A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3Kα Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer

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The primary objective of this phase 2 study in patients with advanced endometrial cancer is to compare the clinical efficacy of MLN0128 + weekly paclitaxel to weekly paclitaxel alone in second- or third-line treatment of advanced, recurrent, or...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Uterine, pelvic and broad ligament disorders
Study type	Interventional

Summary

ID

NL-OMON48725

Source
ToetsingOnline

Brief title
C31004

Condition

- Uterine, pelvic and broad ligament disorders

Synonym
endometrium cancer, uterus cancer

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Millennium Pharmaceuticals;Inc.

Intervention

Keyword: endometrial cancer, endometrial carcinoma, gynecological cancer

Outcome measures

Primary outcome

Primary

• To determine if MLN0128 in combination with weekly paclitaxel improves progression free survival (PFS) compared to weekly paclitaxel alone.

Secondary outcome

Secondary

• To determine if single-agent MLN0128 improves PFS compared to weekly paclitaxel alone.

• To determine if MLN0128 + MLN1117 improves PFS compared to weekly paclitaxel alone.

• To assess the safety and tolerability of single-agent MLN0128, MLN0128 in combination with paclitaxel, and MLN0128 + MLN1117.

• To evaluate improvement in efficacy measures (endpoints other than PFS) of MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128 + MLN1117 to weekly paclitaxel alone.

• To collect plasma concentration-time data with sparse pharmacokinetic (PK) sampling to contribute to future population PK analysis.

Quality of Life (QOL)

• To assess the QOL and symptoms in patients treated with MLN0128 in combination with weekly paclitaxel, single-agent MLN0128, and MLN0128 + MLN1117 to weekly paclitaxel alone.

Exploratory

• To identify clinical response markers in archival and fresh tumor tissue specimens and circulating tumor DNA (ctDNA).

• To identify adaptive response mechanisms to single-agent MLN0128 or MLN0128 + MLN1117.

• To understand the effects of genetic polymorphisms in drug metabolizing enzymes and/or transporters that may be implicated in the disposition of MLN0128 and/or MLN1117 as part of population PK analyses.

Study description

Background summary

Endometrial cancer is the most common gynecological malignancy with an estimated 287,000 new cases per year worldwide.[1] It is the fourth most common malignancy among women in the US, with an estimated 52,000 new cases and 8,600 deaths in 2013.[2]
Endometrial carcinomas are classified into 2 major types (I and II), based upon light microscopic appearance, clinical behavior, and epidemiology. Type I carcinomas include tumors of endometrioid histology that are Grade 1 or 2. These comprise approximately 80% of endometrial carcinomas and typically have a favorable prognosis, are estrogen responsive, and may be preceded by an intraepithelial neoplasm. Type II tumors account for 10% to 20% of endometrial carcinomas and include Grade 3 endometrioid tumors as well as tumors of non endometrioid histology (serous, clear-cell, mucinous, squamous, transitional cell, mesonephric, carcinosarcoma, and undifferentiated). These tumors are often high grade, have a poor prognosis, and are not clearly associated with

