Essai Clinique

Généré le 25 avr. 2024 à partir de

Titre	Étude ouverte de phase 3 à répartition aléatoire visant à évaluer l'innocuité et l'efficacité de l'olaparib en monothérapie ou en association avec le bévacizumab par rapport au bévacizumab en association avec 5-FU chez les participants atteints d'un cancer colorectal non résécable ou métastatique dont la maladie n'a pas progressé après une induction en première intention de FOLFOX en association avec le bévacizumab
Protocole ID	MK-7339-003 (LYNK-003)
ClinicalTrials.gov ID	NCT04456699
Type(s) de cancer	Côlon et rectum
Phase	Phase III
Type étude	Traitement
Institution	CISSS DE LAVAL HOPITAL DE LA CITE-DE-LA-SANTE 1755 boul. René-Laennec, Laval, QC, H7M 3L9
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But étude	Il s'agit d'une étude d'efficacité et d'innocuité de l'olaparib en monothérapie ou en association avec le bévacizumab par rapport au bévacizumab en association avec 5?fluorouracile (FU) chez les participants atteints d'un cancer colorectal (CCR) non résécable ou métastatique dont la maladie n'a pas progressé après une induction en première intention de FOLFOX en association avec le bévacizumab. Hypothèse 1 : l'association olaparib + bévacizumab est supérieure à l'association 5-FU + bévacizumab en ce qui concerne la survie sans progression (SSP) selon les critères RECIST [Response Evaluation Criteria in Solid Tumours] (version 1.1), telle qu'évaluée par un examen central indépendant à l'insu (ECII) pour le traitement du CCR. Hypothèse 2 – l'olaparib est supérieur à l'association 5-FU + bévacizumab en ce qui concerne la SSP selon les critères RECIST version 1.1, telle qu'évaluée par un ECII pour le traitement du CCR.
Critères d'éligibilité	A participant will be eligible for inclusion in the study if the participant: 1. Has a histologically-confirmed metastatic and unresectable (Stage IV as defined by AJCC eighth edition) colorectal adenocarcinoma (NCCN 2018). 2. Has not progressed (ie, achieved a SD, PR, or CR) after a first-line induction course of at least 6 cycles of FOLFOX with bevacizumab as first-line therapy. • Participants must not have received an investigational agent during their FOLFOX + bevacizumab induction course. • Determination of SD/PR/CR will be made by the investigator. • "First-line therapy" is defined as the first systemic chemotherapy regimen given for the diagnosis of unresectable or metastatic CRC. Participants may have received prior adjuvant/neoadjuvant chemotherapy for CRC as long as it was completed at least 6 months prior to initiation of first-line FOLFOX + bevacizumab induction treatment. 3. Has experienced unacceptable toxicity to oxaliplatin that, in the opinion of the treating physician, requires/required the discontinuation of oxaliplatin. Note: As an example, unacceptable toxicity may include (but is not limited to) severe or prolonged neurotoxicity. • Participants must be randomized within a minimum of 2 weeks and a maximum of 6 weeks after their last dose of FOLFOX + bevacizumab (last dose is the day of the last infusion). 4. Has provided to the iCRO at least 1 set of radiographic images taken during the FOLFOX + bevacizumab induction period and at least 42 days prior to the imaging performed during screening. The iCRO must determine the images are of diagnostic quality prior to randomization. 5. Has an ECOG performance status of 0 to 1 within 10 days prior to randomization. 6. Has the ability to swallow and retain oral medication and not have any clinically significant gastrointestinal abnormalities that might alter absorption. 7. Has adequate organ function, as detailed in Table 1; all screening laboratory tests should be performed within 10 days of randomization. Table 1 Adequate Organ Function Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥10.0 g/dL or ≥ 5.6mmol/L
Renal	
Estimated creatinine clearance using the Cockroft-Gault equation	≥51 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase);
AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ULN=upper limit of normal.
1 Criteria must be met without packed red blood cell (pRBC) transfusion within last 2 weeks.
2 Estimated creatinine clearance using Cockcroft-Gault:

(140-age [years] × weight [kg]) (× F)*	(× F)*
Serum creatinine (mg/dL) × 72	

*where F = 0.85 for females and F = 1 for males
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

8. Has provided a tumor tissue sample deemed acceptable by the central lab for biomarker analysis.
   - Notification of acceptability must be received prior to randomization.
   - If a sample is not available at screening, a new tissue sample is required to be collected during screening.

