 4. The most common symptom triggering alerts was pain, with 32 alerts. Pain could be scored from 0 to 10 (higher numbers indicating worse pain control), and the median alerting score was 5 (range 4-8). Pain alerts were detected in 15 (37.5%) patients, among them 9 patients had multiple pain alerts. Red or serious pain alerts occurred in six patients. There was no significant change of reported pain score over

time (p=0.695). The second most frequently reported symptom triggering alerts was absence of passing gas in 11 (27.5%) patients, which were all medium/yellow.

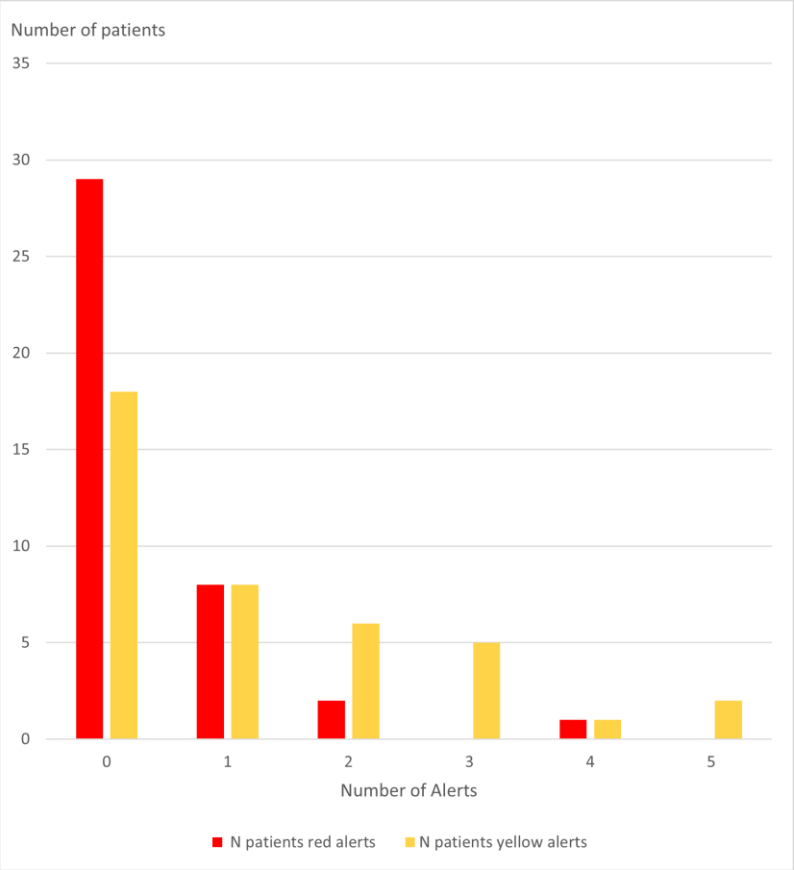

Figure 4. Number of alerts per symptom. The combination of several symptoms may result in a single alert. Yellow denotes alerts of moderate severity, while red denotes severe alerts.

No association was detected between baseline disease or patient variables with higher likelihood of alerts, including active MBO episode at enrollment (p= 0.71), platinum resistant disease (p= 0.63), platinum resistant disease and >3 prior lines of therapy (p= 0.23), ovarian cancer and active MBO episode prior to enrollment vs not (p= 0.81).

Out of the 65 alerts, 47 triggered one or more actions or recommendations from the specialized gynecologic oncology nurses. The remaining 18 alerts did not require recommendations as the patients' symptoms were self-managed or resolved with no interventions needed. The PPV of the alerts to trigger actions was 72% (95% CI: 58-82%). Discharge reasons from the MBOT program were completion of the program (67.5%), patient withdrawn (10%), transfer to hospice care (7.5%), death (5%) or other (10%).

A staff satisfaction survey was offered to nurses managing MBOT nine months after the deployment of the application (Annex 10.6). The survey was completed by 64% of nurses (11). Most of them (4, 57.4%) considered that the electronic version and assessment of bowel symptoms took less of their time than proactive MBO calls, improved patient care and patient experience. All the nurses understood the purpose and were aware of the importance of electronic symptom monitoring.

Safety feedback from nurses favored the electronic monitoring. The majority (4, 57.4%) considered that checking patients' bowel function status through electronic monitoring was as reliable as proactive calls and patients can receive timely responses due to asynchronous messaging, dashboard alerts and email prompts. The overall satisfaction with the electronic system was very good (6, 85.7%) and all the nurses would use the MBOT app again. Electronic monitoring was felt to be convenient to use compared with proactive phone calls by most of them (4, 57.4%).

Nurses provided open-ended feedback on their experiences and perceptions. Advantages were noted as it was a positive tool especially for those patients who like technology and were highly motivated to use it. The secure messaging feature was considered a key component. Yet, limitations of the system, as described by the nurses, included documentation in patient's chart (not integrated with current electronic health record), additional screen to monitor when assigned to triage (e.g., individual email, triage role email, other), patients that are not comfortable with electronics could not use this system, limited to English version only, and patient's adherence to complete pathways.

6- GLOBAL SUMMARY OF DISCUSSION

Cancer therapy can result in significant treatment emergent AEs. The type of toxicity and frequency will vary according to the disease setting, systemic therapy employed and patient characteristics. In the realm of gynecologic malignancies, the overarching goal of novel therapeutic strategies is to extend overall survival and/or enhance QoL for patients with advanced disease. Consequently, a need to meticulously measure and assess AEs arises, especially as we develop maintenance strategies. The generation of reliable data in gynecologic oncology trials is required to inform patient management and enhancing safety protocols. Achieving optimal toxicity assessment and reporting requires the involvement of multiple stakeholders, including clinician and patient reported outcomes. Moreover, the integration of novel toxicity and symptom monitoring systems promises to revolutionize healthcare delivery by enabling continuous monitoring and tailoring of treatment plans, thereby optimizing patient outcomes, and enhancing the overall QoL for individuals undergoing therapy.

6.1 Clinician and institutional reporting of adverse events in gynecologic oncology research studies

The optimal assessment of AEs in clinical trials is crucial for ensuring the accuracy, completeness, and timeliness of toxicity reporting, thereby promoting patient safety, and generating high-quality data to inform new studies and standard of care management. This dissertation contributes valuable insights to the field through the analysis of an institutional clinical trial AE database, as well as AE assessment in early phase clinical trials focusing on ovarian and endometrial cancer.

Analysis of the Princess Margaret AE dataset provided significant insights into the feasibility of clinical trial AE recording at an institutional level. The extensive AE dataset, comprising up to 3,440 participants nested within trials for disease site comparisons and 359 participants within gynecologic cancer trials, collected in real-time by specialized clinical trial nurses, offers reliable toxicity information. The three-year timeframe of individual patient data analysis provides robust findings. Notably, the study highlights certain types of studies or patient cohorts that may

necessitate more vigilant monitoring and introduces novel methodology for assessing clusters of high-grade AEs across trials through social network analysis.

The global analysis of clinician reported AEs enabled the identification of factors associated to a higher likelihood of having grade ≥3 AEs reported in gynecologic oncology clinical trials. These factors include the type of therapy, with lower rates of AEs observed in immunotherapy studies and non treatment combinations. Lower rates of treatment emergent AEs in immunotherapy monotherapy trials have been described in previously published gynecologic oncology trials. For example, in the NINJA clinical trial (JapicCTI-153004), assessing nivolumab vs single agent chemotherapy in platinum resistant ovarian cancer, fewer treatment-related AEs (61.5% vs 98.1%) and related grade 3 or 4 AEs (10.9% vs 65.2%) were observed with nivolumab compared to chemotherapy.[78] Yet, when therapies blocking PD-1 or PD-L1, are combined with other immune modulating agents (such as anti-CTLA4), high grade AEs will probably increase in frequency and duration.[79,80] It is also expected that combination of different therapeutic types, such as anti-angiogenics, targeted therapies or tyrosine kinase inhibitors, may derive in greater grade ≥3 AEs.[24,81-84] The severity and frequency of AEs are dependent on the drug profile. The increase in toxicity in studies assessing therapeutic combination can be derived from the sum of the known toxic effects of each drug, or newly identified or increased due to the combination.

The Princess Margaret AE database analysis showed that the study phase (early vs phase III trials) was not associated with higher likelihood of high-grade AE reporting. Higher odds of AE reporting was detected in the unadjusted model in investigator-initiated/intergroup studies compared to industry sponsored studies. Yet, the results did not reach statistical significance on multivariable analysis when adjusting for patient age, clinical trial phase, sponsor, single vs combination therapy and type of therapy. A systematic review showed that industry-sponsored randomized controlled trials are more likely to exclude elderly patients, those with comorbidities and certain concomitant medications.[85] In the gynecologic clinical trials included in the study more non-industry sponsored trials allowed inclusion of patients with Eastern Cooperative Oncology Group performance status (ECOG) 2 (industry sponsored 8% and non-industry sponsored 47%); although globally only six patients with ECOG 2 were accrued in gynecologic cancer studies in the

AE database timeline. These differences in eligibility may have an impact on treatment tolerability and high-grade AE occurrence.

The patient age emerged as a significant factor, with older patients showing a higher odds of experiencing grade ≥3 AEs. Biological age has been described as a potential factor associated with higher treatment emergent AEs in oncology. In this setting, careful monitoring of frail patients may have a role. The incorporation of comprehensive geriatric assessment tools may be used to evaluate aspects of an older patient's health, including physical, cognitive, psychological, and social factors.[86] This underscores the importance of careful monitoring and the potential incorporation of comprehensive geriatric assessment tools in clinical trial designs to address the needs of this population.

The Princess Margaret AE dataset did not show statistically significant differences in grade 3 or higher AEs in gynecologic oncology clinical trials compared to other disease sites. Prior retrospective work focusing on the NCI phase I database revealed that the reported average of grade 1 or 2 (related and unrelated) and related grade 2 AEs were higher for women with gynecologic cancers, than women or men with other cancers in early phase trials.[37] Yet, the average numbers of all grade 3 to 5 AEs were similar across the 3 groups. The NCI and current study differ in terms of study design (NCI dataset included all AEs), type of treatment assessed, variations in AE reporting among institutions, and in the study phase (the Princess Margaret database included both early and phase III studies).

A component to improve AE reporting from an institutional level includes technology and electronic data capture. The use of electronic data capture systems and electronic health records to streamline AE reporting processes has a role in improving data accuracy and enables real-time monitoring. Importantly, the Princess Margaret AE database analysis demonstrates the feasibility of real-time electronic AE monitoring at an institutional level, paving the way for future advancements in data capture and analysis using artificial intelligence and machine learning techniques to enhance AE prediction and management.

