SYNOPSIS

Study Title	Natural History, Geographical Distribution and Biological Characterization of Patients with Neuroendocrine Tumor (NET) ITMO Multicenter, clinical-biological study
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) no-profit Organization on Clinical Research
Therapeutic Area	Medical Oncology – Natural History
Number of Centers	≥ 10
Trial Design	Longitudinal, prospective, multicenter observational study
Indication	Early- and advanced-stages neuroendocrine tumors
Target Population	Patients with neuroendocrine tumor
Study rationale	Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms characterized by peculiar clinical-biological features that differentiate them from other cancer types. NETs present similar immunohistochemical and morphological features, including the ability to produce hormones or local mediators that can lead to the development of clinical syndromes. Despite these common characteristics, NETs are highly different with regard to biological behavior and clinical outcome. Although until recently NETs were considered as rare neoplasms, their incidence has significantly increased over the last decades prompting an urgent need for earlier diagnosis and therapeutic decisions. Clinical and histobiological features have a relevant impact on the oncologist's approach to NETs management, since on the one hand they influence the diagnosis and prognosis of the disease and the patient's treatment and monitoring on the other. Therefore, a deeper understanding of NETs clinical and biological features along with a correct histopathological characterisation of these neoplasms may provide new decisional tools to surgeons as well as to clinical oncologists. Similarly, a deeper knowledge of NETs natural history and biology

	is an essential requirement for the development of individually tailored treatment plans. Over the last decade, improvements in immunohistochemical, biochemical, morphological and biomolecular techniques have led to remarkable advances in the diagnosis and treatment of NETs. However, to date the relatively low incidence and the pronounced heterogeneity of NETs have not allowed the collection of large case series, thus precluding the development of diagnostic and therapeutic standards and the identification of strict criteria to guide treatment strategies. The aim of this study is to evaluate the diagnostic and therapeutic course as well as follow-up of patients with both early- and advanced-stages neuroendocrine tumors, by taking into account epidemiological characteristics, survival according to histotype, primary tumor site and tumor stage at diagnosis, and the possible correlations between clinicopathological and biological parameters on one hand and disease course on the other. Our final objective is to identify potential prognostic factors that may be able to influence overall survival and to guide at best therapeutic choices.
Objectives	Collection of clinical data from patients with neuroendocrine tumors to evaluate the incidence and distribution of NETs, and to assess and improve outcomes for the whole population of NETs patients. Primary objectives: • To describe the diagnostic and therapeutic course for the cohort of enrolled patients • To assess survival in the cohort of enrolled patients based on histotype, primary tumor site and stage at diagnosis • To identify biomarkers in subgroups of patients with different histological subtypes Secondary obiectives: • To define the clinical features of enrolled patients

	• To estimate the percentages of patients presenting with different histological subtypes of NETs • To estimate the proportions of functioning and non-functioning tumors • To estimate the percentages of patients with family history of NETs and MEN-1 and MEN-2 syndromes • To report the main reasons influencing therapeutic choices, with special reference to symptoms (functioning tumors, typical/atypical syndrome, not full-blown syndrome), tumor primary site, histopathological features, stage at diagnosis, performance status and age
Biological Study	Centralised review of histological samples. All diagnoses will be reclassified according to the latest pathological knowledge on thoracic (WHO 2004) and gastroenteropancreatic (WHO 2010) neuroendocrine tumors. Furthermore, gene expression profiles of neuroendocrine tumor samples will be analysed by means of biomolecular assays in order to identify the potential molecular pathways involved in the progression of disease and to develop a molecular classification for the identification of genes with prognostic and/or predictive value.
Number of Subjects	≥ 8 evaluable cases for center
Duration of Trial Recruitment	5 ± 2 years (depending on accrual)
Follow-Up	10 years
Inclusion Criteria	• Histological diagnosis of neuroendocrine tumor • Early-stage, locally advanced and metastatic neuroendocrine tumors • Written informed consent

Exclusion Criteria	• Concomitant participation in another observational study on neuroendocrine tumors
Statistical Analyses	All patient data will be collected in electronic case report forms (eCRFs) and analysed by using appropriate statistical software. In order to meet the primary objective of the study, the evaluation of the frequency incidence and distribution of neuroendocrine tumors, as well as their diagnostic profile, a descriptive statistical analysis will be used, with summarized as (absolute frequencies and percentages for categorical variables) and cardinal variables summarized as means ± standard deviations. In case of variables with non-normal distribution or in case of ordinal variables, data will be summarized as medians and percentiles. Disease outcome and prognostic factors potentially affecting disease evolution will be analysed by means of longitudinal models such as survival analysis (Kaplan-Meier curves) and Cox regression models. An interim analysis will be performed two years after the start of the study and/or when the submission of data valued as relevant for the clinical management of the enrolled patients will be considered useful/mandatory by the trial investigators.