SYNOPSIS

Protocol Title:	**A Phase II Single Arm Trial Evaluating the Efficacy and Safety of Temozolomide for Second-Line Treatment of metastatic Neuroendocrine Carcinomas Progressing after First-Line Platinum- based Therapy.**
Protocol Name:	TENEC
IMPs:	• Temozolomide
Participating countries	Italy - approximately 5 centres
Background Information and Study Rationale	Recurrent or metastatic Neuroendocrine Carcinoma (NEC) continues to be an incurable disease with a poor prognosis and there is no standard for second line chemotherapy. There are few prospective studies that investigate a second line chemotherapy in these Carcinomas. Temozolomide, administrated with different schedules, seems to be a promising drug both alone or in association with Bevacizumab and Capecitabine [1-5]. Clover study has investigated activity of a three-drug combination including cisplatin, dacarbazine and capecitabine demonstrating that this combination may be an option in NEC with a global overall survival (OS) of 13 months (range=1-29) and a progression-free survival (PFS) of 6 months (range=1-11) [6]. However patients with a metastatic pNEC, progressed after a first line chemotherapy do not have a good Performance Status, generally. In 2011 Welin et al. showed that Temozolomide may be an active, well tolerated, second-line chemotherapy regimen for NEC patients (mainly gastrointestinal) who have progressed after first-line chemotherapy [7]. It seems to be effective also in lung carcinoid [8]. In Glioma, it has been suggested that intermittent dosing (one week on/one week off treatment) may reduce the frequency and severity of hematologic toxicity compared with more extended dosing schedules such as the 21/28-day or extended daily schedules [9;10]. This schedule has been also investigated by Chan et al. in 34 patients with advanced neuroendocrine tumors demonstrating a good profile of toxicity [11]. Metronomic schedules have been reported to potentially overcome MGMT-related drug resistance. At INT Pascale of Naples, we treated a patient with one week on and one week off Temozolomide regimen. The patient had a metastatic pNEC, progressed after a first line chemotherapy cisplatin-based regimen. After 1 month of treatment, a clinical response, with regression of disease-related symptoms and performance status improvement from ECOG PS 2 to 0 was obtained. After 3 months of therapy a RECIST partial response was observed. The treatment was well tolerated without drugrelated side effects. After 18 months of therapy the partial response goes on. Though on the tumor samples of patient the detection test of MGMT

	methylation was positive, we think that this result cannot be due only to the action of the alkylating drug, but needs immunological implications of the chemotherapy. Conventional anticancer chemotherapy is generally thought to act through selective killing of tumor cells or by irreversibly arresting their growth. Cytotoxic drugs act in different phases of cell cycle interfering with DNA synthesis, or inducing a damage on DNA, leading to tumor cell death. Always more evidences indicate that several chemotherapeutic agents are more active against tumors implanted in immunocompetent hosts as compared with tumors in immunodeficient hosts. This clearly indicates the existence of a correlation between the activity of chemotherapeutic agents and the hosts' immune system [12]. Advances in tumor immunology have now explained some key mechanisms that represent the basis of therapeutic synergy with other treatments. In our clinical case, the continuous response after 18 months of treatment, associated with the clinical benefit obtained, indicate a plausible immune activation induced by metronomic temozolomide. Moreover this case report highlights the efficacy and tolerability of this regimen even in a patient with poor performance status and in this particular category of neoplasms, opening new scenarios of treatment for metastatic pNET. Therefore, this regimen has a promising activity that should be evaluated to confirm the efficacy and safety of temozolomide as second-line treatment of Gastro-entero-Pancreatic Neuroendocrine Carcinomas progressing after first-line Platinum-based therapy, especially in selected patients, such as those who have levels of MGMT methylation.
Objective	To assess the efficacy and safety of Temozolomide for second-line treatment of Neuroendocrine Carcinomas progressing after first-line Platinum-based therapy.
Primary Endpoint	- Overall response rate (ORR)
Secondary Endpoint(s)	- Clinical Benefit Rate (CBR) - Second Line Progression Free Survival (PFS) - Overall survival (OS) - 1 Year OS - Safety and tolerability - Duration of response - Quality of Life (QoL)
Study Design	This is a Phase II, multicentre, single-arm study
Number of subjects:	Approximately 35 patients will be recruited over a planned recruitment period of 24

