IDENTIFICATION OF MOLECULAR PREDICTORS OF RESPONSE TO PRRT IN PATIENTS WITH GEP-NETS	
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Tipologia di studio	**Osservazionale x Interventistico □** **Clinico □ Preclinico x** **Retrospettivo x Prospettico x**
Fase	**na x fase 2 □ fase 3 □ fase 4 □**
N. soggetti	Discovery phase: 192 Validation phase: 50
Razionale (max 100 parole)	Tumor SSTR expression as imaged by Octreoscan or ^{68}Ga-DOTATOC PET/CT scan is the only biomarker capable to predict response to peptide receptor radionuclide therapy (PRRT), but more precise predictors of safety and efficacy are needed to optimize patient preselection in the "precision medicine" era. Single nucleotide polymorphisms (SNPs) are gene sequence variations occurring in more than 1% of the general population, and account for approximately 80% of inter-individual genomic heterogeneity. No studies have evaluated so far the impact of the individual genomic background on the safety and efficacy of PRRT in NET patients.
Obiettivo (max 50 parole)	To identify biomarkers of response and/or toxicity for PRRT in patients with GEP-NETs
Endpoint principale	To identify molecular predictors (single SNPs or clusters of SNPs) of

(max 50 parole)	disease control rate (as defined by the percentage of patients who have achieved complete response/partial response according to RECIST 1.1, or stable disease for at least 12 months) after PRRT in patients with GEP-NETs
Endpoints secondari (max 100 parole)	To identify molecular predictors of progression-free survival (PFS) and overall survival (OS) for PRRT in patients with GEP-NETs. To identify molecular predictors of G3/G4 toxicities (according to CTCAE v5.0) for PRRT in patients with GEP-NETs.
Popolazione dello studio (max 100 parole)	This study will enroll a total of 242 patients (192 subjects in the discovery phase; 50 subjects in the validation phase) with GEP-NETs who underwent treatment with PRRT. In the discovery phase, 96 responders (patients achieving CR or PR, or SD for at least 12 months) and 96 non-responders (patients achieving SD for less than 12 months or progressing to the treatment) will be recruited. In the validation phase, 50 consecutive patients with GEP-NETs undergoing treatment with ^{177}Lu-DOTATATE will be enrolled.
Criteri di Inclusione e di esclusione (max 200 parole)	**Inclusion criteria (discovery phase):** • Adult patients (age ≥18) treated with at least one cycle of ^{90}Y- or ^{177}Lu-radiolabeled somatostatin analogs from 2000 to 2017; • Karnofsky performance status ≥ 60; • Histopathological diagnosis of well differentiated (G1/G2) gastroenteropancreatic (GEP) NET; • Locally advanced or metastatic, unresectable disease; • Radiologically measurable disease according to RECIST 1.1 criteria; • Radiological evaluation within 3 months prior to PRRT; • Radiological evaluation within 3 months after treatment completion; • Follow-up of at least 24 months after the last cycle of PRRT; • Available records of adverse effects of any grade according to the CTCAE 5.0 definition reported by the patient and collected during treatment and follow-up. **Inclusion criteria (validation phase):** • Adult patients (age age ≥18) treated with 4 cycles of ^{177}Lu-DOTATATE (cumulative dose: 29.6 GBq); • Follow-up of at least 12 months after the fourth cycle of PRRT with ^{177}Lu-DOTATATE; • All other inclusion criteria listed above. **Exclusion criteria (discovery phase):** • Patients who did not receive at least one cycle of ^{177}Lu-based PRRT; • Patients with high-grade or poorly differentiated neuroendocrine neoplasms; • Patients with non-GEP NETs; • Patients with incomplete recordings of their clinical, laboratory, radiologic or nuclear medicine evaluations before and after

	treatment; • Patients with faint uptake (defined as less than liver uptake) at Octreoscan or ^{68}Ga-PET/CT scan; • Patients lost to follow-up within 24 months from the last cycle of PRRT. **Exclusion criteria (validation phase):** • Patients lost to follow-up within 12 months from the last cycle of PRRT with ^{177}Lu-DOTATATE; • All other exclusion criteria listed above
Trattamento (max 50 parole)	PRRT
Piano Statistico (max 200 parole) ***Includere la giustificazione per il clinical sample size ed il primary hypothesis testing***	We have designed this study to test the null hypothesis that no gene SNP is able to predict objective radiological response (ORR) to ^{177}Lu-DOTATATE in patients with GEP-NETs. Using a two-sided alpha level of 5%, and considering that the ORR reported in the NETTER-1 trial [2] in a molecularly unselected group of patients with midgut NETs was 18% (null hypothesis), the enrollment of 192 patients will have a 80% power to reject the null hypothesis, if the true ORR is at least 37% in patients with a favorable genomic profile (alternative hypothesis).
Nome del Centro Promotore e del PI dello studio	Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro" – **Mauro Cives**, **Raffaele Palmirotta**, **Franco Silvestris**
Nome degli altri Centri partecipanti che hanno già aderito allo studio e dei relativi responsabili	- Department of Abdominal Oncology, Istituto Nazionale Tumori, IRCCS Fondazione "G. Pascale", Naples; **Salvatore Tafuto** - Nuclear Medicine Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola; **Stefano Severi** - Pancreatic Surgery Unit, Pancreas Translational and Clinical Research Center, San Raffaele Scientific Institute, Milan; **Stefano Partelli, Massimo Falconi** - S. Orsola-Malpighi University Hospital, Bologna; **Davide Campana** - Unit of Nuclear Medicine, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia; **Annibale Versari** - Azienda Ospedaliero-Universitaria di Ferrara, Ferrara; **Mirco Bartolomei**
Data di inizio studio	January 1, 2020
Data di fine studio	January 2, 2023
Stato di avanzamento dello studio (aggiornare annualmente)	/
Periodo di arruolamento in mesi	26 months

Data di inizio arruolamento	April 1, 2020
Data di fine arruolamento	June 1, 2022
Data di approvazione Comitato Etico del Centro Promotore*	Parere del CE Policlinico di Bari (seduta del 22/11/2019) atteso per domani 11/12/2019

* 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.