8-79-52030-326 CLARINET FORTE

EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 14 DAYS IN WELL DIFFERENTIATED, METASTATIC OR LOCALLY ADVANCED, UNRESECTABLE PANCREATIC OR MIDGUT NEUROENDOCRINE TUMOURS HAVING PROGRESSED RADIOLOGICALLY WHILE PREVIOUSLY TREATED WITH LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 28 DAYS

Promoteur: IPSEN

Coordonnateur: Mariane PAVEL, Germany

- 11 countries - Belgium, France, Germany, Republic of Ireland, Italy, Spain, the United Kingdom (UK), the Netherlands, Denmark, Poland and the United States of America (USA).
- 30-32 centres, 100 patients (50 per cohort)

Overall duration: 64 months. Recruitment duration 24 months.
2 cohort design: 100 Subjects : two cohorts (NET): 50 x PNET or 50 x MIDGUT NET

Main Inclusion criteria

- Histopathologically confirmed well differentiated (grade 1 or 2 according to the WHO 2010 classification), metastatic or locally advanced, unresectable pNET (pNET cohort) or midgut NET (midgut cohort : CLOSED) with or without hormone related syndromes, with a Ki67 ≤20%.
- Positive SSTR2 as assessed by imaging (scintigraphy or positron emission tomography (PET) scan) in the organs of target lesions.
- Progression as assessed by an independent central reviewer according to RECIST v1.0 from radiological imaging (CT scan or MRI) while receiving first line treatment with lanreotide Autogel® at a standard dose of 120 mg every 28 days for at least 24 weeks (6 injections). Progression must be radiologically documented using the same technique of images (CT scan or MRI) within 24 months prior to enrolment.
- Inclusion into the study must be within 28 days of the radiological imaging that is performed to document progression.
- ECOG Performance Status (PS) 0 to 2.

Main Exclusion criteria

1. Has poorly differentiated grade 3 NET or rapidly progressive NET (within 12 weeks of initiation of lanreotide Autogel® 120 mg every 28 days) as per RECIST v1.0.
2. Has been diagnosed with VIPoma (i.e. Verner Morrison syndrome), insulinoma, foregut (except for pNET), hindgut NET, unknown primary NET or MEN1
3. Has progressed during treatment with Somatostatin Analogues (Sas) other than lanreotide Autogel® 120 mg.
4. Has been previously treated with any antitumour agent for NET other than lanreotide Autogel® 120 mg every 28 days: chemotherapy, molecular targeted therapy, peptide receptor radionuclide therapy (PRRT) or interferon.
5. Has had major surgery related to the studied disease within 3 months prior to entering the study. Previous de-bulking surgery and chemo-embolisation are acceptable as long as tumour burden is measurable (other target lesions).
6. Has gallbladder lithiasis at Screening echography or a history of cholelithiasis with no cholecystectomy since then

PROTOCOL N° UC-0105/1612
ACSE PEMBROLIZUMAB

TRIAL TITLE: Secured access to pembrolizumab for adult patients with selected rare cancer types

Promoteur: UNICANCER 101, rue de Tolbiac 75654 Paris Cedex 13 (France)

