Essai Clinique

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Titre	A Randomised Phase III Double-Blind Placebo-Controlled Study of Regorafenib in Refractory Advanced Gastro-Oesophageal Cancer
Protocole ID	INTEGRATEII
ClinicalTrials.gov ID	NCT02773524
Type(s) de cancer	Estomac
Phase	Phase III
Stade	Maladie réfractaire
Type étude	Traitement
Médicament	Regorafenib
Institution	CIUSSS DU CENTRE-OUEST-DE-L'ILE-DE-MONTREAL HOPITAL GENERAL JUIF SIR MORTIMER B.DAVIS 3755 rue de la Côte Ste. Catherine, Montréal, QC, H3T 1E2
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But étude	Purpose: The purpose of this Phase III study is to determine if regorafenib improves overall survival in patients with Advanced Gastro-Oesophageal Carcinoma.Who is it for: You may be eligible to join this study if you are aged 18 years or above and have been diagnosed with advanced (metastatic or locally recurrent) Gastro-Oesophageal Carcinoma which has not responded to a minimum of 2 and a maximum of 3 lines of prior anti-cancer therapy.Trial Details: Participants will be randomly (by chance) allocated to one of two groups: regorafenib or placebo in 2:1 ratio respectively and will not be aware of their group allocation. Regorafenib or matching placebo will be self-administered by participants orally once daily on days 1-21 of each 28 days cycle. Treatment will continue until disease progression or prohibitive toxicity. Participants will be followed up every 2-4 weeks in order to evaluate their progress on the study.
Critères d'éligibilité	• Adults (18 years or over) with metastatic or locally recurrent gastro-oesophageal cancer which: Note: Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy will be considered as first line treatment where people have relapsed or progressed within 6 months of completing treatment; Radiosensitising chemotherapy given solely for this purpose concurrent with palliative radiation will not be considered as a line of treatment. Ramucirumab monotherapy, or immunotherapy with a checkpoint inhibitor, will be considered a line of treatment. • has arisen in any primary gastro-oesophageal site (oesophago-gastric junction (GOJ) or stomach); and • is of adenocarcinoma or undifferentiated carcinoma histology , and • is evaluable according to Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1) by computed tomography (CT) scan performed within 21 days prior to randomisation. A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrolment; and • has failed or been intolerant to a minimum of 2 and a maximum of 3 lines of prior anti-cancer therapy for recurrent/metastatic disease which must have included at least one platinum agent and one fluoropyrimidine analogue. • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. • Ability to swallow oral medication.

	• Adequate bone marrow function (Platelets ≥100x109/L; Absolute Neutrophil Count (ANC) ≥1.5x109/L and Haemoglobin ≥ 9.0g/dL). • Adequate renal function (Creatinine clearance >50 ml/min) based on either the Cockcroft-Gault formula (Appendix 2), 24-hour urine or Glomerular Filtration Rate (GFR) scan; and serum creatinine ≤1.5 x Upper Limit of Normal (ULN). • Adequate liver function (Serum total bilirubin ≤1.5 x ULN, and INR ≤ 1.5 x ULN, and Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP) ≤2.5 x ULN (≤ 5 x ULN for participants with liver metastases)). Participants being treated with an anti-coagulant, such as warfarin or heparin, will be allowed to participate provided that no prior evidence of an underlying abnormality in these parameters exists. • Adequate cardiac function (Left Ventricular Ejection Fraction (LVEF) ≥ 50% or above the lower limit of normal (LLN) for the Institution (whichever is lower). Cardiac function should be assessed within 3 months prior to randomisation, but after completion of any anthracycline-containing chemotherapy. • Willing and able to comply with all study requirements, including treatment, timing, and/or nature of required assessments and follow-up. • Study treatment both planned and able to start within 7 days after randomisation (note: subjects randomised on a Friday should commence treatment no earlier than the following Monday). • Signed, written informed consent.
Critères d'exclusion	• Known allergy to the investigational product drug class or excipients in the regorafenib. • Poorly-controlled hypertension (systolic blood pressure >140mmHg or diastolic pressure> 90mmHg despite optimal medical management). • Participants with known, uncontrolled malabsorption syndromes. • Any prior anti-VEGF targeted therapy using small molecule VEGF TKIs (e.g. apatinib). Prior anti-VEGF targeted monoclonal antibody therapies (e.g. bevacizumab and ramucirumab) are permitted. • Treatment with any previous drug therapy within 3 weeks prior to randomization. This includes any investigational therapy. • Use of biological response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 3 weeks prior to randomisation. • Concurrent treatment with strong CYP3A4 inhibitors or inducers. • Palliative radiotherapy, unless more than 14 days have elapsed between completion of radiation and the date of registration, and adverse events resulting from radiation have resolved to< Grade 2 according to CTCAE V4.03. • Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization. • Arterial thrombotic or ischaemic events, such as cerebrovascular accident, within 6 months prior to randomization. • Venous thrombotic events and pulmonary embolism within 3 months prior to randomization. • Any haemorrhage or bleeding event ≥ Grade 3 according to CTCAE v4.03 within 4 weeks prior to randomization. • Non-healing wound, ulcer, or bone fracture. • Interstitial lung disease with ongoing signs and symptoms. • Clinical hyperthyroidism or hypothyroidism. Note: non-clinically significant abnormal TFTs (abnormal TSH and abnormal T3 and/or abnormal T4) considered to be due to sick euthyroid syndrome is allowed. • Persistent proteinuria of ≥ Grade 3 according to CTCAE v4.03 (equivalent to > 3.5g of protein over 24 hours, measured on either a random specimen or 24 hour collection). • Uncontrolled metastatic disease to the central nervous system. To be eligible, CNS metastases should have been treated with surgery and/or radiotherapy and the patient should have been receiving a stable dose of steroids for at least 2 weeks prior to randomization, with no deterioration in neurological symptoms during this time. • History of another malignancy within 2 years prior to randomization. Participants with the following are eligible for this study: • curatively treated cervical carcinoma in situ, • non-melanomatous carcinoma of the skin, • superficial bladder tumours (T1a [Non-invasive tumour], and Tis[Carcinoma in situ]), • treated thyroid papillary cancer • Any significant active infection, including chronic active hepatitis B, hepatitis C, or HIV. Testing for these is not mandatory unless clinically indicated. Participants with known Hepatitis B/C infection will be allowed to participate providing evidence of viral suppression has been documented and the patient remains on appropriate anti-viral therapy. • Serious medical or psychiatric condition(s) that might limit the ability of the patient to comply with the protocol. • Pregnancy, lactation, or inadequate contraception. Women must be post-menopausal infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to randomization. Men must have been surgically sterilized or use a barrier method of contraception.