	months
Treatment	All patients will receive: - Temozolomide 75 mg/m2/day seven days followed by seven days of stop (regimen one week on / one week off)
Treatment Duration	Patients enrolled will receive study medication until disease progression, unacceptable toxicity, withdrawal of consent or death, whichever comes first.
Supportive Therapy	N.A.
Efficacy Assessments	Imaging assessments for evaluation of tumor response and disease progression will be done at baseline and every 9 weeks. Once a patient progresses this should be confirmed by imaging according to RECIST v1.1 (Eisenhauer et al. 2009). Efficacy for all patients will be evaluated by objective tumor assessments every 9 weeks from first dosing using the appropriate method as recommended by RECIST criteria. During protocol treatment, periodic assessments should continue until progression of disease occurs. All patients will be assessed until evidence of one of the following: 1. Progression as defined in this protocol 2. Death without evidence of disease progression and will not be followed up after progression of disease (PD) <u>Conventional CT and MRI:</u> Minimum sized lesion should be twice the reconstruction interval, with a minimum lesion size of 15 mm when the reconstruction interval is 7mm. The techniques should be performed with contiguous cuts of 10 mm or less in slice thickness; however, contiguous cuts of 7mm or less is preferable. MRI is acceptable, but when used, lesions must be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Whenever possible, the same scanner should be used. Spiral CT: Minimum size of a baseline lesion may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. This specification applies to the tumors of the chest, abdomen, and pelvis. Please note the following: The same diagnostic method must be used throughout the study to evaluate a lesion. Ultrasound is not an acceptable method of disease assessment.
Safety Assessments	Safety outcome measures are as follows:

	• Incidence and severity of adverse events (AEs),serious adverse events (SAEs), and adverse events of special interest (AESIs) • Laboratory test abnormalities Clinical assessments will be performed every three weeks and recorded on electronic case report forms at every nine weeks . Hemocrome and complete biochemical assessment will be performed at baseline and at day one of every week of treatment (week on). Any clinical AE or abnormal laboratory test value that is serious and which occurs from the signature of the ICF, start of any study specific procedure, during the course of the study will be reported to Sponsor **within 24 hours** of the investigator becoming aware of the event (expedited reporting).
Quality of life assessment	QoL will be assessed using the European Organization for Research and Trial in Cancer QOL core (EORTC QLQ-C30) questionnaire (version 3) and supplemented by disease specific modules for NET, the EORTC QLQ GINET21. EORTC QLQ-C30 and the specific module for NET EORTC QLQ GINET21 Quality of Life Questionnaire will be administrated every 28 days.
Inclusion Criteria	- Signed informed consent prior to initiation of any study-specific procedures or treatment, as confirmation of the patient's awareness and willingness to comply with the study requirements. - Patients ≥18 years of age. - Histologically confirmed Metastatic Neuroendocrine Carcinoma (Ki67>20% Ki67 must be quantified in percentage) with documented progression of disease per investigator assessment following or during first-line platinum-based treatment. - ECOG performance status (PS) of 0-2. - At least 28 days since prior radiation therapy or surgery and recovery from treatment. - Patients must have measurable disease which must be evaluable per RECIST v1.1. - Estimated life expectancy of ≥12 weeks.
Exclusion criteria	- Patients < 18 years of age - Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would prevent the patient from meeting the study requirements. - Serious active infection requiring i.v. antibiotics and/or hospitalization at study entry. - Patients who are treated with any medicinal product that contraindicates the use of the study drug, may interfere with the planned treatment, affects patient

compliance or puts the patient at high risk for treatment-related complications.

- Pregnant or lactating females. Serum pregnancy test to be assessed within 7 days prior to study treatment start, or within 14 days with a confirmatory urine pregnancy test within 7 days prior to study treatment start. Women of childbearing potential (defined as <2 years after last menstruation and not surgically sterile) not using effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly). Perimenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential
- Patients with meningeal carcinomatosis
- Patients with organ allografts requiring immunosuppression
- Patients with known positive HIV status
- Patients with a hypersensitivity to Temozolomide or Dacarbazine
- Any laboratory values at baseline as follows:

<u>Hematology:</u>

a. ANC <1.5x109/L or 1500/mm3
b. Platelet count <100x109/L
c. Hemoglobin <8 g/dL (Note: hemoglobin levels may be supported by transfusion or erythropoietin or other approved hematopoietic growth factors).

<u>Coagulation:</u>

a. INR >1.5 except for patients on stable anticoagulant therapy
b. aPTT ≥1.5 times ULN or greater than the lower limit of the therapeutic range

Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks at the time of Day 1, Cycle 1.

<u>Serum chemistry:</u>

a. Total bilirubin >1.5 times ULN
b. AST or ALT >2 times ULN (>5 times ULN for patients with known liver involvement)
c. ALP >2 times ULN (>5 times ULN for patients with known liver involvement and >7 times ULN for patients with known bone involvement).