Coordonnateur: COORDINATING INVESTIGATOR: Pr Jean-Charles Soria

20 and 50 patients will be enrolled in each cohort

Pembrolizumab 200 mg IV as a 30 minute infusion on Day 1 of every 21 day cycle

Main Inclusion criteria

-Rare malignant neuroendocrine cancer: poorly differentiated digestive tumours refractory after 2 lines of chemotherapy *(CDDP/carbo-VP16 and FOLFIRI),* poorly differentiated non digestive tumours refractory after 2 lines of chemotherapy *(CDDP/carbo-VP16 and any 2d ligne)*
well differentiated tumours refractory after 4 lines of treatment *(2 lines of chemotherapy, everolimus and sunitinib)* ,
carcinoid tumours after 2 lines of treatment (*everolimus and Temozolomide chemotherapy)*
-Metastatic disease or unresectable locally advanced malignancy
-Measurable disease according to RECIST v1.1
- Treatment-free interval of at least 21 days following previous systemic anti-cancer treatments.
For investigational products or targeted therapy a treatment free interval equivalent to 5 half-lives of the product, or 21 days is required, whichever is shortest.
- Adequate hematologic function within 14 days of treatment initiation
- Neutrophil count ≥ 1.0 x109/L, platelets ≥ 100 x109/L, haemoglobin ≥ 9 g/L
Lymphocytes count below 1,000/mm3 and CD4+ count below 500/mm3
Serum bilirubin ≤ 1.5N , ASAT and ALAT≤ 2N. ASAT/ALAT ≤ 5N if liver metastasis.
Serum creatinine < 1.5 xULN or glomerular filtration rate >50 ml/min.
Normal blood levels of calcium and magnesium
-ECOG≤ 1.
-Life expectancy ≥ 90 days.

Main Exclusion criteria

-Prior treatment with an anti-PD1 or anti-PD-L1 antibody.
-Concurrent steroid medication at a dose greater than prednisone 10 mg/day or equivalent.
-Active autoimmune disease that has required systemic treatment in the past 2 years
-Chemo-, hormono-, radio- or immunotherapy or therapy with monoclonal antibodies or small tyrosine kinase inhibitors within 21 days or 5 half-life times prior to the first administration of IP.
-Treatment with other investigational drugs or participation in another clinical trial within 21 days or 5 half-life times (whatever the shortest) prior to the first administration of IP
-Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
-Other malignancies within the past 5 years other than basal cell skin cancer or in situ carcinoma of the cervix.
-Active serious infections, active or chronic hepatitis B, hepatitis C and/or human immunodeficiency virus infection (HIV 1/2 antibodies), or a known history of active Tuberculosis bacillus.

EudraCT NUMBER: 2010-024621-20 FIRSTMAPPP STUDY
FIRST INTERNATIONAL RANDOMIZED STUDY PLACEBO IN MALIGNANT PROGRESSIVE PHEOCHROMOCYTOMA AND PARAGANGLIOMA (PPGL)
Promoteur: Gustave Roussy, Villejuif Coordonnateur France : Eric Baudin Gustave Roussy, Villejuif
NUMBER OF CENTERS: At least 16
NUMBER OF PATIENTS: 74
Randomized, double-blind, phase II, international, multicenter study
Main Inclusion criteria 1- Diagnosis of malignant PPGL, based on imaging or biopsy evidence of metastases in liver, bones, lungs and or lymph nodes, combined with at least one of two further confirmatory diagnoses: 1. diagnosis of PPGL from histopathological review of resected or biopsied tissue performed by a skilled pathologist (centralized review will be performed in all cases either before enrolment in case of any doubt or during the study); 2. or in patients where tumor tissue is unavailable for formal pathological review, from combined biochemical and functional imaging evidence of PPGL (e.g., MIBG scintigraphy combined with consistently and highly elevated plasma or urine levels of metanephrines). 2-Metastatic disease not amenable to surgical resection 3-Pre-treated or not 4-Whatever the genetic status (sporadic or inherited) 6-Evaluable disease according to RECIST 1.1 criteria 6-Progressing disease within 18 months at imaging RECIST. The recent scan indicating progression may be used as the screening scan if within 28 days of randomization 7-ECOG 0-2 8-Adequate bone marrow reserve (Hb > 8, neutrophils ≥ 1500/mm³ and platelets ≥80.000/mm³)
Main Exclusion criteria 1-Patients with cardiac events within the previous 12 months, such as myocardial infarction (including severe/unstable angina pectoris), coronary/peripheral artery bypass graft, revascularization procedure symptomatic congestive heart failure (CHF, ejection fraction <45%),), uncontrolled cardiac arrhythmia, clinically significant bradycardia, cerebrovascular accident or transient ischemic attack, or pulmonary embolism 2-Hypertension that cannot be controlled despite medications (>=160/95 mmHg despite optimal medical therapy) 3-Abnormal cardiac function with 12 lead ECG. Ongoing cardiac dysrhythmias of NCI CTC grade 2, atrial fibrillation of any grade, or prolongation of the QTc interval to >470 msec for males or >480 msec for females 4-Brain metastases (exception if stable and asymptomatic for more than 3 months) –Brain metastases (exception if stable and asymptomatic for more than 3 months) 5-Prior systemic treatment with any tyrosine kinase inhibitors or anti-VEGF angiogenic inhibitors 6-treatment with therapeutic doses of anticoagulants. 7-Prior treatments with chemotherapy, immunotherapy, somatostatine analog therapy drug , thoracic radiotherapy within 4 weeks prior to inclusion 8-Major surgery for any cause or local radiotherapy within one month prior to visit 9-Liver embolisation therapy within the last 3 months prior visit 1 except if progression is demonstrated and embolised lesion not used as targets