estrogen stimulation. A precursor lesion in type II tumors is rarely identified. Systemic treatment for metastatic and relapsed endometrial cancer consists of endocrine therapy or cytotoxic chemotherapy. In nonrandomized trials, paclitaxel with carboplatin or cisplatin demonstrated a response rate > 60% and a possibly prolonged survival compared with historical experience with other nonpaclitaxel-containing regimens. Results from randomized trials showed a similar response when paclitaxel was added to first-line platinum-containing regimens.[3] Based on these results, paclitaxel-based combination regimens are preferred for first-line chemotherapy of advanced and recurrent endometrial cancer.[4] According to the European Society for Medical Oncology (ESMO) guidelines, endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Various agents have been tested in a number of small phase 2 trials in patients previously exposed to chemotherapy, but the available options and response remain limited.[5] Only high-dose paclitaxel has consistently shown a response rate greater than 20%.
Dose-dense weekly administration of paclitaxel is a proven strategy to further enhance anti tumor activity, especially in the re-treatment setting.
Preclinical and clinical studies have proven that the duration of paclitaxel exposure is an important determinant of its cytotoxic effect. Thus, cytotoxicity can be enhanced at fairly low concentrations of paclitaxel provided that the exposure is extended, eg, through weekly administration.[6-8]
Molecular studies showed that endometrioid neoplasms have a different genetic profile than non-endometrioid neoplasms. Endometrioid carcinomas form 3 subgroups. one with high rates of microsatellite instability, one with POLE mutations leading to ultra-high mutation rates, and one with relatively low mutation rates and exhibiting a microsatellite stable phenotype.[35] Broadly, these tumors are defined by high rate of PTEN mutations and a relative lack of TP53 mutations. Specific mutations in FGFR2, ERBB2, PIK3CA, PIK3R1, KRAS, SOX17 and CTNNB1 (*-catenin) genes are also associated with this tumor type.[35,36]
In contrast, serous and serous-like endometrial carcinomas exhibit extensive somatic copy number alterations. Common molecular findings in the serous subtype include p53 and PIK3CA mutations as well as ERBB2 and KRAS amplifications and PTEN deletions.[35,37] Despite these genetic differences between endometrioid and non-endometrioid carcinomas it is apparent that both histological populations show high rates of genomic alterations of the PI3K-AKT-mTOR pathway that may be sensitive to treatment with a dual TORC1/TORC2 inhibitor such as MLN0128. In addition, the combination of a PI3Kα inhibitor (MLN1117) with a TORC1/2 inhibitor (MLN0128) would be expected to provide more robust inhibition of the PI3K AKT mTOR pathway than either agent alone.

Study objective

The primary objective of this phase 2 study in patients with advanced endometrial cancer is to compare the clinical efficacy of MLN0128 + weekly paclitaxel to weekly paclitaxel alone in second- or third-line treatment of advanced, recurrent, or persistent endometrial cancer. In addition, the

clinical efficacy of single-agent MLN0128 and the combination of MLN0128 + MLN1117 will be compared to weekly paclitaxel alone.
This study will test the following 2 hypotheses: 1) that sequential administration of paclitaxel + MLN0128 can potentiate the cytotoxic effects of paclitaxel and improve treatment outcomes compared to single-agent paclitaxel and 2) that TORC1/2 inhibition either with or without additional PI3Kα inhibition will provide better efficacy compared with the single-agent cytotoxic effects of paclitaxel in patients with advanced recurrent endometrial cancer and progressive disease after platinum-containing cytotoxic chemotherapy.

Study design

Eligibility will be determined during the Screening period, which may last for up to 28 days before the Cycle 1 Day 1 visit. Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study.
Study drug will be administered in 28-day treatment cycles.
Approximately 260 patients will be randomized at a ratio of 1:1:1:1 to receive study drug in 1 of 4 treatment arms:
• Arm A: paclitaxel 80 mg/m2 weekly on Days 1, 8, and 15 of a 28-day cycle
• Arm B: paclitaxel 80 mg/m2 weekly on Days 1, 8, and 15 of a 28-day cycle + MLN0128 4 mg on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle
• Arm C: MLN0128 30 mg once weekly (QW) on Days 1, 8, 15, and 22 of a 28-day cycle
• Arm D: MLN0128 4 mg + MLN1117 200 mg on Days 1-3, 8-10, 15-17, and 22-24 of a 28 day cycle
In the event that enrollment into a treatment arm(s) is closed, patients will be randomized 1:1 into the remaining treatment arms.

Intervention

Paclitaxel will be administered intravenously (IV) whereas MLN0128 and MLN1117 will be administered by mouth (PO) throughout the study. Patients in Arm A and Arm B will receive paclitaxel alone or paclitaxel + MLN0128 until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients in Arm B who discontinue paclitaxel before disease progression may continue to receive MLN0128 alone until they experience disease progression, unacceptable toxicity, or withdraw consent. In addition, patients will receive MLN0128 (in Arm C) or MLN0128 + MLN1117 (in Arm D) continuously until they experience disease progression, unacceptable toxicity, or withdraw consent. Patients who discontinue study treatment for reasons other than progressive disease will continue to have PFS follow-up visits every 2 months for the first 6 months after the end-of-treatment (EOT) visit, then every 3 months until disease progression, death, or start of another anticancer therapy, whichever occurs first. After disease progression, patients will be followed for overall survival (OS) every 3 months.

