Titolo dello Studio

An Italian multicenter phase II trial of **me**tronomic **te**mozolomide in unfit patients with advanced neuroendocrine neoplasms (NENs): **MeTe** study.

Informazioni di contatto del Centro promotore:	**Divisione di Oncologia Medica Gastrointestinale e Tumori Neuroendocrini** **Principal investigator: Francesca Spada, M.D., Ph.D.**
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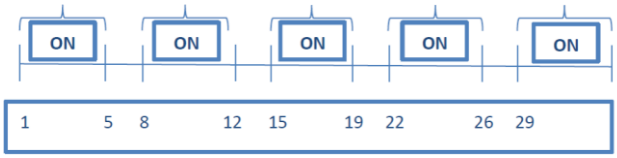
Tipologia di studio	**Osservazionale □ Interventistico □** **Clinico □ Preclinico □** **Retrospettivo □ Prospettico x**
Fase	**na □ fase 2 x fase 3 □ fase 4 □**
N. soggetti	Unlimited
Razionale (max 100 parole)	Chemotherapy in NENs still represents a controversial question as for clinical and biological aspects. Neuroendocrine tumours (NETs) are recognized as highly vascularized cancers therefore chemotherapy could be proposed as conventional or metronomic (m) schedule (low dose continuously) in deeply selected patients. However, to date, a preferred regimen globally shared has not been identified in NENs yet. Temozolomide (TMZ), which is a manageable agent, has been investigated as m-schedule in various malignancies including GEP-NETs and typical/atypical lung carcinoids with different schedules including the metronomic one. However, to date, a preferred regimen globally shared there has not been identified in NENs yet.

Obiettivo (max 50 parole)	To evaluate the activity and safety of mTMZ in patients with advanced low grade NENs considered "frail" and unfit for other systemic treatments. We would also explore the MGMT level. Finally we would also evaluate the quality of life (QoL) of the population through a specific questionnaire (QLQ-GI.NET21) and G8 test for frail patients.
Endpoint principale (max 50 parole)	Progression free survival (PFS) at 12 months
Endpoints secondari (max 100 parole)	• Overall survival (OS) • Safety • Quality of life (QoL) using the a specific questionnaire (QLQ-GI.NET21) and G8 test for frail elderly patients **Exploratory** O6-methylguanine-DNA-methyltransferase (MGMT) status in tumour tissue and peripheral blood to validate the methods of MGMT determining and correlation with clinical outcomes.
Popolazione dello studio (max 100 parole)	Patients with advanced low grade NENs judjed unfit for other systemic treatments.
Criteri di Inclusione e di esclusione (max 200 parole)	**Inclusion criteria:** • Age > 18 years; • Histologically proven diagnosis of low grade GEP-NENs (in accordance with WHO 2019 classification), bronchial carcinoids (in accordance with the Travis classification), low grade of unknown primary sites NENs; • Advanced disease (unresectable locally advanced or metastatic); • ECOG performance status 2 and/or moderate renal failure (eGFR o CrCl 30-59 ml/min – G2) and/or moderate liver failure (Child B 7-9) and/or severe comorbidities and/or > 3 prior systemic antitumor therapies (apart from SSA); • Functioning/non functioning; • Morphological progressive disease (CT scan or MRI); • Clinical progression (as judged by the investigator); **Exclusion criteria** • Patients pretreated with TMZ.

Trattamento (max 50 parole)	• **Standard dose:** Temozolomide 60 mg/day continuously 28-day cycles)  • **Recommended treatment modifications for biochemical or clinical toxicity:** Temozolomide 60 mg/5 days on and 5 days off.  **The TMZ could be required as per the Italian regulatory procedures through the 648/96 law.**
Piano Statistico (max 200 parole) ***Includere la giustificazione per il clinical sample size ed il primary hypothesis testing***	The primary measure of efficacy will be the progression-free survival (PFS). Based on historical data*, a median PFS ≤ 6 months will be expected in our patient population if no treatment is given (null hypothesis). In contrast, a median PFS of 12 months in patient treated with metronomic temozolomide would be considered to be successful (alternative hypothesis). Estimation of the cumulative probability functions for PFS will be performed by means of the Kaplan–Meier product-limit method, and the confidence interval of the median PFS will be computed using the Brookmeyer and Crowley methods. (*Brookmeyer R and Crowley, JJ. A confidence interval for the median survival time. Biometrics, 38, 29-41, 1982*). The null hypothesis will be rejected if the lower bound of the 90% confidence interval of the median OS will be lower than 6 months. Considering an accrual period of 1 year and a total study duration of 2 years, to have a 90% probability of rejecting the null hypothesis, the planned sample size should be **46 patients**. In the alternative hypothesis scenario, the expected number of progressions during the study period is **29**.
Nome del Centro Promotore e del PI dello studio	**IEO, Milano, IRCCS** **Francesca Spada, M.D., Ph.D.**
Nome degli altri Centri partecipanti che hanno già aderito allo studio e dei relativi responsabili	**All the available Italian centres involved in NEN management.**

Data di inizio studio	January 2020
Data di fine studio	January 2021
Stato di avanzamento dello studio (aggiornare annualmente)	
Periodo di arruolamento in mesi	12 months
Data di inizio arruolamento	January 2020
Data di fine arruolamento	January 2021
Data di approvazione Comitato Etico del Centro Promotore*	Ongoing

* 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.