As part of the dissertation, results from two investigator-initiated early phase studies where AE data was reported utilizing CTCAE version 4 are shown. These studies highlighting importance of

AE assessment to find optimal drug dosing and provide safety signals of novel treatments or combinations.

The NEC (NCT03016338) multi-centre, non-randomized, phase II clinical trial assessed niraparib monotherapy (cohort 1), and niraparib with dostarlimab (cohort 2) in 47 patients with recurrent serous or endometrioid endometrial carcinoma. The CTCAE version 4.0 was utilized to assess treatment related toxicity, providing frequencies and proportions of adverse events based on severities and attributions. The toxicity analysis of the drugs did not provide new safety signals, and one patient experienced an AE of special interest with the niraparib and dostarlimab combination, grade 3 myasthenia gravis. The study showed that niraparib monotherapy did not meet the efficacy threshold of clinical benefit in the recurrent setting. The association of niraparib in combination with dostarlimab showed modest activity. The treatment combination tested in the NEC trial have now been moved to the front line setting as maintenance strategies have been assessed as part of the RUBY part-2 clinical trial (NCT03981796).

As novel oncology drugs are employed in clinical trials and standard of care settings, clinicians must have a thorough understanding of the AE profile of the drug, and carefully monitor of patients that are expected to have high grade AEs can be considered. In order to improve future reporting practices and patient safety, a culture of transparency and data sharing should be fostered, promoting the dissemination of AE information and lessons learned from previous trials.

6.2 Incorporation of the patient's perspective in gynecologic oncology research studies

A meticulous evaluation of patient-reported symptoms holds implications for both clinical trials and routine care. Basch and colleagues demonstrated the significant impact of real-time assessment of PROs on overall survival in patients with advanced cancer undergoing systemic therapy.[66] Despite the recognized importance of PROs, their utilization in gynecologic oncology remains largely unexplored. Prior work from our group reported results of a systematic review assessing the frequency of studies incorporating real-time assessment and utilization of PROs, among those assessing PROs (including QoL).[67] The study revealed that only 0.8% (1/117) of studies performed proactive PRO assessment. These results demonstrate that there is room for

improvement. Patients diagnosed with cancer spend a significant amount of time reporting their symptoms and outcomes, and prompt analysis of their PROs could have impact in their outcomes.

Recognizing the value of capturing the patient's perspective in research studies, the thesis highlights the feasibility and relevance of assessing PRO-CTCAE in a phase II randomized clinical trial (NCT02151292) evaluating gemcitabine and adavosertib in patients with recurrent platinum-resistant or platinum-refractory ovarian cancer.[17] Results of the study revealed clinical efficacy of the Wee1 inhibitor adavosertib combined with gemcitabine, with improved progression-free and overall survival. The PRO-CTCAE assessment was an exploratory endpoint of the trial and was performed in two of the participating centres. The thesis demonstrates the feasibility of collecting PRO-CTCAE data in early-phase trials, even among heavily pretreated patients with a high symptom burden. Notably, the incorporation of PRO-CTCAE data provided valuable complementary information to clinician-reported toxicity, enhancing accuracy in toxicity reporting and between-arm comparisons of AEs.

The study identified symptomatic AEs potentially linked to recurrent ovarian cancer, such as abdominal pain and bloating, and those likely exacerbated by gemcitabine and/or adavosertib administration, including diarrhea, fatigue, mucositis, and difficulty swallowing. Notably, disease-related symptoms did not significantly differ between patients receiving gemcitabine/adavosertib and gemcitabine/placebo overall or longitudinally during the initial 12 weeks of therapy. The assessment of PRO-CTCAEs facilitated the isolation of symptomatic AEs attributable or potentially attributable to adavosertib and gemcitabine, shedding light on their safety profiles. Assessment of the incremental AUC at 12 weeks and consideration of the free text reports supported the fact that fatigue, mucositis, and difficulty swallowing appeared to be AEs attributable or potentially attributable to the addition of adavosertib to gemcitabine.

The inclusion of free-text reports in PRO-CTCAE assessments proved to be feasible and yielded meaningful insights. The write-ins related to oral toxicity were helpful in amplifying its potential consequences in patients. Mucositis and/or dysphagia were not commonly observed in the randomized phase II trial (<30% in the profile of clinician reported AEs [not reported in the AE table of main publication]).[17] The analysis of the PRO-CTCAE detected significant differences in

mouth sores and difficulty swallowing between the adavosertib and placebo arms. In addition, free-text symptoms may have reflected the severity and consequences of oral toxicity, including periodontal disease, tooth pain, and cheilosis. Similarly, rash as a write-in was reported by six patients in the adavosertib arms, and none in the gemcitabine/placebo arm. Using clinician assessed CTCAE rash was observed in 44% of patients in the gemcitabine/adavosertib arm and 9% in the gemcitabine/placebo arm, also mirroring the between-arm difference observed in the write-ins. These findings hold implications for the selection of PRO-CTCAE items for future studies.

It's worth noting that differences in treatment duration between study arms may have influenced reported toxicities. The median number of cycles were three in the gemcitabine/adavosertib arm and two in the gemcitabine/placebo arm. To mitigate this potential confounding factor, longitudinal assessments, and incremental AUC analyses, which adjusts for baseline symptoms, were conducted at the 12-week mark, minimizing the impact of treatment duration discrepancies.

In summary, the thesis shows the importance of assessing CTCAE and PRO-CTCAE data in tandem to provide a comprehensive safety profile of therapeutic agents. These findings inform the implementation of preventive and supportive measures, such as oral hygiene and symptom management strategies in patients receiving adavosertib and gemcitabine.

6.3 Impact of research procedures in gynecologic oncology

Early-phase oncology clinical trials may mandate biopsies for correlative endpoints. However, data on the impact of research biopsies on PROs and distress caused by the procedure are limited. A comprehensive understanding of the physical and emotional toll of this procedure on patients is important for obtaining true informed consent for research biopsies. The thesis dissertation includes results of surveys administered to patients diagnosed with gynecologic cancers before and after research biopsies.

Existing literature predominantly reports clinician-assessed biopsy complications. Retrospective data indicate that obtaining sequential tissue samples in early-phase trials is feasible, with successful and safe procurement of paired biopsies in 88% of patients.[87] Most studies report low

complication rates, with serious adverse events occurring in 0.8% to 1.6% of patients and other complications in 10% of patients. [88,89] For instance, a series from MD Anderson evaluating phase I trial biopsies showed an 86% success rate with a 1.4% risk of serious complications. [89] However, the results presented in this thesis offer a different perspective, as the impact and symptoms are directly reported by patients. The survey findings revealed that patient-reported complications were higher than those reported by clinicians in the literature. Approximately 60% of patients experienced pain at the biopsy site during the procedure and in the first week afterward. Additionally, 13% of patients felt embarrassment and 12% experienced a loss of dignity during the procedure. There was a significant decline in anxiety levels before versus after the procedure, underscoring the importance of considering psychosocial support and providing a comfortable environment to enhance patients' experiences. This study accurately incorporated the patient perspective on biopsy-related complications and symptoms, which will be invaluable for consent processes and providing adequate information and education before the procedure.

Notably, 16% of patients expressed reluctance or unwillingness to consent for a second biopsy. Factors influencing patient willingness for serial research biopsies included higher Hospital Anxiety and Depression Scale (HADS) scores, physical discomfort, embarrassment, loss of dignity during the biopsy, and post-biopsy flu-like symptoms or shivering. Pain at the biopsy site during the procedure or within the week after the biopsy did not correlate with patient's willingness to undergo a second biopsy. The study was able to identify potentially modifiable factors that influence a patient's willingness to consent for serial research biopsies, which has an important role in the development of new biomarker driven treatment strategies for gynecologic malignancies.

Acknowledging the significance of biopsy-related complications, including emotional effects, pre-procedure education, risk information, and developing coping strategies are crucial for improving patient experiences and the success rate of achieving serial biopsies. As research biopsies remain integral to some gynecologic oncology trials, addressing these concerns is paramount.

6.4 Novel technological advances in symptom monitoring in gynecologic oncology

Remote symptom monitoring plays a pivotal role in fostering a patient-centered model of care in both oncology and palliative care settings. Numerous studies have underscored the benefits of electronic PROs in routine practice, enabling clinicians to promptly detect AEs and intervene in symptom management, ultimately leading to improved patient comfort, satisfaction, and even survival.[66] The utility of electronic PROs has also been explored in palliative care settings.[90]

A previous initiative at Princess Margaret Cancer Centre demonstrated the success of a program wherein specialized oncology nurses conducted proactive phone calls for monitoring MBO symptoms, providing early intervention and support to patients with gynecologic malignancies.[69] Compared to historical controls, patients enrolled in this program experienced shorter hospital admissions, received more palliative chemotherapy, underwent fewer surgeries, and achieved longer median overall survival. A qualitative study further highlighted that the outpatient monitoring program fostered increased support, reduced isolation, and enhanced patient knowledge on self-management.[76] Building upon this groundwork, the thesis includes findings from a research program evaluating the feasibility of an electronic MBO monitoring program for patients with gynecologic cancers. This electronic monitoring program aimed to address limitations of the proactive phone-call program, such as extensive nursing time consumption and challenges in implementation across centers with limited resources.

The "My Bowels on Track" (MBOT) application enrolled forty patients with gynecologic cancers, demonstrating the feasibility of electronic PRO collection via smartphone application in 65% of participants. Common symptoms were identified among participants, with 60% of participants experiencing alerts. Many of these alerts had actions or recommendations associated. The PPV of the alerts to trigger recommendations to the patients was high, mainly dietary, and laxative adjustments.

The MBOT pilot program had some limitations. The total number of enrolled patients was limited (n=40), and that questionnaires were only provided in English. A specialized gynecology nursing triage system that was already familiar with the outpatient management of MBO was available to run the program, which may not be available in other centres and may limit the expansion of

the program. A limitation of the electronic PRO approaches is that they are not suitable for all patients, as some patients may not be comfortable with technology. Future solutions may involve the development of more interactive and user-friendly technologies, such as automatized mobile phone messaging or phone-call-based virtual clinical assistants. Other solutions may include integration of the app with wearable sensors or medical devices capable of monitoring physiological parameters relevant to bowel obstruction, such as abdominal girth, or vital signs to provide real-time insights and early detection of complications.

