Diagnosis and main criteria for inclusion

All patients must meet all of the following criteria:

1. Written informed consent
2. Male or female ≥18 years of age
3. Histologically confirmed diagnosis of well-differentiated neuro-endocrine tumour of non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET), tumour grade G1 or G2 (Ki-67 ≤20%), unresectable or metastatic, in a patient who is either treatment-naïve (1 st line) or who has progressed under prior therapy (2 nd line)
4. Availability of existing biopsy specimen from primary tumour or metastasis or, if unavailable, willingness to undergo current biopsy for secondary central analysis
5. Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥1 cm in longest diameter, and ≥2 radiological tumour lesions in total. A maximum of 5 target lesions visible on CT/MRI will be defined, thereof not more than 2 lesions per organ
6. Somatostatin receptor positive (SSTR +) disease, as evidenced by SSTR imaging (SRI) within 4 months prior to randomisation, as locally authorised, by:
   - 68 Ga-based SSTR positron emission tomography (PET) imaging (68 Ga-edotreotide or 68 Ga-DOTATATE), or
   - 111 In-pentetreotide SSTR SPECT/planar imaging, or
   - 99m Tc-octreotide SSTR SPECT/planar imaging
   - 64 Cu-based SSTR PET imaging (64 Cu-DOTATATE), if approved, according to local regulations

   All target lesions and ≥90% of non-target lesions need to be positive for SSTR; this relates to lesions of at least 15 mm in diameter acquired on SRI images with SPECT, and of at least 10 mm in diameter acquired on SRI images with PET systems.
7. The patient must have progressive disease based on RECIST 1.1 Criteria as evidenced by two morphological imaging examinations made with the same imaging method (either CT or MRI), within a maximum of 36 months prior to randomisation. The most recent scan must not be older than 90 days prior to randomisation date. The minimum interval between the two scans must be ≥90 days.
8. Karnofsky performance status (KPS) scale ≥70
9. Life expectancy allows the patient to participate in the study based on the investigator's assessment
10. Glomerular filtration rate (GFR, CKD-EPI) ≥60 mL/min/1.73 m2
11. For patients included in France only, verification and confirmation of their affiliation with a social security
12. Patients with functional P-NETs who require SSA for symptom control may continue SSA treatment throughout the study, on condition that:
    a) they have been on a stable dose for at least three months prior to study enrolment
    b) that progressive disease has been diagnosed while under such stable dose

Exclusion criteria

A patient will be excluded from participation in the trial if one or more of the following criteria are met:

1. Known hypersensitivity to edotreotide or everolimus
2. Known hypersensitivity to DOTA, lutetium-177, or any excipient of edotreotide or everolimus or any other Rapamycin derivative
3. Known hypersensitivity to lysine, arginine, or any excipient of the nephroprotective amino acid solution
4. Prior exposure to any peptide receptor radionuclide therapy (PRRT), including 177 Lu-edotreotide, 90 Y-edotreotide or other SSTR-targeting agents (e.g. 177 Lu-octreotate or high-dose 111 In-pentetreotide)
5. Prior therapy with mTOR inhibitors
6. Prior EFR (external field radiation) to GEP-NET lesions within 90 days before randomisation or radioembolisation therapy (e.g. 90 Y microspheres, 131 I-lipiodol) with administration to the liver
7. Prior therapy with chemotherapy, immunotherapy, interferon, chemo-embolisation, bland embolisation, cyclosporine-A within 4 weeks before randomisation; any new cancer treatment between screening and randomisation
8. Therapy with an investigational compound and/or medical device within 30 days or 5 half-life periods (whichever is longer) prior to randomisation
9. Subjects who have received a live vaccine up to 4 weeks prior to first dose
10. Current therapy with any prohibited medication (see Section 6.1.1)
11. Ongoing toxicity grade 2 according to CTCAE version 4.03 from previous standard or investigational therapies
12. Indication for surgical lesion removal with curative potential
13. Planned (for the period of study participation): chemotherapy, immunotherapy, interferon, radiation therapy, chemo-embolisation, bland embolisation, radio-embolisation, treatment with cyclosporine-A
14. Neuroendocrine tumours, not meeting the inclusion criteria:
    - With known non-GEP-NET origin (e.g. pulmonary or gonadal primaries)
    - Functional GE-NET
    - Explicit diagnosis of unknown primary (CUP)
    - G3 neuroendocrine tumours and neuroendocrine carcinomas
    - NET for which no histological specimen for secondary histological analysis can be obtained
15. Total hepatic tumour burden >70%
16. Brain metastases
17. Other malignancy within previous 5 years (except basal cell carcinomas and in situ squamous cell carcinomas of the skin)
18. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator

19. Clinically relevant renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments, as follows:
    - Renal
        - Renal obstruction
    - Hepatic
        - Total bilirubin >1.5 x ULN
        - AST or ALT >2.5 x ULN
        - Alkaline phosphatase >5 x ULN
        - Albumin <3 g/dL, unless prothrombin time is within normal range
    - Cardiovascular
        - New York Heart Association classification III & IV
        - Uncontrolled hypertension
    - Haematopoietic
        - Platelets 80 × 10 9 /L
        - Absolute neutrophil count (ANC) <1 x 10 9 cells/L
20. Pregnant or breast-feeding women. Female patients of childbearing potential or male patients with female partners of childbearing potential, unless willing to practice full and true sexual abstinence or who are surgically/permanently sterile (bilateral tubal occlusion, hysterectomy, or vasectomy), or female patients whose male partners have medically successful vasectomy (provided the partner is the sole sexual partner of the female patient of childbearing potential), or who are not willing to practice highly effective contraception in combination with a barrier method of contraception (e.g. condom). Contraception methods that are considered highly effective are: oral or non-oral (injected or implanted) non-oestrogen progesterone-based hormonal method; oral, intravaginal, or transdermal combined oestrogen and progesterone-based hormonal methods; and/or intrauterine device (IUD), and/or intrauterine hormone-releasing system (IUS). Sexual abstinence or the contraception methods described above must be followed throughout the entire study period and for 56 days after treatment in the everolimus group and 66 days in the PRRT group (10 half-lives of 177 Lu) after the last treatment cycle.
21. Subjects not able to declare meaningful informed consent on their own (e.g. with legal guardian for mental disorders) or any other vulnerable population to that sense (e.g. persons institutionalised, incarcerated etc.).