Code promoteur : 69HCL17_0700

N°IDRCB : 2018-A00037-48

BEVANEC STUDY

Assessment of the efficacy of **bevacizumab in combination with Folfiri as second-line** treatment (versus folfiri) after the failure of the cisplatin (or carboplatin)-etoposide combination in patients suffering from an advanced inoperable **poorly differentiated neuroendocrine carcinoma of an unknown or gastroentero-pancreatic primary cancer**.
A phase 2 non-comparative randomized study (1:1)

Promoteur: Hospices Civils de Lyon

Coordonnateur: Dr. Catherine LOMBARD-BOHAS, Edouard Herriot Hospital HCL, LYON

26 centers of reference within the FFCD and/or from the RENATEN

Length of the inclusion period: 30 months
Duration of participation of each patient: 24 months
Total duration of the study: 54 months

Main Inclusion criteria

-Poorly differentiated neuroendocrine carcinoma (NEC) from a GEP gastrointestinal tract (from esophagus to anal canal) and biliopancreatic primary or an unknown primary cancer, locally advanced and/or metastatic ; Mixed tumor if the NEC component is > 70%
-Centralized review in TENPATH network
-Progressive disease RECIST criteria v.1.1 after a first-line chemotherapy treatment by cisplatin (or carboplatin) + etoposide or in the event of progression in the 6 months following
- at least one measurable target lesion according to RECIST v.1.1, in an area not previously irradiated,
- PS $\leq$ 2 (WHO)

Main Exclusion criteria

-Any of the following uncontrolled progressive diseases in the 6 months before randomization: liver failure, renal insufficiency, respiratory distress, congestive heart failure (NYHA III-IV), unstable angina, myocardial infarction, significant arrhythmia
-All uncontrolled progressive disease within 1 month prior to randomization: grade 3-4 gastrointestinal bleeding, infectious disease or intestinal inflammation, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event
-Known deficiency in dihydropyrimidine dehydrogenase, Known Gilbert's syndrome
-Chronic uncontrolled diarrhea, unresolved intestinal occlusion or subocclusion
-Uncontrolled wound and important surgery within the last 28 days
-Uncontrolled brain metastases (by local treatment)
-All treatment with concomitant anticonvulsive agents, CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine), discontinued for at least 7 days
-Previous local therapy allowed if completed > 6 weeks prior to randomization
-Anticoagulant treatment with an unstable dose of a vitamin K antagonist treatment, and/or having an abnormal INR (>3) in the four weeks before the randomization,
-Uncontrolled high systolic blood pressure >140 mmHg or diastolic pressure >90 mmHg
Total bilirubin level >2N; AST and/or ALT >5N; TP <50%; lipase, amylase >2N
Neutrophils <1.5x10^9/l, platelets <100x10^9/l, hemoglobin < 9 g/dl
Creatinine clearance (MDRD) <50 ml/min
Serum albumin <3.0 g/dL HbA1c > 8.5%
Proteinuria above or equal to 1g/24 hours measured from 24 hours