7- CONCLUSIONS

i. Real-time assessment and recording of adverse events reported in clinical trials within an institutional database is feasible. This approach enables a comprehensive global assessment of the results, facilitating the identification of trends in high-grade adverse events.

ii. Various patient and trial factors have been identified to influence the likelihood of experiencing high grade adverse events while on a gynecologic oncology clinical trial. Analysis of the gynecology oncology studies of the Princess Margaret clinical trial adverse event database revealed higher likelihood of having treatment-related high grade adverse events in non-immunotherapy trials, studies assessing treatment combinations, and among patients aged 65 years and over.

iii. The longitudinal assessment of patient reported symptomatic toxicity utilizing patient reported outcome CTCAE (PRO-CTCAE) in early phase clinical trials involving patients with heavily pre-treated ovarian cancer is feasible.

iv. The PRO-CTCAE analysis of the PHL093 phase II trial provides a complementary and objective assessment of drug tolerability from a patient's perspective. Longitudinal symptom assessment revealed higher severity of difficulty swallowing and fatigue in patients receiving gemcitabine and adavosertib compared to those receiving gemcitabine and placebo.

v. Symptomatic adverse events and distress resulting from research biopsies are under reported. Factors associated with patients' willingness to undergo future research biopsies in gynecological cancers include experiencing embarrassment or loss of dignity during the biopsy, post-biopsy flu-like symptoms or feverish sensations, and higher anxiety before the procedure. Addressing these potentially modifiable psychosocial aspects may enhance the experience of patients undergoing biopsies.

vi. Electronic patient reported outcomes assessments facilitated by a smartphone application, have demonstrated feasibility in 65% of patients with gynecologic cancers with or at risk of malignant bowel obstruction. The "My Bowels on Track" application

effectively tracked symptoms of bowel obstruction in 60% of participants, with a positive predictive value of 72% for triggering recommendations based on alerts.

8- FUTURE DIRECTIONS

The experience gained during the conduction of my thesis aims to improve outcomes of patients diagnosed with gynecologic malignancies by integrating clinical, psychosocial, and technological innovations to their care. The encouraging results provided by the analyses presented in the dissertation have permitted me to obtain research funding as an independent investigator, including financial support from the American Society of Clinical Oncology (ASCO) and Spanish Society of Medical Oncology (SEOM).

The analysis of the Princess Margaret AE dataset has led to the initiation of two ongoing projects. Firstly, a comprehensive global analysis encompassing clinical trial AEs across various disciplines, including medical oncology and hematology, has been conducted. This analysis, which is currently pending publication, aims to identify trends in high-grade AE reporting and to pinpoint patients who may require more vigilant monitoring during their trial participation. Leveraging social network analysis, we are also investigating global clinical trial enrollment patterns and high-grade AE trends to inform future research and clinical practice. Secondly, an ongoing project is focused on refining AE reporting methods through the utilization of AI within the Princess Margaret AE database. By harnessing AI capabilities, we aim to predict patterns of toxicity, thereby enhancing our ability to anticipate and manage AEs effectively. The outcomes of this project hold the potential to facilitate the development of novel tools or algorithms aimed at streamlining data collection and analysis for AE prediction, ultimately enhancing patient safety and trial efficiency.

The thesis examined the potential of remote monitoring technologies to enhance real-time AE reporting, symptom management, and communication between patients and healthcare providers. Specifically, the "My Bowels on Track" smartphone application demonstrated the utility of symptom monitoring in patients with or at risk of malignant bowel obstruction. Building upon these findings, a new prospective trial is underway in Spain to evaluate the effectiveness of automated calls, powered by artificial intelligence, in detecting symptoms of concern in patients at risk of malignant bowel obstruction. I am the principal investigator of this trial, that has received funding support from SEOM and is currently ongoing. Additionally, the thesis findings demonstrated the feasibility of integrating PROs captured through the PRO-CTCAE assessment

tool in patients with advanced gynecologic malignancies and significant symptom burden. In line with the goal of further integrating patient-reported outcomes into routine clinical practice, I am currently leading the development of a digital health tool based on electronic PRO-CTCAE surveys for patients with gynecologic malignancies. The study design and smartphone application development have been completed, with implementation anticipated in the second quarter of 2024.

The research conducted for this thesis has motivated me to actively contribute to the development of PRO measures tailored to individuals with gynecologic malignancies. Currently, I am leading the efforts to translate and validate the MOST questionnaires into Spanish, in collaboration with the Spanish Group of Gynecologic Cancers (GEICO). These questionnaires, originally created by the GCIG-Symptom Benefit group, are designed to comprehensively assess both physical and psychological symptoms experienced by patients undergoing treatment and surveillance. Furthermore, I am engaged in collaborative efforts to develop questionnaires aimed at assessing "time-to-toxicity" and to update existing measures as part of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life group. Notably, the ovarian cancer module of the EORTC (EORTC QLQ OV28) was initially developed in 1997. Given the advancements in treatment options for ovarian cancer patients since then, including the availability of new therapies that offer extended disease control, there is a pressing need to refine and update these assessment tools to better reflect the contemporary landscape of ovarian cancer care.

In summary, the thesis highlighted the need to incorporate systematically PROs for patients with gynecological cancer. This pivotal knowledge is relevant for my future work as a clinician investigator, to implement in research studies and continue developing strategies to assess it in usual care practice.

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10- ANNEX

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- US Department of Defense.
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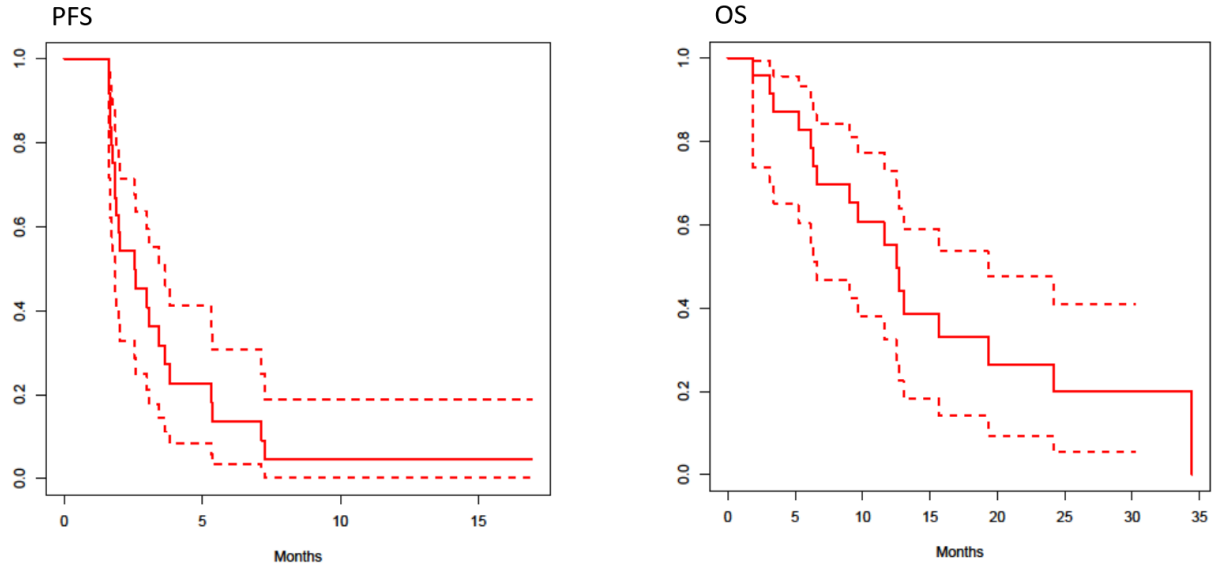
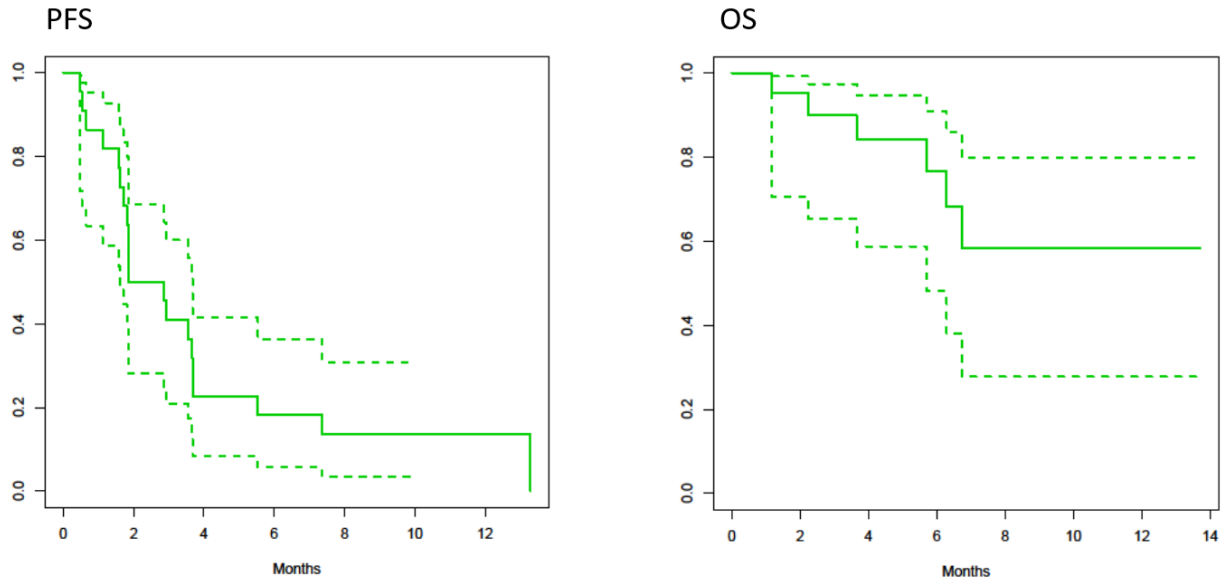
10.2 Clinical outcome and biomarker assessments of a multi-centre phase II trial assessing niraparib with or without dostarlimab in recurrent endometrial carcinoma: Supplementary Material

