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Cabozantinib and temozolomide in patients with advanced progressive neuroendocrine tumors: a phase 2 study

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Treatment options for patients with advanced neuroendocrine tumors (NETs) are limited. Preclinical and early clinical evidence suggest that cabozantinib and temozolomide may exert synergistic antitumor activity. We performed an open-label, single-arm, phase 2 study (NCT04893785) to assess the safety and efficacy of cabozantinib and metronomic temozolomide in patients with advanced, progressive, well-differentiated NETs of gastroenteropancreatic, pulmonary or unknown origin. Patients received cabozantinib 40 mg daily and temozolomide 100 mg/m^2/day one week on/one week off. The primary endpoint was overall response rate (ORR) by blinded local review. Secondary endpoints included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR), duration of response (DOR) and safety. Of the 37 patients enrolled, 14 harbored gastrointestinal NETs, 12 pancreatic NETs, 9 lung NETs and 2 NETs of unknown primary. Neoplasms were classified as G1, G2 or G3 in 9, 24 and 4 cases respectively. While all enrolled patients were assessable for toxicity, 33 met the criteria for per protocol assessment of efficacy. The ORR was 15% (95% CI, 5-31%) and did not meet the primary endpoint. However, after a median follow-up of 19.2 months, the CBR was 100% (95% CI, 89.5-100%) and the median PFS was 28.5 months (95% CI, 16.8-28.5 months). The median OS was not reached, with a 3-year OS rate of 68.5% (± 9.1%). The median DOR was 19.5 months. Lymphopenia (16%), thrombocytopenia (11%), diarrhea (8%) and colitis (8%) emerged as the most frequent grade ≥3 treatment-related adverse events. No treatment-related deaths were recorded. Deficiency of O^6-methylguanine–DNA methyltransferase (MGMT) and c-MET expression were associated with response. The proportion of the patients benefitting of the treatment and its safety profile justify larger, controlled studies to further investigate the added role of combining cabozantinib with metronomic temozolomide. ClinicalTrials.gov identifier: NCT04893785.

Neuroendocrine tumors (NETs) are heterogeneous malignancies originating from the diffuse neuroendocrine system[1]. According to the most updated analysis of the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI), the annual age-adjusted incidence of NETs is 8.52 per 100,000[2]. Most commonly, NETs arise in the gastrointestinal tract, lungs, and pancreas, and substantial differences have been described in terms of biology, clinical behavior, and response to treatments according to the site of origin[1].

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The treatment landscape of advanced NETs has recently expanded. Treatment options for extrapancreatic NETs include somatostatin analogs (SSAs)[3,4] and everolimus[5]. Sunitinib[6] or alkylating agent chemotherapy, particularly with temozolomide-based regimens[7], can also be considered for pancreatic NETs. Radioligand therapy with ^{177}Lu-dotatate is approved for the treatment of patients with somatostatin receptor (SSTR)-positive gastroenteropancreatic (GEP)-NETs progressive on SSA[8]. Based on the results of the NETTER-2 study[9], ^{177}Lu-dotatate has been recently approved by FDA but not EMA as frontline therapy in patients with advanced, well-differentiated GEP-NETs with a Ki-67 proliferative index of 10–55%. Cabozantinib, an oral small-molecule inhibitor of multiple tyrosine kinases including VEGF receptors, MET, AXL, and RET has been recently investigated in the double-blind, randomized, placebo-controlled CABINET trial[10]. The tyrosine kinase inhibitor (TKI) significantly improved progression-free survival (PFS) in patients with previously treated, progressive, advanced pancreatic and extrapancreatic NETs, receiving approval by both FDA and EMA.

Preclinical and early clinical evidence suggest that cabozantinib and temozolomide may exert synergistic antitumor activity. While cabozantinib has been described to enhance the sensitivity of glioblastoma, sarcoma, and neuroblastoma cell lines to temozolomide through downregulation of the c-MET and ERK pathway[11–13], sub-toxic doses of temozolomide are known to exert antiangiogenic effects[14,15], thus potentially enhancing the microvasculature remodeling determined by cabozantinib. The safety of combining cabozantinib and temozolomide has been already investigated in phase 1 or 2 clinical trials of patients with newly diagnosed glioblastoma or pretreated sarcomas[16,17]. The combination appeared tolerable, particularly when cabozantinib was administered at 40 mg daily. In a phase 2 study of patients with uterine and soft tissue sarcomas, the combination of cabozantinib and temozolomide exceeded the PFS rates expected with TKIs or alkylating agents in similar disease settings[17]. Among patients with heavily pretreated uterine leiomyosarcoma, addition of cabozantinib to temozolomide and bevacizumab was associated with an overall response rate (ORR) of 50% and a clinical benefit rate (CBR) of 100%, whereas ORR and CBR were 35% and 78% in patients who received only temozolomide and bevacizumab[18].

Here, we show the results of an open-label, single-arm, phase 2 study that evaluated the safety and efficacy of cabozantinib and temozolomide in patients with progressive, advanced, well-differentiated pulmonary or GEP-NETs. The primary endpoint selected was ORR given the difficulty of interpreting PFS outcomes in a single-arm trial. Although the primary endpoint was not met, the combination of cabozantinib and temozolomide was associated with a CBR of 100% (95% CI, 89.5–100%) and a median PFS was 28.5 months (95% CI, 16.8–28.5 months).