CC-90011-ST-001
Study CC-90011-ST-001 is an open-label, Phase 1a, dose escalation and expansion, FIH clinical study of CC-90011 in subjects with relapsed and/or refractory advanced unresectable solid tumors : Neuroendocrine Prostate Cancer (NEPC) and Bronchial NETS (Typical Carcinoid (TC) ; Atypical carcinoid (AC), Large Cell Neuroendocrine Carcinoma (LCNEC)
Promoteur: Celgene Corporation, Summit, New Jersey 07901 - United States
Investigateur Coordonnateur: Docteur Nicolas Isambert Unité de Phases Précoces U2P/Oncologie Médicale, 21079 Dijon - France
Length of the inclusion period: 12-18 months Duration of participation of each patient: 4-28months Total duration of the study: 6 years **Part B** : 20 patients per cohort
CC-90011 will initially be administered orally (60 mg) once weekly in each 4-week (28 day) Cycle. CC-90011 is a reversible, potent, and selective inhibitor of the epigenetic target LSD1 (histone-modifying enzyme that removes methyl groups and hence regulates the expression of many genes –histone methytransferase)
Main Inclusion criteria Relapsed and/or refractory advanced unresectable solid tumors : Neuroendocrine Prostate Cancer (NEPC) and Bronchial NETS (Typical Carcinoid (TC) ; Atypical carcinoid (AC), Large Cell Neuroendocrine Carcinoma (LCNEC) - Subjects must have progressed on (or not been able to tolerate due to medical comorbidities or unacceptable toxicity), or following standard anticancer therapy or for whom no other approved conventional therapy exists or is acceptable. - Progressive disease RECIST criteria v.1.1 after the last therapy - Subject consents to mandatory tumor biopsies (Screening and on treatment) - ECOG 0-1. Neutrophils <1.5x10^9/l, platelets <150x10^9/l, hemoglobin < 10 g/dl Serum creatinine >1.5N or Creatinine clearance <50 ml/min ; INR <1.5N Total bilirubin level <3N; AST and/or ALT <5N ; Serum albumin >3.0 g/dL
Main Exclusion criteria - Anti-cancer therapy (either approved or investigational) ≤ 4 weeks or 5 half-lives -Treatment with other investigational drugs or participation in another clinical trial within 28 days or 5 half-life times prior to the first administration, < 42 days for nitrosoureas or mitomycine C - Major surgery ≤ 4 weeks or minor surgery ≤ 2 weeks prior to Cycle 1 Day 1 - Any radiation treatment < 4 weeks prior to Cycle 1 Day 1 or < 2 weeks for palliative bone radiotherapy (single fraction). - Symptomatic and untreated or unstable central nervous system (CNS) metastases. - Subject recently treated with whole brain radiation or stereotactic radiosurgery for CNS metastases must have completed therapy at least 4 weeks prior to Cycle 1, Day 1 and have a follow-up brain CT or MRI demonstrating either stable or improving metastases 4 or more weeks after radiotherapy - Subject must be asymptomatic and off steroids or ≤10 mg/day prednisone equivalent - Concurrent steroid medication at a dose greater than prednisone 10 mg/day or equivalent. - Chronic active hepatitis B or C virus (HBV, HCV) infection. -Any of the following uncontrolled diseases: liver failure, renal insufficiency, respiratory distress, congestive heart failure (NYHA III-IV ,FEV<45%) , unstable angina, myocardial infarction, significant arrhythmia (BB, long QT, QTc> 480 ms) gastrointestinal bleeding, infectious disease or intestinal inflammation, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event, intestinal malapsorption, chronic diarrhea, hemorrhage CTAE>2 - Uncontrolled high systolic blood pressure >160 mmHg or diastolic pressure >95 mmHg - Patients receiving anticoagulant treatment and/or having an abnormal INR (>3), HBPM authorized