Patients will attend the EOT visit 30 to 40 days after receiving their last dose of study drug.
Sparse PK samples will be collected from patients enrolled in Arms B, C, and D for determination of the plasma concentration of MLN0128 and/or MLN1117 during Cycle 1 at prespecified time points. Data generated in this study will be combined with data from other studies in which the PK of MLN0128 is characterized for population PK analysis. For correlative biomarker analysis, fresh and archival tumor samples will be obtained during screening, as well as a blood sample for ctDNA at prespecified time points. In addition, fresh tumor samples will be obtained on Cycle 1 Day 22 from patients in Arms C and D to identify adaptive response mechanisms to treatment of MLN0128 or MLN0128 + MLN1117.
Radiological tumor evaluations (computed tomography [CT] scan with IV contrast or magnetic resonance imaging [MRI] with contrast, as clinically indicated) of the chest, abdomen, and pelvis will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1).
Changes in QOL disease-specific symptoms will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and the Endometrial Cancer Module (EORTC QLQ-EN24).
Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events. Adverse events will be assessed, and laboratory values, vital signs, and electrocardiograms will be obtained to evaluate the safety and tolerability of MLN0128 in combination with paclitaxel, single-agent MLN0128, and MLN0128 + MLN1117.

Study burden and risks

The most common TEAEs observed with MLN0128 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual mTORC1/2 inhibitors. The TEAEs observed across the MLN0128 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite. Potential overlapping toxicities associated with MLN0128 and MLN1117, the identified and potential risks of both drugs, including data from nonclinical and clinical studies for each product, have been reviewed. More detailed information on the identified and potential risks of both drugs is included in the individual single-agent IBs. Class effects of mTOR inhibitors (for MLN0128) and PI3K inhibitors (for MLN1117) have also been considered. Potential overlapping toxicities for both agents include:
• Dermatologic disorders (pruritus, rash)
• Gastrointestinal disorders (diarrhea, mucosal inflammation, nausea, stomatitis, vomiting)
• Generalized disorders (anorexia, asthenia, decreased appetite, fatigue)
• Hematologic disorders (lymphoid, bone marrow depletion)

• Metabolic disorders (decreased blood chloride, hypercholesterolemia, hyperglycemia)
On the basis of current clinical experience and the previous list of potential overlapping toxicities, hyperglycemia, diarrhea, nausea, vomiting, fatigue, and rash are the most anticipated TEAEs associated with the MLN0128 + MLN1117 combination regimen. These events are expected to be manageable.
During this study, risk mitigation strategies include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of TEAEs and serious adverse events (SAEs) by the sponsor.
The benefits of MLN0128 and MLN0128 + MLN1117 are discussed in Sections 1.2 and 1.3 of the protocol, respectively.
Further details are presented in the current editions of the MLN0128, MLN0128 + MLN1117, and MLN1117 IBs.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologic or cytologic diagnosis of endometrial carcinoma (including endometrioid, serous, mixed adenocarcinoma, clear-cell carcinoma, or carcinosarcoma)
2. Evidence that the endometrial cancer is advanced, recurrent, or persistent and has relapsed or is refractory to curative therapy or established treatments.
3. At least 1 prior platinum-based chemotherapeutic regimen, but not more than 2 prior chemotherapeutic regimens, for management of endometrial carcinoma. Prior treatment may include chemotherapy, chemotherapy/radiation therapy, and/or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primaryradiation as a radio-sensitized therapy will be considered a systemic chemotherapy regimen.
4. Measureable disease by RECIST 1.1, defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded). Each lesion must be >= 10 mm in long axis when measured by CT, MRI, or caliper measurement by clinical exam. Lymph nodes must be >= 15 mm in short axis when measured by CT or MRI.
5. Tumor accessible and patient consents to undergo fresh tumor biopsies.
6. Female patients 18 years or older.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
8. Female patients who:
- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method of contraception, and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 90 days (or longer, as mandated by local labeling [eg, USPI,
SmPC, etc.]) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg,calendar, ovulation, symptothermal, postovulation methods] and
withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
9. Clinical laboratory values as specified below within 4 weeks before the first dose of study drug:
- Bone marrow reserve consistent with absolute neutrophil count (ANC) >= 1500/uL; platelet count >= 100,000/uL; hemoglobin A1c (HbA1c) <6.5%.
- Total bilirubin must be less than or equal to 1.5 x the upper limit of normal (ULN).
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be less than or equal to 2.5 the upper limit of the normal range. AST and ALT may be elevated up to 5 times the ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in liver.
- Creatinine clearance >= 50 mL/min/1.73 m2 based either on Cockcroft-Gault estimate or based on a 12- or 24-hour urine collection.
- Fasting serum glucose < 130 mg/dL and fasting triglycerides <= 300 mg/dL.