Results

Patient population

Demographic variables and clinical characteristics of 37 patients enrolled in the study are listed in Table 1. Patients were enrolled between June 2021 and July 2023. Overlapping enrollment on the final recruitment days determined the slight over-enrollment against the protocol-specified sample size of 35 patients. The median age of the patient population was 59 (31–78) years. Twenty patients (54%) were of female gender and thirty-one of them (84%) had a performance status of 0. Most patients had grade 2 or 3 well-differentiated tumors (76%). The Ki-67 index ranged between 1% and 50%, with a median of 7%. Primary tumor sites included pancreas (12 patients), small bowel ($n = 10$), lung ($n = 9$), colon ($n = 2$), unknown ($n = 2$), stomach ($n = 1$) and gallbladder ($n = 1$). Ten patients had carcinoid syndrome. Homogeneous lesion uptake on ^{68}Ga-DOTApeptide PET/CT was observed in 33/37 patients. The primary tumor had been resected in 17/37 patients before enrollment in the trial. Patients had received a median of two lines of prior systemic therapy; 33 received prior somatostatin analogs, 19 received prior ^{177}Lu-based radioligand therapy, 5 had prior cytotoxic chemotherapy (including etoposide/cisplatin, mFOLFOX6 and cyclophosphamide/epirubicin/vincristine), 5 had prior everolimus, 1 had prior sunitinib, 1 received prior interferon-α, and 5 had prior investigational agents (including axitinib, lenvatinib and surufatinib). At study entry, 19/37 patients (51%) remained on somatostatin analogs.

Duration of therapy

The disposition of all enrolled patients is shown in the CONSORT diagram (Fig. 1). All patients received the study treatment and were evaluable for safety. Of these, 33 (89%) completed at least one cycle of study treatment and met the criteria for per-protocol assessment of efficacy. Reasons for treatment discontinuation before the end of the first cycle included rapid clinical worsening ($n = 2$) and G4 thrombocytopenia ($n = 2$). Overall, patients evaluable for efficacy ($n = 33$) received a median of sixteen 28-day treatment cycles. Eighteen patients (49%) had at least one dosing interruption (<14 days) of cabozantinib, and 5 patients (14%) required a permanent dose reduction of the TKI. Toxicities leading to cabozantinib dose reduction included diarrhea ($n = 3$), fatigue ($n = 1$) and hand-foot syndrome ($n = 1$). Cabozantinib dose reductions always resolved the adverse event, allowing the patients to continue therapy. Ten patients (27%) had at least one dosing interruption (<14 days) of temozolomide. Permanent dose reduction and discontinuation of temozolomide were required in 6 (16%) and 4 (11%) patients, respectively. Toxicities, including neutropenia ($n = 2$), thrombocytopenia ($n = 2$), fatigue ($n = 1$), and nausea ($n = 1$) were the primary reasons for temozolomide dose reduction. Temozolomide dose reductions resolved the adverse event in 2/6 cases (1 neutropenia and 1 nausea case). Reasons for temozolomide discontinuation included neutropenia ($n = 3$) and nausea ($n = 1$). All patients discontinuing temozolomide were able to continue cabozantinib monotherapy. The median time to permanent temozolomide discontinuation was 2.6 months (95% CI, 1.7-4.3 months). In the overall cohort ($n = 37$), reasons for discontinuation of the study treatment included unacceptable toxicity ($n = 8$), radiographic tumor progression ($n = 6$), symptomatic decline ($n = 6$), worsening of pre-existing complicating diseases ($n = 4$) and withdrawal of consent ($n = 3$). Ten patients remained on study treatment at the time of data analysis. Toxicities leading to study treatment discontinuation included thrombocytopenia ($n = 4$), diarrhea ($n = 2$), fatigue ($n = 1$) and bowel perforation ($n = 1$). Figure 2 integrates individual patient treatment durations with recorded reasons for study discontinuation, timing of radiographic response, and stratification by tumor primary site.

Radiological and biochemical response

Among the 33 patients evaluable for efficacy, ORR was 15% (95% CI, 5–31%) and CBR was 100% (95% CI, 89.5–100%). When best response to therapy was evaluated, 5/33 patients (15%; 95% CI, 5.1–31%) had partial response (PR) and 28 patients (85%; 95% CI, 68–95%) experienced stable disease (SD) according to RECIST 1.1 criteria. After excluding the patients who discontinued treatment due to symptomatic decline, the ORR was 14% (95% CI, 4–32%), which remained comparable to the rate observed in the overall study population. Stratified by primary site, the ORR was 8% (95% CI, 0.2–38%) for gastrointestinal NETs, 17% (95% CI, 2–48%) for pancreatic NETs, and 25% (95% CI, 3–65%) for lung NETs. Overall, 19 patients (58%; 95% CI, 40–75%) experienced a reduction in tumor size from baseline, with sustained response for more than 18 months in 12/33 patients (36%; 95% CI, 21–53%). As depicted in Fig. 3A, B, most patients experiencing tumor shrinkage harbored pancreatic or lung NETs and G2 malignancies. The median DOR was 19.5 months (range, 4.8–38.3 months). No change in tumor volume or continued tumor growth was observed in 38% (13/34; 95% CI, 22–56%) of the cohort (Fig. 3C). Characteristics of patients deriving an objective

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Table 1 | Patient demographics and clinical characteristics

