IT.A.NET
Italian Association for Neuroendocrine Tumors

THE ROLE OF TUMOR MICROENVIRONMENT IN NET BEHAVIOR AND PROGRESSION	
Informazioni di contatto del Centro promotore:	IRCCS Istituto Clinico Humanitas
Indirizzo (Città, CAP):	Via Manzoni n.56, 20089 Rozzano (Mi)
Phone/Fax:	Phone: 02-82244658
e-mail:	andrea.lania@hunimed.eu
Tipologia di studio	**Osservazionale** □ **Interventistico** □ **Clinico** □ **Preclinico** x **Retrospettivo** □ **Prospettico** □
Fase	**na** x **fase 2** □ **fase 3** □ **fase 4** □
N. soggetti	NA
Razionale (max 100 parole)	Neuroendocrine tumors (NETs) are rare neoplasms showing a wide spectrum of clinical behaviors. Therapeutic options available are rarely curative as NETs frequently show resistance to therapy. Tumor microenvironment represents a potential therapeutic target that is yet to be explored. Although different studies support the use of tumor-associated macrophages (TAMs) as potential biomarkers for cancer prognosis, their role in NET progression has not been clearly demonstrated. Interestingly, metformin (anti-diabetic drug), octreotide (somatostatin analog) and everolimus (mTOR inhibitor), shows anti-inflammatory properties in different tumors, however their impact on tumor microenvironment in NET remains unknown. Finally, better insight into immunological characterization of NETs is necessary for innovative immunotherapeutic strategies.

Obiettivo (max 50 parole)	The translational study outlined here is expected to provide original information related to the identification of new pathways involved in NET progression and clarify the involvement of tumor microenvironment, particularly of TAMs, in mediating both clinical behavior and response to medical treatment.
Endpoint principale (max 50 parole)	1. To study the immune profile of NETs, to correlate TAM and TIL markers with clinicopathological features and overall survival of NET patients. 2. To examine macrophages role in NET progression and behavior.
Endpoints secondari (max 100 parole)	A. To analyze the circulating leukocyte subsets in patients with NETs. B. To evaluate the ability of metformin, octreotide and everolimus to modulate macrophage phenotype. C. To identify novel activated pathway in NET cells, after macrophages CM treatment. D. To study the impact of NET cells on macrophages and on resistance to therapy. E. The role of macrophages in NET metastasis and angiogenesis in zebrafish model.
Popolazione dello studio (max 100 parole)	Patients affected by pancreatic and neuroendocrine tumors clinically diagnosed
Criteri di Inclusione e di esclusione (max 200 parole)	Inclusion criteria: Both sex, age > 18 years; ability to give informed consent according to ICH/EU GCP, and national/local regulations. Exclusion criteria: Pregnancy; childbearing potential; known allergies to local anesthetics; current medical conditions; major known coagulation defects; drug or alcohol abuse.
Trattamento (max 50 parole)	Patients involved in the study will be provided standard therapy.
Piano Statistico	The study will be conducted retrospectively and prospectively in patients with NETs of different

(max 200 parole) ***Includere la giustificazione per il clinical sample size ed il primary hypothesis testing***	aggressiveness. In all patients that will give informed consent, clinical and biochemical data will be recorded by an on line clinical reporting form, accessible via secure username and password. Correlation between clinical, hormonal, pathological and molecular data will be carried out by $\chi 2$ test (dichotomous variables) or Student's t test (Gaussian continuous variables). Wilcoxon's test will be used in case on non-normal distributions. When three or more group comparisons are required, ANOVA, followed by post hoc test (Dunnett's test or Bonferroni post hoc test) will be used. Study population is estimated to be about 10 patients/year, which will be consecutively enrolled in the next 3 years. Due to rareness of the disorder, no preliminary considerations about statistical power and sample size have been made. P less than 0.05 will be considered statistically significant. Calculations will be carried out by SPSS software and Graphpad Prism 7.0
Nome del Centro Promotore e del PI dello studio	Humanitas Clinical and Research Hospital Prof. Andrea Lania
Nome degli altri Centri partecipanti che hanno già aderito allo studio e dei relativi responsabili	Prof. Giovanni Vitale, Istituto Auxologico Italiano IRCCS Unità di chirurgia pancreatica IRCCS Istituto Clinico Humanitas Unità di chirurgia toracica IRCCS Istituto Clinico Humanitas
Data di inizio studio	1 December 2019
Data di fine studio	31 December 2021
Stato di avanzamento dello studio (aggiornare annualmente)	
Periodo di arruolamento in mesi	NA
Data di inizio arruolamento	NA
Data di fine arruolamento	NA
Data di approvazione Comitato Etico del Centro Promotore*	Protocollo BIO-NET 6-02-2018

* Allegare copia del documento attestante approvazione dello studio da parte del CE del Centro promotore, oppure autocertificazione da parte del PI dello studio attestante che l'approvazione del CE del proprio Ente non è richiesta per lo studio in oggetto.