TROPHAMET

Essai de phase I/II avec Avelumab associé au Methotrexate chez des patientes atteintes de tumeur trophoblastique gestationnelle (TTG) de bas risque en 1ère ligne thérapeutique

Phase : II, Précoce

Type d'essai : Académique / Institutionnel

Thème spécifique : Cancers Rares

Etat de l'essai : Ouvert

Résumé / Schéma de l'étude

Experimental : Avelumab combined with methotrexate and folinic acid Avelumab administration at 800 mg every 2 weeks and methotrexate administration at 1mg/kg/day during 4 months ½ (median).

Critères d'inclusion

1. Woman older than 18 years.
2. Low-risk gestational trophoblastic neoplasia according to FIGO score (FIGO score ≤ 6) with indication of methotrexate as first line treatment.
3. Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
4. Patients with adequate bone marrow function measured within 28 days prior to administration of study treatment as defined below :
    1. Absolute granulocyte count ≥ 1.5 x 10^9/L.
    2. Platelet count ≥ 100 x 10^9/L.
    3. Haemoglobin ≥ 9.0 g/dL (may have been blood transfused).
5. Patients with adequate renal function : Calculated creatinine clearance ≥ 30 ml/min according to the Cockcroft-Gault formula (or local institutional standard method).
6. Patients with adequate hepatic function : Serum bilirubin ≤ 1.5 x UNL and AST/ALT ≤ 2.5 X UNL (≤ 5 X UNL for patients with liver metastases).
7. Patients must have a life expectancy ≥ 16 weeks.
8. Confirmation of non-childbearing status for women of childbearing potential.
9. An evolutive pregnancy can be ruled out in the following cases :
    1. In case of a previous hysterectomy.
    2. If serum hCG level ≥ 2 000 IU/L and no intra or extra-uterine gestational sac is detected on pelvic ultrasound.

3. If serum hCG level < 2 000 IU/L on a first measurement and serum hCG increases < 100% on a second measurement performed 3 days later.

10 Highly effective contraception if the risk of conception exists. (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential must agree to use 2 highly effective contraceptions, defined as methods with a failure rate of less than 1% per year. Highly effective contraception is required at least 28 days prior, throughout and for at least 12 months after avelumab treatment.

11 Patients who gave its written informed consent to participate to the study.

12 Patients affiliated to a social insurance regime.

13 Patient is willing and able to comply with the protocol for the duration of the treatment.

Critères de non-inclusion

1 Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti- CTLA 4 antibody (including ipilimumab, tremelimumab or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways).

2 Illness, incompatible with avelumab, such as congestive heart failure; respiratory distress; liver failure; uncontrolled epilepsy; allergy.

3 Patients with a known allergic hypersensitivity to methotrexate or any of the other ingredients (sodium chloride, sodium hydroxide, and hydrochloric acid if excipient).

4 Patients with second primary cancer, except : adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥ 5 years.

5 All subjects with brain metastases, except those meeting the following criteria :

1. Brain metastases that have been treated locally and are clinically stable for at least 2 weeks prior to enrolment, No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).

2. Subjects with brain metastases must be either off steroids except a stable or decreasing dose of < 10mg daily prednisone (or equivalent).

6 Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment with study drug.

7 Persistent toxicities (≥ grade 2) with the exception of alopecia and sensory neuropathy, caused by previous cancer therapy.

8 Treatment with other investigational agents.

9 Bowel occlusive syndrome, inflammatory bowel disease, immune colitis, or other gastro-intestinal disorder that does not allow oral medication such as malabsorption.

10 Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease.

11 Clinically significant (i.e., active) and severe cardiovascular disease according to investigator opinion such as myocardial infarction (< 6 months prior to enrollment).

12 Patients with immune pneumonitis, pulmonary fibrosis.

13 Known severe hypersensitivity reactions to monoclonal antibodies, any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of partially controlled asthma Global Initiative for Asthma 2011).

14 Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.

15 Active infection requiring systemic therapy..Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive).

16 Administration of a live vaccine within 30 days prior to study entry.

17 Current or prior use of immunosuppressive medication within 7 days prior to start of study treatment. *The following are exceptions to this exclusion criterion :

1. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection).

2. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.

3. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

18 Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents.

19 Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

20 Female patients who are pregnant or lactating, or are of childbearing potential and not practicing a medically acceptable method of birth control.

21 Treatment with oral anticoagulant such Coumadin.

22 Alcoholism (patient interview, investigator judgment).

23 Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome. Torsades de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation, bradycardia defined as < 50 bpm), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association Class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.

24 Prior organ transplantation, including allogeneic stem cell transplantation (excluding autologous bone marrow transplant).

25 Patients under guardianship.

Calendrier prévisionnel

Lancement de l'étude : Février 2020
Fin estimée des inclusions : Juin 2023
Nombre de patients à inclure : 26

Etablissement(s) participant(s)

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