SYNOPSIS

Study Title	An open label, single arm, phase II study to evaluate the activity and toxicity of Panitumumab in pre-treated patients with advanced well differentiated neuroendocrine tumor (G1 and G2)
Coordinating Center	Istituto di Oncologia (I.D.O.) - Policlinico di Monza Via Carlo Amati 111, 20900 Monza- Itlay
Sponsor	I.T.M.O (Italian Trials in Medical Oncology)
Therapeutic Area	Medical Oncology
Clinical Phase	II
Number of Centers	$\geq$ 10 Italian Centers
Trial Design	Multicentric, not randomized, optimal 2-stage design (Simon, 1989) phase II study
Indication	Well differentiated neuroendocrine tumor (G1 and G2)
Target Population	Metastatic or not eligible for surgery well differentiated neuroendocrine tumor (G1 and G2)after somatostatine analogues
Drugs/Dose/Route/Regimen	Panitumumab 6 mg/kg day 1, q 14 i.v.
Rationale	The neuroendocrine tumors are rare neoplasm, no standard therapeutic approach are recognized. The somatostatin analogues represent the gold standard in tumors with carcinoid syndrome. Up to date the role of this drug is well recognized for symptoms control, but has not been shown a direct effect on the control of tumor growth. Studies with the use of chemotherapy showed different rates in terms of objective response, however, there is no evidence of a real impact on survival. Panitumumab works by binding to the extracellular domain of the EGFR (epidermal growth factor receptor) preventing its activation. This in turn, results in halting of the cascade of intracellular signals dependent on this receptor. Epidermal growth factor receptor is expressed and activated in gastrointestinal carcinoids and pancreatic neuroendocrine tumors.
Primary Objective	To evaluate the activity and efficacy of panitumumab in metastatic or not eligible for surgery well differentiated neuroendocrine tumor after somatostatine analogues and possible chemotherapy.
Secondary Objectives	To evaluate activity (on further parameters: see §2.4), efficacy and tolerability of panitumumab in metastatic or not eligible for surgery well differentiated neuroendocrine tumor after somatostatine analogues and chemotherapy.
Primary Endpoints	Activity is defined as *Non-progression rate*, (RECIST criteria version 1.1), as evaluated at 6 months.

Secondary Enpoints	Best *objective response* (CR + PR according to RECIST criteria version 1.1): complete plus partial responses, as evaluated at 6 months Biochemical response (changes of tumor marker values) Time to progression (TTP) and overall survival (OS), as estimated by the Kaplan-Meier method. Adverse reaction definition and grading according to CTC-AE v.3.0
Biological Study and Endpoints	Evaluation of tissue molecular markers expression in relation to the activity of Panitumumab Central review (EGFR and KRAS)
Number of Subjects	32 evaluable patients
Duration of Treatment for subject/patient	The treatment will be given until unacceptable toxicity or progression disease
Duration of Trial Recruitment	12 months +/- 6 months
Follow-Up	24 months
Inclusion Criteria	• Histological diagnosis of well-differentiated neuroendocrine tumor (G1 and G2) of gastro-entero-pancreatic district or of unknown primary site. • Disease progression after treatment with somatostatin analogues • Previous treatment with everolimus, sunitinib or bevacizumab is admitted. • One chemotherapy is admitted. • Metastatic or not eligible for surgery disease. • Male or female, age > 18 years. • Absence carcinoid syndrome. • ECOG performance status 0-1. • Expectancy of life > 6 months • Written informed consent • Adequate liver function as shown by: serum bilirubin ≤1.5 x ULN; ALT and AST ≤ 2.5x ULN (≤ 5x ULN in patients with liver metastases) • Adequate bone marrow function: ANC ≥ 1.5 x 109/L;PLT ≥ 100 x 109/L; Hb > 9 g/dL • Creatinine clearance ≥ 50 ml/min • Magnesium and calcium ≥ lower limit of normal • At least one measurable lesion at CT scan as defined by RECIST • Women of childbearing potential must have had a negative serum or urine pregnancy test within 7 days prior to the administration of the study treatment start, and must use an acceptable form of contraception

Exclusion Criteria	• Patients with a known hypersensitivity to panitumumab • Histological diagnosis of poorly differentiated neuroendocrine carcinoma (G3) • Histological diagnosis of lung neuroendocrine tumors (typical or atypical carcinoid, small cell lung cancer, large cell neuroendocrine carcinoma) • 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, myocardial infarction ≤ 12 months prior to first study treatment, serious uncontrolled cardiac arrhythmia; severely impaired lung function; uncontrolled diabetes; 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; non-malignant 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 due to which 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; uncontrolled hyperlipidemia • History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan. • Patients with serious neurological or psychiatric disorders • Patients with central nervous system (CNS) metastases • Patients who have a history of another primary malignancy with the exception of basal or squamous cell skin cancer, in situ cancer, and any cancer from which the patient has been disease free for 5 years • Immunocompromised patients, including positive HIV test. An HIV test is not required to enter the study • Female patients who are pregnant or breast feeding • Patients of reproductive potential who are not using appropriate contraceptive methods. Appropriate forms of contraception are: IUD, oral or depot contraceptive or the barrier method plus spermicide.
Statistical Analyses	The sample size (see statistical section) was calculated to both reduce the number of patients to be treated with an eventually poor drug and evidence an activity of panitumumab at the **75**% success level. A "success" was defined as no evidence of Progressive Disease (PD) according to RECIST at the time of planned evaluation. tumor assessments will be made at baseline and thereafter every three months, according to visit schedule. Patients lost to follow-up/not evaluated for activity before 6 months were considered as a non success.. The optimal 2-stage design to test the null hypothesis that the success rate P<=**0.60** versus the alternative hypothesis that P>=**0.75** has an

	expected sample size of **22.03** and a probability of early termination of **0.367**. If the drug is actually non active, there is a **0.198** probability of concluding that it is (the target for this value is **0.20**). If the drug is actually active, there is a 0.198 probability of concluding that it is not (the target for this value is 0.20). After testing the drug on **10** patients in the first stage, the trial will be terminated if **5** or fewer successes. If the trial goes on to the second stage, a total of **32** patients will be studied. If the total number responding is less or equal to **21**, the drug is rejected.
Duration of the Study	Recruitment period: 12 months +/- 6 months Follow up period: 24 months