Essai Clinique

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Titre	A Phase 1, Open-Label, Dose Escalation and Expansion Study of TH1902 in Patients With Advanced Solid Tumors
Protocole ID	TH1902-CTR-0001
ClinicalTrials.gov ID	NCT04706962
Type(s) de cancer	Tumeurs solides
Phase	Phase I
Type étude	Clinique
Médicament	TH1902
Institution	CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL
Ville	
Investigateur principal	Dre Diane Provencher
Coordonnateur	Adeline Hamon 514-890-8000 poste 30737
Statut	Actif en recrutement
Date d'activation	27-11-2023
But étude	Open label first-in-human study of TH1902 in solid cancer, with 4 sequential parts: **Part 1 (dose escalation)**: patients with recurrent advanced solid tumors (all comers) that have relapsed or are refractory to standard chemotherapy, surgery, radiation therapy, and for which no known effective therapies exist. **Part 2 (expansion):** selected patient populations with recurrent advanced TNBC, HR+ breast cancer, epithelial ovarian cancer, endometrial cancer, cutaneous melanoma, thyroid cancer, SCLC, prostate cancer and other cancers known to express SORT1 that are refractory to standard therapy.**Part 3 (optimization):** patients diagnosed with histologically or cytologically confirmed high grade serous ovarian cancer, including high grade peritoneal or fallopian tube cancer, or high grade endometrioid cancer, that is refractory or resistant to standard therapies, should not be considered platinum sensitive, and where current therapy is not considered to be providing benefit**Part 4 (basket expansion):** selected cancer type diagnosed with histologically or cytologically confirmed cancers, where TH1902 has been studied and/or showed activity (in Parts 1 to 3), that is refractory or resistant to standard therapies, and where current therapy is not considered to be providing benefit.
Critères d'éligibilité	**Parts 1, 2, 3 and 4** Patients must meet all the following criteria to be eligible to participate in the study: • Are ≥18 years old males or females. • Are capable of understanding and have voluntarily signed the informed consent document and willing to comply with study requirements. • Have histologically or cytologically confirmed diagnosis of metastatic or advanced-stage solid tumor that is refractory to standard therapy (For Part 1 only; see modified inclusion criteria #13, 15 and 18 for Parts 2, 3, and 4, respectively). • Have measurable disease according to the RECIST 1.1. • Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. • Have an expected survival of at least 3 months. • Have a negative pregnancy test result confirmed by a serum beta-human chorionic gonadotropin (β-HCG) test (for women of childbearing potential [WOCBP]) performed at Screening and have a negative pregnancy urine test result on Cycle 1, Day 1. This is not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy, salpingectomy, tubal ligation and/or hysterectomy or postmenopausal or those that have had definitive radiation therapy to the pelvis. WOCBP are considered postmenopausal if 12 months of spontaneous amenorrhea, or 6 months of spontaneous

amenorrhea with serum follicle-stimulating hormone levels > 40 mIU/mL, or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

