CABOZANTINIB AND TEMOZOLOMIDE IN PATIENTS WITH ADVANCED PROGRESSIVE NEUROENDOCRINE TUMORS: A PHASE 2 STUDY

Supplementary Table 1. Antibodies and experimental conditions for immunohistochemistry.

Target	Ab clone	Species	Supplier	Dilution	Incubation time	Positive control
MGMT	MT3.1	Mouse	Abcam	1:100	60 min	Glioblastoma
c-MET	D1C2	Rabbit	Cell signaling technology	1:300	20 min	Renal cell carcinoma
AXL	C89E7	Rabbit	Cell signaling technology	1:100	20 min	Renal cell carcinoma
VEGFR2	D5B1	Rabbit	Cell signaling technology	1:300	20 min	Renal cell carcinoma

Supplementary Table 2. Baseline patient characteristics by duration of clinical/radiographic benefit. Two-sided Fisher's exact test, Mann-Whitney U test or Kruskal Wallis test were used, as appropriate.

Characteristics	Benefit <18 months (*n*=21) *n* (%)	Benefit ≥18 months (*n*=12) *n* (%)	*p*
Age (years)			
Median	58	57.5	
Range	31-78	39-70	
Gender			
Male	8 (38)	8 (67)	0.16
Female	13 (62)	4 (33)	
ECOG Performance Status			
0	18 (86)	12 (100)	0.28
1	3 (14)	0 (0)	
Location of primary tumor			
Pancreas	6 (29)	6 (50)	0.5
Small bowel	5 (24)	2 (17)	
Lung	6 (29)	2 (17)	
Colon	1 (5)	1 (8)	
Unknown primary	2 (8)	0 (0)	
Gallbladder	1 (5)	0 (0)	
Stomach	0 (0)	1 (8)	
Metastatic sites number			
1	6 (29)	0 (0)	0.06
≥2	15 (71)	12 (100)	
Metastasis sites			
Liver	18 (86)	11 (92)	0.67
Lymph nodes	11 (52)	8 (67)	
Bone	9 (43)	5 (42)	
Lung	2 (9)	4 (33)	
Peritoneum	2 (9)	1 (8)	
Others	7 (33)	2 (16)	
Functional status			
Non-functioning	13 (62)	10 (84)	0.26
Functioning	8 (38)	2 (16)	
Carcinoid syndrome	8	2	
Tumor grade			
G1	6 (29)	3 (25)	0.3
G2	12 (57)	9 (75)	
G3	3 (14)	0 (0)	
SSTR positivity by imaging			
Yes	18 (86)	12 (100)	0.17
No	3 (14)	0 (0)	
Elevated baseline CgA			
Yes	17 (81)	7 (58)	0.16
No	4 (19)	5 (42)	
Baseline CgA (xULN)			
Median	2.9	1.42	
Mean	6,5	4,7	
Median time from diagnosis (months)	32	30.3	
Primary tumor resected			
Yes	13 (62)	3 (25)	0.07
No	8 (38)	9 (75)	
Prior lines of systemic therapy			
Median	2	2	

Range	1-4	1-6	
Previous systemic therapy			
SSAs	20 (95)	11 (92)	0.63
^{177}Lu-based radioligand therapy	11 (52)	5 (42)	
Y-90-based radioligand therapy	2 (9)	1 (8)	
Everolimus	1 (5)	2 (16)	
Chemotherapy	2 (9)	1 (8)	
Axitinib	1 (5)	2 (16)	
Sunitinib	0 (0)	1 (8)	
Lenvatinib	1 (5)	0 (0)	
Surufatinib	1 (5)	0 (0)	
IFNα	0 (0)	1 (8)	
Previous liver-directed therapy			
Yes	4 (19)	1 (8)	0.6
No	17 (81)	11 (92)	
Concurrent on study SSA			
Yes	11 (52)	8 (67)	0.49
No	10 (48)	4 (33)	
MGMT promoter methylation			
Yes	2 (10)	2 (16)	0.77
No	8 (38)	5 (42)	
Unknown	11 (52)	5 (42)	
MGMT expression (H-score)			
High	6 (28)	5 (42)	0.68
Low	5 (24)	3 (25)	
Unknown	10 (48)	4 (33)	
c-MET expression			
Positive	2 (10)	3 (25)	0.39
Negative	9 (42)	3 (25)	
Unknown	10 (48)	6 (50)	
Baseline plasma VEGF-A concentration			
High			
Low	6 (29)	7 (58)	0.24
Unknown	9 (42)	3 (25)	
	6 (29)	2 (17)	
ΔVEGF-A concentrations			
High (> median value)	9 (42)	3 (25)	
Low (< median value)	6 (29)	7 (58)	0.22
Unknown	6 (29)	2 (17)	

ΔVEGF-A concentrations: absolute changes in VEGF-A concentrations from best RECIST response to baseline.

Supplementary table 3. Correlative analyses cohort: patient demographics and clinical characteristics.

Characteristics	Number of patients (*n*=19)	%
Age (years)		
Median	55	
Range	36-75	
Gender		
Male	10	53
Female	9	47
ECOG Performance Status		
0	16	84
1	3	16
Location of primary tumor		
Pancreas	10	53
Small bowel	4	21
Lung	4	21
Colon	1	5
Number of metastatic sites		
1	4	21
≥2	15	79
Metastasis sites		
Liver	16	84
Lymph nodes	12	63
Bone	6	32
Lung	2	11
Peritoneum	2	11
Others	1	5
Functional status		
Non-functioning	16	84
Functioning	3	16
Carcinoid syndrome	3	
Tumor grade		
G1	6	32
G2	13	68
Ki-67 labeling index		
<10%	11	58
≥10%	8	42
SSTR positivity by imaging		
Yes	18	95
No	1	5
Elevated baseline CgA		
Yes	12	63
No	7	37
Baseline CgA (xULN)		
Median	1.61	
Mean	5.24	
Median time from diagnosis (months)	35.8	
Primary tumor resected		
Yes	9	47
No	10	53
Prior lines of systemic therapy		
Median	2	
Range	1-6	
Previous systemic therapy		
SSAs	18	95

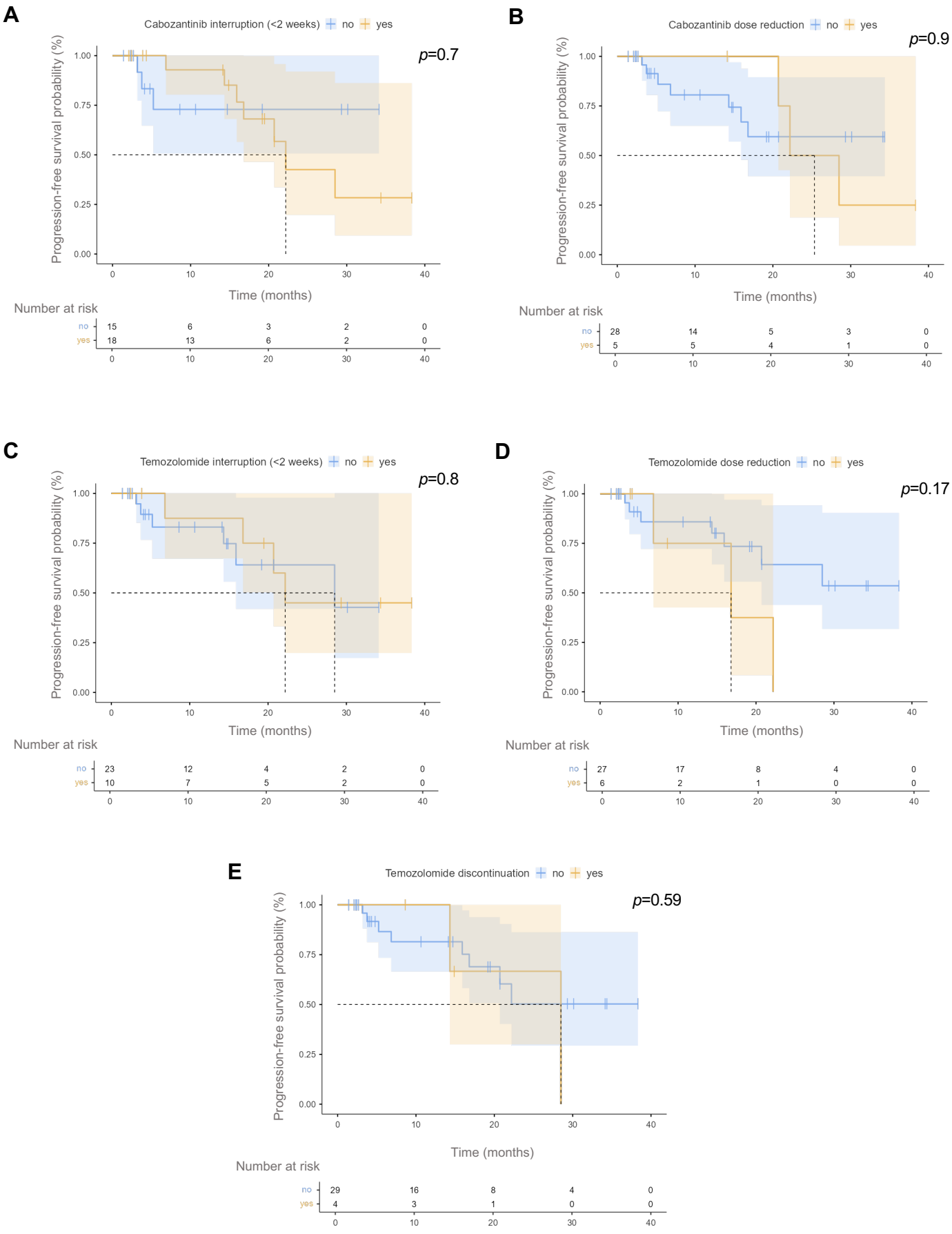
^{177}Lu-based radioligand therapy	9	47
^{90}Y-based radioligand therapy	2	11
Everolimus	3	16
Chemotherapy	2	11
Axitinib	1	5
Sunitinib	1	5
Lenvatinib	1	5
IFNα	1	5
Previous liver-directed therapy		
Yes	2	11
No	17	89
Concurrent on study SSA		
Yes	11	58
No	8	42

CgA: Chromogranin A; ECOG: Eastern Cooperative Oncology Group; IFNα: interferon α; SSA: somatostatin analog; SSTR: somatostatin receptor; ULN: upper limit of normal.

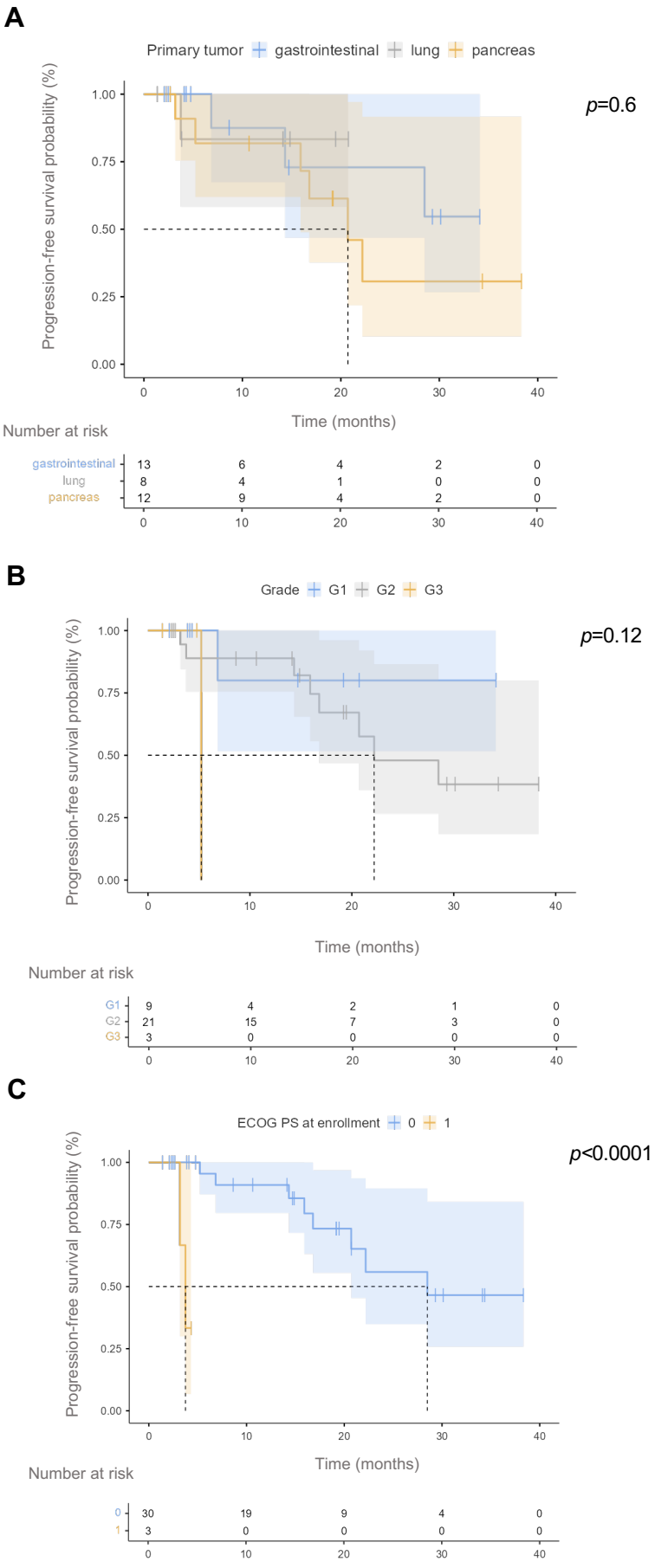
Supplementary Table 4 – Association between MGMT assessment methods.