Demographics
9. Is male or female, at least 18 years of age, at the time of signing the informed consent.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

10. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days (if on Arm 2) or 180 days (if on Arm 1 or Arm 3) after the last dose of study intervention:

• Refrain from donating sperm

PLUS either:

• Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

	• Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below: - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration. • Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex. **Female Participants** 11. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: • Is not a WOCBP OR • Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 30 days (if on Arm 2) or 180 days (if on Arm 1 or Arm 3) after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. • A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. • If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. • Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. **Informed Consent** 12. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research. Hemoglobin ≥10.0 g/dL or ≥5.6 mmol/L1 Hemoglobin ≥10.0 g/dL or ≥5.6 mmol/L1 Hemoglobin ≥10.0 g/dL or ≥5.6 mmol/L1
Critères d'exclusion	The participant must be excluded from the study if the participant: **Medical Conditions** 1. Has known hypersensitivity to the components and/or excipients in bevacizumab, 5-FU, or olaparib. 2. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression for at least 28 days by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid intervention for at least 14 days prior to first dose of study intervention). 3. Has an active infection requiring systemic therapy. 4. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority. 5. Has a known history of or is positive for hepatitis B (HBsAg reactive) or hepatitis C (HCV RNA [qualitative] is detected). Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority. 6. Has a known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study. 7. Has MDS/AML or with features suggestive of MDS/AML. 8. Has hemoptysis or hematemesis within 28 days prior to randomization. 9. Has evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation). 10. Has clinically significant bleeding within 28 days prior to randomization. 11. Is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent. 12. Has 1 or more conditions that, in the opinion of the treating physician, make the participant ineligible for treatment with bevacizumab. These conditions may include:

- Uncontrolled hypertension or a history of hypertensive crisis or hypertensive encephalopathy
- History of nephrotic syndrome or moderate proteinuria
- History of gastrointestinal perforation.
- History of non-gastrointestinal fistula formation
- History of RPLS

Prior/Concomitant Therapy

13. Has received prior systemic anticancer therapy (other than FOLFOX + bevacizumab induction) including investigational agents within 28 days prior to randomization.

Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline.

14. Has received prior therapy with olaparib or with any other PARP inhibitor.

15. Is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to randomization is 2 weeks.

16. Is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (eg. bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to randomization is 5 weeks for phenobarbital and 3 weeks for other agents.

Note: A current list of strong/moderate inhibitors or inducers of CYP3A4 can be found at the following website:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-druginteractions-table-substrates-inhibitors-and-inducers

17. Has undergone major surgery within 2 weeks of randomization or has not recovered adequately from toxicities and/or complications from any major surgery prior to randomization.

18. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

Prior/Concurrent Clinical Study Experience

19. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 28 days prior to the first dose of study intervention.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 28 days after the last dose of the previous investigational agent.

Diagnostic Assessments

20. Has a known additional malignancy that is progressing or has required active therapy within the past 5 years.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

22. Has clinically significant (eg, active) cardiovascular disease, including:

- Myocardial infarction or unstable angina within ≤ 6 months of randomization
- CHF ≥Grade 2 (as per New York Heart Association)
- Poorly controlled cardiac arrhythmia despite medication (patient with rate controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on resting ECG (eg, QTC ≥450 msec detected on 2 or more time points within a 24-hour period)
- Peripheral vascular disease ≥Grade 3 (eg, symptomatic and interfering with activities of daily living requiring repair or revision)

23. Has DPD deficiency

Other Exclusions

24. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 90 days after the last dose of study intervention.