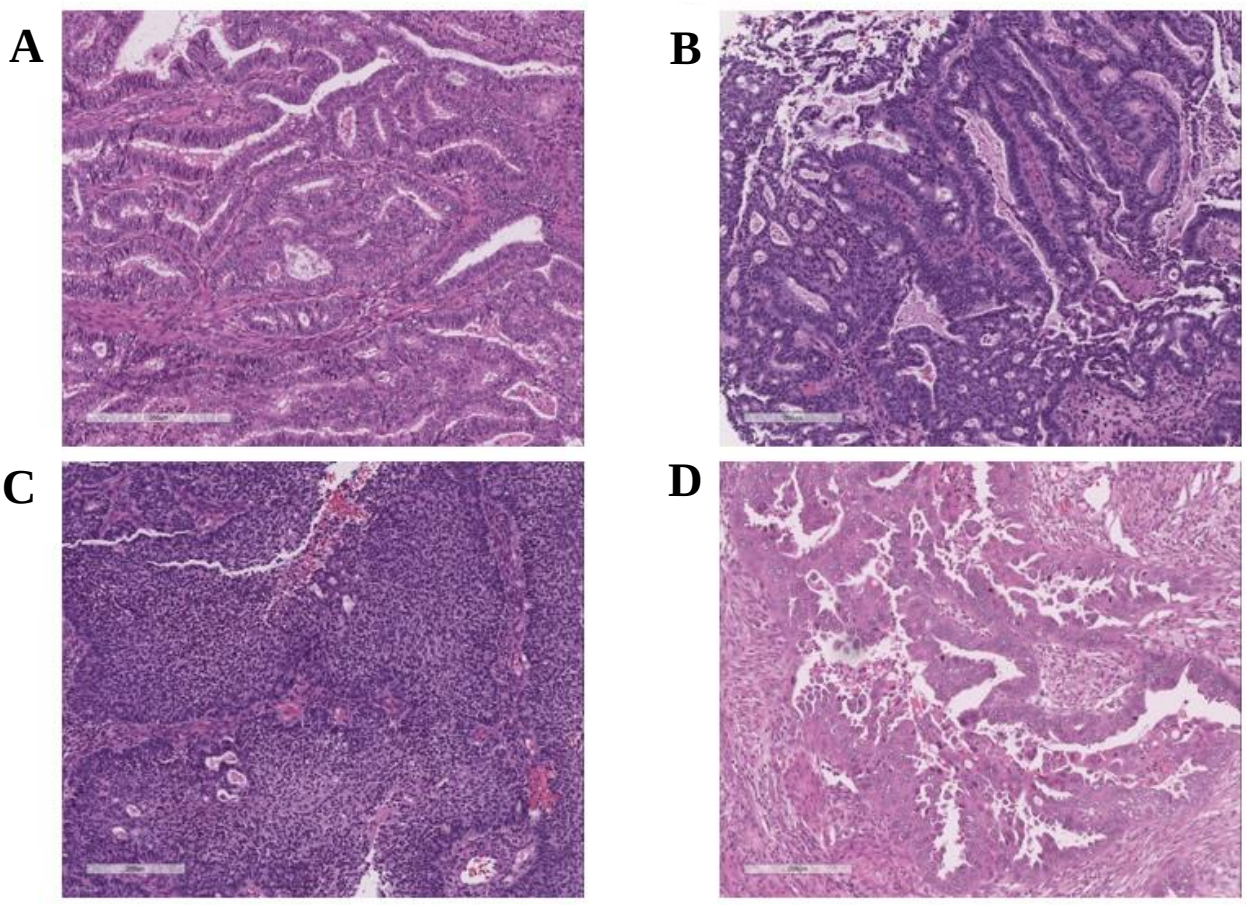
Cohort 1 – Niraparib (n=25)



Cohort 2 – Niraparib + Dostarlimab (n=22)



Supplementary Figure 1. Progression free survival and overall survival per cohort.


A
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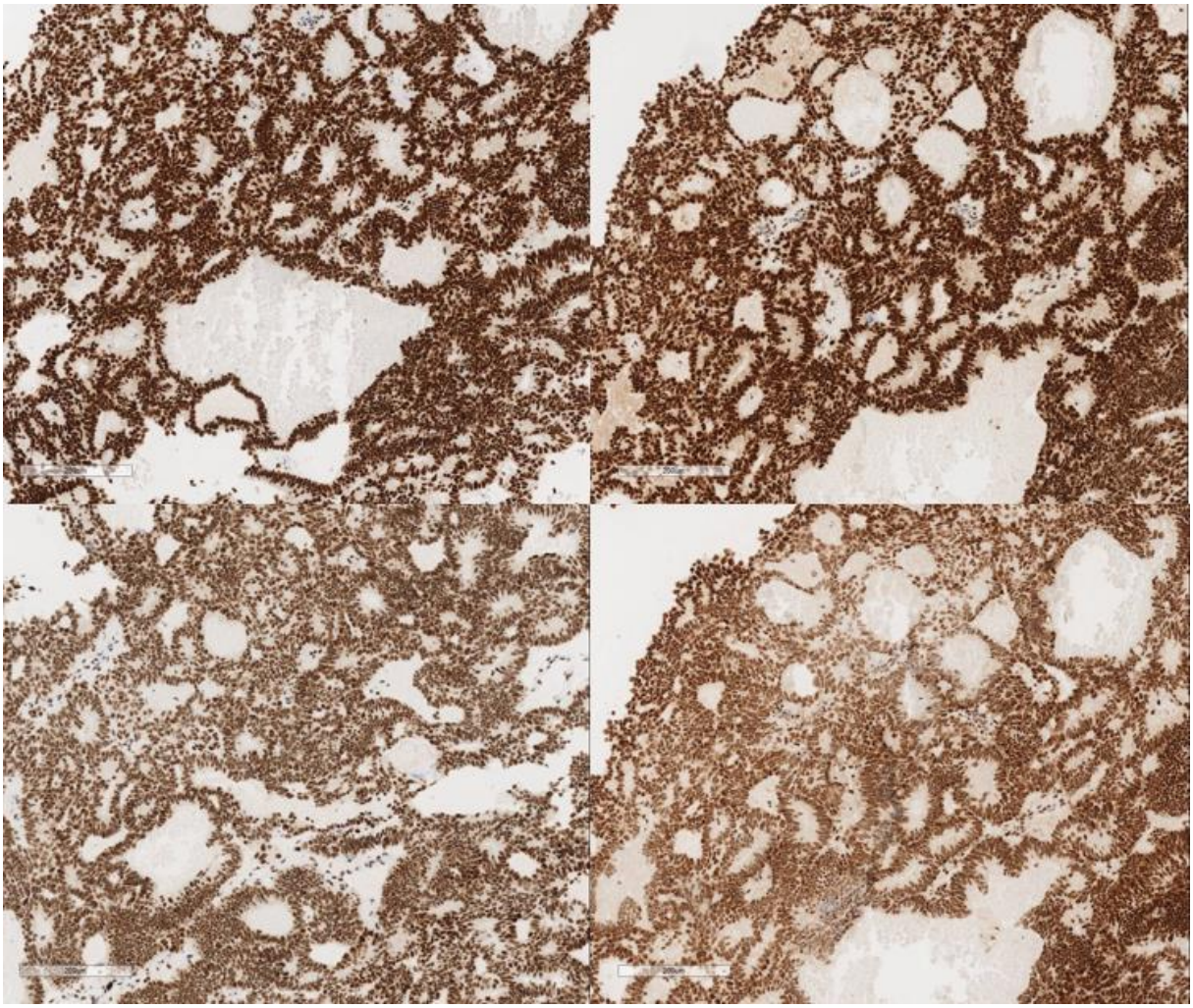

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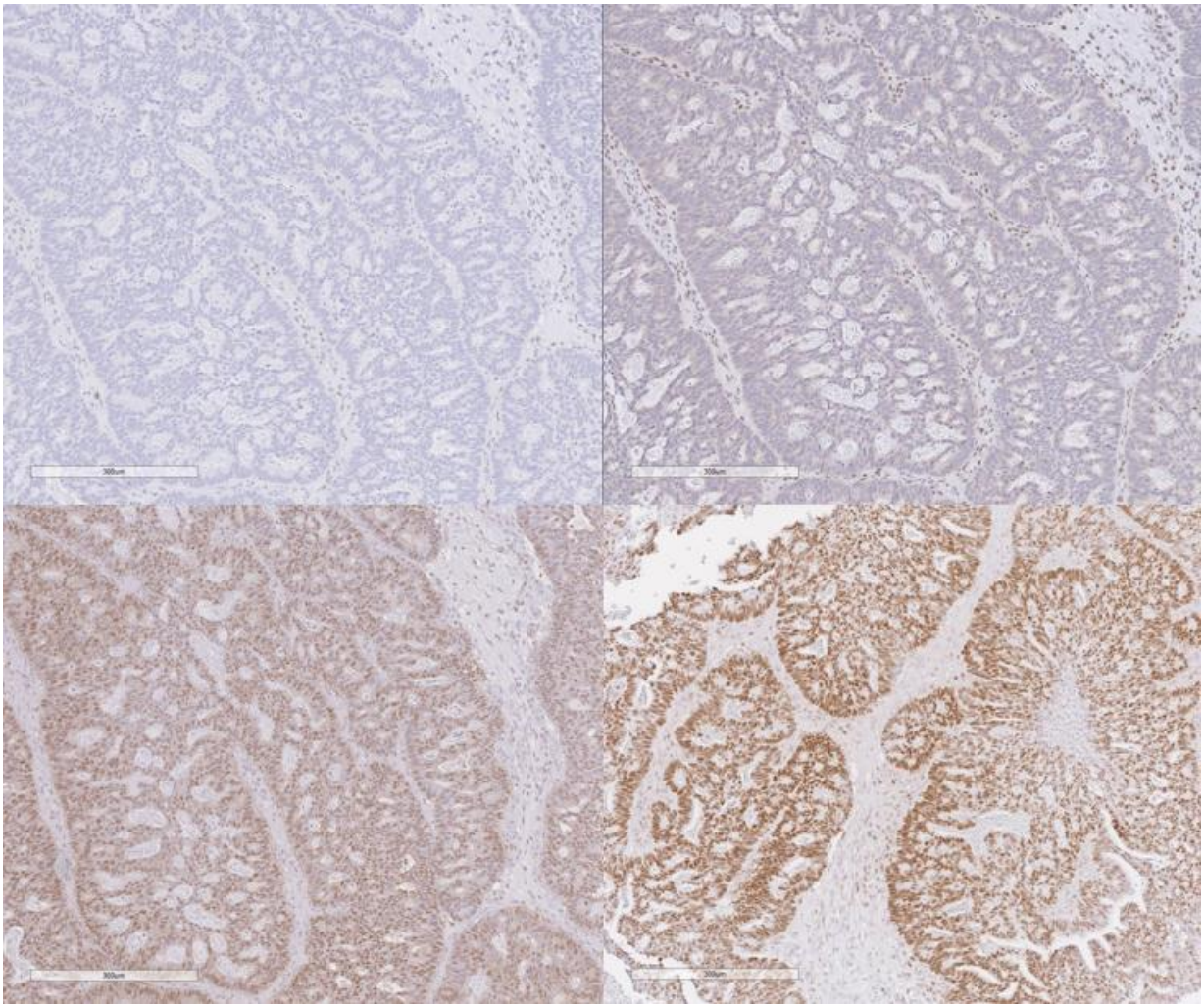