Characteristics	Number of patients (*n* = 37)	%
Age (years)		
Median	59	
Range	31–78	
Gender		
Male	17	46
Female	20	54
ECOG performance status		
0	31	84
1	6	16
Location of primary tumor		
Pancreas	12	33
Small bowel	10	27
Lung	9	24
Colon	2	5
Unknown primary	2	5
Gallbladder	1	3
Stomach	1	3
Number of metastatic sites		
1	7	19
≥2	30	81
Metastasis sites		
Liver	32	87
Lymph nodes	20	54
Bone	17	46
Lung	7	19
Peritoneum	4	11
Others	11	30
Functional status		
Non-functioning	27	73
Functioning	10	27
Carcinoid syndrome	10	27
Tumor grade		
G1	9	24
G2	24	65
G3	4	11
Ki-67 labeling index		
<10%	21	57%
≥10%	16	43%
SSTR positivity by imaging		
Yes	33	89
No	4	11
Elevated baseline CgA		
Yes	26	70
No	10	27
Unknown	1	3
Baseline CgA (xULN)		
Median	2	
Mean	5.5	
Median time from diagnosis (months)	31.2	
Primary tumor resected		
Yes	17	46
No	20	54

Table 1 (continued) | Patient demographics and clinical characteristics

Characteristics	Number of patients (*n* = 37)	%
Prior lines of systemic therapy		
Median	2	
Range	1–6	
Previous systemic therapy		
SSAs	33	89
^{177}Lu-based radioligand therapy	18	49
^{90}Y-based radioligand therapy	3	8
Everolimus	5	14
Chemotherapy	5	14
Axitinib	3	8
Sunitinib	1	3
Lenvatinib	1	3
Surufatinib	1	3
IFNα	1	3
Previous liver-directed therapy		
Yes	5	14
No	32	86
Concurrent on study SSA		
Yes	19	51
No	18	49

CgA chromogranin A, *ECOG* Eastern Cooperative Oncology Group, *IFNα* interferon α, *SSA* somatostatin analog, *SSTR* somatostatin receptor, *ULN* upper limit of normal.

response as a result of the investigational treatment are detailed in Table 2. Characteristics of patients experiencing clinical and radiographic benefit (absence of PD) exceeding 18 months are outlined in Supplementary Table 2.

Among 22 patients with baseline elevated (>ULN) serum CgA levels and at least one repeat measurement, 6 patients (27%; 95% CI, 11–49%) experienced major reduction (>50%) or normalization of the tumor marker. Differences between the median baseline CgA concentration and their lowest value following initiation of treatment were statistically significant ($p < 0.0001$; Fig. 3D). Among patients who experienced major reductions of CgA levels, 1/6 experienced PR and 5/6 experienced tumor shrinkage.

Progression-free and overall survival

At the time of data cut-off, 12 patients had died and 25 were alive, with a median follow-up duration of 19.2 months (range, 0.9–38.5 months). Among patients who met the protocol criteria for efficacy analysis ($n = 33$), 8 patients had died and 25 were alive, with a median follow-up duration of 19.5 months (range 3.2–38.5 months). As depicted in Fig. 4A, the median PFS was 28.5 months (95% CI, 16.8–28.5 months), and the 12-month PFS rate was 84.4% (±7.2). A sensitivity analysis excluding the patients who discontinued treatment due to symptomatic decline yielded efficacy estimates consistent with the primary analysis (median PFS: not reached; 95% CI, 22.2 months to not reached). As shown in Supplementary Fig. 1, no significant difference was seen in terms of PFS when comparing patients who required cabozantinib dose reduction or interruption or temozolomide dose reduction, interruption of permanent discontinuation versus those who did not. Stratified by tumor group, the median PFS of patients with pancreatic NETs, gastrointestinal NETs and lung NETs was 20.7 months (95% CI, 15.9–22.2 months), not reached (95% CI, 14.3 months to not reached) and not reached (95% CI, not reached) respectively ($p = 0.6$; Supplementary Fig. 2). By grade, the median PFS

