Phase 2 Study of MLN0128, Combination of MLN0128 With MLN1117, Paclitaxel and Combination of MLN0128 With Paclitaxel in Women With Endometrial Cancer

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2016 by Takeda

Sponsor:
Millennium Pharmaceuticals, Inc.

Collaborators:
European Network of Translational Research in Ovarian Cancer - EUTROC
European Network of Individualized Treatment in Endometrial Cancer - ENITEC

Information provided by (Responsible Party):
Takeda (**Millennium** Pharmaceuticals, Inc.)

ClinicalTrials.gov Identifier:
NCT02725268

First received: March 28, 2016
Last updated: November 2, 2016
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History of Changes

Purpose

The primary purpose of this study is to determine if MLN0128 in combination with weekly paclitaxel improves progression-free survival (PFS) compared to weekly paclitaxel alone.

Condition	Intervention	Phase
Endometrial Neoplasms	Drug: Paclitaxel Drug: MLN0128 Drug: MLN1117	Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: 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

Resource links provided by NLM:

Drug Information available for: Paclitaxel

U.S. FDA Resources

Further study details as provided by Takeda:

Primary Outcome Measures:

- Progression Free Survival (PFS) [Time Frame: Up to 30 months]

  PFS is defined as the time from the date of randomization to the date of first documentation of progressive disease or death due to any cause, whichever occurs first. For a participant who has not progressed and is last known to be alive, PFS will be censored at the last response assessment that is stable disease (SD) or better.

Secondary Outcome Measures:

- Percentage of Participants who Experience at Least One Treatment-emergent Adverse Event (TEAE) [Time Frame: From the first dose of study drug through 30 days after the last dose of study drug (Up to 30 Months)]

- Overall Survival (OS) [Time Frame: Up to 30 months]

  OS is defined as the time from the date of randomization to the date of death. Participants without documentation of death at the time of analysis will be censored at the date last known to be alive.

- Time to Progression (TTP) [Time Frame: Up to 30 months]

  TTP is defined as the time from the date of randomization to the date of first documentation of progression. For a participant who has not progressed, TTP will be censored at the last response assessment that is stable disease (SD) or better.

- Overall Response Rate (ORR) [Time Frame: Up to 30 months]

  ORR is defined as the percentage of participants who achieve a best response of a complete response (CR) or partial response (PR) using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. CR: Disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR: At least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions.

- Clinical Benefit Rate (CBR) [Time Frame: Up to 30 months]

  CBR is defined as the percentage of participants with complete response (CR) or partial response (PR) or stable disease (SD).

- Clinical Benefit Rate (CBR) at Week 16 (CBR-16) [Time Frame: Up to 30 months]

  CBR-16 is defined as the percentage of participants who achieve CR or PR of any duration or have SD with a duration of at least 16 weeks.

Estimated Enrollment:	260
Study Start Date:	June 2016
Estimated Study Completion Date:	December 2018
Estimated Primary Completion Date:	December 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Paclitaxel 80 mg/m^2 Paclitaxel 80 mg/m^2, IV, weekly on Days 1, 8, and 15 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent.	Drug: Paclitaxel Paclitaxel intravenous solution
Experimental: Paclitaxel 80 mg/m^2 + MLN0128 4 mg Paclitaxel 80 mg/m^2, IV, weekly on Days 1, 8, and 15 of a 28-day cycle along with MLN0128 4 mg, capsule, orally on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent.	Drug: Paclitaxel Paclitaxel intravenous solution Drug: MLN0128 MLN0128 capsules
Experimental: MLN0128 30 mg MLN0128 30 mg, capsule, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent.	Drug: MLN0128 MLN0128 capsules
Experimental: MLN0128 4 mg + MLN1117 200 mg MLN0128 4 mg, capsule, orally and MLN1117 200 mg, capsule, orally on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent.	Drug: MLN0128 MLN0128 capsules Drug: MLN1117 MLN1117 capsules

Detailed Description:

The drugs being evaluated in this study are MLN0128 and MLN1117. MLN0128 is being evaluated as a single agent and in combination with paclitaxel or MLN1117 to treat women with advanced, recurrent, or persistent endometrial cancer. This study will evaluate the efficacy and safety of each drug or drug combination.

