Essai Clinique

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Titre	ATARI: ATr Inhibitor in Combination With Olaparib in Gynaecological Cancers With ARId1A Loss
Protocole ID	ATARI
ClinicalTrials.gov ID	NCT04065269
Type(s) de cancer	Endomètre Ovaire
Phase	Phase II
Type étude	Clinique
Médicament	AZD6738 avec olaparib
Institution	CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL
Ville	
Investigateur principal	Dre Diane Provencher
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Statut	Fermé
But étude	ATARI is a multi-centre, open-label, multiple two-stage parallel cohorts phase II clinical trial for patients with relapsed gynaecological cancers, with ARID1A-deficient ('loss') and "no loss."The trial tests the ATR inhibitor drug AZD6738 and a PARP inhibitor drug olaparib to assess the response in groups of patients selected based on their cancer cell subtype and the presence of an abnormality in ARID1AThe treatment groups are: 1A - Women with clear cell subtype with (ovarian/uterus) ARID1A loss treated with AZD6738. 1B - Women with clear cell subtype with (ovarian/uterus) ARID1A loss treated with AZD6738 + olaparib. 2 - Women with clear cell subtype (ovarian/uterus) with no ARID1A loss treated with AZD6738 and olaparib. 3 - Women with other rare gynaecological cancers (carcinosarcoma, cervical, endometrioid type) irrespective of ARID1A loss treated with AZD6738 and olaparib.

Critères d'éligibilité	• Histologically confirmed progressive or recurrent gynaecological carcinomas of the following histological subtypes:
	  • Ovarian and endometrial clear cell (>50% clear cell carcinoma with no serous differentiation)
	  • Endometrioid
	  • Cervical - adenocarcinomas and squamous
	  • Carcinosarcomas Note: patients who have an original diagnosis based on cytology only will not be eligible for entry into the study unless a biopsy confirming above histology is performed
	• Histological tissue specimen (tissue block or 8-10 unstained slides) must be available (specimen can be the sample at diagnosis or taken at relapse). Otherwise, a biopsy must be carried out to obtain sufficient tissue for histological assessment
	• Evidence of radiological disease progression since last systemic anti-cancer therapy and prior to trial entry
	• Patients who have progressed after ≥1 prior platinum containing regimen. Platinum-based therapy does not need to be the last treatment prior to study entry. For patients who have disease progression within 6 months of last dose of a platinum-containing regime, no more than two further lines of systemic therapy are permitted prior to trial entry
	• Measurable disease by RECIST criteria v1.1, which can be accurately assessed at baseline by CT (or MRI where CT is contradicted or unclear). Patients with CA125 progression in the absence of measurable disease will NOT be eligible
	• ECOG performance status 0 or 1 with no deterioration over the previous 2 weeks
	• Life expectancy > 16 weeks
	• Adequate hepatic, bone marrow, coagulation and renal function as defined by the following

values within 14 days prior to starting treatment:
    - Haemoglobin ≥10.0 g/dL with no blood transfusion in the past 14 days
    - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
    - Platelet count ≥ 100 x 109/L with no platelet transfusion in the past 28 days
    - Creatinine clearance ≥51 mL/min (estimated using Cockcroft-Gault equation or measured GFR clearance test as appropriate); • Total bilirubin ≤1.5 x ULN (where bilirubin rise > 1.5 x ULN due to Gilbert's syndrome a conjugated bilirubin ≤1.5 x ULN is required)
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5 x ULN if no demonstrable liver metastases or ≤5 times ULN if patient has documented liver metastases
- No significant medical illness which in the opinion of the Investigator would preclude entry to ATARI
- Women of child-bearing potential who are confirmed NOT to be pregnant. This should be evidenced by a negative urine or serum pregnancy test within 72 hours prior to start of trial treatment. Patients will be considered to be not of child-bearing potential if they are:
    - Post-menopausal - defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, OR women under 50 years old who have been amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments and have serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and plasma oestradiol levels in the post-menopausal range for the institution
    - Able to provide documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
    - Radiation or chemotherapy-induced oophorectomy or menopause with > 1 year since last menses
- Patients with prior synchronous tumours or history of prior malignancy are eligible provided that there is biopsy evidence that the disease measurable on CT and/or MRI is of the histological subtypes stated in 1
- Willingness to commit to scheduled visits, treatments plans, laboratory tests and study procedures
- Able to swallow, absorb, retain oral medication
- Able to provide written, informed consent