10. Ability to swallow oral medications, willingness to perform mucositis prophylaxis, and suitable venous access for the study-required blood sampling.
11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion criteria

1. Positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug. Women who are lactating and breastfeeding are not eligible.
2. Previous treatment with any weekly taxane regimen.
3. History of severe hypersensitivity reactions to paclitaxel or any of its excipients.
4. Previous treatment with PI3K, AKT, dual PI3K/mTOR inhibitors,TORC1/2 inhibitorsor TORC1 inhibitors.
5. Initiation of treatment with hematopoietic growth factors, transfusions of blood and blood products, or systemic corticosteroids (either IV or oral steroids, excluding inhalers) within 1 week before administration of the first dose of study drug (patients already receiving erythropoietin on a chronic basis for >= 4 weeks are eligible).
6. Patients who are taking proton pump inhibitors (PPIs) within 7 days of the first dose of study drug or who require treatment with PPIs throughout the trial or those who are taking H2 receptor antagonists within 24 hours of the first dose of study drug.
7. A prothrombin time (PT) or activated partial thromboplastin time (aPTT) above the ULN or a history of a coagulopathy or bleeding disorder.
8. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
9. Sensory or motor neuropathy >= Grade 2.
10. Central nervous system (CNS) metastasis, endometrial leiomyosarcoma, or endometrial stromal sarcoma.
11. Manifestations of malabsorption due to prior gastrointestinal surgery, gastrointestinal disease, or for some other reason that may alter the absorption of MLN0128 or MLN1117. In addition, patients with enteric stomata are also excluded.
12. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active CNS disease, active infection, or any other condition that could compromise participation of the patient in the study.
13. Known human immunodeficiency virus infection.
14. History of any of the following within the last 6 months before administration of the first dose of study drug:
- Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures.
- Ischemic cerebrovascular event, including transient ischemic attack and arteryrevascularization procedures.
- Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).

- Placement of a pacemaker for control of rhythm.
- New York Heart Association Class III or IV heart failure (see Section 14.3).
- Pulmonary embolism.
15. Significant active cardiovascular or pulmonary disease before administration of the first dose of study drug, including:
- Uncontrolled hypertension (ie, either systolic blood pressure >180 mm Hg; diastolic blood pressure > 95 mm Hg).
- Uncontrolled asthma or oxygen saturation < 90% by arterial blood gas analysis or pulse oximetry on room air.
- Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention; or history of valve replacement.
- Medically significant (symptomatic) bradycardia.
- History of arrhythmia requiring an implantable cardiac defibrillator.
- Baseline prolongation of the rate-corrected QT interval (QTc; eg, repeated demonstration of QTc interval > 480 ms, or history of congenital long QT syndrome or torsades de pointes).
16. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type
are not excluded if they have undergone complete resection.
17. Patients with endometrioid histology and histologically confirmed expression of estrogen receptors (ER) and/or progesterone receptors (PgR) who have not received prior endocrine therapy and for whom endocrine therapy is currently indicated.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-04-2018

Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MLN0128
Generic name:	n/a
Product type:	Medicine
Brand name:	MLN1117
Generic name:	n/a
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-005394-37-NL
ClinicalTrials.gov	NCT02725268
CCMO	NL61519.018.17