Essai Clinique

Généré le 18 mai 2024 à partir de

Titre	An Open-label, Multicenter, Multicohort, Phase 2 Study to Evaluate Enfortumab Vedotin in Subjects With Previously Treated Locally Advanced or Metastatic Malignant Solid Tumors
Protocole ID	7465-CL-202 (EV-202)
ClinicalTrials.gov ID	NCT04225117
Type(s) de cancer	Tumeurs solides
Phase	Phase II
Stade	Maladie avancée ou métastatique
Type étude	Clinique
Médicament	Enfortumab Vedotine
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
Ville	
Investigateur principal	Dr Wilson Miller
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Statut	Actif en recrutement
But étude	The primary purpose of this study is to determine the antitumor activity of enfortumab vedotin as measured by confirmed objective response rate (ORR). This study will also assess other measures of antitumor activity; overall survival (OS); as well as the safety and tolerability of enfortumab vedotin.

Critères d'éligibilité	• Subject is considered an adult according to local regulation at the time of signing the informed consent form (ICF).
	• Subject has measurable disease by RECIST Version 1.1.
	• Subject has accessible archival tumor tissue from either the primary tumor or a metastatic site, for which source and availability have been confirmed prior to study treatment. If no archival tumor tissue is available, the subject will have a biopsy to obtain tumor tissue prior to study treatment. If the subject is unable to undergo a biopsy due to safety concerns, enrollment into the study must be discussed with the medical monitor.
	• Subject has ECOG performance status of 0 or 1.
	• Subject has the following baseline laboratory data. If a subject has received a recent blood transfusion, the hematology tests must be obtained ≥ 28 days after any blood transfusion.
	  • absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L
	  • platelet count ≥ 100 × 10^9/L
	  • hemoglobin ≥ 9 g/dL
	  • serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
	  • creatinine clearance (CrCl) ≥ 30 mL/min as estimated per institutional standards or as measured by 24-hour urine collection (glomerular filtration rate [GFR] can also be used instead of CrCl).
	  • alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN
	• Subject agrees not to participate in another interventional study while receiving study treatment in the present study.
	• Additional contraceptive requirements exist for male and female subjects.
	
	Disease Specific Inclusion Criteria:

- Evidence of progression on or after the last regimen received.
- Locally advanced or metastatic disease that is not amenable to curative intent treatment.

Cohort 1: HR+/HER2- breast cancer

- Subject has evidence of radiographic progression on or after the last regimen received.
- Subject has histologically- or cytologically-confirmed HR+/HER2- (estrogen receptor [ER] positive and/or progesterone receptor [PR] positive, and HER2 negative) breast cancers and are not considered a candidate for further hormonal therapy. Subject will be considered HR+ if biopsies show ≥ 1% expression of ER or PR as per current American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.
- Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
- Subject must have received a taxane or anthracycline in the neoadjuvant, adjuvant or incurable, locally advanced or metastatic setting.
    - Prior cytotoxic regimen received in the neoadjuvant or adjuvant setting will count as a prior cytotoxic regimen if disease recurrence occurred during or within 6 months of completing the regimen.
- Subject has progressed, relapsed, or discontinued for toxicity during or after at least 1 prior standard of care cytotoxic regimen in the incurable, unresectable locally advanced or metastatic setting, and has not received > 2 prior lines of cytotoxic therapy in the locally advanced or metastatic setting. No limit applies to endocrine therapies. Poly(ADP-ribose) polymerases (PARP) inhibitors do not count as a line of cytotoxic therapy.
- Subject has progressed, relapsed, or discontinued for toxicity during or after receiving endocrine therapy or with hormonally-directed therapy with cyclin-dependent kinase (CDK) inhibitors. Prior therapy with CDK inhibitors is not required.

Cohort 2: triple negative breast cancer (TNBC)

- Subject has evidence of radiographic progression on or after the last regimen received.
- Subject has histologically- or cytologically-confirmed TNBC; defined as unequivocal TNBC histology (ER-negative/PR-negative/HER2-negative). This is defined by < 1% expression of ER and PR by immunohistochemistry (IHC), and that are, for HER2, either 0 to 1+ by IHC, or IHC 2+ and fluorescence in situ hybridization (FISH) negative (not amplified) as per current ASCO/CAP guidelines.
- Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
- Subject must have received a taxane or anthracycline in the neoadjuvant, adjuvant or incurable, locally advanced or metastatic setting.
    - Prior cytotoxic regimen received in the neoadjuvant or adjuvant setting will count as a prior cytotoxic regimen if disease recurrence occurred during or within 6 months of completing the regimen.
- Subject has progressed, relapsed, or discontinued for toxicity during or after at least 1 prior standard of care cytotoxic regimen in the incurable, unresectable locally advanced or metastatic setting, and has not received > 2 prior lines of cytotoxic therapy in the locally advanced or metastatic setting. Poly(ADP-ribose) polymerases (PARP) inhibitors do not count as a line of cytotoxic therapy.
- Subject has received prior therapy with an anti-programmed cell death protein-1 (PD-1) or an anti-programmed cell death-ligand 1 (PD-L1) based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohort 3: squamous non-small cell lung cancer (NSCLC)

