Titre: Sensibilisation par la radiothérapie externe (stéréotaxique) de l'efficacité d'une immunothérapie anti-PD1 dans les tumeurs neuro-endocrines métastatiques bien différenciées.

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Essai de phase 2 inter-groupe PROGIGE (FFCD, GTE, Unicancer, GERCOR)

Title: Sensitization to anti-PD1 immunotherapy by (Stereotactic Body (SB)) External Radiation Therapy in neuroendocrine tumor

Acronym: Immun(SB)RTNET)

Rational: This is a study to investigate the efficacy and safety of a sensitizing immunotherapy strategy combining anti-PD1 immunotherapy and (SB) External Radiation Therapy in patients with advanced or metastatic, well-differentiated, (only non-functional ?) neuroendocrine tumors of pancreatic, gastrointestinal or thoracic origin. GM-CSF, which is a potent immune adjuvant to dendritic cell maturation, might induce abscopal responses in metastatic solid tumours.
Our hypothesis is that (SB) External Radiation Therapy could sensitize the tumor to immune therapy by anti-PD1 immunotherapy. We aim to test in patients with stable (or progressive) disease whether the addition of (SB) External Radiation Therapy to a small fraction of the disease associated with GM-CSF applied with treatment with anti-PD1 immunotherapy and GM-CSF may be able to induce tumor objective response following immunotherapy.

Commenté [TL1]: ou autre cible immune check point ??
Choix de l'anti-PD1 immunotherapy (ou autre cible immune check point) parmi les suivants :
Novartis : anti-PD-1 monoclonal antibody PDR001 et/ou anti-LAG-3 monoclonal antibody LAG525
BMS : Nivolumab
MSD : pembrolizumab
……

Objectives:
The primary objective is to evaluate efficacy of anti-PD1 after (SB) External Radiation Therapy associated with GM-CSF.
The secondary objectives in this study are: to evaluate safety of the combination between (SB) External Radiation Therapy and anti-PD1 immunotherapy; to find early markers for response to immune therapy, by immunomonitoring and pharmacokinetic study (translational research)

Eligibility Criteria:
- Pathologically confirmed, unresectable, advanced metastatic well-differentiated (G1 or G2) neuroendocrine tumor of GI, pancreatic or thoracic origin
- At least three metastatic lesions
- No severe functional syndrome associated with neuroendocrine tumor
- Patients must have been no pretreated for advanced disease within 6 months before the first dose of study treatment (systemic or locoregional treatment, except somatostatin analogs)
- (Tumor biopsy material must be provided for all patients for the purpose of biomarker analysis)
- Radiological documentation of disease stabilisation (Disease stabilisation must have been observed within 6 months prior to start of study treatment) or progression

Primary outcomes measure: Confirmed Overall Response Rate, i.e. complete or partial response according to RECIST 1.1 criteria at (3 and) 6 months after inclusion (RECIST evaluation should not use the lesion treated by (SB) External Radiation Therapy as a target lesion).

Secondary outcomes measures: ORR according to mRECIST and irRECIST criteria during the study period ; Time to progression according to RECIST, mRECIST, irRECIST criteria ; Progression free survival according to RECIST, mRECIST, irRECIST criteria ; Overall survival ; Toxicity according to CTCAE v4.03

Treatment: Anti-PD1 immunotherapy should be started within 1 week following inclusion (?? mg every ?? weeks, until progression). (SB) External Radiation Therapy to one lesion, targeting a destruction diameter of 2 to 4 cm, total dose of ?? Gy delivered in ?? fractions, combined with anti-PD1 immunotherapy ?? mg every ?? weeks, until progression.

The radiotherapy should start within ?? (3?) weeks following inclusion. The radiotherapy might target only partial volume of a lesion, the goal not being local control but the enhancement of systemic response. The targeted lesion should be chosen to avoid potential at-risk organs. However, in the case of all targetable lesion would be close to at-risk organs, adaptation to the dose for a schedule delivering ?? Gy in ?? fractions could be proposed.

Granulocyte-macrophage colony-stimulating factor (125 µg/m² subcutaneously injected daily for 2 weeks, starting during the second week of radiotherapy – A VOIR EN FCT DU SCHEMA DE RT)

Collateral Research: Pre- and post-treatment biopsy (A DISCUTER) and immunomonitoring for all patients pre-treatment and post-treatment biopsy for all patients: PD-1, PD-L1, PD-L2 expression. Complementary analysis of pre-treatment and post-treatment biopsy (mutational load, immune infiltrate), and circulating biomarkers: Immunomonitoring (T cell proliferation, Treg function, circulating cytokines); pharmacokinetic study of anti-PD1 immunotherapy.

Statistical Plan: An open-label, single-arm phase II prospective clinical trial. The primary efficacy end-point is confirmed Overall Response Rate at 6 months. The simple size calculation is based on the assumption that a true ORR of ≥ 30% (H1) is necessary to consider the investigational treatment sufficiently active to pursue in further studies, whereas a true ORR of ≤ 5% (H0) is not yield further interest in this treatment. The sample size is chosen based on a one-sided α level of 5% and a power of 85%. The calculated sample size is 20 patients. With a proportion of 5% not evaluable patients, we need to include 21 patients.