		MGMT (IHC)		
		Low (1-2)	**High (3)**	**Total**
MGMT (MSP)	**Positive**	3	1	4
	Negative	5	8	13
	Total	8	9	17

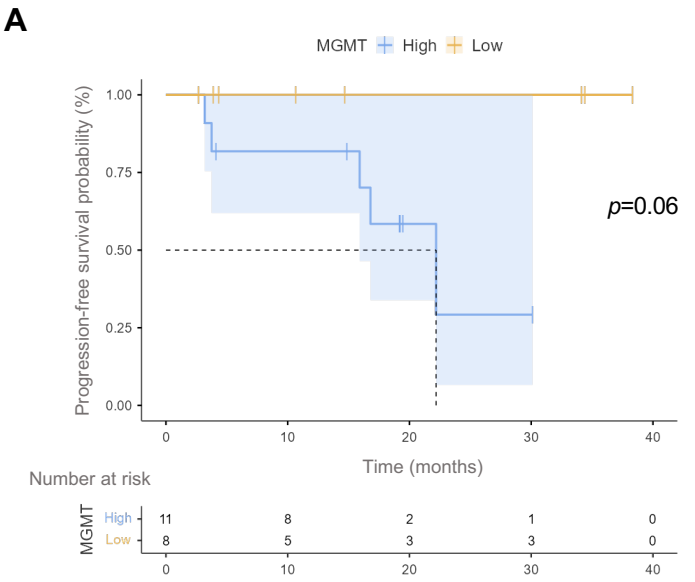
IHC: immunohistochemistry; MSP: methylation-specific PCR
Counts are shown for tumors that underwent MGMT testing by both methods (*n*=17)

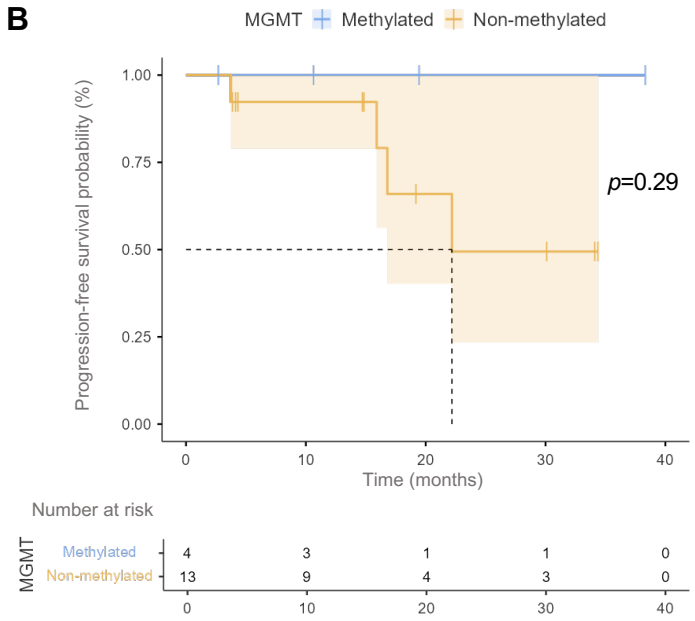


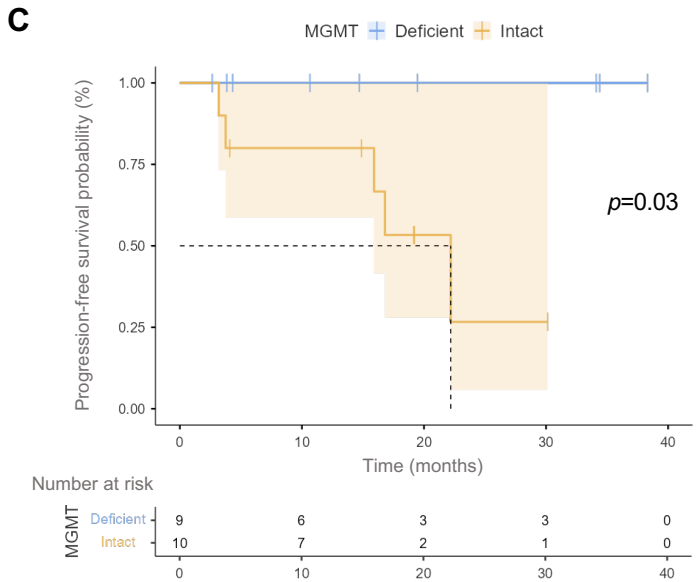
Supplementary Figure 1



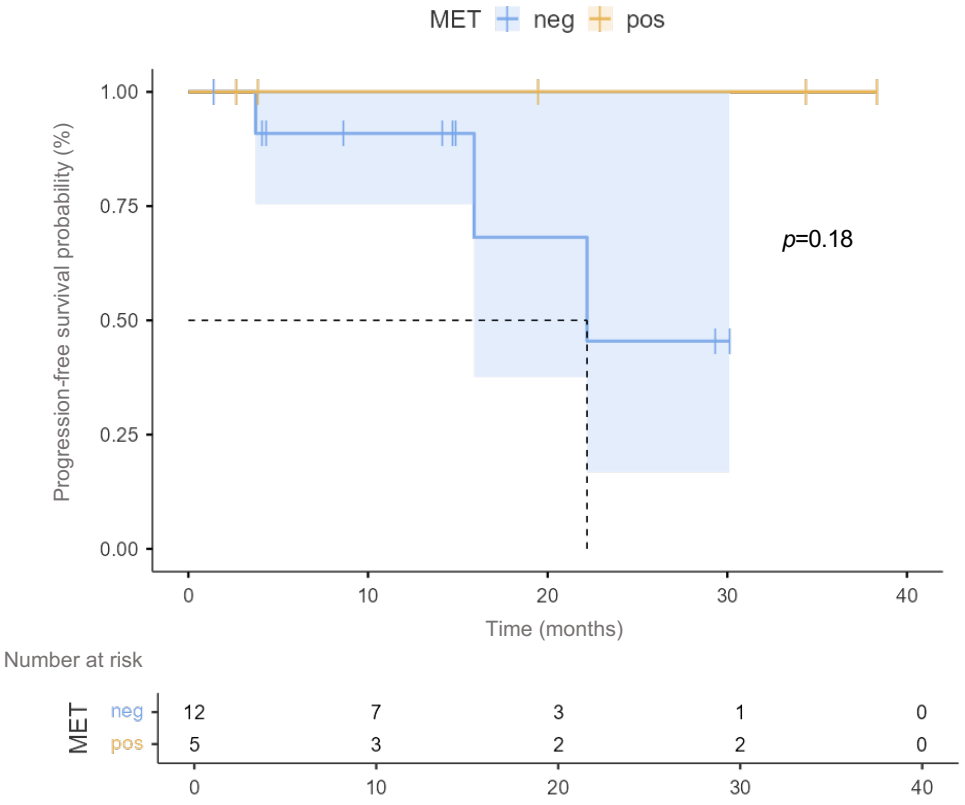
Supplementary Figure 2



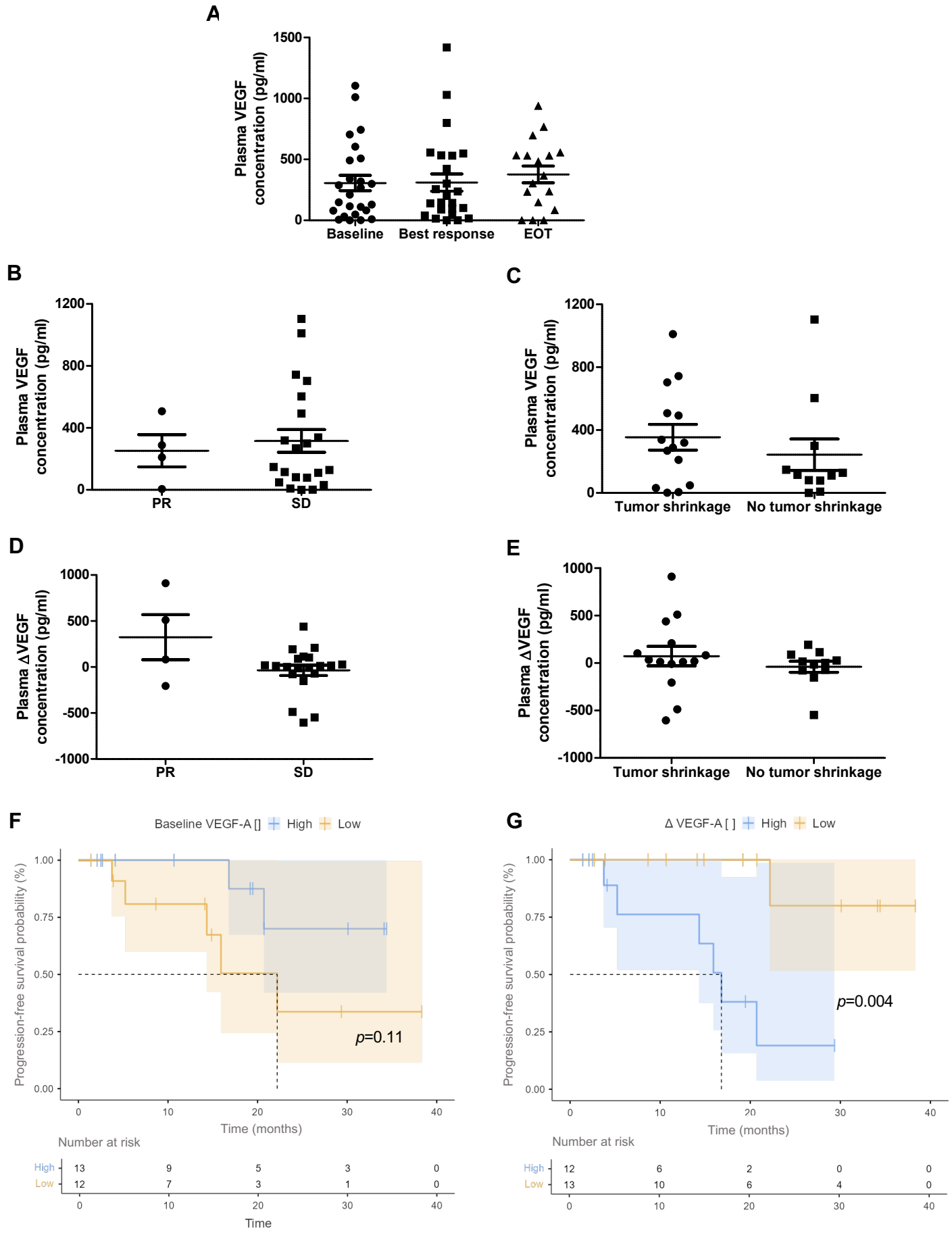




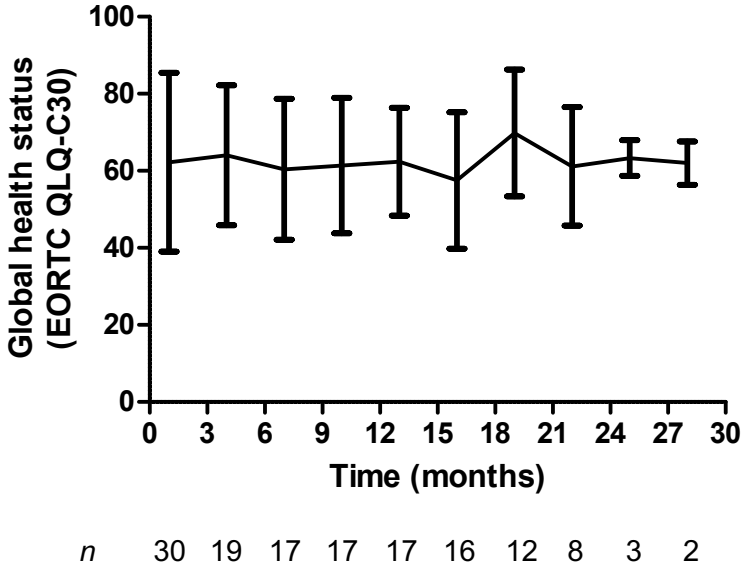
Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure 6

Supplementary Figure Legends

Supplementary Figure 1 – PFS according to dose modifications: cabozantinib dose reduction (A), cabozantinib temporary interruption (B), temozolomide dose reduction (C), temozolomide temporary interruption (D), temozolomide permanent discontinuation (E). In the Kaplan-Meier curves, the colored lines show the estimated survival proportion, while the shadow areas represent the 95% CI. The black dashed line indicates the 50% survival probability point estimate. The initial sample size (*n*=33) and the number of patients at risk over time are shown in the table below each x-axis; *p*-values, displayed in each panel as exact values, were calculated using the two-sided log-rank test. No adjustments were made for multiple comparisons. Source data are provided as a Source Data file.