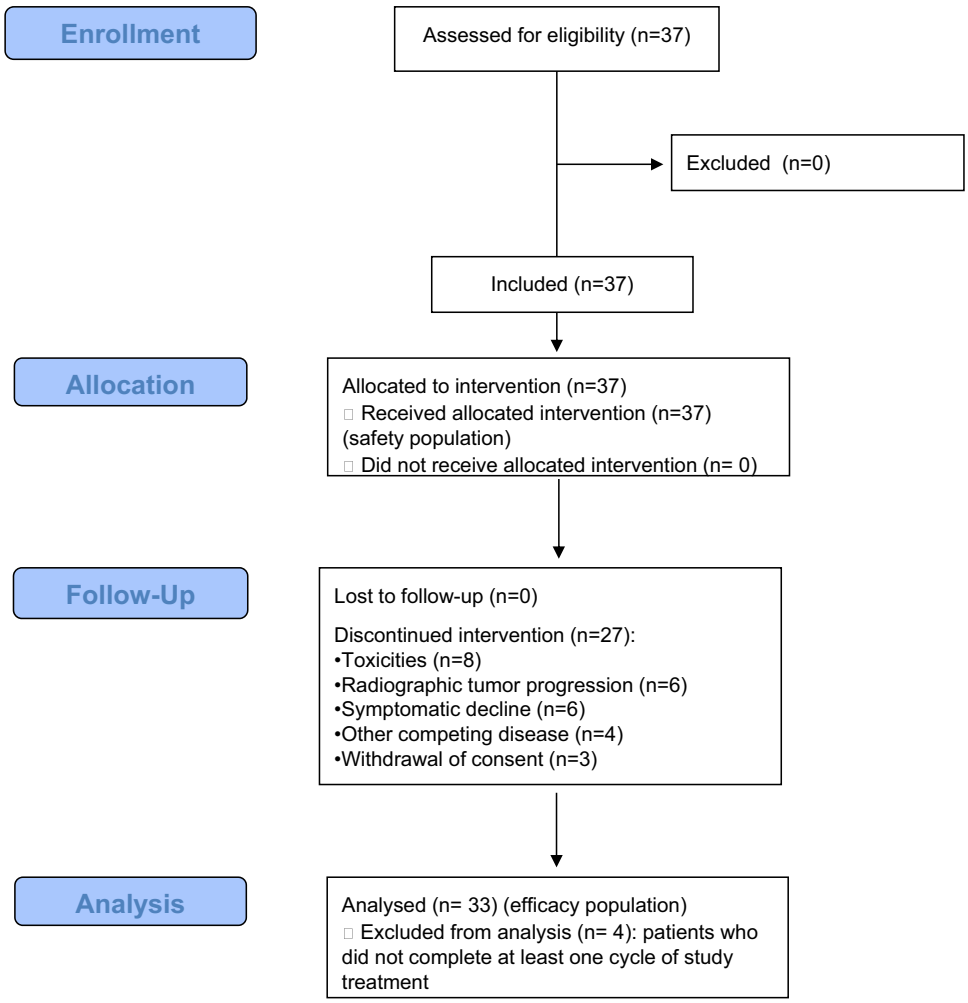

Fig. 1 | CONSORT diagram. Flow of participants through each stage of the study, including enrollment, treatment allocation, follow-up and analysis.

of patients with grade 1, 2 and 3 tumors was not reached (95% CI, 6.8 months to not reached), 22.2 months (95% CI, 16.8–28.5 months) and 5.2 months (95% CI, not reached; $p = 0.12$) respectively. A significant difference in PFS was observed between patients with ECOG performance status of 0 (28.5 months; 95% CI, 20.7–28.5 months) and 1 (3.7 months; 95% CI, 3.2–3.7 months) at study entry ($p < 0.0001$). The median PFS of patients with baseline elevated CgA was 20.7 months (95% CI, 14.3–28.5 months), whereas it was not reached (95% CI, 22.2 months to not reached) in patients with baseline normal CgA ($p = 0.04$). Age and gender were not associated with the risk of progression. Multivariable Cox regression analysis revealed that high baseline CgA levels were the only factor associated with a higher risk of progression (HR: 0.09, 95% CI 0.01-0.87; $p = 0.04$). The median TTF was 16.8 months (95% CI, 5.2–22.2).

The median OS was not reached (95% CI, not reached; Fig. 3B). The 12-, 24-month and 36-month OS rates were 82.2% (±6.6%), 73.3% (±8.4%) and 68.5% (±9.1%). OS did not significantly differ by age, gender, primary site and baseline CgA levels. Grade ($p = 0.03$) and ECOG performance status at study entry ($p < 0.0001$) predicted OS. Grade ($p = 0.005$) and ECOG performance status ($p = 0.002$) retained prognostic impact after multivariable analysis.

Safety

All study patients were evaluated for toxicity. The side effects considered at least possibly related to the treatment are listed in Table 3. Grade ≥3 toxicities occurred in 9/37 (24%) patients. The most frequent grade ≥3 treatment-related adverse events were lymphopenia (16%), thrombocytopenia (11%), colitis (8%), diarrhea (8%), anemia, abdominal pain, hand-foot syndrome, hyperbilirubinemia and oral mucositis (3% each). No opportunistic infections related to lymphopenia occurred during the study. More broadly, all cases of lymphopenia were asymptomatic and without clinical consequences. Grade ≥3 thrombocytopenia tended to occur early during the investigational treatment (during the first cycle in 3/4 patients, during the second cycle in 1/4 patients). Platelet transfusions were required in all patients who developed grade ≥3 thrombocytopenia. Grade 4 thrombocytopenia occurred in patients already exposed to chemotherapeutic agents or ^{177}Lu-dotatate (4/4 patients) and displaying extensive skeletal involvement (3/4 patients). Among patients who experienced colitis, one experienced a life-threatening bowel perforation requiring urgent surgery. Hypertension was considered a toxicity of special interest and developed in 7/37 (19%) patients. Anti-hypertensive agents were efficacious in controlling such toxicity in 100% of individuals. Other common adverse events included fatigue (65%), nausea (51%), decreased appetite (46%), dyspepsia (30%), constipation (16%), hypothyroidism (16%) and erectile dysfunction (16%). No treatment-related death was reported. No detrimental changes in cardiac function were reported over time by repeat echocardiography.

Tissue biomarkers

Of the 33 patients included in the per-protocol efficacy analysis, 19 (58%) had archival pathology specimens available for IHC and promoter methylation analysis. Demographics of patients who had tissue available for correlative analyses is summarized in Supplementary