Critères d'exclusion

- Prior treatment with ATR or PARP inhibitors, including AZD6738 and olaparib
- Patients receiving, or having received:
    - cytotoxic treatment for their malignancy within 21 days prior to Cycle 1 Day 1
    - exposure to a small molecule IP within 30 days or 5 half-lives (whichever is longer) prior to Cycle 1 Day 1. The minimum washout for immunotherapy is 42 days
    - treatment with bevacizumab within 30 days prior to Cycle 1 Day 1
    - palliative radiotherapy within 21 days prior to Cycle 1 Day 1
- Treatment with any other investigational medicinal product within the 4 weeks prior to trial entry
- Receiving, or having received, concomitant medications, herbal supplements and/or foods that are strong or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index that significantly modulate CYP3A4 or P-gp activity (washout period 5 half-lives or three weeks for St. John's Wort). Note these include common azole antifungals, macrolide antibiotics and other medications (Refer to Section 11 and Appendix A5 for further details)
- Pregnant or lactating women.
- Women of childbearing age and potential who are not willing to use one highly effective form of contraception and a condom as detailed in Section 5.5
- Any other malignancy which has been active or treated within the past three years, with the exception of cervical intra-epithelial neoplasia and non-melanoma skin cancer
- Clinical/radiological evidence of bowel obstruction (e.g. hospitalisation) or symptoms of sub-acute bowel obstruction within 6 weeks prior to trial entry
- Any clinically significant haematuria (as deemed by the investigator)
- With the exception of alopecia, any unresolved toxicities from prior therapy should be no greater than CTCAE Grade 2 at trial entry
- Clinically significant cardiac disease currently or within the last 6 months including: a. Pre-existing arrhythmia: i. Mean resting QTc >470 msec obtained from 3 electrocardiograms (ECGs) performed 2-5 minutes apart at study screening (within 14 days prior to Cycle 1 Day 1) using the Fredericia formula ii. Clinically important abnormalities in rhythm, conduction or morphology of resting ECG (including complete left bundle-branch block, third degree heart block) b. Any factor increasing the risk of QTc prolongation or arrhythmia, including: i. Hypokalaemia ii. Congenital long QT syndrome iii. Immediate family history of long QT syndrome or unexplained sudden death below the age of 40 years c. Unstable angina pectoris d. Acute myocardial infarction e. Unstable cardiac arrhythmias f. Cardiac failure i. Known reduced LVEF <55% ii. New York Heart Association (NYHA) class II, III or IV cardiac failure
- Clinically relevant orthostatic hypotension
- Patients who have a diagnosis of ataxia telangiectasia
- Major surgery within 4 weeks prior to entry to the study (excluding placement of vascular access) or minor surgery (excluding tumour biopsies) within 2 weeks of entry into the study (excluding placement of vascular access)
- Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)

- Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days
- Known leptomeningeal involvement or brain metastases, unless asymptomatic, treated (with no evidence of progression since completion of CNS-directed therapy), presence of disease outside the CNS and stable off steroids for at least 4 weeks prior to registration
- Known hypersensitivity to investigational drugs or excipients
- Receiving, or having received during the four weeks prior to registration, corticosteroids at a dose >10mg prednisolone/day or equivalent for any reason
- Any haemopoietic growth factors (e.g., G-CSF, GM-CSF) and blood transfusions within 14 days prior to trial entry. Use of erytropoeitin is not permitted for 4 weeks prior to Cycle 1 Day 1 and for the duration of the study
- As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases e.g., severe hepatic impairment, extensive interstitial lung disease on high resolution CT scan (bilateral, diffuse, parenchymal lung disease), uncontrolled chronic renal diseases (glomerulonephritis, nephritic syndrome, Fanconi Syndrome or Renal tubular acidosis), current unstable or uncompensated respiratory or cardiac conditions, active bleeding diatheses or active infection including hepatitis B, hepatitis C, and immunocompromised patients e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV). Screening for chronic conditions is not required
- Judgment by the Investigator that the patient is unsuitable to participate in the study and/or the patient is unlikely to comply with study procedures, restrictions and requirements
- Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of study drug
- Patients with uncontrolled seizures
- Active infection requiring systemic antibiotics, antifungal or antiviral drugs
- Patients with myelodysplastic syndromes (MDS)/acute myeloid leukaemia (AML), or with features suggestive of MDS/AML
- Concurrent severe and/or uncontrolled medical condition (e.g., severe COPD, severe Parkinson's disease, active inflammatory bowel disease) or psychiatric condition (e.g. psychiatric disorder prohibiting obtaining informed consent)
- Any contraindication to the combination of AZD6738 and olaparib as per local prescribing information
- Patients unable to swallow orally administered medication