Supplementary Figure 2 – PFS of patients with NETs of gastroenteropancreatic, lung or unknown primary treated with cabozantinib and metronomic temozolomide by primary tumor site (A), grading (B) and ECOG performance status at enrollment (C). In the Kaplan-Meier curves, the colored lines show the estimated survival proportion, while the shadow areas represent the 95% CI. The black dashed line indicates the 50% survival probability point estimate. The initial sample size (*n*=33) and the number of patients at risk over time are shown in the table below each x-axis; *p*-values, displayed in each panel as exact values, were calculated using the two-sided log-rank test. No adjustments were made for multiple comparisons. ECOG: Eastern Cooperative Oncology Group; PS: performance status. Source data are provided as a Source Data file.

Supplementary Figure 3 – PFS of patients with NETs treated with cabozantinib and metronomic temozolomide by MGMT status as assessed by immunohistochemistry (A) and methylation-specific PCR (B). In (C), MGMT deficiency is defined as either low IHC expression or positive promoter methylation. In the Kaplan-Meier curves, the blue line shows the estimated survival proportion, and the shadow area represents the 95% CI. The black dashed line indicates the 50% survival probability point estimate. The initial sample size (*n*=19 in A and C; *n*=17 in B) and the number of patients at risk over time are shown in the table below each x-axis; *p*-values, displayed in

each panel as exact values, were calculated using the two-sided log-rank test. No adjustments were made for multiple comparisons. Source data are provided as a Source Data file.

Supplementary Figure 4 – PFS of patients with NETs treated with cabozantinib and metronomic temozolomide by c-MET expression as assessed by immunohistochemistry. In the Kaplan-Meier curves, the colored lines show the estimated survival proportion, while the shadow areas represent the 95% CI. The black dashed line indicates the 50% survival probability point estimate. The initial sample size (n=17) and the number of patients at risk over time are shown in the table below each x-axis; p-values, displayed in each panel as exact values, were calculated using the two-sided log-rank test. No adjustments were made for multiple comparisons. Source data are provided as a Source Data file.

Supplementary Figure 5 – Plasma VEGF-A concentrations at different time points and their association with clinical outcomes. (A) Plasma VEGF-A concentrations measured at study entry, at the time of first best response, and at study discontinuation (n=25). Longitudinal changes in VEGF-A levels were assessed using a two-sided linear mixed-effects model with timepoint as a fixed effect and patient as a random intercept to account for repeated measurements ((F(2, 41.1)=1.67; p=0.2). (B) Baseline VEGF-A concentrations in patients who achieved a partial response versus those who did not (n=25; p=0.97). (C) Baseline VEGF-A concentrations in patients whose tumors exhibited any shrinkage during treatment versus those who did not (n=23; p=0.31). (D) Absolute changes in VEGF-A concentrations from best RECIST response to baseline (ΔVEGF-A) in patients who achieved a partial response versus those who did not (n=24; p=0.2). (E) ΔVEGF-A in patients whose tumors exhibited any shrinkage during treatment versus those who did not (n=25; p=0.34). In B-E, differences between groups were assessed using a two-sided Mann-Whitney U test. Row concentration values, medians, and interquartile range are represented in A-E. (F) PFS of patients with plasma baseline VEGF-A concentrations above and below the median VEGF-A level (210 pg/ml). (G) PFS of patients with ΔVEGF-A higher or lower than the median ΔVEGF-A (-15 pg/ml). In the Kaplan-Meier curves, the colored lines show the estimated survival proportion, while the

shadow areas represent the 95% CI. The black dashed line indicates the 50% survival probability point estimate. The initial sample size (n=25) and the number of patients at risk over time are shown in the table below each x-axis; p-values, displayed in each panel as exact values, were calculated using the two-sided log-rank test. No adjustments were made for multiple comparisons. VEGF: vascular endothelial growth factor; EOT: end of treatment; PR: partial response; SD: stable disease. Source data are provided as a Source Data file.

Supplementary Figure 6 – Health-related quality of life (HR-QoL) by EORTC QLQ-C30. Mean HR-QoL scores and standard deviations are represented. The initial sample size (n=37) and the number of patients who completed the questionnaire at each time point is also shown. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30. Source data are provided as a Source Data file.

Clinical Study Protocol

Study Title:	**CABOTEM** A Phase II Single Arm Interventional Trial Evaluating the Activity and Safety of combination between Cabozantinib and Temozolomide in Lung and GEP-NENs progressive after SSAr, everolimus, sunitinib or PRRT.
Short study title:	**The CABOTEM Study:** Cabozantinib and Temozolomide in progressive Lung and GEP-NENs.
Development phase:	Phase II
EudraCT number:	2020-001898-78
Protocol Version:	2
Protocol Date:	28 Gennaio 2021
Chief Investigator:	dr. Salvatore Tafuto
Study coordinators:	d.ssa Ottavia Clemente, dr. Giuseppe Di Lorenzo
Study nurse:	d.ssa Sabrina Lamia
	ENETs Center of Excellence Istituto Nazionale per lo Studio e la Cura dei Tumori, I.R.C.C.S. – Fondazione "G. Pascale" - Naples, ITALY
Sponsor:	No-profit trial

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Sponsor: no-profit trial

Clinical Trial Monitoring Centre:

Data management will be carried out by Bambin Gesù Hospital in Rome, under the supervision of Dr. Valeria Antenucci.

Coordinating Centre (Global and Italy):
S.C. Sarcomi e Tumori Rari
ENETs Center of Excellence
I.R.C.C.S. Ist. Naz. Tumori di Napoli "G. Pascale" - Naples,
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dott. Francesco Fiore Onco Interventional Radiology, Istituto Nazionale Tumori "Fondazione G. Pascale", IRCCS, 80131, Naples, Italy

IMP Supply:

IPSEN will provide cabozantinib tablets and cabozantinib powder according with the Quality Technical Agreement. Temozolomide tablets will be provided by the sponsor.
The IMP tablets will be re-labelled locally in the sponsor site.

Laboratories:

1. Functional Genomics, Istituto Nazionale Tumori "Fondazione G. Pascale", IRCCS, 80,131, Napoli, Italia
2. Unit of Molecular Biology and Viral Oncology, Department of Research, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italia
3. Division of Laboratory Medicine, Department of Pathology and Laboratory Diagnostics, Istituto Nazionale Tumori "Fondazione G. Pascale", IRCCS, 80,131, Naples, Italy.

Abbreviations

Abbreviation/Term	Explanation
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CI	Chief investigator
CR	Complete response (RECIST)
CRF	Case report form
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITTS	Intent to treat analysis set
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
M2	Meter Square
mg	Milligrams
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NE	Non-evaluable (RECIST)
NENs	Neuroendocrine Neoplasms
NTL	Non-Target Lesion
ORR	Objective response rate

OS	Overall survival
PD	Progressive disease
pNENs	Pancreatic Neuroendocrine Neoplasms
PFS	Progression Free Survival
PR	Partial response
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease (RECIST)
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TL	Target Lesion
ULN	Upper Limit of Normal

PROTOCOL APPROVAL

"A Phase II Single Arm Interventional Trial Evaluating the Activity and Safety of combination between Cabozantinib and Temozolomide in Lung and GEP-NENs progressive after SSAs, everolimus, sunitinib or PRRT".

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practices and local regulations and requirements.

Investigator:

Name: _____

Signature: _____

Date: _____

1 INTRODUCTION AND RATIONALE

1.1 Metastatic NENs

Neuroendocrine neoplasms (NENs) are a heterogeneous group of neoplasms mainly originating from neuroendocrine cells in the gastro-entero-pancreatic system and the lung, although they are potentially ubiquitous throughout the body. Due to the difficulty in early diagnosis, most of the patients present at diagnosis with an advanced and/or metastatic disease. Metastatic NENs are associated with poorer prognosis and lower overall survival [1].

Patients with well-differentiated (grade 1, 2 and 3 NETs, WHO 2017) locally advanced and metastatic non-operable lung and GEP NENs usually could receive treatment with somatostatin analogues (SSAs), targeted therapies (Everolimus, Sunitinib), chemotherapy (Streptozotocina [STZ]-based regimes, capecitabine, temozolomide), and/or Peptide Receptor Radionuclide Therapy (PRRT) [2-13]. The treatment choice depends on many clinical and pathological factors, such as functional vs non-functional disease status, grade of differentiation and prior treatment history. However, no therapy has demonstrated a clear survival advantage over another and the sequential use of the above-mentioned therapies is the most frequent approach.
Thus, no standard treatment and no optimal sequence of treatment exist for patients with advanced NENs. Furthermore, a prompt disease progression is reported after an initial response to all the approved treatments. The treatment options for these progressive diseases are still limited and new treatment modalities are needed to improve clinical outcome and maintain the quality of life for patients with advanced, progressive NENs. Additionally, data on the role of the therapies sequences and the definition of new biological predictors of outcome and prognosis are strongly recommended.

1.2 Cabozantinib

Cabozantinib is an oral, multi tyrosine kinases inhibitor (TKI) that targets vascular endothelial growth factor receptor2 (VEGFR2), hepatocyte growth factor (c-MET), AXL, and RET.

Cabozantinib is currently approved for treatment of advanced renal cell carcinoma and progressive, metastatic medullary thyroid cancer.

Preclinical data suggested that cabozantinib has activity in lung and GEP-NENs. In particular, it demonstrated *in-vitro* antiproliferative and antiinvasive effects [14] (Reuther et al. 2016), and reduced *in-vivo* tumor growth, invasion and metastasis in pancreatic NEN mice models [15]. These positive results led to a phase II clinical trial, which preliminary results added evidence to cabozantinib activity in NENs. In fact, a median progression free survival (mPFS) of 31.4 months (mo) (95% CI, 8.5 mo-NR) and 21.8 mo (95% CI, 8.5-32.0 mo) was reported after cabozantinib treatment in patients with progressive, well differentiated, grade 1-2 carcinoid and pNET, respectively. In addition, in both groups an ORR of 15% was achieved [16].

Final results of this trial are awaited in April 2022. Furthermore, a phase III study, evaluating the PFS in 395 patients with advanced or metastatic or not surgically resectable NENs (CABINET study, NCT03375320) is currently ongoing in USA.

1.3 Temozolomide

Temozolomide (TMZ) is an orally active alkylating agent analogue of the dacarbazine. TMZ showed activity in pre-treated patients affected by NENs, either in monotherapy and in combination with other drugs (i.e. capecitabine, everolimus, bevacizumab, octreotide, lanreotide, pazopanib) [17-27]. The schedule and the dose of TMZ vary within different trials, ranging from the standard dose (i.e. 150-200 mg/m2 once daily for 5 every 28 days) to metronomic or one-week on/one-week off schedule. The different schedules have no difference in terms of efficacy, but the metronomic and intermittent schedule seems to be better tolerated.