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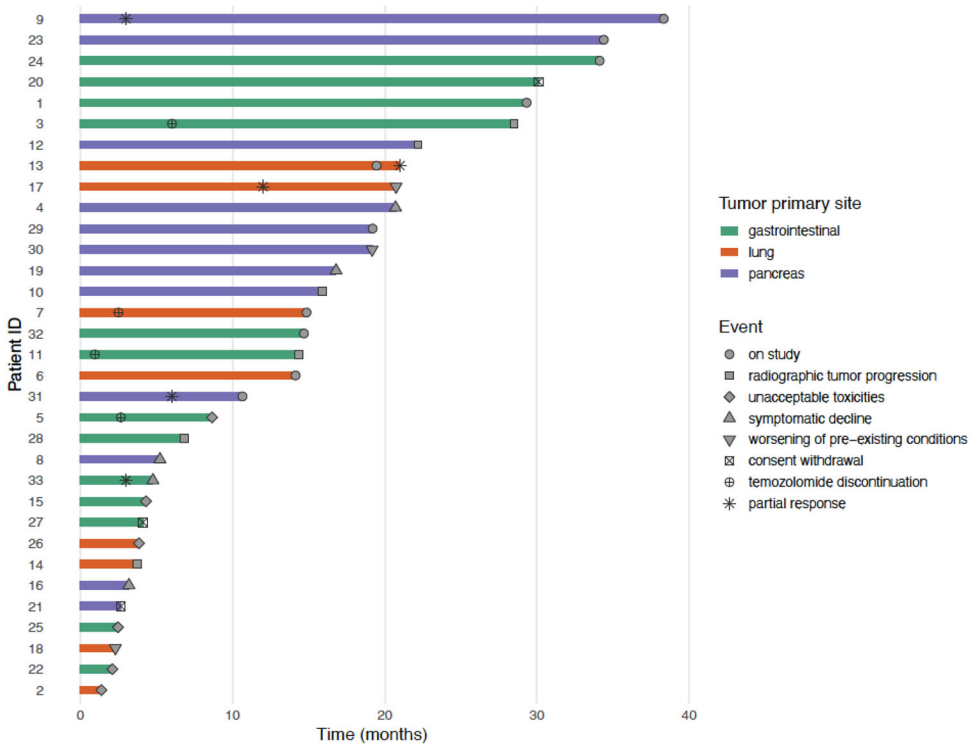

Fig. 2 | Swimmer plot of individual patient treatment timelines. Each bar represents an individual patient's duration of therapy from treatment initiation to discontinuation. Bars are color-coded according to tumor primary site. Symbols on each bar denote the timing of radiographic response or permanent temozolomide discontinuation. Termination points indicate the reason for treatment discontinuation. The plot provides a visual summary of treatment exposure, response dynamics, and discontinuation patterns across the study cohort ($n = 33$). CgA chromogranin A. Source data are provided as a Source data file.

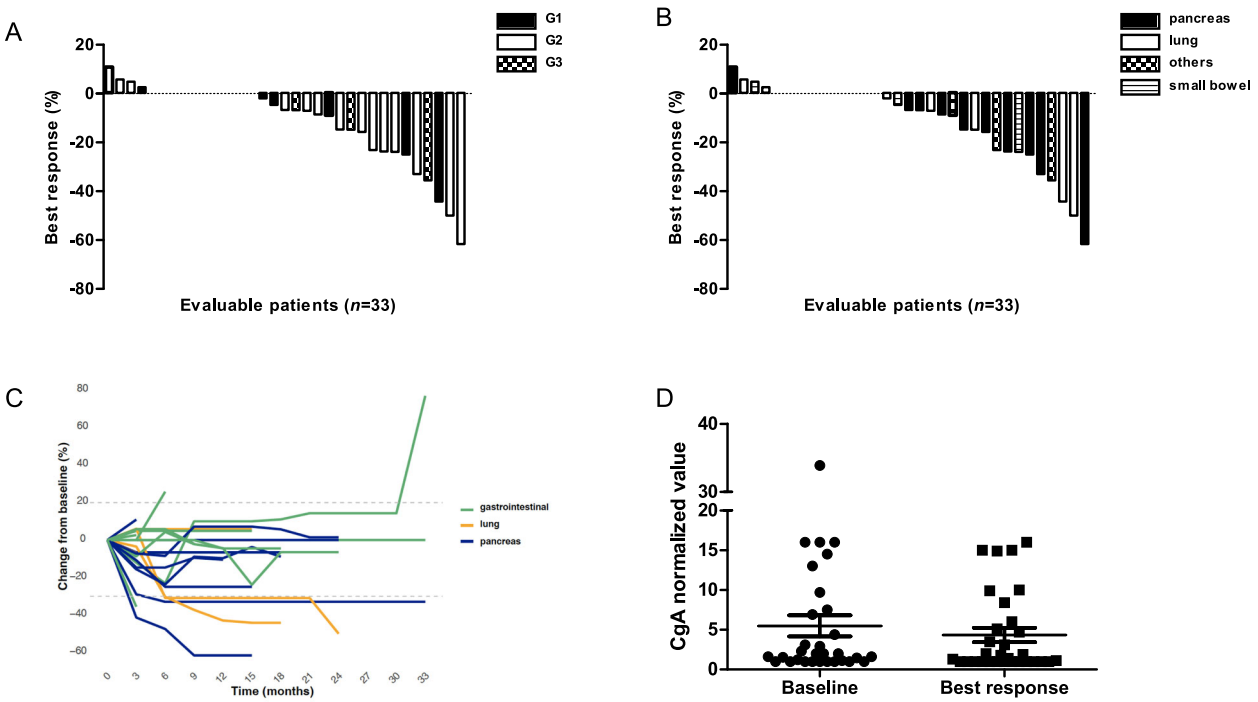

Fig. 3 | Antitumor activity of cabozantinib and temozolomide in patients with advanced, progressive NETs of gastroenteropancreatic, lung or unknown origin. Waterfall plot illustrating best radiographic response (% change) in each enrolled patient ($n = 33$), stratified by grading (**A**) and tumor primary site (**B**). **C** Spider plot showing the evolution of relative tumor size from the first dose of study treatment until the last tumor evaluation ($n = 33$). **D** Biochemical response following treatment with cabozantinib and metronomic temozolomide. The decrease in CgA concentrations was statistically significant ($p < 0.0001$) by two-sided Wilcoxon-matched pairs signed rank test. Paired row values, median change, and interquartile range are represented ($n = 31$). Source data are provided as a Source data file.