- Subject has evidence of radiographic progression on or after the last regimen received.
- Subject has histologically or cytologically-confirmed squamous NSCLC.
    - Subjects with mixed histology NSCLC are eligible provided there is not any component of neuroendocrine histology.
    - Subjects with known epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), reactive oxygen species (ROS), BRAF, or other actionable mutations are eligible if treated with mutation targeted therapy and have progressed, relapsed, or discontinued treatment due to toxicity.
- Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
- Subject has progressed, relapsed, or discontinued treatment due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    1. Subjects with locally advanced disease who previously received curative intent treatment with platinum-based standard of care regimen in the adjuvant or neoadjuvant setting or as part of concomitant chemoradiation therapy are eligible if they have progressed or relapsed within 6 months of completion.
    2. Maintenance therapy does not constitute a new chemotherapy regimen provided there was no progression after the initial platinum-based regimen.
    3. Changing chemotherapy agents during platinum-based treatment for the management of toxicities does not constitute a new chemotherapy regimen provided no progression had occurred while on the initial therapy.
- Subject has received prior therapy with an anti-programmed cell death protein-1 (PD-1) or

anti-programmed cell death-ligand 1 (PD-L1) based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohort 4: non-squamous non-small cell lung cancer

- Subject has evidence of radiographic progression on or after the last regimen received.
- Subject has histologically- or cytologically-confirmed non-squamous NSCLC.
    - Subjects with mixed histology NSCLC are eligible provided there is not any component of neuroendocrine histology.
    - Subjects with known EGFR, ALK, ROS, BRAF, or other actionable mutations are eligible if treated with mutation targeted therapy and have progressed, relapsed, or discontinued treatment due to toxicity.
- Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
- Subject has progressed, relapsed, or discontinued treatment due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    1. Subjects with locally advanced disease who previously received curative intent treatment with platinum-based standard of care regimen in the adjuvant or neoadjuvant setting or as part of concomitant chemoradiation therapy are eligible if they have progressed or relapsed within 6 months of completion.
    2. Maintenance therapy does not constitute a new chemotherapy regimen provided there was no progression after the initial platinum-based regimen.
    3. Changing chemotherapy agents during platinum-based treatment for the management of toxicities does not constitute a new chemotherapy regimen provided no progression has occurred while on the initial therapy.
- Subject has received prior therapy with an anti-PD-1 or anti-PD-L1 based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohort 5: head and neck cancer

- Subject has evidence of radiographic progression on or after the last regimen received.
- Subject has histologically- or cytologically-confirmed head and neck cancer.
    - Primary tumor site must arise from the oral cavity, oropharynx, hypopharynx, and larynx; tumors arising from the nasopharynx are excluded. Salivary gland tumors and/or parotid gland tumors are not eligible for Cohort 5.
- Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
- Subject has progressed, relapsed, or discontinued treatment due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    - Subjects with locally advanced disease who previously received curative intent treatment with platinum-based standard of care regimen in the adjuvant or neoadjuvant setting or as part of concomitant chemoradiation therapy are eligible if they have progressed or relapsed within 6 months after completion.
- Subject has received prior therapy with an anti-PD-1 or anti-PD-L1 based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohorts 6, 7 and 8: gastric or gastroesophageal junction (GEJ) or esophageal adenocarcinoma

- Subject has evidence of radiographic progression on or after the last regimen received.
- Subject has histologically- or cytologically-confirmed gastric, GEJ, or esophageal cancer.
- Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
- Subject has progressed, relapsed, or discontinued due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    - Neoadjuvant or adjuvant cytotoxic regimens will count as a prior regimen if relapsed or progressed ≤ 6 months after completion.
- Subject must have received a HER2 directed therapy if known to have HER2 positive cancer.
- Subject has received prior therapy with an anti-PD-1 or anti-PD-L1 based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Critères d'exclusion

- Subject has preexisting sensory or motor neuropathy Grade ≥ 2.
- Subject has active central nervous system (CNS) metastases. Subjects with treated CNS metastases are permitted on study if all the following are true:
    - CNS metastases have been clinically stable for ≥ 6 weeks prior to screening
    - If requiring steroid treatment for CNS metastases, the subject is on a stable dose ≤ 20 mg/day of prednisone or equivalent for ≥ 2 weeks
    - Baseline imaging scans show no evidence of new or enlarged brain metastasis
    - Subject does not have leptomeningeal disease
- Subject has ongoing clinically significant toxicity (Grade 2 or higher with the exception of

alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery).

- Subjects with ongoing ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded. Subjects with ongoing immunotherapy-related colitis, uveitis, myocarditis or pneumonitis, or subjects with other immunotherapy-related AEs requiring high doses of steroids (> 20 mg/day of prednisone or equivalent), are excluded. Subject with ≤ Grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may be enrolled when well maintained/controlled on a stable dose of hormone replacement therapy (if indicated).
- Subject has a history of uncontrolled diabetes mellitus within 3 months before the first dose of study treatment. Uncontrolled diabetes (within 3 months before first dose) is defined as hemoglobin A1c (HbA1c) ≥ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained. The lowest HbA1c during the screening period will be used to determine eligibility.
- Subject has prior treatment with enfortumab vedotin or other monomethyl auristatin E (MMAE) based antibody-drug conjugates (ADCs).
- Subject has a second malignancy diagnosed within 3 years before first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with non-melanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.
- Subject is currently receiving systemic antimicrobial treatment for viral, bacterial, or fungal infection at the time of first dose of study treatment. Routine antimicrobial prophylaxis is permitted.
- Subject has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or active hepatitis C (e.g., hepatitis C virus [HCV] RNA [qualitative] is detected).
- Subject has known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2).
- Subject has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug.
- Subject has major surgery within 4 weeks prior to first dose of study drug.
- Subject had radiotherapy, chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.
- Subject has known hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate and polysorbate 20) OR subject has known hypersensitivity to biopharmaceutical produced in Chinese hamster ovary cells.
- Subject has known active keratitis or corneal ulcerations. Subject with superficial punctate keratitis is allowed if the disorder is being adequately treated.
- Subject has any condition which makes the subject unsuitable for study participation.