The majority of these trials have investigated the role of TMZ in pNENs, and although these data are still evolving, TMZ may replace STZ-based regimens in pNENs due to its better tolerability and side effect profile. There is evidence that TMZ could also be used in the subgroup of well-differentiated G3 NETs, and preliminary data suggest that TMZ may be effective in selected patients with intestinal and bronchial NETs [28].

In Italy STZ is not registered. Therefore, in this country for metastatic GEP NET patients undergoing to chemotherapy, TMZ in order to law n.648 (1996, Dec 23) paragraph 4 art. 1, is allowed.

In our experiences, an intermittent schedule of metronomic TMZ is effective and safe in patients with advanced progressive G2-G3 NEN, with Performance Status 2 (PS) showing to be a feasible second line treatment in this setting, for its excellent toxicity profile. In fact, in the trial, no G3/G4 toxicity was recorded according to NCI-CTCAE v 5.0 criteria. [29]. This schedule has been also investigated in association with anti-VEGF bevacizumab to treat 34 patients with advanced neuroendocrine tumours demonstrating a good efficacy and safety profile [24].

In another study, a patient with progressing pancreatic NEN G3 after cisplatin and etoposide was treated with TMZ as a second-line treatment. An intermittent and metronomic administration regimen of Temozolomide (75 mg/m2/day - one-week on/one-week off) was chosen for the patient's expired clinical condition (PS 2) and in order to reduce iatrogenic toxicity. The patient achieved significant clinical benefit (PS = 0) and total body CT showed a RECIST partial response at all disease sites. No drug-related side effects were reported by the patient. After 18 months of therapy, treatment continues without significant toxicity and with further remission of metastases. Treatment with metronomic TMZ "one-week on/one-week off" may be considered a good treatment option in patients with poor performance status, suffering from pancreatic NEN G3.

Moreover, it is possible to refer to the AIOM Guidelines for Neuroendocrine Neoplasms – 2019 (paragraphs 2.7.2; 3; 5.3.2; 6.4.1) to consider the use of TMZ in patients with well-differentiated pulmonary NEN and patients with gastro-entero-pancreatic neuroendocrine disease [35] and to refer to paragraph 6.1 of this trial for further clarifications regarding the achievement of the Primary Objective of the trial.

1.4 Rationale for the study

Temozolomide is currently an approved treatment for progressive NENs.

The emerging data of the ongoing Chan's trial and CABINET trial could have important clinical implications for the use of cabozantinib in NENs.

Shiff et al. demonstrated that cabozantinib at a dose of 40/60 mg daily plus TMZ for patients with newly diagnosed high-grade glioma was generally well tolerated even with the addition of radiotherapy, and also demonstrated no pharmacokinetic interactions with concurrent TMZ [30]. *In-vitro*, downregulation of c-MET pathway, enhances the sensitivity of glioblastoma cell lines to temozolomide [31].

Therefore, cabozantinib, through the inhibition of c-MET pathway, could enhance the sensitivity of NENs to temozolomide. In addition, the intermittent metronomic schedule of TMZ has a proven anti-angiogenic activity [32-34] that could be additive and/or enhance the anti-angiogenic effect of cabozantinib.

It is also possible to refer to other evidences present in the literature such as *M. Bupathi et al*. [38] and *M.A. Bhave et al*. [27-38].

Thus, this current study seeks to evaluate the efficacy and safety of cabozantinib in combination with temozolomide as a treatment for progressive well differentiate lung and GEP-NENs. In addition, the expression of HGF, RET, c-MET, VEGFR2, AXL and the MGMT status in the tumour samples of treated patient will be evaluated to identify possible predictive factors and/or markers of response and/or resistance.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

Objective	Endpoint
To assess the efficacy of the combination of cabozantinib and one-week-on/one-week-off temozolomide, based on overall response rate (ORR)	ORR (as assessed by RECIST v1.1) defined by complete response (CR) or partial response (PR).

2.2 Secondary Objectives and Endpoints

Objective	Endpoint
1. To assess the activity of the combination of cabozantinib and one-week-on one-week-off temozolomide according to Progression Free Survival (PFS)	PFS (as assessed by RECIST v1.1) defined as time from study entry to first evidence of disease progression or death due to any cause.
2. To assess the activity of the combination of cabozantinib and one-week-on one-week-off temozolomide according to Clinical Benefit Rate (CBR)	CBR (as assessed by RECIST v1.1) defined by complete response (CR) or partial response (PR) or stable disease (SD).
3. To assess the activity of the combination of cabozantinib and one-week-on one-week-off temozolomide according to Overall Survival (OS)	OS defined as time from study entry to death due to any cause or to study termination.
4. To assess the activity of the combination of cabozantinib and one-week-on one-week-off temozolomide according to duration of response (DOR)	DOR defined as time from study entry to change in response from CR or PR to Stable Disease (SD) or Progressive Disease (SD) (as assessed by RECIST v1.1).
5. To assess the safety and tolerability of the combination of cabozantinib and one-week-on one-week-off temozolomide	Safety and tolerability as assessed by adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. After five patients, it will be perform a detailed safety report based on CTCAE v.5.0
6. To assess the predictive role of MGMT Methylation Status on response to the combination of cabozantinib and one-week-on one-week-off temozolomide	MGMT Methylation Status will be assessed and any correlation with the efficacy endpoints will be evaluated.
7. To assess the activity of the combination of cabozantinib and one-week-on one-week-off	1 year overall survival (OS)

temozolomide at 1 year from the start of the treatment	

2.3 Exploratory Objectives and Endpoints

Objective	Endpoint
2.1 Biological approach	Exploratory endpoints include the evaluation of biomarkers and biologic studies.
2.2 To assess the *in-vitro* effect of cabozantinib and temozolomide	**A) c-MET and HGF expression in NENs patients and NET cell lines.** Expression of cabozantinib molecular targets will be assessed in NENs patients and cell lines, the human pancreatic-BON cells and the human bronchial-net NCI-H727 cells. c-MET, VEGFRr2, RET, AXL and HGF expression will be evaluated through immunohistochemistry on formalin-fixed and paraffin-embedded (FFPE) from primary diagnosis and, possible, secondary lesions biopsies. the following antibodies will be used: for c-MET (anti-c-MET antibody [ep1454y]) and HGF (anti-HGF antibody (ab83760), Anti-Axl antibody (ab227871), Anti-Ret antibody (ab214791) c-MET and HGF will be measured in BON and NCI-H727 cells by Western Blot (same antibodies). c-MET, MET, AXL and HGF RNA expression will be evaluated by Real Time PCR using previously described methods (10.1016/S0002-9440(10)64096-5). Moreover, HGF (1.25 nM)-mediated downstream activation in presence of Cabozantinib (2.5 µM) in BON and NCI-H727 cells will be investigated by Western Blot at 10, 30 and 60 min of HGF stimulation, using the following antibodies: Rabbit monoclonal antibodies for (Thr202/Tyr204), S6K1, p-S6K1(Thr389), 4EBP1, p-4EBP1, p-P38 (Thr180/Tyr182), P38, Erk1/2, p-Erk1/2 (Thr202/ Tyr204), p-Akt (Ser473) and AKT **B) In vitro Cytotoxic/Apoptotic/Senescent effect of Cabozantinib and TMZ by SRB, Annexin V and Cell Senescence assays**. The effect of cabozantinib on BON and NCI-H727cells will be determined by proliferation assay. BON and NCI-H727 cells will be plated into 6-well plates (50 x 10^4 cells/well) in duplicate. After 24 hrs the cells will be treated with Cabozantinib (2.5 µM). Cell growth will be assessed at 24-48 and 72hrs after treatment by manual cell counting. The combinatory effect of Cabozantinib plus Temozolomide will be evaluated through Cytotoxicity, Apoptosis and Senescence assays. Citotoxicity: BON and NCI-H727 cells will be seeded in 96-well plates (Nalgene Nunc International)

	at a concentration of 1×10^4 cells/well in 100 µl of complete medium. The cells will be allowed to adhere and 24 hours later will be treated for 72 hours with increasing concentration of TMZ (0.1-500 uM) in presence or not of Cabozantinib (2.5 µM) and evaluated through Sulphorhodamine B cytotoxicity assay. Combined drug effects, such as synergism and inhibition will be investigated with Calcusyn software. Apoptosis and senescence on BON and NCI-H727 cells treated with different concentration of TMZ (0.1-500 uM) in presence or not of Cabozantinib (2.5 µM) at different time points, will be evaluated by flow cytometry using the FITC Annexin V Apoptosis Detection Kit I (BD, cat n. 556547) and the Cellular Senescence Flow Cytometry Assay (Cell Biolabs, CBA-232) respectively according to manufactures instructions. **C) Generation of TMZ-resistant BON and NCI-H727 cell lines.** TMZ resistant BON and NCI-H727 cells will be established through exposure to increasing TMZ concentrations for up to 8 months or until they become 100x resistant compared to parental cell lines. In vitro effect of Cabozantinib on TMZ resistant BON and NCI-H727 cell lines. The effect of Cabozantinib on Temozolomide resistant BON and NCI-H727 cells in restoring TMZ sensitivity will be evaluated through Cytotoxicity, Apoptosis and Senescence assays as previously described (Task 2.2). c-MET, HGF, AXL and RET will be measured in TMZ resistant BON and NCI-H727 cells by Western Blot. c-MET, MET, AXL and HGF RNA expression will be evaluated by Real Time PCR using previously described methods (10.1016/S0002-9440(10)64096-5). Moreover HGF (1.25nM)-mediated signalling will be evaluated in the presence of Cabozantinib (2.5 µM) in TMZ resistant NET cells as above described at using the following antibodies: Rabbit monoclonal antibodies for (Thr202/ Tyr204), S6K1, p-S6K1(Thr389), 4EBP1, p-4EBP1, p-P38 (Thr180/Tyr182), P38, Erk1/2, p-Erk1/2 (Thr202/ Tyr204), p-Akt (Ser473) and AKT. MGMT promoter methylation status will be evaluated with two techniques: methylation specific-polymerase chain reaction or pyrosequencing.
2.3 To assess the activity of the combination of cabozantinib and one-week-on one-week-off temozolomide according to the quality of life (QOL)	QOL evaluated through the responses of patients to EORCT-QLQ-C30 questionnaire combined with QLQ-GINET21 questionnaire

2.4 Benefit-Risk Assessment

Assuming that the primary objective of the study is to evaluate the efficacy of the combination of cabozantinib and temozolomide one week-on/one week-off, based on the overall response rate (ORR) and that the evaluation of the activity of the combination of cabozantinib and temozolomide one week-ON/one week-OFF based on the Clinical Benefit Rate (CBR) and the safety and tolerability assessment of the combination of cabozantinib and temozolomide one week-on/one week-off are among the secondary objectives of the study, in order to carry out an appropriate risk assessment. benefit it is possible to refer to the following scientific evidence:

- in the phase I study Cabozantinib 40 or 60 mg daily in combination with Temozolomide was generally well tolerated and showed no pharmacokinetic interactions with concomitant Temozolomide standard dose administered [30];
- in the above study the most frequently reported grade 3/4 adverse events were thrombocytopenia (31%), leukopenia (27%, including 5 patients with neutropenia) and deep vein thrombosis and / or pulmonary embolism (23 %) [30];
- in a study on the activity and safety of metronomic Temozolomide in second line of treatment, previous clinical experience has shown that Temozolomide is active against NEN at standard doses of 150 to 200 mg / m2 per day and has not been recorded G3 / G4 toxicity. The study found that the administration of metronomic Temozolomide is a suitable treatment for NEN G2 and G3 particularly in patients with Performance Status 2 (PS) [29];
- in the aforementioned study, the analysis of the efficacy and safety results after treatment with second-line Temozolomide Metronomic confirmed an ORR of 19%; in particular, the ORR in patients with NEN G2 was 9% while for those with NEN G3 the ORR was 27% [29];
- in a further study of Temozolomide Metronomic in second line of treatment a patient with G3 neuroendocrine neoplasia of the pancreas progressing with PS 2 underwent an intermittent and metronomic regimen of Temozolomide (75 mg / m2 / day - one week on/one week off). The patient achieved significant clinical benefit (PS = 0) and total body CT showed a partial RECIST response at all disease sites. No side effects were recorded [36].