The study will enroll approximately 260 patients. Participants will be randomly assigned (by chance, like flipping a coin) to one of 4 treatment groups:

- Paclitaxel 80 mg/m^2 weekly
- Paclitaxel 80 mg/m^2 weekly + MLN0128 4 mg 3 consecutive days each week
- MLN0128 30 mg weekly
- MLN0128 4 mg + MLN1117 200 mg both given 3 consecutive days each week

Participants will receive either Paclitaxel intravenous (IV) weekly, Paclitaxel IV along with MLN0128 orally, MLN0128 orally, or MLN0128 and MLN1117 orally.

This is a multicenter, multinational trial. Participants will make multiple visits to the clinic, with an end of treatment visit (EOT) which will occur 30 to 40 days after receiving their last dose of study drug or before the start of any subsequent anticancer therapy. After EOT, participants will be followed for PFS and overall survival (OS).

Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Sexes Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

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 primary radiation as a radio-sensitized therapy will be considered a systemic chemotherapy regimen.
4. Measureable disease by Response Evaluation Criteria in Solid Tumors (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 computed tomography (CT), magnetic resonance imaging (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, United States Prescribing Information (USPI), Summary of Product Characteristics (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], 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/μL; platelet count ≥ 100,000/μL; hemoglobin A1c (HbA1c) < 6.5%.
    - Total bilirubin must be ≤ 1.5 x the upper limit of normal (ULN).
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be ≤ 2.5 x 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 m^2 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 phosphoinositide 3-kinase (PI3K), serine/threonine-specific protein kinase (AKT), dual PI3K/ mammalian (or mechanistic) target of rapamycin (mTOR) inhibitors, target of rapamycin complex 1/2 (TORC1/2) inhibitors or TORC1 inhibitors.
5. Treatment with strong inhibitors and/or inducers of cytochrome P450 3A4 (CYP3A4), CYP2C9, or CYP2C19 within 1 week preceding the first dose of study drug.
6. Initiation of treatment with hematopoietic growth factors, transfusions of blood and blood products, or systemic corticosteroids (either intravenous (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).
7. 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.
8. A prothrombin time (PT) or activated partial thromboplastin time (aPTT) above the ULN or a history of a coagulopathy or bleeding disorder.
9. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
10. Sensory or motor neuropathy ≥ Grade 2.
11. Central nervous system (CNS) metastasis, endometrial leiomyosarcoma, or endometrial stromal sarcoma.

12. 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.
13. 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.
14. Known human immunodeficiency virus infection.
15. 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 artery revascularization 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.
    - Pulmonary embolism.
16. 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 or diastolic blood pressure > 95 mm Hg).
    - Pulmonary hypertension.
    - 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).
17. 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.
18. 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.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02725268

Contacts

Contact: Takeda Study Registration Call Center +1-866-835-2233 GlobalOncologyMedinfo@takeda.com

Show 62 Study Locations

Sponsors and Collaborators

Millennium Pharmaceuticals, Inc.

European Network of Translational Research in Ovarian Cancer - EUTROC

European Network of Individualized Treatment in Endometrial Cancer - ENITEC

Investigators

Study Director: Medical Monitor **Millennium** Pharmaceuticals, Inc.

More Information

Responsible Party:	**Millennium** Pharmaceuticals, Inc.
ClinicalTrials.gov Identifier:	NCT02725268 History of Changes
Other Study ID Numbers:	**C31004** U1111-1168-1824 (Registry Identifier: WHO) 2014-005394-37 (EudraCT Number)
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Keywords provided by Takeda:
Drug Therapy

Additional relevant MeSH terms:

Endometrial Neoplasms	Paclitaxel
Uterine Neoplasms	Albumin-Bound Paclitaxel
Genital Neoplasms, Female	Antineoplastic Agents, Phytogenic
Urogenital Neoplasms	Antineoplastic Agents
Neoplasms by Site	Tubulin Modulators
Neoplasms	Antimitotic Agents
Uterine Diseases	Mitosis Modulators
Genital Diseases, Female	Molecular Mechanisms of Pharmacological Action

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