

RAMSETE (RAD001 in Advanced Metastatic Silent NeuroEndocrine Trial in Europe)

Purpose/rationale	The purpose of this study is to assess activity and safety of RAD001 10 mg/day in the treatment of advanced non syndromic neuroendocrine carcinoma patients. The primary objective is to determine the response rate (CR + PR) in at least 50 patients treated with RAD001 10 mg/day.
Study design	<p>This is a single-arm multicenter , exact binomial single-stage phase II study to evaluate the safety and the preliminary efficacy of RAD001 10 mg p.o. q.d. in approximately 50 patients with advanced non syndromic neuroendocrine carcinoma.</p> <p>An independent central radiology review committee will be set up to review radiology studies as provided by investigational sites. All CT scans and MRIs obtained at baseline, during the treatment period and the follow-up period will be sent to the independent central radiologist. The primary analysis of ORR will be based on the central radiological assessments. Tumour assessments are performed until documented disease progression as assessed by both central and local radiologists.</p> <p>Duration of Treatment: Patients will be treated with RAD001 until tumour progression is documented per RECIST or until any other reasons for treatment discontinuation as outlined within the protocol.</p> <p>Follow-Up: Patients who have not progressed at the time of discontinuation of study treatment will be followed with tumour assessments until progression is documented at the investigative site. During this follow up period the site will continue to send radiological studies for central review.</p> <p>In addition patients will be followed for safety until at least 28 days after study treatment discontinuation and for survival until the final analysis.</p>

Inclusion/exclusion criteria	<p>Inclusion</p> <ul style="list-style-type: none"> • Adult male or female patients ≥ 18 years of age • Advanced (unresectable or metastatic) biopsy-proven non syndromic neuro-endocrine carcinoma, low- or intermediate grade • Radiological documentation of disease progression within 12 months prior to study entry. If patients received anti-tumour therapy during the past 12 months, they must have radiological documentation of progression of disease while on or after receiving the therapy. • Patients may have received previous treatment (chemotherapy, biotherapy, peptide-receptor radionuclide therapy); an overall maximum of 3 systemic treatments is allowed, as follows: <ul style="list-style-type: none"> ○ previous ≤ 1 CT regimen for advanced disease; ○ previous ≤ 1 RT regimen; ○ previous ≤ 1 Biotherapy (e.g. IFN etc); ○ previous ≤ 1 VEGFi therapy (e.g. bevacizumab, sunitinib etc); • Measurable disease as defined by RECIST using instrumental assessment (CT or MRI) • Adequate bone marrow function as shown by: <ul style="list-style-type: none"> ○ ANC $\geq 1.5 \times 10^9/L$, ○ Platelets $\geq 100 \times 10^9/L$, ○ Hb >9 g/dL • Adequate liver function as shown by: <ul style="list-style-type: none"> ○ Serum bilirubin $\leq 1.5 \times ULN$ ○ INR < 1.3 (or < 3 on anticoagulants) ○ ALT and AST $\leq 2.5x ULN$ ($\leq 5x ULN$ in patients with liver metastases) • Adequate renal function: serum creatinine $\leq 2.0 \times ULN$ • Fasting serum cholesterol ≤ 200 mg/dL OR ≤ 5 mmol/L AND fasting triglycerides ≤ 200mg/dL. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication. • ECOG performance status of 0-2 • Life expectancy ≥ 6 months • Women of childbearing potential must have had a negative urine pregnancy test within 72 hours prior to the administration of the study treatment start. • Patients who give a written informed consent obtained according to local guidelines <p>Exclusion</p> <ul style="list-style-type: none"> • Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma are not eligible • Patients with carcinoid with hormone related symptoms (diarrhea ≥ 4 stools per day and/or flushes) • Patients with Islet Cell carcinomas or pancreatic NET • Patients who receive currently following therapies have to undergo washout period prior to study entry <ul style="list-style-type: none"> ○ cytotoxic CT: 4 weeks ○ Biotherapy: 4 weeks ○ Biotherapy short acting: 48 hours ○ Radiotherapy: 4 weeks. • The patient should have recovered from the treatment and have a good clinical condition before entering this study. • Patients who received peptide-receptor radionuclide therapy within 3 months prior to study entry
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- Patients who received VEGFi therapy within 4 weeks prior to study entry.
- Patients who received hepatic artery embolisation within the last 6 months (1 month if there are other sites of measurable disease), or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months of study entry
- Patients who received prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus)
- Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients
- Patients with uncontrolled central nervous system (CNS) metastases.
- Patients with an active, bleeding diathesis.
- Patients receiving chronic systemic treatment with corticosteroids (dose of ≥ 10 mg/day methylprednisone equivalent) or another immunosuppressive agent. Inhaled and topical steroids are acceptable.
- Patients with a known history of HIV seropositivity.
- Patients with autoimmune hepatitis.
- Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
 - unstable angina pectoris, symptomatic congestive heart failure (NYHA II, III, IV), myocardial infarction ≤ 6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia
 - severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O₂ saturation that is 88% or less at rest on room air
 - uncontrolled diabetes as defined by fasting serum glucose >2.0 x ULN
 - any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study
 - nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with this study treatment, such as severe hypertension that is not controlled with medical management and thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication
 - liver disease such as cirrhosis, decompensated liver disease, chronic active hepatitis or chronic persistent hepatitis
 - fatal or life-threatening autoimmune and ischemic disorders.
- Patients who have a history of another primary malignancy and off treatment for ≤ 3 years, with the exception of non-melanoma skin cancer and carcinoma in situ of uterine cervix
- Patients that are currently, or in the 4 weeks preceding initiation of study treatment, receiving other investigational agents
- Patients unwilling or unable to comply with the requisites of the protocol
- Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Oral contraceptives are not acceptable.