Taking into account the toxicity of the two molecules, as reported in the corresponding SmPCs, and the benefit the therapeutic combination could bring to patients, Cabozantinib with Temozolomide represents a promising approach for patients with progressive thoracic (T-NENs) and gastro-entero-pancreatic (GEP - NENs) neuroendocrine tumors after a first line of treatment. To confirm the activity of the combination drugs in this trial will be used lower doses than phase I studies done, and this choice could certainly offer adverse events more manageable. Moreover, according to the evidence present in the Temozolomide SmPC, phase I studies have shown that the administration of TMZ with other drugs does not produce alterations on the absorption of temozolomide. Therefore, as TMZ does not undergo hepatic metabolism and is characterized by low protein binding, it is unlikely to affect the pharmacokinetics of other medicinal products.

The current unmet need is to carry out further clinical investigations to clarify the exposure-efficacy/safety relationship of Temozolomide-Cabozantinib combination to define a new second line therapy for this setting of patients.

3 STUDY DESCRIPTION

3.1 Design

This is a phase II, open-label, single-arm, multicentre study of Cabozantinib in combination with Temozolomide in patients with lung and GEP-NENs progressed after SSAs, Everolimus, Sunitinib or PRRT.

The study is designed to evaluate the activity and safety of the combination Cabozantinib and Temozolomide.

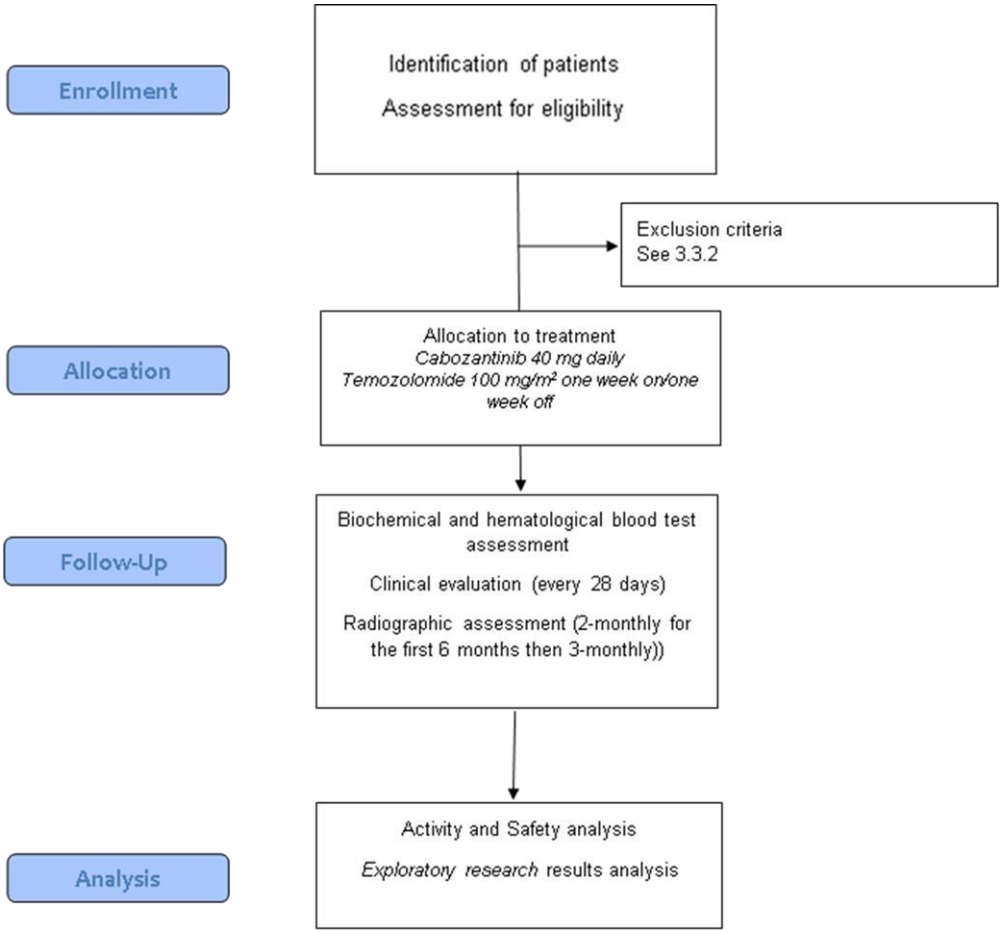
Toxicities will be assessed as follows:

- all the patient with Grade G4 - G5 toxicities will be discontinued according to the NCI -CTCAE v. 5.0;
- regarding the occurrence of episodes of diarrhea:
  - for non-syndromic patients, grades G4-G5 will be excluded
  - for syndromic patients, grade G3 will be excluded;
- AST or ALT <3 x ULN and total bilirubin <2 x ULN in combination will be tolerated to prevent liver injury;
- all cases where AEs are not resolved in 7 days will be excluded.

All patients will be treated with Cabozantinib 40 mg per os daily continuously, and Temozolomide 100 mg/m^2/day seven days followed by seven days of stop (regimen one week on / one week off).

Patients enrolled will receive study medication until disease progression, unacceptable toxicity, withdrawal of consent or death, whichever comes first.

3.2 Study Flowchart



3.3 Study Population

Approximately 35 patients will be enrolled over a planned recruitment period of 24 months.

3.3.1 Inclusion Criteria

Patients who meet all of the following inclusion criteria will be considered eligible for this study:

1. 18 years and older patients
2. Signed informed consent prior to initiation of any study-specific procedures or treatment, as confirmation of the patient's awareness and willingness to comply with the study requirements.
3. Documented histological or cytological diagnosis of well differentiated Lung and GEP-NENs (NET G1, NET G2, NET G3 in WHO 2017 classification) progressing after a first line of therapy with SSAs, sunitinib, everolimus, chemotherapy and/or PRRT or documented histological or cytological diagnosis of Large cells neuroendocrine carcinoma patients with Ki67< 55% progressed after platinum-based first line chemotherapy.
4. Subjects must have evidence of progressed disease, radiologically documented in the 12 months previous study entry.
5. Subjects must have evidence of measurable disease as determined by the investigator. Target lesions must have shown evidence of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 criteria in the 12 months prior to study entry. Patients must have measurable disease per RECIST 1.1 by computer tomography (CT) scan or magnetic resonance imaging (MRI). Gallium 68 PET Scan can be considered useful before and during the treatment.
6. Subject must have adequate swallowing capacity.
7. Subjects with functional (associated with a clinical hormone syndrome) and non functional tumors are eligible for the study.
8. The concurrent use of somatostatin analogues is allowed provided that the patient has been on a stable dose for at least two months.
9. At least 4 weeks of wash-out from previous targeted therapies.
10. At least 6 months of wash-out from previous PRRT treatment.
11. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2
12. Subjects must have adequate organ function, including the following:
13. Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥1.5 x10^9/L; platelet count ≥ 100 x 10^9/L; haemoglobin ≥ 9 g/dL;
14. Hepatic: total bilirubin ≤ 1.5 x upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT] and alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT]) ≤ 2.5 x ULN (< 5 x ULN if liver metastases are present);
15. Renal: normal serum creatinine or calculated creatinine clearance ≥ 60 mL/min (Cockroft-Gault formula);
16. Recovery from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.
17. Estimated life expectancy of ≥12 weeks.

18. Sexually active fertile female subjects must agree to use effective contraceptive methods during the course of the study and for 4 months after the last dose of study treatment. While sexually active fertile male subjects must agree to use effective contraceptive methods during the course of the study and up to 6 months after the last dose of study treatment;
19. For women of child-bearing potential, negative serum pregnancy test within 14 days prior to the first study drug administration;
20. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures and willingness to comply with the study requirements.

3.3.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be considered eligible for this study:

1. Receipt of any type of anticancer therapy within 4 weeks before study entry.
2. Previous treatment with Temozolomide or cabozantinib
3. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before recruitment.
4. Previous PRRT treatment: Systemic treatment with radionuclides within 6 months before study entry.
5. Subjects with clinically relevant ongoing complications from prior radiation therapy and/or surgery are not eligible.
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 3 months before study entry
7. Concomitant anticoagulation at therapeutic doses with oral anticoagulants or platelet inhibitors.
8. Chronic hepatitis B infection (both active or not).
9. Chronic treatment with corticosteroids or other immuno-suppressive agents.
10. Serious illness other than cancer including, but not limited to, the following conditions:
    a. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation: i.e. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before recruitment. Note: Complete healing of an intra-abdominal abscess must be confirmed prior to recruitment.

    b. Cavitating pulmonary lesion(s) or endobronchial disease

    c. Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Subjects with lesions invading the portal vasculature are eligible.

    d. Clinically significant bleeding risk including the following within 3 months of recruitment: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors

    e. Other clinically significant disorders such as:

i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness.
ii. Serious non-healing wound/ulcer/bone fracture

iii. Malabsorption syndrome iv. Uncompensated/symptomatic hypothyroidism v. Requirement for hemodialysis or peritoneal dialysis vi. History of solid organ transplantation

11. Uncontrolled congestive heart failure (NYHA II, III, IV). Patients with history of congestive heart failure who do not violate this exclusion criterion will undergo an evaluation of their cardiac ejection fraction prior to recruitment, preferably via gated equilibrium radionuclide ventriculography. The results from an earlier assessment (not exceeding 30 days prior to recruitment) may substitute the evaluation at the discretion of the Investigator, if no clinical worsening is noted. The patient's measured cardiac ejection fraction in these patients must be >40% before recruitment.
12. QTcF > 470 msec for females and QTcF > 450 msec for males or congenital long QT syndrome.
13. Patients with rare hereditary problems of galattose intolerance, congenital lactase deficiency or glucose-galattose malabsorption.
14. Major surgery within 3 months before study entry. Complete wound healing from major surgery must have occurred 1 month before study entry and from minor surgery at least 10 days before study entry.
15. Pregnant or lactating females.
16. History of another malignancy within 2 years before study entry, except for superficial skin cancers.
17. Serious and/or unstable pre-existing medical or psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
18. Patients on chronic treatment with drugs that are contraindicated to with cabozantinib and temozolomide treatment according to the SmPC of each product. For further information, please refer to what is reported in section 4.2.1.2.

3.4 Procedures and Measurements

3.4.1 Screening

Each patient will undergo screening during the 28 days prior to admission to confirm eligibility, as per Table 1. Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided they comply with the protocol specified timelines. Written informed consent will be obtained before the subject undergoes any study specific procedures.

Once consent has been obtained the patient should be added to the Electronic Case Report Form (eCRF), where a unique Screening ID will be allocated, which should be used in all correspondence during the screening period.

A complete record of all patients who enter screening for the study, and those who go on to be enrolled, must be maintained at each site. The local investigator is responsible for ensuring that this record includes the allocated trial ID as well as the patient identifiable data including name, hospital number (if any) and date of birth.

Eligible patients who take part in the study must meet all of the listed inclusion criteria (refer to 3.3.1) and none of the exclusion criteria (refer to 3.3.2).

3.4.2 Allocation

After eligibility has been confirmed, patients will be enrolled in the study and allocated for treatment. Patients should receive the first dose of study treatments no later than 3 calendar days after enrolment into the study. Patients who fail the screening can be screened again and eventually entered into the study, as long as all inclusion/exclusion criteria are met.

3.4.3 Treatment Period

Patients will receive study treatment until disease progression, unacceptable toxicity or withdrawal. Patients will be required to attend clinic on Day 1, Day 8, Day 14 and Day 22 of every 4 week cycle. Assessments to be performed during treatment are outlined in table 1.

3.4.4 Follow-up

Patients will return to clinic at 30 days (+/- 5 days) of their last dose of cabozantinib or temozolomide (whichever is discontinued last), for an end of treatment visit.

Following their end of treatment visit patients will be followed-up 3-monthly during routine clinic appointments to collect data on further anti-cancer treatment and survival. Follow-up will continue until 6 months after the last patient stops study treatment or up to 18 months after the last patient is randomised, whichever is sooner. Assessments and data collection to be performed during follow-up are outlined in Table 1.

3.5 Visit Schedule

While receiving study treatment patients will be reviewed every 28 days until disease progression or unacceptable study treatment-related toxicity. For assessment details see table 1.