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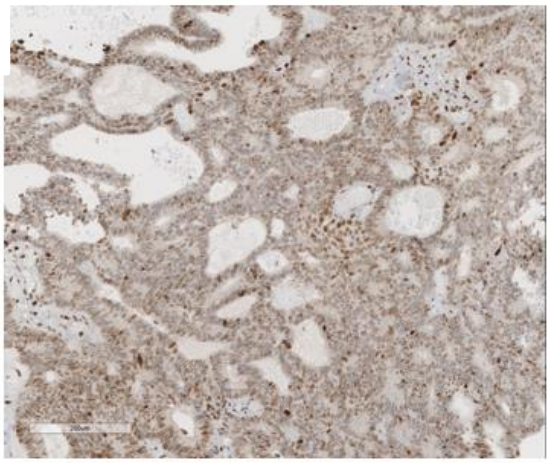

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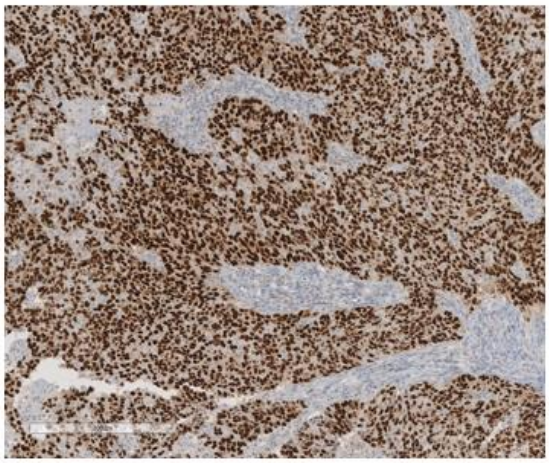

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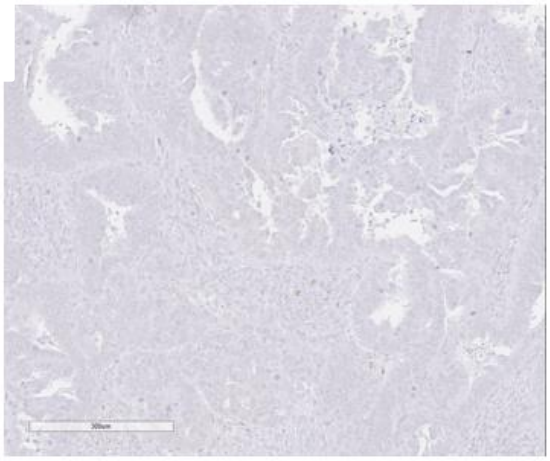

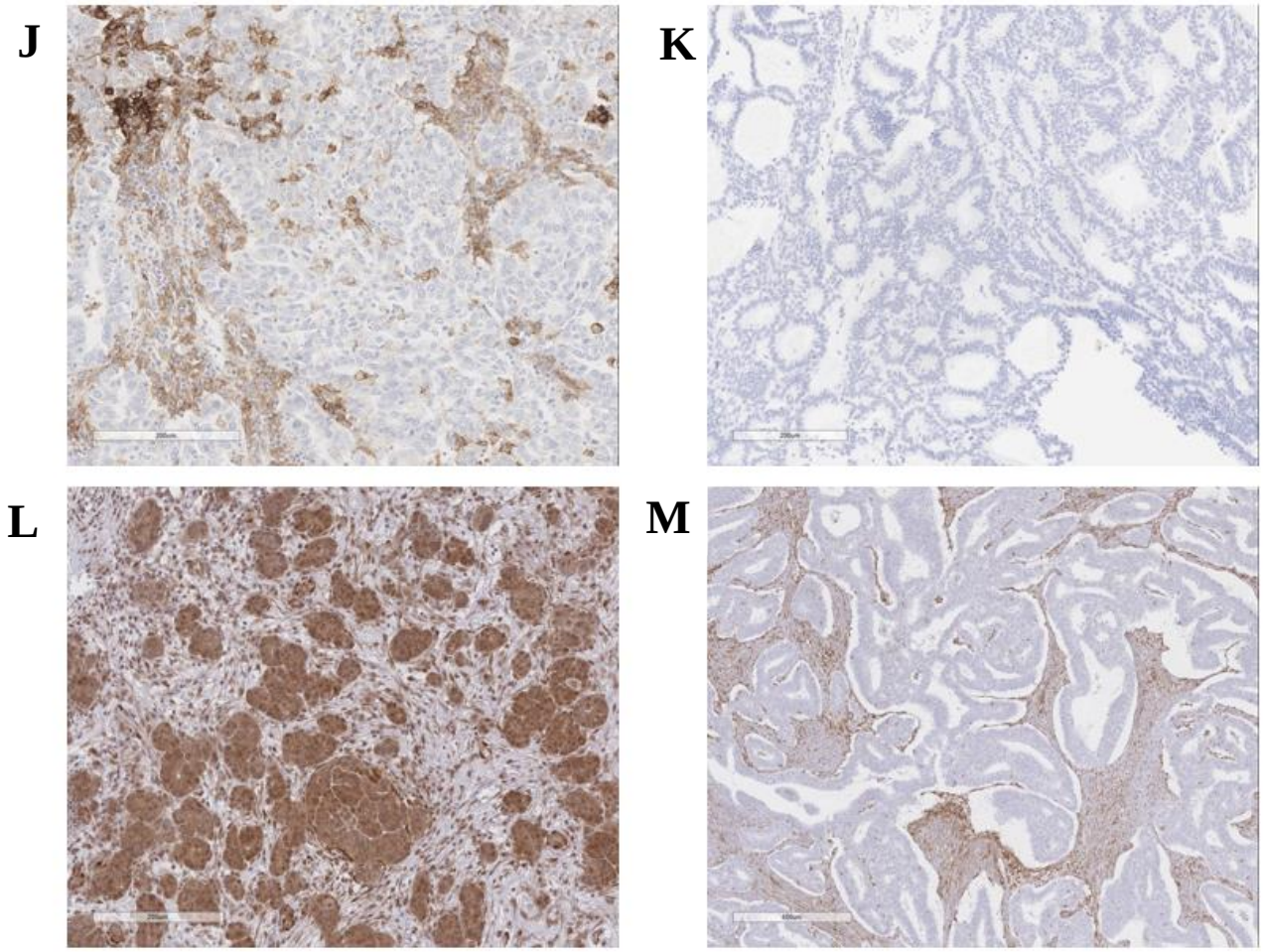

Supplementary Figure 2. Immunohistochemistry markers used in the study.

A) Endometrioid endometrial carcinoma, FIGO grade 1, showing <5% solid growth (H&E stain)
B) Endometrioid endometrial carcinoma, FIGO grade 2, showing between 5% and 50% solid/microacinar growth (H&E stain)
C) Endometrioid endometrial carcinoma, FIGO grade 3, showing >50% solid/microacinar growth (H&E stain)
D) Serous carcinoma, characterized by papillary/tufted architecture, irregular luminal borders, high-grade cytologic atypia and brisk mitotic activity (H&E stain)
E) Mismatch repair proficient (MMRp) endometrial carcinoma – intact nuclear staining seen in tumor cells stained with MLH1, PMS2, MSH2 and MSH6 (clockwise from top left)
F) Mismatch repair deficient (MMRd) endometrial carcinoma – loss of nuclear staining with MLH1 and PMS2 (note the retained staining in peritumoral stromal and inflammatory cells) with intact nuclear expression of MSH2 and MSH6 (clockwise from top left)
G) Normal p53 staining (wild-type pattern) in endometrial carcinoma, whereby a proportion of tumor nuclei show positive nuclear expression of variable intensity
H) Abnormal p53 staining (overexpression pattern) in endometrial carcinoma, in which >80% of tumor nuclei show strong positivity

I) Abnormal p53 staining (null pattern) in endometrial carcinoma; no staining is seen in is seen in tumor cell nuclei. Note the presence of faint wild-type staining in background non-tumor nuclei, serving as an internal positive control.
J) Positive PD-L1 staining in endometrial carcinoma, predominantly seen in intratumoral immune cells, with lesser expression in viable tumor cells
K) PD-L1-negative endometrial carcinoma
L) Endometrial carcinoma with retained PTEN staining
M) Loss of PTEN expression in endometrial carcinoma; note retained staining in peritumoral stroma, serving as a positive internal control

	Cohort	**n (%)**	**Serous**	**Endometrioid low grade**	**Endometrioid high grade**	**Mixed**
PTEN IHC status	C1	Retained	8 (57%)	4 (67%)	0 (0%)	1 (100%)
		Lost	4 (29%)	1 (17%)	3 (100%)	0 (0%)
		Heterogeneous	2 (14%)	1 (17%)	0 (0%)	0 (0%)
		NA	1	0	0	0
	C2	Retained	6 (67%)	1 (20%)	4 (57%)	0 (0%)
		Lost	3 (33%)	4 (80%)	3 (43%)	1 (100%)
		Heterogeneous	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		NA	0	0	0	0
	Overall	Retained	14 (61%)	5 (45%)	4 (40%)	1 (50%)
		Lost	7 (30%)	5 (45%)	6 (60%)	1 (50%)
		Heterogeneous	2 (8.7%)	1 (9.1%)	0 (0%)	0 (0%)
		NA	1	0	0	0
***PTEN* mutation**	C1	no	10 (83%)	2 (40%)	1 (33%)	1 (100%)
		yes	2 (17%)	3 (60%)	2 (67%)	0 (0%)
		NA	3	1	0	0
	C2	no	9 (100%)	1 (20%)	3 (43%)	0 (0%)
		yes	0 (0%)	4 (80%)	4 (57%)	1 (100%)
		NA	0	0	0	0
	Overall	no	19 (90%)	3 (30%)	4 (40%)	1 (50%)
		yes	2 (9.5%)	7 (70%)	6 (60%)	1 (50%)
		NA	3	1	0	0
***PTEN* mutation with oncogenicity as per OncoKB**	C1	Negative	10 (83%)	3 (60%)	1 (33%)	1 (100%)
		Oncogenic	2 (17%)	2 (40%)	2 (67%)	0 (0%)
		NA	3	1	0	0
	C2	Negative	9 (100%)	1 (20%)	3 (43%)	0 (0%)
		Oncogenic	0 (0%)	4 (80%)	4 (57%)	1

