Essai Clinique

Généré le 02 mai 2024 à partir de

Titre	Étude internationale de phase III à répartition aléatoire visant à évaluer l'efficacité du traitement d'entretien par le cédiranib et l'olaparib ou par l'olaparib en monothérapie chez les patientes atteintes d'un cancer de l'ovaire récidivant après une réponse à la chimiothérapie à base de platine
Protocole ID	ICON9
ClinicalTrials.gov ID	NCT03278717
Type(s) de cancer	Ovaire
Phase	Phase III
Type étude	Clinique
Médicament	Théapie de maintien avec olaparib et cediranib versus olaparib seul
Institution	CHU DE QUEBEC – UNIVERSITE LAVAL L'HOTEL-DIEU DE QUEBEC ET CRCEO 11 Côte du Palais, Québec, QC, G1R 2J6
Ville	
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But étude	ICON 9 will assess the efficacy, safety and tolerability of maintenance olaparib in combination with cediranib compared to maintenance olaparib alone following a response to platinum-based chemotherapy in women with relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer. Prognostic and predictive factors will be studied from tumour and blood samples.
Critères d'éligibilité	Registration Inclusion Criteria: 1. Provision of informed consent prior to any study specific procedures and the ability to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations. 2. Females aged ≥ 18 years with previous histologically proven diagnosis of high grade serous or endometrioid carcinoma of the • Ovary • Fallopian tube • or peritoneum, progressing >6 months after day 1 of the last cycle of first-line platinum-based chemotherapy and requiring treatment with platinum-based chemotherapy on the basis of radiological evidence of disease or following surgical resection of recurrent disease. 3. Patients must have had CT or MRI proven relapsed disease (measureable or non-measureable abnormalities supported by GCIG CA125 criteria of progression), or have had debulking surgery for first relapse. 4. Patients showing response to chemotherapy mid-treatment (post 3 or 4 cycles), either by CA125, on a CT/MRI scan, or no evidence of progression having undergone surgical debulking, should be approached for ICON9 trial registration to allow for BRCA mutation status to be assessed (germline and/ or somatic). 5. Prior front-line maintenance therapy with bevacizumab is permitted. 6. ECOG performance status 0-1. 7. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary cancer or from secondary debulking surgery with adequate neoplastic cell content (>30%), must be available for central BRCA testing. For inclusion in i) the genetic HRD Test and ii) the biomarker research, patients must complete the consent form. Translational blood samples are also required, see Laboratory Manual for further details.

8. Patients should have a life expectancy ≥ 16 weeks.
9. Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days prior to study treatment and confirmed prior to treatment on day 1Postmenopausal is defined as age ≥60 years, or:
    - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
    - Radiation-induced oophorectomy with last menses >1 year ago
    - Chemotherapy-induced menopause with >1 year interval since last menses
    - Surgical sterilisation (bilateral oophorectomy or hysterectomy)
10. Adequately controlled blood pressure (systolic blood pressure [SBP] ≤140 mmHg; diastolic blood pressure [DBP] ≤ 90mmHg) on maximum of 2 antihypertensive medications.
11. Adequately controlled thyroid function, with no symptoms of thyroid dysfunction.

Randomisation Inclusion Criteria:

1. Patients must have received at least 4 cycles, and a maximum of 6 cycles of second-line platinum-based chemotherapy.
2. In patients with measurable disease, end of treatment scans must have a RECIST v1.1 'partial response' or 'complete response' and meet one of the following CA125 requirements:
    1. If the first screening CA125 value is below the ULN the patient is eligible for randomisation and a second CA125 assessment is not required.
    2. If the first screening CA125 value is greater than ULN then a second assessment is required at least 7 days after the first to confirm eligibility. If the second CA125 value has risen by ≥ 15% then the patient will not be eligible.
3. In patients with non-measurable disease, who have not undergone debulking surgery, they must have had a GCIG CA125 response to chemotherapy and meet one of the following CA125 requirements:
    1. If the first screening CA125 value is below the ULN the patient is eligible for randomisation and a second CA125 assessment is not required.
    2. If the first screening CA125 value is greater than ULN then a second assessment is required at least 7 days after the first to confirm eligibility. If the second CA125 value has risen by ≥ 15% then the patient will not be eligible.
4. Patients who have had debulking surgery at first relapse must have no evidence of disease progression on imaging (CT or MRI) and meet one of the following CA125 requirements:
    1. If the first screening CA125 value is below the ULN the patient is eligible for randomisation and a second CA125 assessment is not required.
    2. If the first screening CA125 value is greater than ULN then a second assessment is required at least 7 days after the first to confirm eligibility. If the second CA125 value has risen by ≥ 15% then the patient will not be eligible.
5. Expected to be able to commence treatment within 7 days post randomisation, and within 4-8 weeks post day 1 of the last cycle of chemotherapy.
6. Adequate bone marrow function as defined below:
    - Absolute Neutrophil Count (ANC) ≥ 1.5 x 109/l
    - Platelet (Plt) ≥ 100 x 109/l
    - Haemoglobin (Hb) ≥ 100g/l required and no packed blood transfusions in the 14 days prior to starting trial treatment
7. Adequate liver function as defined below:
    - Serum bilirubin ≤ 1.5 x ULN (or ≤ 3 for cases of known Gilbert's syndrome)
    - Serum transaminases ≤3 x ULN
    - Serum transaminases ≤ 5 x ULN if liver metastasis present
8. Adequate renal function as defined below: • Serum creatinine ≤ 1.5 x ULN and calculated glomerular filtration rate (GFR) ≥50ml/min (calculated as per local practice)
9. Urine dipstick for proteinuria <2+. If urine dipstick is ≥ 2+ on two occasions more than one week apart then a 24-hour urine must demonstrate ≤ 1 g of protein in 24 hours or protein/creatinine ratio < 1.5.
10. Germline and/or somatic BRCA mutation status must be known prior to randomisation.

Critères d'exclusion

1. Non-epithelial ovarian cancer, carcinosarcoma, clear cell carcinoma and mucinous carcinomas.
2. Arterial thrombotic event (including transient ischemic attack, cerebrovascular accident, and peripheral arterial embolus) within the last 12 months.
3. Patients unable to swallow orally administered medication and patients with gastrointestinal impairment that could affect ability to take, or absorption of oral medicines including sub-acute or complete bowel obstruction.
4. Clinically significant signs and/or symptoms of bowel obstruction within 3 months prior to starting treatment.
5. History of intra-abdominal abscess within 3 months prior to starting treatment.
6. History of GI perforation. Patients with a history of abdominal fistula will be considered eligible if the fistula was surgically repaired, there has been no evidence of fistula for at least 6 months prior to starting treatment, and patient is deemed to be at low risk of recurrent fistula.
7. Symptomatic or clinically significant inflammatory bowel disease (Crohn's disease or ulcerative colitis).
8. Patients with an ileostomy will be excluded.
9. Evidence of severe or uncontrolled cardiac disease.
    1. Myocardial infarct or unstable angina within the last 6 months
    2. New York Health Association (NHYA) ≥ grade 2 congestive heart failure

3. Cardiac ventricular arrhythmias requiring medication
4. History of 2nd or 3rd degree atrioventricular conduction defects

10. Resting ECG with QTcF > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.
11. Evidence of active bleeding or bleeding diathesis. Significant haemorrhage of >30ml in a single episode within the last 3 months or any haemoptysis (>5ml fresh blood in last 4 weeks).
12. Malignancy treated within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS) of the breast, Stage 1, grade 1 endometrial carcinoma.
13. Previous treatment with VEGFR tyrosine kinase inhibitors or PARP inhibitors are not permitted.
14. Patients with a known hypersensitivity to excipients of cediranib or olaparib.
15. Persisting ≥ grade 2 CTCAE toxicity (except alopecia and neuropathy) from previous anti-cancer treatment.
16. Major surgery within 14 days before anticipated start of treatment and patients must have recovered from any effects of major surgery.
17. Inability to attend or comply with treatment or follow-up scheduling.
18. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contra-indicated the use of an investigation drug or puts the patients at high risk for treatment-related complications.
19. Pregnant or breast-feeding women are excluded. Women of childbearing potential will be excluded unless effective methods of contraception are used from signing of the informed consent, throughout the period of taking study treatment and for at least 6 weeks after last dose of trial drug(s).
20. Treatment with any other investigational agent, or participation in another interventional clinical trial within 28 days prior to enrolment.
21. Concomitant use of known CYP3A4 inhibitors (such as ketoconazole, itraconazole, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir, telithromycin and clarithromycin or moderate CYP3A inhibitors (e.g. Ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.
22. Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
23. Patients with myelodysplastic syndrome/acute myeloid leukaemia.
24. Other psychological, psychiatric, social or medical condition, physical examination finding or a laboratory abnormality that the Investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results.
25. Patients with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids.
26. Immunocompromised patients e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy.
27. Patients with symptomatic uncontrolled brain or meningeal metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment.
28. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
29. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).