ESSAIS CLINIQUES CENTRE ENETS IPC – RENATEN PACA Septembre 2018

EudraCT NUMBER: 2017-003863-37

GCO-001 NIPINEC

Etude GCO étudiant l'efficacité et la tolérance du nivolumab en monothérapie ou de l'association nivolumab – ipilimumab chez les patients pré-traités présentant un carcinome neuroendocrine (CNE) peu différencié de stade avancé pulmonaire ou gastroentéropancréatique.

Promoteur: **I**ntergroupe **F**rancophone de **C**ancérologie **T**horacique (IFCT)

Coordonnateurs : Prs Nicolas Girard et Thomas Walter (PARIS-LYON)

Groupes : Fédération Française de Cancérologie Digestive (FFCD)
GERCOR – Groupe Coopérateur Multidisciplinaire en Oncologie

180 patients seront randomisés (90 par cohorte)
Période d'inclusion : 3 ans, période de suivi : 2 ans

Randomized, double-blind, phase II, international, multicenter study

Main Inclusion criteria

- OMS 0-2.
- Carcinome neuroendocrine (CNE) peu différencié : grande et petites cellules pour les CNE gastro-entéro-pancréatiques et grandes cellules uniquement pour les CNE pulmonaires indépendant du statut PD-L1 ; les tumeurs mixtes avec un CNE proéminent (> 70%) sont éligibles.
- Progression tumorale après une ou deux lignes de traitement, incluant au moins une ligne de chimiothérapie à base de platine.
-Stade localement avancé non résécable ou métastatique.
-Maladie mesurable selon les critères RECIST 1.1
-Clairance de la créatinine ≥ 50 mL/min (formule de Cockcroft) ; neutrophiles ≥ 1500/mm3 ; plaquettes ≥ 100 000/mm3 ; Hémoglobine ≥ 9 g/dL ; enzymes hépatiques < 3 x LNS (Limite Normale Supérieure) avec bilirubine totale ≤ 2 x LNS sauf pour les patients avec métastases Hépatiques ≤ 3,0 mg/dL.
-Matériel tumoral disponible pour la revue centralisée et pour la recherche translationnelle.

Main Exclusion criteria

-Mutation activatrice connue de l'EGFR, réarrangement connu du gène ALK ou ROS1 pour les CNE pulmonaires.
-Métastases cérébrales sauf si traitées par chirurgie ou radiothérapie stéréotaxique sans évolution dans les 3 mois précédant l'inclusion et que le patient est asymptomatique.
- autres cancers < 2 ans précédant la randomisation
-Antécédent d'immunodéficience primaire, de transplantation d'organe nécessitant un traitement immunosuppresseur, traitement immunosuppresseur dans les 28 jours précédant la randomisation ou antécédent de toxicité sévère (grade 3 ou 4) à médiation immunitaire
- corticothérapie orale (> 10 mg par jour de prednisone ou équivalent) ou autres traitements immunosuppresseurs dans les 14 jours précédant la randomisation.
-Antécédent connu de pneumopathie interstitielle ou signes de pneumopathie interstitielle au scanner
-Maladie auto-immune active connue ou suspectée incluant le lupus érythémateux ou la granulomatose de Wegener (diabète de type I ou hypothyroïdie ou une maladie cutanée incluables.
-Maladie active ou antécédent de pathologie inflammatoire du colon ou chronique gastrointestinale
- Infection active ou non contrôlée ou maladie sévère, tuberculose active, Hépatite B ou C aigue, VIH
-Traitement antérieur par un anticorps anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 ou traitement ciblant la co-stimulation des lymphocytes T ou les voies du checkpoint.
-chimiothérapie ou de radiothérapie < 3 semaines avant la randomisation.