						(100%)
		NA	0	0	0	0
	Overall	Negative	19 (90%)	4 (40%)	4 (40%)	1 (50%)
		Oncogenic	2 (9.5%)	6 (60%)	6 (60%)	1 (50%)
		NA	3	1	0	0
MMR status	C1	Intact	12 (92%)	3 (50%)	2 (67%)	1 (100%)
		Deficient	0 (0%)	3 (50%)	1 (33%)	0 (0%)
		Equivocal (Subclonal)	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)
		NA	2	0	0	0
	C2	Intact	9 (100%)	2 (40%)	7 (100%)	1 (100%)
		Deficient	0 (0%)	3 (60%)	0 (0%)	0 (0%)
		Equivocal (Subclonal)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		NA	0	0	0	0
	Overall	Intact	21 (95%)	5 (45%)	9 (90%)	2 (100%)
		Deficient	0 (0%)	6 (55%)	1 (10%)	0 (0%)
		Equivocal (Subclonal)	1 (4.5%)	0 (0%)	0 (0%)	0 (0%)
		NA	2	0	0	0
PDL1 status	C1	Negative	9 (64%)	5 (83%)	0 (0%)	0 (0%)
		Positive	5 (36%)	1 (17%)	3 (100%)	1 (100%)
		NA	1	0	0	0
	C2	Negative	2 (22%)	2 (40%)	3 (43%)	1 (100%)
		Positive	7 (78%)	3 (60%)	4 (57%)	0 (0%)
		NA	0	0	0	0
	Overall	Negative	11 (48%)	7 (64%)	3 (30%)	1 (50%)
		Positive	12 (52%)	4 (36%)	7 (70%)	1 (50%)
		NA	1	0	0	0
p53 IHC	C1	Abnormal	14 (100%)	0 (0%)	0 (0%)	0 (0%)
		Wild-type	0 (0%)	6 (100%)	2 (100%)	0 (0%)
		Overexpressed	0 (0%)	0 (0%)	0 (0%)	1 (100%)
		NA	1	0	1	0
	C2	Abnormal	9 (100%)	0 (0%)	2 (29%)	1 (100%)
		Wild-type	0 (0%)	5 (100%)	5 (71%)	0 (0%)
		Overexpressed	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		NA	0	0	0	0

	Overall	Abnormal	23 (100%)	0 (0%)	2 (22%)	1 (50%)
		Wild-type	0 (0%)	11 (100%)	7 (78%)	0 (0%)
		Overexpressed	0 (0%)	0 (0%)	0 (0%)	1 (50%)
		NA	1	0	1	0
***TP53* mutation**	C1	yes	12 (100%)	0 (0%)	3 (100%)	1 (100%)
		no	0 (0%)	5 (100%)	0 (0%)	0 (0%)
		NA	3	1	0	0
	C2	yes	9 (100%)	0 (0%)	2 (29%)	1 (100%)
		no	0 (0%)	5 (100%)	5 (71%)	0 (0%)
		NA	0	0	0	0
	Overall	yes	21 (100%)	0 (0%)	5 (50%)	2 (100%)
		no	0 (0%)	10 (100%)	5 (50%)	0 (0%)
		NA	3	1	0	0
***TP53* mutation with oncogenicity as per OncoKB**	C1	Oncogenic	11 (92%)	0 (0%)	2 (67%)	0 (0%)
		Negative	0 (0%)	5 (100%)	0 (0%)	0 (0%)
		VUS	1 (8.3%)	0 (0%)	1 (33%)	1 (100%)
		NA	3	1	0	0
	C2	Oncogenic	9 (100%)	0 (0%)	2 (29%)	1 (100%)
		Negative	0 (0%)	5 (100%)	5 (71%)	0 (0%)
		VUS	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		NA	0	0	0	0
	Overall	Oncogenic	20 (95%)	0 (0%)	4 (40%)	1 (50%)
		Negative	0 (0%)	10 (100%)	5 (50%)	0 (0%)
		VUS	1 (4.8%)	0 (0%)	1 (10%)	1 (50%)
		NA	3	1	0	0
HRR gene alterations	C1	yes	7 (58%)	4 (80%)	2 (67%)	0 (0%)
		No	5 (42%)	1 (20%)	1 (33%)	1 (100%)
		NA	3	1	0	0
	C2	yes	6 (67%)	3 (60%)	6 (86%)	1 (100%)
		No	3 (33%)	2 (40%)	1 (14%)	0 (0%)
		NA	0	0	0	0
	Overall	yes	13 (62%)	7 (70%)	8 (80%)	1 (50%)
		No	8 (38%)	3 (30%)	2 (20%)	1 (50%)
		NA	3	1	0	0
HRR alterations	C1	Negative	9 (75%)	1 (20%)	2 (67%)	1 (100%)

with oncogenicity as per OncoKB		Oncogenic NA	3 (25%) 3	4 (80%) 1	1 (33%) 0	0 (0%) 0
	C2	Negative Oncogenic NA	7 (78%) 2 (22%) 0	3 (60%) 2 (40%) 0	2 (29%) 5 (71%) 0	0 (0%) 1 (100%) 0
	Overall	Negative Oncogenic NA	16 (76%) 5 (24%) 3	4 (40%) 6 (60%) 1	4 (40%) 6 (60%) 0	1 (50%) 1 (50%) 0
HRR alterations, excluding *ARID1A*, with oncogenicity as per OncoKB	C1	negative positive NA	11 (92%) 1 (8.3%) 3	3 (60%) 2 (40%) 1	2 (67%) 1 (33%) 0	1 (100%) 0 (0%) 0
	C2	negative positive NA	7 (78%) 2 (22%) 0	4 (80%) 1 (20%) 0	3 (43%) 4 (57%) 0	1 (100%) 0 (0%) 0
	Overall	negative positive NA	18 (86%) 3 (14%) 3	7 (70%) 3 (30%) 1	5 (50%) 5 (50%) 0	2 (100%) 0 (0%) 0
TMB high	C1	no yes NA	11 (92%) 1 (8.3%) 3	2 (40%) 3 (60%) 1	3 (100%) 0 (0%) 0	1 (100%) 0 (0%) 0
	C2	no yes NA	8 (89%) 1 (11%) 0	4 (80%) 1 (20%) 0	4 (57%) 3 (43%) 0	1 (100%) 0 (0%) 0
	Overall	no yes NA	19 (90%) 2 (9.5%) 3	6 (60%) 4 (40%) 1	7 (70%) 3 (30%) 0	2 (100%) 0 (0%) 0

Supplementary Table 1. Immunohistochemistry and genomic alterations per histological subtype. Data is presented per cohort, and overall.
C1: Cohort 1, C2: Cohort 2, NA: Not available.

Study number	**New variants seen in ctDNA alone**
NEC-005	CHEK2 (NM_007194.3) c.283C>T (p.Arg95*, aka p.R95*) AF: 1.7%, likely onc
NEC-012	TP53 (NM_000546.5) c.808T>C (p.Phe270Leu, aka p.F270L) AF: 1.5%; VUS

NEC-016	ATR (NM_001184.3) c.6793G>A (p.Val2265Ile, aka p.V2265I) AF: 1.4%; VUS
NEC-022	FANCD2 (NM_033084.3) c.3931C>T (p.Pro1311Ser, aka p.P1311S) AF: 1.0%; VUS
NEC-027	TP53 (NM_000546.5) c.827C>A (p.Ala276Asp, aka p.A276D) AF: 11.7%; VUS
NEC-032	ATRX (NM_000489.4) c.2677G>A (p.Gly893Ser, aka p.G893S) AF: 1.9%; VUS

Supplementary Table 2. New variants seen in baseline ctDNA, not detected in archival tissue, in cohort 1 (n=5, NEC-005 to NEC-027) and cohort 2 (n=1, NEC-032).

NEC study number	1st ctDNA sample	2nd ctDNA sample
NEC-011	no variant detected	no variants detected
NEC-016	**ATR (NM_001184.3) c.6793G>A (p.Val2265Ile, aka p.V2265I) AF: 1.4%** BAP1 (NM_004656.2) c.878C>T (p.Pro293Leu, aka p.P293L) AF: 45.6% FANCA (NM_000135.2) c.308C>T (p.Ser103Leu, aka p.S103L) AF: 47.0% NBN (NM_002485.4) c.1361C>A (p.Ser454Tyr, aka p.S454Y) AF: 44.6%	**ATR (NM_001184.3) c.6793G>A (p.Val2265Ile, aka p.V2265I) AF: 3.4%** BAP1 (NM_004656.2) c.878C>T (p.Pro293Leu, aka p.P293L) AF: 44.7% FANCA (NM_000135.2) c.308C>T (p.Ser103Leu, aka p.S103L) AF: 47.9% NBN (NM_002485.4) c.1361C>A (p.Ser454Tyr, aka p.S454Y) AF: 46.7%
NEC-044	**PTEN (NM_000314.4) c.277C>T (p.His93Tyr, aka p.H93Y) AF: 2.8%; Onc** **ARID1A (NM_006015.4) c.4495C>T (p.Gln1499*, aka p.Q1499*) AF: 2.4%; Onc** **ARID1A (NM_006015.4) c.4856del (p.Pro1619Glnfs*7, aka p.P1619Qfs*7) AF: 1.8%; Onc** **PTEN (NM_000314.4) c.697C>T (p.Arg233*, aka p.R233*) AF: 2.6%; Onc** **ATRX (NM_000489.4) c.110G>A (p.Arg37Gln, aka p.R37Q) AF: 2.1%; VUS** BRCA2 (NM_000059.3) c.7522G>A (p.Gly2508Ser, aka p.G2508S) AF: 46.8%; VUS FANCL (NM_018062.3) c.677G>A (p.Arg226His, aka p.R226H) AF: 50.5%; VUS	BRCA2 (NM_000059.3) c.7522G>A (p.Gly2508Ser, aka p.G2508S) AF: 48.8% FANCL (NM_018062.3) c.677G>A (p.Arg226His, aka p.R226H) AF: 48.0%