Table 1: Scheduled assessment

Time-point → / Assessments ↓	Screening / Baseline	
	Within 28 days	**Within 14 days**
Informed Consent	X	
Demographics	X	
Medical History	X	
Vital signs		X
Height		X
Weight		X
ECOG Performance Status		X
Complete Physical Examination		X
12-lead ECG and ECHOCARDIOGRAFY	X	
Hematology[1]		X
Biochemistry[2]		X
Coagulation (INR, PTT)		X
Fasting Serum Glucose		X
Fasting Lipid Profile		X
Thyroid profile[19]		X
Urinalysis[3]		X
Serum Pregnancy Test[4]		X
Research Blood Sample		X
Archival Tumour Tissue or fresh biopsy (**optional**)	X	

Radiographic (CT/MRI) Assessments[6]	X	
^{68}Ga-Dotatoc	X	
Tumour Markers[7]	X	
EORTC-QLQ-C30/GINET21 questionnaire		X
Adverse Events (NCI CTCAE version 5.0)	X	
Concomitant Medications	X	

Assessments ↓ / Time-point →	Each Treatment Cycle						End of Treatment Visit	Follow-up
	Week 1		Week 2		Week 3	Week 4	30 days post last treatment (±5 days)	Every 3 months (±5 days)
Days →.	1	2-7	8-13	14	15-21	22-28		
Vital signs	X[8,9]						X	
Weight	X[8,9]						X	
ECOG Performance Status	X[8,9]						X	
Physical Examination[10]	X[8,9]			X			X	
12-lead ECG[11] and ECHOCARDIOGRAPHY	X						X	
Hematology[1]	X[8]		X	X		X	X	
Biochemistry[2]	X[8]			X			X	
Coagulation (INR, PTT)	X[8,9]						X	
Fasting Serum Glucose	X[8]						X	
Fasting Lipid Profile[12]	X[8,9]						X	
Thyroid profile[19]	X[8,9]			X			X	
Urinalysis[3]	X[1,2]						X	
Serum or Urine Pregnancy Test[4]	X[1,2]							
Research Blood Sample	X						X	
Radiographic (CT/MRI) Assessments	X[13]						X[14]	
^{68}Ga-Dotatoc							X	
Tumour Markers[7]	X[8]						X	X
Temozolomide Administration/Compliance [15]	X				X			
Cabozantinib Administration / Compliance [16]	X							
Adverse Events (NCI CTCAE version 5.0)	X		X	X		X	X	X
EORTC-QLQ-C30/GINET21 questionnaire	X							
Concomitant Medications [17]	X						X	
Record of Future Treatments								X
Record of Overall Survival								X
Fresh Biopsy (Optional) [18]							X	

1. Haematology includes white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct), and platelet count. A weekly monitoring of complete cell blood count will be ensured during treatment with temozolomide. The complete blood count will have to be available before starting the new weekly- administration of temozolomide
2. Full chemistry panel includes sodium [Na], potassium [K] chloride [Cl], bicarbonate [CO_2], blood urea nitrogen [BUN], creatinine [Cr], glucose, liver function tests (LFTs - ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, calcium, phosphate, and magnesium.
3. Urinalysis will include macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (levels should be recorded if available) and microscopic analysis should be performed if an abnormality is noted. In addition, 24-hour urine collection will be required for assessment of 5-HIAA levels
4. Only for patients of child-bearing potential. Either serum or urine pregnancy test will be done at screening and on Day 1 of every 3 cycles.
5. Fresh biopsy of the primary or metastatic lesion is optional prior to initiation of treatment on C1D1.
6. Computerized tomography (CT) (with contrast)/magnetic resonance imaging (MRI) of chest, abdomen and pelvis must be obtained
7. Relevant tumour markers (e.g., CgA, NSE and Urine-5-HIAA) will be obtained.
8. These assessments must be undertaken prior to dosing
9. The assessment does not need to be repeated if it was done within 3 days prior to the first dose.
10. Complete physical examination will be performed at Day 1 of every cycle, and at the end of treatment visit. Symptom directed physical examination will be done at all other scheduled time-points. Particularly, before initiation and during treatment with cabozantinib will be performed assessments for signs and symptoms associated with thyroid dysfunction (peripalpebral edema, tachycardia, exophthalmos, goiter).
11. ECGs should be collected as clinically indicated during trial treatment
12. Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein (LDL-C), and triglycerides will be performed at Screening/Baseline, pre-dose on Day 1 of every cycle and at the end of treatment visit.

13. Computerised tomography (CT) (with contrast)/magnetic resonance imaging (MRI) of chest, abdomen and pelvis must be obtained every 2 cycles (± 7 days) for the first 6 months, starting at C3D1 for response assessment by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 Subsequently, will be performed every 3cycles. If CT and/or MRI was obtained within 14 days prior treatment initiation it does not need to be repeated on day 1.
14. Tumour assessments will only be done on patients who have not previously demonstrated disease progression in the study, unless completed within the previous 4 weeks.
15. Temozolomide will be administered at 100 mg/m^2 daily on the first and third week of each cycle (1 week on/1 week off). Compliance will be recorded using a patient diary.
16. Cabozantinib will be administered at 40 mg daily until disease progression or unacceptable toxicity. Compliance will be recorded using a patient diary.
17. Co-administration of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution. Chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort [Hypericum perforatum]) with cabozantinib should therefore be avoided. For further drugs interactions, please refer to point 4.2.1.2
18. An **optional** fresh biopsy of the progressed site is required after tumour progression and prior initiation of any future tumour treatment
19. TSH, FT3 and FT4 will be performed at Screening/Baseline, pre-dose on Day 1 and Day 14 of every cycle and at the end of treatment visit.

3.6 Clinical Assessments and Procedures

Please refer to Table 1 detailing the schedule of assessments.

3.6.1 Demographic Data

Subject date of birth, race / ethnicity and smoking status (smokes or not / habitual or occasional) will be collected at screening.

3.6.2 Medical History

Both past medical history (including cancer history) and concomitant medical conditions will be collected.

3.6.3 Physical Examination

A complete physical examination will be performed at screening and at Day 1 of every cycle. Symptom directed physical exams may be performed at other time-points. The following examinations should be undertaken in the complete physical examinations: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen and neurological. The outcome of the examinations will be assessed as normal or abnormal, and whether clinically significant.

3.6.4 ECOG Performance Status

Performance status will be assessed at baseline and subsequent assessments as indicated in table 1 according to ECOG criteria as follows:

Table 2: ECOG Performance Status

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

3.6.5 Vital Signs

Vital signs including weight, pulse and blood pressure will be measured as indicated in table 1. Vital signs may be assessed at any time during the visit; however, blood pressure and pulse should be measured after 10 minutes rest. Height will be measured at initial screening visit only.

3.6.6 ECG and ECHOCARDIOGRAPHY

A standard 12-lead ECG and ECOCARDIOGRAPHY should be performed at baseline and as indicated in table 1.

Details of rhythm, ECG intervals and an overall evaluation will be collected.

3.6.7 Laboratory Evaluations

Blood samples for haematology and clinical chemistry and urinalysis will be taken at scheduled visits and analysed at the local laboratory using standard methods for routine tests.

The following variables will be measured at the time-points indicated in table 1

- Biochemistry: sodium [Na], potassium [K] chloride [Cl], bicarbonate [CO_2], blood urea nitrogen [BUN], creatinine [Cr], glucose, liver function tests (LFTs - ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, calcium, phosphate, and magnesium.
- Hematology: White blood cell count (WBC) with differential, hemoglobin (Hb), hematocrit (Hct), and platelet count. A weekly monitoring of complete cell blood count will be ensured during treatment with temozolomide. The complete blood count will have to be available before starting the new weekly-administration of temozolomide.
- Fasting serum glucose
- Fasting Lipid Profile: Total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein (LDL-C), and triglycerides
- Coagulation: INR and PTT
- Urinalysis: Macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (levels should be recorded if available) and microscopic analysis should be performed if an abnormality is noted. 5-hydroxyindoleacetic acid (5-HIAA) in the 24-h-urine sample

- Tumour markers: Cromogranina A (CgA), Enolasi Neurono-Specifica (NSE), Urine-5-HIAA
- Serum or urine pregnancy test for subjects of child bearing potential

Thyroid profile: TSH, FT3 and FT4Laboratory values that have changed significantly from baseline and are considered to be of clinical concern must be recorded as an adverse event and followed up as appropriate.

3.6.8 Treatment Compliance (Patient Diary)

Patients will be required to keep a detailed record of all cabozantinib and temozolomide tablets that they take in patient diaries. Date and time of administration and drug dose will be collected.

3.6.9 Patient Reported Outcomes (Quality-of-Life Assessments)

The EORCT-QLQ-C30 questionnaire combined with QLQ-GINET21 questionnaire will be used in this trial. The QLQ-C30 is a 30-question questionnaire designed to measure quality of life (QoL) in patients with different types of cancer. The QLQ-GINET21 is a 21-item model, which complements the general QLQ-C30 questionnaire with items specific to QoL in neuroendocrine cancer. The QLQ-C30 and QLQ-GINET21 will be completed at baseline and every 3 weeks thereafter, until study drug discontinuation and/or PD.

3.6.10 Clinical Safety Assessments

The NCI-CTCAE version 5.0 will be used to evaluate the clinical safety of the treatment in this study. Patients will be assessed for AEs at each clinical visit throughout the treatment phase of the study and during follow-up. All AEs need to be recorded in the eCRF. After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). SAEs are immediately reportable to the study coordinator as described in specific section.

3.6.11 Tumour Assessments

Tumour assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at the time-points indicated in table 1. The same method used for assessment at baseline must be used at all subsequent time points.

Tumour assessment will include: if disease is measurable or non-measurable (at least one lesion must be measurable), date of assessment, imaging method used, site, longest diameter of each target lesion and sum of longest diameters for all target lesions.

Patient response to treatment will be assessed using RECIST v1.1 criteria. Tumour size, Progression Free Survival and Objective Response Rate will all be determined. The RECIST v1.1 (January 2009) guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are detailed in Appendix A.

Tumour Size will be assessed at baseline and on scans at subsequent time points and recorded as the sum of the longest diameters of the target lesions. Baseline assessment should be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of study treatment; it should include all areas known for possible neuroendocrine tumour metastases. Subsequent tumour assessments will be

conducted every two cycles for the first 6 months and then 3-monthly, the window for each assessment is ± 7 week.

3.6.12 Record of Future Treatments

All anti-cancer treatment following the end of treatment visit until the study is closed will be recorded.

3.6.13 Record of Overall Survival

A record of overall survival will be made.

3.6.14 Exploratory Research

The following samples will be collected for exploratory research. Further details on sample processing, handling and shipment will be provided in the Laboratory Manual.

3.6.14.1 Archival Tumour Tissue

An archival tissue sample (either from the diagnostic tumour or a metastatic site) in the form of formalin fixed paraffin embedded (FFPE) tumour block will be collected from each patient. If it is not possible to obtain the entire tumour block, 30 slides of unstained 5-micron sections may be provided instead. Tumour samples will be tested for oncology biomarkers.

The following details will be collected: whether archival or fresh tumour, sample tissue type (primary or metastatic), whether representative tumour tissue is present, biopsy site, biopsy type, and histology sample ID.

Archival tumour blocks will be returned to source at the end of the study or earlier, upon request, if required.

3.6.14.2 Research Fresh Tumour Biopsies

Fresh biopsy is optional but recommended prior to initiation of treatment on C1D1. An optional biopsy of the progressed site is required and optional after radiologically documented progression.

The following details will be collected: date of biopsy collection, biopsy site, biopsy type and histology sample ID.

3.6.14.3 Research Blood Samples

Blood samples (2 x 10ml) will be collected to provide one sample of plasma and one sample of serum per time point, as indicated in table 1. These will be analysed for a range of oncology biomarkers, which may correlate with drug response. The date of collection and sample IDs will be recorded on the eCRF.

3.6.14.4 ***Chain of Custody of Biological Samples***

In all cases, patients will be consented for the collection and use of their biological samples and a full chain of custody will be maintained for all samples throughout their lifecycle.

The investigator at each site is responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal. Any person(s) responsible for temporarily holding samples, e.g. sub-contracted service provider keeps full traceability of samples from initial receipt of sample to further shipment or disposal (as appropriate).

INT Pascale keeps overall oversight of the entire lifecycle through internal procedures and monitoring of study sites.

4 TRIAL TREATMENT

Trial treatment must begin within 3 days of the patient being enrolled into the study.

4.1 IMP Administration and Schedule

Cabozantinib will be supplied in yellow triangle film-coated tablets at a dose of 40 mg for oral dosing. The tablets have no score and are debossed with “XL” on one side and “40” on the other side of the tablet. Cabozantinib 40 mg daily, will be self-administered orally on an empty stomach during continuous treatment. The tablet should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before, through 1 hour after taking cabozantinib. On each clinic day, the subject should return any unused study drug.

Cabozantinib will be administrated according to the EMA and AIFA label (Cabometyx® package insert), physicians prescribing cabozantinib must know and follow special warnings and precautions for use included in this label, as well as be aware of any cabozantinib interaction with other drugs (please refer also to point 4.2).