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Table 2 | Baseline patient characteristics by best response according to RECIST 1.1 criteria

Characteristics	PR (*n* = 5) *n* (%)	SD (*n* = 28) *n* (%)	*p*
Age (years)			
Median	56	58.5	
Range	44-68	31-78	
Gender			
Male	4 (80)	12 (43)	0.17
Female	1 (20)	16 (57)	
ECOG performance status			
0	5 (100)	25 (89)	1
1	0 (0)	3 (11)	
Location of primary tumor			
Pancreas	2 (40)	10 (36)	0.2
Small bowel	0 (0)	7 (25)	
Lung	2 (40)	6 (21)	
Colon	0 (0)	2 (7)	
Unknown primary	0 (0)	2 (7)	
Gallbladder	1 (20)	0 (0)	
Stomach	0 (0)	1 (4)	
Metastatic sites number			
1	0 (0)	5 (18)	0.57
≥2	5 (100)	23 (82)	
Metastasis sites			
Liver	5 (100)	24 (86)	0.54
Lymph nodes	1 (20)	17 (61)	
Bone	3 (60)	11 (39)	
Lung	2 (40)	4 (14)	
Peritoneum	1 (20)	2 (7)	
Others	0 (0)	2 (7)	
Functional status			
Non-functioning	5 (100)	18 (64)	0.29
Functioning	0 (0)	10 (36)	
Carcinoid syndrome	0 (0)	10 (36)	
Tumor grade			
G1	1 (20)	8 (29)	0.9
G2	3 (60)	18 (64)	
G3	1 (20)	2 (7)	
SSTR positivity by imaging			
Yes	4 (80)	26 (93)	0.36
No	1 (20)	2 (7)	
Elevated baseline CgA			
Yes	3 (60)	21 (75)	0.49
No	2 (40)	7 (25)	
Baseline CgA (xULN)			
Median	3,1	2	
Mean	4, 3	6, 2	
Median time from diagnosis (months)	81, 9	31, 6	
Primary tumor resected			
Yes	2 (40)	14 (50)	0.68
No	3 (60)	14 (50)	
Prior lines of systemic therapy			
Median	3	2	
Range	1-6	1-3	

Table 2 (continued) | Baseline patient characteristics by best response according to RECIST 1.1 criteria

Characteristics	PR (*n* = 5) *n* (%)	SD (*n* = 28) *n* (%)	*p*
Previous systemic therapy			
SSAs	5 (100)	26 (93)	0.08
^{177}Lu-based radioligand therapy	3 (60)	13 (46)	
Y-90-based radioligand therapy	1 (20)	2 (7)	
Everolimus	3 (60)	0 (0)	
Chemotherapy	1 (20)	2 (7)	
Axitinib	1 (20)	2 (7)	
Sunitinib	1 (20)	0 (0)	
Lenvatinib	0 (0)	1 (4)	
Surufatinib	0 (0)	1 (4)	
IFNα	0 (0)	1 (4)	
Previous liver-directed therapy			
Yes	1 (20)	4 (14)	0.74
No	4 (80)	24 (86)	
Concurrent on study SSA			
Yes	4 (80)	15 (54)	0.86
No	1 (20)	13 (46)	
MGMT promoter methylation			
Yes	3 (60)	1 (4)	0.001
No	0 (0)	13 (46)	
Unknown	2 (40)	14 (50)	
MGMT expression (H-score)			
High (3)	1 (20)	10 (36)	0.63
Low (1–2)	2 (40)	6 (21)	
Unknown	2 (40)	12 (43)	
c-MET expression			
Positive	2 (40)	3 (11)	0.05
Negative	0 (0)	12 (43)	
Unknown	3 (60)	13 (46)	
Baseline plasma VEGF-A concentration			
High (>median value)	3 (60)	10 (36)	0.57
Low (<median value)	1 (20)	11 (39)	
Unknown	1 (20)	7 (25)	
ΔVEGF-A concentrations			
High (>median value)	1 (20)	11 (39)	0.60
Low (<median value)	3 (60)	10 (36)	
Unknown	1 (20)	7 (25)	

ΔVEGF-A concentrations: absolute changes in VEGF-A concentrations from best RECIST response to baseline.
Two-sided Fisher's exact test, Mann-Whitney U test or Kruskal Wallis test were used, as appropriate.

Table 3. Two samples failed the methylation-specific PCR, providing indeterminate results and were therefore not further analyzed. Table 4 shows response by MGMT as measured via IHC and promoter methylation. The ORR in patients whose tumors had low or high MGMT expression was 25% (95% CI, 3.2–65.1%) and 9% (95% CI, 0.–41.3%), respectively, corresponding to an odds ratio (OR) of 3.3 (95% CI, 0.3–38.2; $p = 0.5$). The ORR in patients whose tumors scored positively by methylation-specific PCR was 75% (95% CI, 21.9–98.7%), while it was 0% (95% CI, 0–24.7%) in those whose tumors scored negatively, corresponding to an OR of 63 after Haldane-Anscombe correction (95% CI, 3.2–1234; $p = 0.002$). The overall concordance rate between MGMT promoter methylation status and MGMT protein