NEC-045	**PTEN (NM_000314.4) c.518G>A (p.Arg173His, aka p.R173H) AF: 1.4%** ARID1A (NM_006015.4) c.5965C>T (p.Arg1989*, aka p.R1989*) AF: 85.2% ATM (NM_000051.3) c.2002G>T (p.Glu668*, aka p.E668*) AF: 34.0% ATM (NM_000051.3) c.2510C>A (p.Ser837*, aka p.S837*) AF: 39.5% **ATR (NM_001184.3) c.7075G>T (p.Glu2359*, aka p.E2359*) AF: 3.1%** **ATR (NM_001184.3) c.7756G>T (p.Glu2586*, aka p.E2586*) AF: 1.3%** ATRX (NM_000489.4) c.271G>T (p.Glu91*, aka p.E91*) AF: 21.0% ATRX (NM_000489.4) c.6997G>T (p.Glu2333*, aka p.E2333*) AF: 28.9% BLM (NM_000057.2) c.503C>A (p.Ser168*, aka p.S168*) AF: 8.0% **BRCA1 (NM_007294.3) c.2158G>T (p.Glu720*, aka p.E720*) AF: 4.1%** BRCA2 (NM_000059.3) c.289G>T (p.Glu97*, aka p.E97*) AF: 34.5% BRCA2 (NM_000059.3) c.4552G>T (p.Glu1518*, aka p.E1518*) AF: 38.7% BRCA2 (NM_000059.3) c.6082G>T (p.Glu2028*, aka p.E2028*) AF: 36.2% BRCA2 (NM_000059.3) c.926C>A (p.Ser309*, aka p.S309*) AF: 36.3% CHEK2 (NM_007194.3) c.235G>T (p.Glu79*, aka p.E79*) AF: 6.5% **MRE11A (NM_005591.3) c.571C>T (p.Arg191*, aka p.R191*) AF: 15.4%** POLE (NM_006231.3) c.1270C>A (p.Leu424Ile, aka p.L424I) AF: 41.2% PTEN (NM_000314.4) c.388C>T (p.Arg130*, aka p.R130*) AF: 36.7% TP53 (NM_000546.5) c.637C>T (p.Arg213*, aka p.R213*) AF: 40.5% TP53 (NM_000546.5) c.916C>T (p.Arg306*, aka p.R306*) AF: 41.4% Additional Variants: ARID1A (NM_006015.4) c.148A>G (p.Met50Val, aka p.M50V) AF: 53.8% ATM (NM_000051.3) c.7199G>T (p.Arg2400Ile, aka p.R2400I) AF: 37.8% ATR (NM_001184.3) c.440A>C (p.Lys147Thr, aka p.K147T) AF: 39.3% **ATR (NM_001184.3) c.6208C>A (p.Leu2070Ile, aka p.L2070I) AF: 18.3%** **ATRX (NM_000489.4) c.1671G>T (p.Glu557Asp, aka p.E557D) AF: 1.2%** ATRX (NM_000489.4) c.1964G>T (p.Arg655Ile, aka p.R655I) AF: 32.7%	POLE (NM_006231.3) c.5609G>T (p.Arg1870Leu, aka p.R1870L) AF: 48.1% RAD51C (NM_058216.1) c.640C>T (p.Arg214Cys, aka p.R214C) AF: 46.0%

	ATRX (NM_000489.4) c.2716G>T (p.Asp906Tyr, aka p.D906Y) AF: 7.0% ATRX (NM_000489.4) c.2958A>C (p.Lys986Asn, aka p.K986N) AF: 32.1% **ATRX (NM_000489.4) c.3804G>T (p.Glu1268Asp, aka p.E1268D) AF: 7.9%** **ATRX (NM_000489.4) c.4441C>T (p.Arg1481Trp, aka p.R1481W) AF: 7.2%** ATRX (NM_000489.4) c.6236G>A (p.Arg2079Gln, aka p.R2079Q) AF: 27.0% ATRX (NM_000489.4) c.7210T>G (p.Cys2404Gly, aka p.C2404G) AF: 4.3% **BARD1 (NM_000465.2) c.1409A>G (p.Asn470Ser, aka p.N470S) AF: 6.0%** BRCA1 (NM_007294.3) c.3237A>C (p.Lys1079Asn, aka p.K1079N) AF: 41.3% **BRCA1 (NM_007294.3) c.7T>G (p.Leu3Val, aka p.L3V) AF: 1.7%** BRCA2 (NM_000059.3) c.3668A>G (p.His1223Arg, aka p.H1223R) AF: 5.5% BRCA2 (NM_000059.3) c.4416G>T (p.Lys1472Asn, aka p.K1472N) AF: 35.1% BRCA2 (NM_000059.3) c.4676T>G (p.Phe1559Cys, aka p.F1559C) AF: 37.6% BRCA2 (NM_000059.3) c.4949G>T (p.Ser1650Ile, aka p.S1650I) AF: 30.0% **BRCA2 (NM_000059.3) c.7850G>T (p.Arg2617Ile, aka p.R2617I) AF: 12.6%** **BRCA2 (NM_000059.3) c.8618T>G (p.Phe2873Cys, aka p.F2873C) AF: 5.3%** BRIP1 (NM_032043.2) c.3723T>G (p.Asn1241Lys, aka p.N1241K) AF: 26.7% BRIP1 (NM_032043.2) c.3734T>G (p.Phe1245Cys, aka p.F1245C) AF: 24.1% **BRIP1 (NM_032043.2) c.479G>T (p.Arg160Ile, aka p.R160I) AF: 5.6%** **CHEK1 (NM_001274.5) c.1136G>A (p.Arg379Gln, aka p.R379Q) AF: 1.2%** **CHEK1 (NM_001274.5) c.215G>A**	

	(p.Gly72Asp, aka p.G72D) AF: 7.2% **FANCA (NM_000135.2) c.334C>A (p.Leu112Ile, aka p.L112I) AF: 1.0%** **FANCC (NM_000136.2) c.238A>C (p.Ile80Leu, aka p.I80L) AF: 14.3%** **FANCD2 (NM_033084.3) c.4373T>C (p.Val1458Ala, aka p.V1458A) AF: 5.8%** **MRE11A (NM_005591.3) c.1380A>C (p.Glu460Asp, aka p.E460D) AF: 12.3%** **MRE11A (NM_005591.3) c.391G>A (p.Asp131Asn, aka p.D131N) AF: 5.8%** **NBN (NM_002485.4) c.927A>T (p.Glu309Asp, aka p.E309D) AF: 1.6%** POLE (NM_006231.3) c.1269T>A (p.Asn423Lys, aka p.N423K) AF: 41.3% POLE (NM_006231.3) c.3446C>T (p.Ala1149Val, aka p.A1149V) AF: 35.9% POLE (NM_006231.3) c.5609G>T (p.Arg1870Leu, aka p.R1870L) AF: 43.9% PTEN (NM_000314.4) c.424C>T (p.Arg142Trp, aka p.R142W) AF: 42.6% PTEN (NM_000314.4) c.460T>G (p.Phe154Val, aka p.F154V) AF: 40.6% **RAD50 (NM_005732.3) c.3080G>T (p.Arg1027Ile, aka p.R1027I) AF: 11.3%** RAD51C (NM_058216.1) c.640C>T (p.Arg214Cys, aka p.R214C) AF: 42.7% **FANCF (NM_022725.3) c.459G>T (p.Glu153Asp, aka p.E153D) AF: 7.2%** FANCL (NM_018062.3) c.288G>T (p.Lys96Asn, aka p.K96N) AF: 34.8% **FANCL (NM_018062.3) c.358A>C (p.Thr120Pro, aka p.T120P) AF: 5.7%** WRN (NM_000553.4) c.1486A>C (p.Lys496Gln, aka p.K496Q) AF: 22.4% **WRN (NM_000553.4) c.1781T>G (p.Val594Gly, aka p.V594G) AF: 2.3%** WRN (NM_000553.4) c.269A>C (p.Asn90Thr, aka p.N90T) AF: 39.2%	

Supplementary Table 3. Variants detected in patients were two ctDNA samples were tested.

10.3 "My bowels on track" smartphone application electronic surveys

10.3.1 General questionnaire

Question 1	When was your last bowel movement?
Options	1. Today 2. Yesterday 3. More than 2 days ago
Logic	○ If today or yesterday, proceed to question 2. ○ If more than 2 days ago, proceed to question 4.
Question 2	Display image of UHN Stool Chart (health tip)
Question 2	What type was your last bowel movement (poo)?
Options	○ Type 1: Hard, separate hard lumps, like nuts (hard to pass) ○ Type 2: Hard, sausage-shaped by lumpy ○ Type 3: Formed, like a sausage but with cracks on the surface ○ Type 4: Formed, like sausage or snake, smooth and soft ○ Type 5: Formed, soft blobs with clear-cut edges (passed easily) ○ Type 6: Loose, fluffy pieces with ragged edges, a mushy stool ○ Type 7: Watery, no solid pieces, all liquid.
Logic	▪ If Type 6 or 7, proceed to question 3 ▪ If Type 1, 2, 3, 4, or 5, proceed to question 4
Question 3	How many times have you had diarrhea?
Options	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ More than 5
Question 4	Have you taken any medications to help your bowels move?
Options	○ Yes ○ No
Logic	• If Yes, proceed to question 5 • If No, proceed to question 6
Question 5	Which medications have you taken?
Options	- Senokot - RestoraLAX/Lax-A-Day - Lactulose

	- Other: _____Free text_____
Question 6	Are you passing gas?
Options	• Yes • No
Question 7	How nauseous are you?
Options	1. User to respond with a scale of 0-10 (0 is no nausea, 10 is the most nauseous)
Question 8	Did you throw up in the last 24 hours?
Options	• Yes • No
Logic	- If Yes, proceed to question 9 - If No, proceed to question 10
Question 9	How many times did you throw up in the last 24 hours?
Options	○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ More than 5
Question 10	How many glasses of fluid (such as water) are you drinking in a day?
Options	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ More than 5
Question 11	How much pain do you have in your stomach or abdomen (tummy)?
Options	○ User to respond with a scale of 0 to 10 (0 is no pain, 10 is worse pain)
Question 12	Is your stomach (tummy) bloated or swollen?
Options	▪ Yes ▪ No
Logic	○ If Yes, proceed to question 13 ○ If No, complete questionnaire

Question 13	Does eating a small amount of food make you feel full?
Options	○ Yes ○ No

10.3.2 Questionnaire for patients with an ostomy

Question 1	When was your last bowel movement?
Options	- Today - Yesterday - More than 2 days ago
Logic	○ If today or yesterday, proceed to question 2. ○ If more than 2 days ago, proceed to question 4.
Question 2	Display image of UHN Stool Chart (health tip)
Question 2	What type was your last bowel movement (poo)?
Options	○ Type 1: Hard, separate hard lumps, like nuts (hard to pass) ○ Type 2: Hard, sausage-shaped by lumpy ○ Type 3: Formed, like a sausage but with cracks on the surface ○ Type 4: Formed, like sausage or snake, smooth and soft ○ Type 5: Formed, soft blobs with clear-cut edges (passed easily) ○ Type 6: Loose, fluffy pieces with ragged edges, a mushy stool ○ Type 7: Watery, no solid pieces, all liquid.
Logic	○ *If Type 6,7, proceed to question 3* ○ *If Type 1, 2, 3, 4, or 5, proceed to question 4*
Question 3	How many times have you had diarrhea?
Options	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ More than 5
Question 4	How many times did you empty your ostomy in the last 24 hours?
Options	▪ 0 ▪ 1 ▪ 2 ▪ 3 ▪ 4