- WOCBP who are sexually active with a non-sterilized male partner (sterilized males should be ≥6 months post vasectomy and have obtained documentation of the absence of sperm in the ejaculate) should agree to remain abstinent (refrain from sexual intercourse of any kind) or use 2 effective methods of contraception, including at least 1 method with a failure rate of <1% per year, during the treatment period and for at least 6 months for both female and male patients, following the last dose of TH1902. Periodic abstinence (e.g., calendar, symptothermal, and post-ovulation), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together. Effective contraceptive measures include the following:
    - Intrauterine device (e.g., IUD) or intrauterine system plus one barrier method.
    - Oral, intravaginal, or transdermal combined (estrogen and progestogen) hormonal contraceptive associated with the inhibition of ovulation plus one barrier method.
    - Oral, implantable, or injectable progestogen-only hormonal contraceptive associated with the inhibition of ovulation plus one barrier method.
    - Bilateral tubal occlusion at least 6 weeks before study drug administration.
    - Sterilization of male partner (at least 6 months prior to screening). For WOCBP in on the study, the vasectomized male partner should be the sole partner for that patient and must have obtained documentation of the absence of sperm in the ejaculate.
    - True sexual abstinence when this is in line with the preferred and usual lifestyle of the study patient.
    - Effective barrier methods are male or female condoms, diaphragms, and spermicides.
- WOCBP must agree to ongoing pregnancy testing during the course of the study and must agree not to donate ova during and after treatment with TH1902. Male patients must refrain from donating sperm during the study and for at least 6 months following the last dose of TH1902.
- Male patients with WOCBP partners must agree to remain abstinent (refrain from sexual intercourse of any kind) or use a condom (latex condom is recommended) during the treatment period and for at least 6 months after the last dose of TH1902 to avoid exposing the embryo, if the vasectomy has been performed less than 6 months or documentation of the absence of sperm in the ejaculate has not been obtained. Periodic abstinence (e.g., calendar, symptothermal, and post-ovulation,), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.
- Patients with known Human Immunodeficiency Virus (HIV)/Hepatitis B (HBV)/Hepatitis C (HCV) will be allowed to enter the study provided the following criteria are met:
    - Patients with HIV infection must have CD4+ T-cell (CD4+) counts ≥ 350 cells/μL.
    - The following eligibility criteria are for patients with evidence of chronic HBV infection or patients with history of chronic HCV or who are virologically suppressed on HCV treatment:
        - Liver-related laboratory eligibility criteria should be the same as that for the general population.
        - Exceptions: Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and bilirubin criteria may be less stringent in patients with cancers such as hepatocellular carcinoma and cholangiocarcinoma in whom hepatic function based on Child-Pugh score should be used.
        - Patients with chronic HBV infection with active disease who meet the criteria for anti-HBV therapy should be on a suppressive antiviral therapy prior to initiation of cancer therapy.
        - Patients on concurrent HCV treatments must have HCV below the limit of quantification.
        - Patients with untreated and stable HCV can be enrolled provided that the patient is not at risk for hepatic decompensation.
- Recovered from any previous therapy related toxicity to ≤Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia) (for Parts 1 and 2 only; see modified inclusion criteria #14 for Part 3 and 17 for Part 4).
- **Part 2** Patients must meet the following modified criterion to enter Part 2 of the study:
- Histologically or cytologically confirmed TNBC, HR+ breast cancer, epithelial ovarian cancer, endometrial cancer, cutaneous melanoma, thyroid cancer, SCLC, prostate cancer or other cancer known to express SORT1 that is refractory or resistant to standard therapy (replaces inclusion criterion #3).
- **Part 3** Patients must meet the following additional and/or modified inclusion criteria to enter Part 3 of the study:
- Recovered from any previous therapy related toxicity to ≤Grade 1 at study entry (except for ≤Grade 2 alopecia) (replaces inclusion criterion #12).
- Diagnosed with histologically or cytologically confirmed high grade serous ovarian cancer, including high grade peritoneal or fallopian tube, or high grade endometrioid cancer, that is refractory or resistant to standard therapies, not considered platinum sensitive, and where current therapy is not considered to be providing benefit. Patients with clear-cell, mucinous, low grade serous ovarian cancer or carcinosarcoma are not eligible for the study (replaces inclusion criterion #3).
- Patient received a maximum of 8 prior cancer treatment regimens, including adjuvant/neoadjuvant.
- **Part 4** Patients must meet the following additional and/or modified inclusion criteria to enter Part 4 of the study:
- Recovered from any previous therapy related toxicity to ≤Grade 1 at study entry (except for ≤Grade 2 alopecia) (replaces inclusion criteria #12 and #14).
- Diagnosed with histologically or cytologically confirmed cancers, where TH1902 has been

studied and/or showed activity, that is refractory or resistant to standard therapies, and where current therapy is not considered to be providing benefit (replaces inclusion criteria #3 and #15).
- Patient received a maximum of 8 prior cancer treatment regimens, including adjuvant/neoadjuvant

Critères d'exclusion

Parts 1, 2, 3 and 4 Patients who meet any one of the following criteria at baseline will be excluded from study participation:

1. Have received chemotherapy, biologic therapy, immunotherapy, radiotherapy (except palliative radiation delivered to <20% of bone marrow), or investigational agents within 4 weeks before the first dose of study drug. Patients who have received targeted therapy (investigational or approved) must not have received their last dose within 4 weeks, or within 5 half-lives (whichever is shorter) prior to treatment with the study drug (Cycle 1, Day 1).
2. Have known hypersensitivity to taxanes, including docetaxel, or to any excipients in the TH1902 study drug (e.g., polysorbate 80, predominantly known as Tween® 80).
3. Have experienced severe toxicity with previous taxane treatment.
4. Patients with leptomeningeal disease or spinal cord compression or active brain metastases are ineligible for enrollment. Patients with treated brain metastasis that are stable for 4 weeks or longer, and not requiring steroids, are eligible for treatment. Patients with history of brain metastasis should have a magnetic resonance imaging (MRI) within 4 weeks of initiating treatment. For patients where MRI is contraindicated (e.g., due to tissue expanders), brain computerized tomography (CT) may be obtained after discussion with Sponsor.
5. Pregnant, breastfeeding, or planning to become pregnant during the treatment period.
6. Had any acute viral (including COVID-19), bacterial, or fungal infection that requires parenteral therapy within 14 days prior to treatment with study drug (Cycle 1, Day 1).
7. Have received a live vaccine within 30 days prior to administration of the study drug.
8. Had treatment with cytochrome P450 CYP3A4 or CYP3A5 enzyme-inducing or enzyme inhibiting drugs within 14 days prior to treatment with the study drug (Cycle 1, Day 1).
9. Have any of the following hematologic abnormalities at baseline:
    - Hemoglobin: <9 g/dL rounded value (90 g/L) for Parts 1 and 2; <8 g/dL rounded value (80 g/L) for Parts 3 and 4. Patients may be transfused with packed red blood cells (within the 21-day screening period) prior to TH1902 infusion, if clinically warranted. A post-transfusion hemoglobin assessment may qualify the patient for participation.
    - Absolute neutrophil count < 1.5 x 109/L (1500/mm3)
    - Platelet count < 100 x 109/L (100,000/mm3)
10. Have any of the following serum chemistry abnormalities at baseline:
    - Bilirubin > upper limit of normal (ULN).
    - AST and/or ALT > 1.5 times the upper limit of reference range (ULRR) (For Parts 1 and 2), or >5 times ULRR for patients with documented liver metastases.o Concomitant with alkaline phosphatase > 2.5 times ULN (for Parts 3 and 4).
    - Creatinine clearance (CrCl) < 50 mL/min (calculated according to the Cockcroft and Gault formula):
        - Female CrCl = (140 - age in years) × weight in kg × 0.85 / (serum creatinine in mg/dL x 72)
        - Male CrCl = (140 - age in years) × weight in kg × 1.00 / (serum creatinine in mg/dL x 72)
11. Baseline corrected interval between Q and T waves on electrocardiogram (ECG) (QTc) ≥ 470 msec using Fridericia's formula.
12. Have unstable or uncompensated respiratory, cardiac, hepatic, or renal disease or any other organ system dysfunction, medical condition, or laboratory abnormality which, in the opinion of the investigator, would either compromise the patient's safety or interfere with the evaluation of the study drug safety and anti-tumor activity.
13. Have evidence of persistent Grade 2 or greater neurotoxicity.
14. Have any of the following ocular conditions at baseline:
    - Active or chronic corneal disorder, including but not limited to Sjogren's, Fuch's corneal dystrophy, history of corneal transplantation, active herpetic keratitis, as well as other active ocular conditions requiring ongoing therapy.
    - Any clinically significant corneal disease that prevents adequate monitoring of drug-induced keratopathy.
    - Laser in-situ keratomileusis (LASIK) procedure performed within 1 year or less.
    - Cataract surgery within 3 months or less.
    - Patients will not be allowed to use contact lenses unless advised by an eye care provider for adverse event treatment during the study treatment.

    For Part 2, there is no specific additional or modified exclusion criteria. For Parts 3 & 4, patients who meet any one of the following additional exclusion criteria at baseline will be excluded from study participation
15. Patients that failed >1 taxane-containing regimen, defined as experiencing disease progression while receiving, or within 6 months of completing a taxane-containing regimen.
16. Patients with clinically significant ascites, who need frequent paracentesis (greater than on a weekly basis).
17. Patients with > grade 1 peripheral neuropathy and/or any identified or patient reported muscular weakness (assessed by neuropathy score) regardless of grade at baseline will be excluded from the study.
18. Patients with leptomeningeal disease or spinal cord compression or active brain metastases are ineligible for enrolment. Patients with treated spinal cord compression that is stable and is not active at time of screening, nor is likely to interfere with the patient survival for at least 3

months, or ability to stay on treatment for at least 2 cycles, are eligible for treatment. Patients with treated brain metastasis that are stable for 4 weeks or longer, and not requiring steroids, are eligible for treatment. Patients with history of brain metastasis should have a magnetic resonance imaging (MRI) within 4 weeks of initiating treatment. For patients where MRI is contraindicated (e.g., due to tissue expanders), brain computerized tomography (CT) may be obtained after discussion with Sponsor (replaces exclusion criterion #4).

19. Have evidence of persistent ≥ grade 2 ocular toxicity (in addition to exclusion criterion #14).