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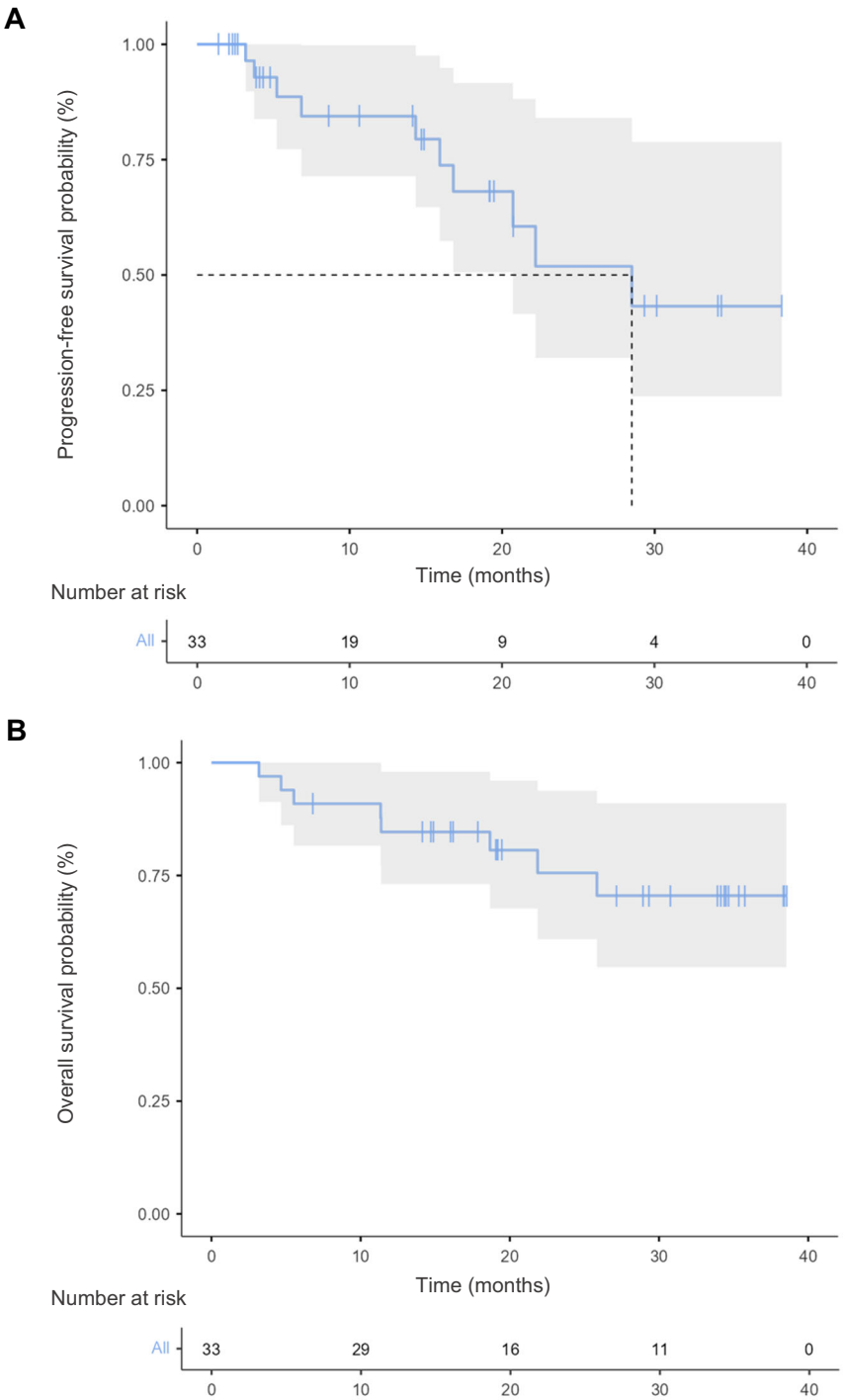

Fig. 4 | PFS and OS of patients with NETs of gastroenteropancreatic, lung or unknown origin treated with cabozantinib and metronomic temozolomide. Kaplan-Meier estimates of progression-free survival (**A**) and overall survival (**B**). The blue line shows the estimated survival proportion and the shadow area 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. Source data are provided as a Source data file.

expression by IHC was 65% (95% CI, 41.3–82.7%), based on agreement between methylation-positive cases with low MGMT expression and methylation-negative cases with high MGMT expression (Supplementary Table 4). When defined as either low IHC expression or positive promoter methylation, MGMT deficiency significantly predicted longer PFS ($p = 0.03$; Supplementary Fig. 3). No association was observed between MGMT status and toxicities (data not shown).

We next evaluated whether primary targets of cabozantinib such as c-MET, AXL and VEGFR2 could predict the response to the investigational treatment. Of 19 tumor samples, 2 lacked an internal positive control for all markers by IHC and were therefore not further analyzed. As shown in Fig. 5, both AXL and VEGFR2 were not expressed by tumor cells, while c-MET was expressed in 5/17 samples (29%). In all cases, the expression of c-MET was scored as weak. The ORR in patients whose