In order to manage the toxicity, the potential dose reduction measures will be introduced by administration of 20 mg tablets.

Temozolomide will be supplied in hard gelatin capsules, with white opaque cap and body, imprinted in black ink. The cap is imprinted with '893'.

Temozolomide will be self-administrated orally in the fasting state at 100 mg/m^2/day for seven days followed by seven days of stop (regimen one week on / one week off). The capsules must be swallowed whole with a glass of water and must not be opened or chewed. Anti-emetic therapy may be administered prior to or following administration of temozolomide. On each clinic day, the subject should return any unused study drug.

Temozolomide will be administrated according to the FDA label, physicians prescribing temozolomide must know and follow special warnings and precautions for use included in this label, as well as be aware of any temozolomide interaction with other medical products.

Cabozantinib tablets will be provided by IPSEN and Temozolomide capsules will be provided by the COORDINATOR CENTER.

4.2 Dose Modifications

4.2.1 CABOZANTINIB

If a patient experiences study drug-related toxicity which requires treatment with cabozantinib to be interrupted, a delay of up to 14 days is permitted to allow for resolution of toxicity. Toxicities must have resolved to ≤Grade 1 or to baseline for treatment to recommence.

For Grade 1 or Grade 2 (tolerable) toxicity, the patient may resume dosing at the same Dose Level. For ≥Grade 2 (intolerable) toxicity, the patient may resume cabozantinib at 20 mg (Table 2).

If, after a 14-day delay, toxicity has not resolved to Grade ≤1 or to baseline, the patient should be withdrawn from the study.

Table 3: Dose Modification of cabozantinib for Toxicity

Adverse reaction and severity	Treatment Modification
Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. Add supportive care as indicated.
Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 3 adverse reactions (except clinically not relevant laboratory abnormalities)	Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.
Grade 4 adverse reactions (except clinically not relevant laboratory abnormalities)	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue cabozantinib.

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4)

4.2.1.1 Cautions in Cabozantinib administration

Cautions must be taken during cabozantinib administration for the following conditions:

- Hypertension—discontinue treatment if uncontrolled despite medical intervention;
- palmar-plantar erythrodysaesthesia syndrome—consider treatment interruption if severe and restart at a lower dose when resolved to grade 1;
- patients at increased risk of fistulas, gastro-intestinal perforation, abdominal abscess —consult product literature;
- patients at risk of hemorrhage (including tumour involvement of the trachea or bronchi)—discontinue if symptoms develop;
- patients at risk of thromboembolic events including myocardial infarction—discontinue if symptoms develop;
- risk of osteonecrosis of the jaw — consider discontinuing treatment at least 28 days before elective invasive dental procedures and monitor for symptoms before and during treatment and discontinue if osteonecrosis develops.;
- susceptibility to QT-interval prolongation (e.g. cardiac disease, electrolyte disturbances, bradycardia, concomitant use of drugs that prolong the QT interval)—monitor ECG and electrolytes periodically
- This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, congenital lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.2.1.2 Interaction with other medicinal products and other forms of interaction

Interaction between Cabozantinib and strong inhibitors/inducers of CYP3A4 have been documented. In addition, interaction with other medicinal products have been proposed and/or tested. In particular:

- Administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance (by 29%) and increased single-dose plasma cabozantinib exposure (AUC) by 38%. Therefore, **co-administration of strong CYP3A4 inhibitors** (e.g., ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be **approached should be avoided**.
- Administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance (4.3-fold) and decreased single-dose plasma cabozantinib exposure (AUC) by 77%. Therefore, **chronic co-administration of strong CYP3A4 inducers** (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort [Hypericum perforatum]) with cabozantinib should therefore be **avoided**.
- No dose adjustment is indicated when gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) are co-administered with cabozantinib.
- MRP2 inhibitors in vitro data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations.
- Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown.
- The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.
- Because of high plasma protein binding levels of cabozantinib a plasma protein displacement interaction with warfarin may be possible. In case of such combination, INR values should be monitored.

- Cabozantinib was an inhibitor (IC50 = 7.0 µM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

For additional information on Cabozantinib toxicities management or interaction, as for a possible surgical and/or radiotherapy approach, please refer to the latest version of the SmPC and IB of Cabozantinib.

With regard to Interaction with other medicinal products and other forms of interaction related to Temozolomide, the following is evident:

- The administration of TMZ with ranitidine did not alter the absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).
- Administration of TMZ with food decreases the Cmax by 33% and the area under the curve (AUC) by 9%. Since it cannot be excluded that the change in Cmax is of clinical significance, Temozolomide should be administered without food.
- Population pharmacokinetic evaluations of phase II studies suggest that co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2 receptor antagonists or phenobarbital does not alter the clearance of Temozolomide. Co-administration of valproic acid is associated with a slight, but statistically significant, decrease in Temozolomide clearance.
- Temozolomide does not undergo hepatic metabolism and is characterized by low protein binding, it is unlikely to affect the pharmacokinetics of other medicinal products[1].
- The use of Temozolomide in combination with other myelosuppressive agents can increase the possibility of myelosuppression.

[1]For additional information please refer to the section 5.2 of the SmPC of Temozolide.

For additional information on Temozolomide toxicities management or interaction, as for a possible surgical and/or radiotherapy approach, please refer to the latest version of the SmPC of Temozolomide.

4.2.1.3 Discontinuation criteria

Cabozantinib should be discontinued for the following AEs:

- visceral perforation or fistula formation,
- severe hemorrhage,
- serious arterial thromboembolic events,
- nephrotic syndrome,
- ipertensive emergency,
- persistent uncontrolled hypertension despite optimal medical management,
- posterior reversible encephalopathy syndrome (RPLS). RPLS should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function,
- drug-related ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN without other reasonable explanation, consistening with drug-induced liver injury (DILI)

Table 4: Management of Liver Function Laboratory Abnormalities Related to Cabozantinib

Severity of ALT, AST, Total Bilirubin Elevations by CTCAE v4	Treatment Dose Modification
Grade 1	Dose adjustment is usually not required. Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated.
Grade 2	Interrupt study treatment if lasting longer than 1 week and consider more frequent monitoring of ALT, AST, and bilirubin. Restart study treatment after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline.
Grade ≥ 3	Interrupt study treatment and consider more frequent monitoring of ALT, AST, and bilirubin. Restart study treatment at a reduced dose after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline. Discontinue if lab abnormalities cannot be reversed despite interruption of study treatment

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE v4, Common Terminology Criteria for Adverse Events version 4

4.2.2 TEMOZOLOMIDE

Dose reductions and discontinuations of temozolomide should be applied according to Tables 5 and 6. During treatment with temozolomide a complete blood count will be obtained weekly. The dose should be reduced or administration discontinued according to Table 5.

If a patient experiences study drug-related toxicity which requires treatment with temozolomide to be interrupted, a delay of up to 14 days is permitted to allow for resolution of toxicity.

If a patient further presents temozolomide toxicities that warrant treatment interruption then should be either withdrawn from the study or may continue receiving cabozantinib as a single agent until disease progression (unless unacceptable toxicity, death or withdrawal of consent.) In this case the patient will still be considered in the study.

Table 5: TMZ dose levels

Dose level	TMZ dose (mg/m^2/day)	Remarks
-2	50	Reduction for prior toxicity not manageable with dose level -1
-1	75	Reduction for prior toxicity
1	100	Dose during all cycles of treatment in absence of toxicity

Table 6: TMZ dose reduction or discontinuation for adverse events

Toxicity	Reduce TMZ by 1 dose level[a]	Discontinue TMZ
Absolute neutrophil count	≥ 0,5 e < 1,5 x 10^9/l	< 0,5 x 10^9/l
Thrombocyte count	≥ 10 e < 100 x 10^9/l	< 10 x 10^9/l
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 o 4

[a]: TMZ dose levels are listed in Table 5 Treatment with TMZ concomitant can be continued when all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9/l; thrombocyte count ≥ 100 x 10^9/l; CTC non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting).

For additional information on Temozolomide toxicities management or interaction, please refer to the latest italian version of the Temozolomide SmPC.

4.3 Permanent Discontinuation of Study Treatment and Withdrawal from Study

4.3.1 Permanent discontinuation of study treatment

Subjects may discontinue study medication for the following reasons:

- Disease progression
- At the request of the subject
- Adverse event / Serious Adverse Event
- Allergic reaction to IMP
- If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

Date of permanent discontinuation and the reason will be recorded.

Once study medication is permanently discontinued it cannot be restarted.

If monitoring and/or verification reveals a serious and/or persistent non-compliance by an investigator/institution, the sponsor will discontinue the investigator/institution's participation in the trial. Where an investigator/institution's participation in a study is terminated due to non-compliance, the sponsor will promptly notify regulatory authorities.

If the Sponsor stops the study early, for any reason, it will ensure that the regulatory authorities, ethics committees and all investigators involved become aware of the decision and take appropriate action.

4.3.2 Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Subject decision
- Loss to follow-up
- Death

If a patient dies whilst participating in the study a “Statement of Death” CRF must be completed. The following details will be collected: date of death, whether autopsy performed, whether death was related to the disease under investigation, primary cause of death, secondary cause of death, and any other details.

4.3.3 Procedures for Withdrawal from Study

If the patient is withdrawn from the study, the date of withdrawal and the reason must be recorded. If possible, the investigator should arrange for the end of treatment assessments to be completed. Where the patient has withdrawn due to an AE, the investigator should follow the procedures in section 5.0.

5 PHARMACOVIGILANCE

5.1 Adverse Event (AE) and Pharmacovigilance

In accordance with the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP. Pre-existing conditions which worsen during a study are to be reported as AEs.

The deadline to report resulting-in-death and potentially life-threatening Adverse Events is seven (7) calendar days for the Interventional Clinical Study and is fifteen (15) calendar days for other serious reactions.

5.1.1 Disease Progression

Disease progression is a worsening of a patient's condition attributable to the disease for which the study medication is being given. This may be an increase in severity of the disease or increase in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

5.1.2 New Cancers

The development of a new cancer should be regarded as an AE and reported accordingly. Generally, it will also meet at least one of the serious criteria.

5.2 Adverse Event recording

AEs will be collected throughout the study, from the point of consent until the end of follow-up; they will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. Serious Adverse Events (SAEs) will also be recorded throughout the study.

Any AEs which remain unresolved at the patient's last visit in the study should be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF.

The following details will be collected in the eCRF for each AE:

- AE description / diagnosis
- Date of onset and date of resolution
- CTCAE grade maximum intensity
- Seriousness
- Investigator causality rating against the study medication (yes or no)
- Action taken with regard to study medication
- Outcome

5.2.1 Severity of Adverse Events

Severity is a measure of intensity; whereas seriousness is defined by the criteria in section 5.4.

Severity will be assessed using the grading scales found in the National Cancer Institute CTCAE version 5.0 (November 2017) for all adverse events with an assigned CTCAE term. For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate and severe into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded at the following link https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf .

5.2.2 Causality of Adverse Events

The Investigator will assess causal relationship between the investigational product and the combination treatment and each AE.

Unassessable:	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship[1]
Unrelated:	No evidence of any causal relationship
Unlikely:	There is little evidence to suggest there is a causal relationship (e.g. event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible:	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable:	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite:	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

[1] For the classification of adverse events as "Unassessable" it is possible to refer to the definitions of the WHO of 2002.

All adverse events being assessed as "Unassessable, Possible, Probable, Definite" should be considered as related to the IMPs while "Unrelated and Unlikely" will be considered as not related to the IMPs.

5.2.3 Treatment and Follow-up of AEs

The treatment and follow up of all the AEs should follow the indication provided below.

- For Related AEs, follow until one of the following occurs:
  - Resolved or improved to baseline;
  - Relationship is reassessed as unrelated;
  - Death;
  - Investigator confirms that no further improvement can be expected;
  - Clinical or safety data will no longer be collected, or final database closure.

- For Unrelated severe or life-threatening AEs, follow until one of the following occurs:
  - Resolved or improved to baseline;
  - Severity improved to Grade 2;
  - Death;
  - Investigator confirms that no further improvement can be expected;
  - Clinical or safety data will no longer be collected, or final database closure.

The final outcome of each AE must be recorded on the CRF.