	▪ 5 ▪ More than 5
Question 5	Have you taken any medications to help your bowels move?
Options	○ Yes ○ No
Logic	▪ *If Yes, proceed to question 5* ▪ *If No, proceed to question 6*
Question 6	Which medications have you taken?
Options	○ Senokot ○ RestoraLAX/Lax-A-Day ○ Lactulose ○ Other: _____Free text_____
Question 7	Are you passing gas?
Options	• Yes • No
Question 8	How nauseous are you?
Options	▪ User to respond with a scale of 0-10 (0 is no nausea, 10 is the most nauseous)
Question 9	Did you throw up in the last 24 hours?
Options	○ Yes ○ No
Logic	• If Yes, proceed to question 9 • If No, proceed to question 10
Question 10	How many times did you throw up in the last 24 hours?
Options	• 1 • 2 • 3 • 4 • 5 • More than 5
Question 11	How many glasses of fluid (such as water) are you drinking in a day?
Options	• 0 • 1 • 2 • 3

	• 4 • 5 • More than 5
Question 12	How much pain do you have in your stomach or abdomen (tummy)?
Options	• User to respond with a scale of 0 to 10 (Zero is no pain, 10 is worse pain)
Question 13	Is your stomach (tummy) bloated or swollen?
Options	○ Yes ○ No

10.3.3 Questionnaire for patients on parenteral nutrition

Question 1	How nauseous are you?
Options	○ User to respond with a scale of 0-10 (0 is no nausea, 10 is the most nauseous)
Question 2	Did you throw up in the last 24 hours?
Options	○ Yes ○ No
Logic	○ If Yes, proceed to question 3 ○ If No, proceed to question 4
Question 3	How many times did you throw up in the last 24 hours?
Options	▪ 1 ▪ 2 ▪ 3 ▪ 4 ▪ 5 ▪ More than 5
Question 4	How many glasses of fluid (such as water) are you drinking in a day?
Options	▪ 0 ▪ 1 ▪ 2 ▪ 3 ▪ 4 ▪ 5 ▪ More than 5
Question 5	How much pain do you have in your stomach or abdomen (tummy)?

Options	▪ User to respond with a scale of 0 to 10 (Zero is no pain, 10 is worse pain)
Question 6	Do you feel more bloated than usual?
Options	- Yes - No
Question 7	Have you had diarrhea?
Options	- Yes - No
Logic	o If Yes, proceed to question 8 o If No, end
Question 8	How many times have you had diarrhea?
Options	o 1 o 2 o 3 o 4 o 5 o More than 5

10.4 “My bowels on track” smartphone application alert system

The alerting system includes red or high-level alerts, and yellow or medium level alerts. The level of the alerting system is used to prioritize the phone calls and patient assessment.

10.4.1 Alerting system for patients answering the general questionnaire.

Passing Gas & Bowel Movement/Constipation

	Constipated (>2 days)	**Not constipated (Today, yesterday)**
Passing Gas	Yellow	No alert
Not passing gas	Red	No alert

Vomiting & Fluid Consumption

Frequency	**0 - 1 cups of fluid**	**2 or more cups of fluid**
Vomiting = 1	Yellow	No alert
Vomiting = 2 or = 3	Red	Yellow
Vomiting = 4 or more	Red	Red

Stomach Pain

Level of pain	
Stomach pain (0-3)	No alert
Stomach pain (4-6)	Yellow
Stomach pain (7-10)	Red

Nausea & Fluid Consumption

Severity	**0-1 cups of fluid**	**2 or more cups of fluid**
Low nausea (0-3)	No alert	No alert
Medium nausea (4-6)	Yellow	No alert
High nausea (7-10)	Red	Yellow

Diarrhea

Frequency	
0-3	No alert
4-5	Yellow
more than 5	Red

10.4.2 Alerting system for patients with a colostomy.

Vomiting & Fluid Consumption

Frequency	0 - 1 Cups of Fluid	2 or more Cups of Fluid
Vomiting = 1	Yellow	No alert
Vomiting = 2 or = 3	Red	Yellow
Vomiting = 4 or more	Red	Red

Stomach Pain

Level of pain	
Stomach pain (0-3)	No alert
Stomach pain (4-6)	Yellow
Stomach pain (7-10)	Red

Emptying Ostomy Bag

Frequency	
0	Red
1 to 4	No alert
5	Yellow
more than 5	Red

Type of Bowel Movement (based on Bristol stool chart)

Type 1	Red
Type 2	Red
Type 3	No alert
Type 4	No alert
Type 5	No alert
Type 6	No alert
Type 7	Red

Passing gas and bowel movement/constipation

	Constipated (more than 2 days)	Not constipated (Today, Yesterday)
Passing Gas	Yellow	No alert
Not passing gas	Red	No alert

Diarrhea

Frequency	
0-3	No alert
4-5	Yellow
more than 5	Red

10.4.3 Alerting system for patients with an ileostomy.

Vomiting and fluid consumption

Frequency	0 - 1 cups of fluid	2 or more cups of fluid
Vomiting = 1	Yellow	No alert
Vomiting = 2 or = 3	Red	Yellow
Vomiting = 4 or more	Red	Red

Stomach Pain

Level of pain	
Stomach pain (0-3)	No alert
Stomach pain (4-6)	Yellow
Stomach pain (7-10)	Red

Emptying Ostomy Bag

Frequency	
0	Red
1 to 4	No alert
5	Yellow
more than 5	Red

Type of bowel movement (based on Bristol stool chart)

Type 1	Red
Type 2	Red
Type 3	Yellow
Type 4	No alert
Type 5	No alert
Type 6	No alert
Type 7	Yellow

Passing gas and bowel movement/constipation

	Constipated (more than 2 days)	Not constipated (today, yesterday)
Passing Gas	Yellow	No alert
Not passing gas	Red	No alert

10.4.4 Alerting system for patients on parenteral nutrition.

Vomiting and fluid consumption

Frequency	0 - 1 cups of fluid	2 or more cups of fluid
Vomiting = 1	Yellow	No alert
Vomiting = 2 or = 3	Red	Yellow
Vomiting = 4 or more	Red	Red

Stomach pain

Level of pain	
Stomach pain (0-3)	No alert
Stomach pain (4-6)	Yellow
Stomach pain (7-10)	Red

Diarrhea

Frequency	
0-3	No alert
4-5	Yellow
more than 5	Red

Bloating and stomach pain

Bloating	Stomach Pain 0-4	Stomach Pain 5-7	Stomach Pain 8-10
Yes	No Alert	Yellow	Red
No	No Alert	No Alert	No Alert

10.5.5 Alerting system for patients not answering the questionnaires.

1st day receiving the questionnaire	No alert
2nd day receiving the questionnaire	Non-compliance alert

10.5 "My bowels on track" smartphone application patient self-management recommendations

Passing gas and constipation alerts

	Constipated (more than 2 days)	
Passing Gas	Yellow	Please remember to eat a low fibre diet. For more information, please check out your resource library for additional tips to help alleviate constipation.
Not passing gas	Red	Please wait for a phone call from your nurse.

Vomiting and Fluid Consumption

Frequency	**0 - 1 Cups of Fluid**		**2 or more Cups of Fluid**	
Vomiting = 1	Yellow	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.	No alert	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.
Vomiting = 2 or 3	Red	Please wait for a phone call from your nurse.	Yellow	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.
Vomiting = 4 or more	Red	Please wait for a phone call from your nurse.	Red	Please wait for a phone call from your nurse.

Stomach Pain

Level of pain	**Alert**	
Stomach pain (0-3)	No alert	N/A
Stomach pain (4-6)	Yellow	Please wait for a phone call from your nurse.
Stomach pain (7-10)	Red	Please wait for a phone call from your nurse.

Nausea and fluid Consumption

Severity of nausea	0-1 Cups of Fluid		2 or more Cups of Fluid	
No nausea (0)	No alert	N/A	No alert	N/A
Low nausea (1-3)	No alert	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.	No alert	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.
Medium nausea (4-6)	Yellow	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.	No alert	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.
High nausea (7-10)	Red	Please wait for a phone call from your nurse.	Yellow	Please try to keep yourself hydrated and remember to follow your anti-nausea strategies. For more information, please check out your resource library for additional tips.

Diarrhea

Frequency	Alert	
0-3	No alert	N/A
4-5	Yellow	Please wait for a phone call from your nurse.
more than 5	Red	Please wait for a phone call from your nurse

10.6 “My bowels on track” smartphone application nurse satisfaction survey

Thank you for agreeing to participate in the survey. If you return the questionnaire, you will be agreeing to analyze the feedback you provided. Your responses will be anonymous and no personal health information about yourself will be collected.

1- How comfortable are you with reviewing the electronic assessment?
   - o High
   - o Medium
   - o Low

2- Do you feel the electronic assessment for malignant bowel obstruction takes less of your time than regular phone calls?
   - o Yes, it takes less
   - o No, it takes more time
   - o It’s similar

3- Do you think that an electronic version of malignant bowel obstruction monitoring has impacted patient care?
   - o It has improved
   - o It has worsened
   - o It’s similar

4- Do you think that an electronic version of malignant bowel obstruction monitoring has impacted patient experience?
   - o It has improved
   - o It has worsened
   - o It’s similar

5- Has the electronic version of malignant bowel obstruction impacted in your nursing’s satisfaction with care delivery?
   - o It has improved
   - o It has worsened
   - o It’s similar

6- Perception:
“I understand advantages and disadvantages of electronic monitoring.”
   - o Yes
   - o No

7- Safety:
“I can check patients' MBO condition through electronic monitoring as in-phone follow ups”
   - o Yes
   - o No

“Patients reporting severe symptoms will receive timely responses through app alerts on the desktop.”

- Yes
- No

8- Satisfaction:
“Electronic monitoring is convenient to use compared with the phone follow up.”
- Yes
- No

“Overall, I am satisfied with this electronic monitoring system.”
- Yes
- No

“I would use electronic monitoring services again.”
- Yes
- No

9- Necessity:
“In emergent situations, such as COVID-19 pandemic, electronic monitoring of MBO is needed.”
- Yes
- No

“Electronic monitoring of MBO is needed regardless of emergent situations such as COVID-19”
- Yes
- No

“Electronic monitoring of MBO can reduce nurse-led proactive phone calls to only responding to severe symptoms.”
- Yes
- No

Please note that by completing and submitting the questionnaire you agree the answers will be used for research purpose.