5.3 Abnormal Laboratory Test Results

Clinically significant laboratory test results will be recorded on the laboratory results pages of the eCRF. Any laboratory result abnormality fulfilling the criteria for a SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Clinically significant treatment-emergent abnormal laboratory results are those meeting one or more of the following conditions:

- Accompanied by clinical symptoms.
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation).
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.
This does not apply to:

- Any abnormal laboratory result, which falls outside the laboratory reference range but does not meet the clinical significance criteria. These results will be analysed and reported as laboratory abnormalities.
- Any abnormal laboratory result that is considered AEs of the type explicitly exempted by the protocol;
- Any abnormal laboratory result of an AE that has been already reported.

The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor.

5.4 Serious Adverse Events (SAE)

5.4.1 Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalization or prolongation of existing patient's hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Is another Important Medical Event**

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Any important adverse events/reactions that is not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting.

5.4.2 Reporting of SAEs (immediately reportable)

Any clinical AE, or abnormal laboratory test value assessed as serious (as defined above), AESI or pregnancy case, occurred during the course of this study from the enrolment visit (start of study screening procedures), including long term follow-up, must be reported to Sponsor and within **within 24 hours** of the Investigator becoming aware of the event (expedited reporting). If the investigator becomes aware of safety information that appears to be drug related, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor. In addition, report of Adverse Events will be done, according to current local law, to local Health Authorities.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial eCRF.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting.

5.5 Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the subject.

5.6 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

5.6.1 Reporting of SUSARs

SUSARs should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report.

A SUSAR which is not fatal or life-threatening will be reported within 15 days.
Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

5.7 Pregnancy and Subjects of Reproductive Potential

All women of childbearing potential (defined as women who have had any menstrual bleeding in the last 24 months and who have not had a hysterectomy) should be informed of the potential risks to their unborn child should they fall pregnant whilst receiving treatment. All men receiving the treatment should be informed of the potential risks to their unborn child should their partners fall pregnant.

The investigator should report all pregnancies within 24 hours to the sponsor.

Adverse effects in the reproductive and developmental toxicity studies of cabozantinib in rats and rabbits, including embryotoxicity, fetal visceral malformations, and reduced fertility, occurred at plasma drug exposures lower than those measured in subjects receiving cabozantinib at clinically-relevant doses in ongoing trials. Female subjects with cancer must have negative pregnancy test at screening and throughout the duration of the study and must agree to use effective contraception while on the study and for 4 months after discontinuing study treatment (or longer depending on the requirements of the protocol). Additional local regulations regarding contraception may apply. Females who are pregnant or breast feeding are excluded from clinical studies with cabozantinib. Sexually active males may be included in clinical studies with cabozantinib if they agree to use effective contraception, use a barrier method (eg, condom) to avoid transmission of cabozantinib in semen, and refrain from donating sperm while on the study and for 4 months after discontinuing study treatment (or longer depending on the requirements of the protocol).

Sexually active fertile male subjects must agree to use effective contraceptive methods during the course of the study and up to 6 months after the last dose of study treatment and should be informed about the possible irreversible infertility related to temozolomide intake.

In accordance with the 2014 CTFG the highly effective contraceptive methods for IMPs with demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - injectable
  - implantable [2]

- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence [4]

If a female subject has a confirmed pregnancy during the study, she should be counseled appropriately about the potential risks to the fetus with discussion of adequate treatment and follow-up for the subject's cancer. She will be taken off study treatment and will be followed through the outcome of her pregnancy, and infants exposed in utero will be followed for at least 6 months after birth. The investigator should be informed of the pregnancy immediately. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to the investigator.

Subjects will be informed of the potential reproductive and developmental risks and the requirements for contraception during the study in the informed consent form.

It is unknown whether cabozantinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for SADRs in nursing infants from cabozantinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in according with the guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4 In the context of the Raccomandation sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

5.8 Safety data exchange requirement

The Sponsor will provide Ipsen with a copy of any SAE report received by the Investigators. All SAEs must be forwarded to Ipsen as soon as possible, but no later than 1 business day of Sponsor awareness; a copy of SUSARs must be sent to Ipsen no later than 1 business day of Sponsor awareness. Pregnancy and Lactation reports must be sent within 24 hours of Sponsor awareness. The final study report should be sent to Ipsen no later than 30 calendar days of study completion.

6 STATISTICAL CONSIDERATIONS

6.1 Sample Size and Power Calculation

We hypothesize that the administration of cabozantinib in combination with temozolomide for in the second-line progressive lung and GEP-NENs will double the response obtained with temozolomide in monotherapy.

Being the null hypothesis settled at a theoretical 25% of ORR, which is a realistic historical ORR of TMZ in monotherapy in the second-line progressive lung and GEP-NENs. This is confirmed by our experience, where in the *Statistical Considerations* section of the study, ORR was considered as the sum of CR + PR, respectively defined as complete remission, i.e. the disappearance of all lesions (CR) and partial remission (PR) or a decrease of 30% or more in the sum of the longest diameters. The analysis of the results, regarding the efficacy and safety after treatment with Temozolomide Metronomico (mTMZ) in the second line confirmed an ORR of 19%; in particular, the ORR in patients with NEN G2 was 9% while for those with NEN G3 the ORR was 27% [29].

To support our arguments, it is also possible to refer to the statistical considerations and the results demonstrated with the standard treatments already used for the pathology object of the CABOTEM study: *Raymond E et al.* (the objective response rate was 9.3% in the Sunitinib group) [9], *Yao JC et al.* (confirmed objective responses were recorded in 2% of patients receiving Everolimus) [7] and *Strosberg J et al*. [37].

The following parameters are used to calculate the sample size: 90% statistical power, one-sided alpha error of 0.1, a null hypothesis (H0) of 25% ORR, an alternative hypothesis (H1) of 50% ORR, a power of 90%. Twenty-nine patients will be accrued to correctly test the previous statistical boundaries and twelve months of follow up are planned.

The sample size will be increased up to 35 patients, taking into account a 15% dropout.

Statistical analysis will be performed by Medcalc software v.17.6

6.2 Analysis Plan

6.2.1 Safety

- **Safety Analysis Population**

All patients who received at least one dose of study medications will be included in the safety population. The safety population will be used for all safety analyses. After five patients, we will perform a detailed safety report based on CTCAE v. 5.0

- **Safety Data Analysis**

All safety parameters will be summarized and presented in tables based on the safety population.

All AEs and clinically significant abnormal laboratory variables will be assessed and captured in the eCRF and clinical database according to the NCI-CTCAE v 5.0 grading system.

Separate listings will be produced for DLTs, SAEs, discontinuations due to AEs, and events of ≥Grade 3 severity.

All AEs commencing prior to dosing with study drugs will be excluded from the tabulation but will be fully listed. Summary statistics by dose cohort and time point will be produced for vital signs, 12-lead ECG parameters and laboratory safety data, together with changes from baseline. The incidence of laboratory test results showing shifts of more than one CTCAE grade will be summarized by dose cohort, time point and overall.

6.2.2 Efficacy

- **Efficacy Analysis Population**

The Efficacy Analysis Population will include all patients who receive ≥1 cycle of cabozantinib + temozolomide and undergo a post-treatment assessment of response.

Patients who on review do not meet the protocol inclusion/exclusion criteria or have a major protocol deviation may be excluded from the efficacy analysis.

- **Methods of Analysis**

Efficacy outcomes will be assessed using RECIST (version 1.1). Such outcomes will be determined by the local Investigator. The outcomes determined by local review will serve as the data source for the primary analysis.

The primary efficacy endpoint is ORR. ORR will be based on the best overall response (BOR).

In general, descriptive summaries of continuous data will present the group mean, standard deviation (SD), median, minimum, maximum, and sample size. Descriptive summaries of discrete data will present the number of patients and incidence as a frequency and as a percentage. Unless otherwise specified, for all estimates, 95% confidence intervals will be calculated.

For The duration of objective response and clinical benefit response will be described descriptively using the Kaplan-Meier method.

6.2.3 Interim Analyses

An interim analysis has not been planned as it would produce a poorly significant statistical result. This is justified by the small sample size.

In the study will be involved the participation of an Independent Data Monitoring Committee (IDMC). The IDMC will deal with the analysis of the data in accordance with the procedures and timelines set out in the 2006 CHMP Guideline on Data Monitoring Committees. The IDMC, as required by the guidelines, will consist of expertise from different scientific areas: qualified clinicians, biostatistical expertise and member with expertise in ethical questions.

The Promoter must inform Ipsen of any recommendations given as a result of any security problem.

7 REGULATORY, ETHICAL AND LEGAL ISSUES

7.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 1964 Declaration of Helsinki, and any subsequent restrictions.

7.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

7.3 Independent Ethics Committee Approval

The study will be performed in compliance with each country's national requirements. Approval from an appropriate Independent Ethics Committee (IEC) must be obtained prior to the start of the study. In addition, the IEC must approve amendments prior to their implementation (as instructed by the Sponsor; with the exception of urgent safety measures).

7.4 Regulatory Authority Approval

The study will be performed in compliance with each country's regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory Authorities must be obtained prior to the start of the study. In addition, the Regulatory Authorities must approve amendments prior to their implementation (as instructed by the Sponsor; with the exception of urgent safety measures which will be submitted after implementation), receive SUSAR reports, Development Safety Update Reports, and be notified of the end of the trial.

7.5 Trial Registration

The study will be registered on a trial database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

7.6 Informed Consent

The Principal Investigator at each site will:

- Ensure that each patient is given full and adequate oral and written information about the study including the background, purpose and risks/benefits of participation
- Ensure that each patient is notified that they are free to withdraw from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed sufficient time to read and understand the information sheet
- Ensure each patient provides signed, dated informed consent before undergoing any study specific procedure
- Ensure the original copy of the signed, dated Informed Consent Form is stored in the patient's medical records and a copy is also filed in the Investigator site file
- Ensure that each patient receives a copy of the signed, dated Informed Consent Form

7.7 Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner (where applicable) by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

7.8 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and IECs.

7.9 Data Protection

Precautions will be taken to ensure that patient confidentiality is preserved at all times. The Patient Consent form will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient.

7.10 End of Trial

The end of the trial is defined as the last data capture for the last patient on study; this will be 6 months after the last patient stops study treatment or up to 18 months after the last patient is randomised, whichever is sooner.

7.11 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

7.12 Disclosure of Data and Publication

Data management and data analysis will be carried out by Bambin Gesù Hospital in Rome, under the supervision of Dr. Valeria Antenucci, upon payment of € 20 000 to be paid at the end of the study.

They will be provide the electronic database development to conduct data review and manage queries and ensure data accuracy and integrity with regular reports.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor and CI. The investigator may use this information for the purposes of the study only.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor and CI.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

The results may be published or presented by the investigator(s), but only with the permission of the Sponsor and CI.

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APPENDICES

Appendix A: Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

** Guidance Document Version 2.0 date 17th November 2014*

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumour lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definition of Disease Parameters

Measurable disease Must be accurately measured in a least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5mm; when CT scans have slice thickness >5mm, the minimum size should be twice the slice thickness).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 20mm by chest X-ray.

Note: Tumour lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measureable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Malignant lymph nodes Criteria for lymph nodes given as ≥15mm short axis for target lesions and 10mm to <15mm for non-target lesions. Nodes under 10mm to be considered non-pathological.
Non-measurable disease All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include; leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Note: Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.

'Cystic lesions' thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements. All measurements should be recorded in metric notation using calipers if clinically assessed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumour regression in the

measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target lesions All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

Methods of Measurement

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

CT/MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g. for body scans but not for lung).

Chest x-ray Lesions on chest x-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial and ≥10mm in diameter as assessed using calipers. For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound (US) should not be used to measure tumour lesions.

Tumour markers Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology Can be used in rare cases (e.g. for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease).

Endoscopy, Laparoscopy Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

New Lesions

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is no PD.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- When patient has measurable disease – to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- When patient has none-measurable disease – there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localised to widespread.

Evaluation of Best Overall Response

Summary of overall response status calculation at each time point, for patients who have measurable disease at baseline.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once >4 wks. from baseline**
Not all evaluated	Non-PD	No	Not evaluated	
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, (taking as reference for PD the smallest measurements recorded on study).

Duration of stable disease: SD is measured from the start of the treatment (from the date of recruitment) until the criteria for disease progression are met, taking as reference the smallest sum on study (if baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of SD varies for different studies and diseases. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study. If the proportion of patients achieving stable disease for a minimum

period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Response Review

For trials where the objective response (CR and PR) is the primary endpoint it is recommended that all responses be reviewed by an expert(s) independent of the study. Simultaneous review of the patients' files and radiological images is the best approach.