Table 3 | Treatment-related adverse events according to CTCAE version 5.0

Adverse event	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)	Overall *n* (%)
Fatigue	19 (51%)	5 (14%)	1 (3%)	0	25 (68%)
Nausea/Vomiting	12 (32%)	7 (19%)	0	0	19 (51%)
Anorexia	12 (32%)	5 (14%)	0	0	17 (46%)
Diarrhea	6 (16%)	6 (16%)	3 (8%)	0	15 (41%)
Dyspepsia/GERD	11 (30%)	0	0	0	11 (30%)
Abdominal pain	10 (27%)	0	1 (3%)	0	11 (30%)
Anemia	3 (8%)	6 (16%)	1 (3%)	0	10 (27%)
Palmar-plantar erythrodysesthesia syndrome	7 (19%)	3 (8%)	1 (3%)	0	9 (29%)
Lymphopenia	2 (5%)	1 (3%)	6 (16%)	0	9 (29%)
Platelet count decreased	1 (3%)	3 (8%)	0	4 (11%)	8 (22%)
Hypertension	1 (3%)	5 (14%)	0	0	6 (16%)
Constipation	6 (16%)	0	0	0	6 (16%)
Hypothyroidism	4 (11%)	2 (5%)	0	0	6 (16%)
Mucositis oral	4 (11%)	1 (3%)	1 (3%)	0	6 (16%)
Erectile dysfunction	4 (11%)	2 (5%)	0	0	6 (16%)
Colitis	0	2 (5%)	2 (5%)	1 (3%)	4 (13%)
Neutropenia	1 (3%)	3 (8%)	0	0	4 (11%)
Hemorrhoids	2 (5%)	1 (3%)	0	0	3 (8%)
Nasal congestion	3 (8%)	0	0	0	3 (8%)
Paresthesia	1 (3%)	1 (3%)	0	0	2 (5%)
Blood bilirubin increased	0	0	1 (3%)	0	1 (3%)

GERD gastro-esophageal reflux disease.

Table 4 | RECIST v1.1 response by MGMT

	IHC (H-score)			Promoter methylation		
RECIST response	Low (1–2)	High (3)	Total	Negative	Positive	Total
No	6	10	16	13	1	14
Yes	2	1	3	0	3	3
Total	8	11	19	13	4	17
	OR = 3.3; 95% CI, 0.3–38.2 (p = 0.5)			OR = 63[a]; 95% CI, 3.2–1234 (p = 0.002)		

Associations were assessed using a two-sided Fisher's exact test, and the odds ratios (OR) with 95% confidence intervals (CI) were calculated, applying the Haldane-Anscombe correction when necessary.

[a]After Haldane-Anscombe correction.

tumors had positive or negative c-MET expression was 40% (95% CI, 11–77%) and 0% (95% CI, 0–14%), respectively, corresponding to an OR of 17.9 (95% CI, 0.69–466; p = 0.07). PFS status by c-MET expression in depicted in Supplementary Fig. 4.

Circulating biomarkers

Blood samples at baseline, at the time of first occurrence of best response and at study discontinuation (or at the last available follow-up for patients who were still on treatment) were available for 25/33 (76%) patients included in the per-protocol efficacy analysis. As shown in Supplementary Fig. 5, plasma VEGF-A concentrations were similar at baseline (median: 210 pg/ml; 95% CI, 175.4–436.3 pg/ml), time of first best response (median: 146.3 pg/ml; 95% CI, 164–456.4 pg/ml) and study discontinuation (median: 367 pg/ml; 95% CI, 230.8–523.4 pg/ml) (p = 0.6), with no significant differences detected by linear mixed-effects modeling (F(2,41.1) = 1.67, p = 0.2). No difference was seen when comparing baseline plasma VEGF-A concentrations with VEGF-A levels at study discontinuation in patients who underwent either radiological PD or radiological/clinical progression (n = 8; p = 1 and p = 0.9, respectively). Baseline plasma VEGF-A concentrations were similar when compared among patients who achieved a PR to the investigational treatment (n = 4; median concentration: 249 pg/ml) and those who did not (n = 21; median concentration: 148 pg/ml; p = 0.97). Similarly, no significant differences were observed in baseline VEGF-A concentrations when comparing patients whose tumors showed any shrinkage (n = 14; median VEGF concentration: 304 pg/ml; 95% CI, 178–532 pg/ml) during treatment versus those whose tumors remained stable or increased in size (n = 11; median VEGF concentration: 115.6 pg/ml; 95% CI, 21–466 pg/ml) (p = 0.31). We then evaluated whether absolute changes in VEGF-A concentrations from best RECIST response to baseline (ΔVEGF-A) were associated with objective responses or tumor shrinkage. ΔVEGF-A levels appeared similar in patients who achieved a PR compared with those who did not (p = 0.2), as well as in patients who experienced tumor shrinkage versus those who did not (p = 0.34). When dichotomized according to their median values, baseline plasma VEGF-A concentrations did not predict PFS (p = 0.1). A significant association was instead seen between ΔVEGF-A concentrations (grouped using the median value as a threshold) and PFS (p = 0.004).

Health-related quality of life

Overall, health-related quality of life remained stable over time among patients who completed questionnaires (Supplementary Fig. 6). No over-time changes were seen in the remaining domains explored by QLQ-C30 and QLQ-GINET21.

Discussion

This phase 2 study evaluated the combination of cabozantinib and temozolomide in patients with advanced, progressive, well-differentiated NETs of GEP, pulmonary or unknown primary. The investigational treatment achieved an ORR of 15%, a CBR of 100% and a median PFS of 28.5 months. The median DoR was 19.5 months, and approximately one third of the enrolled patients derived a clinical benefit lasting >18 months. Although the primary endpoint of the trial (ORR > 50%) was not met, the long median PFS and the evidence of clinical benefit in all enrolled patients are in our opinion encouraging, particularly when weighted against the characteristics of the study population. Our cohort was indeed mostly composed of patients harboring multiple adverse prognostic features such as G2/G3 grading (76%), Ki-67 ≥10% (43%), >2 metastatic sites (81%), high baseline CgA levels (70%) and prior exposure to multiple lines of systemic anticancer treatment (median number of prior systemic treatment lines: 2, range 1–6; median time from diagnosis: 31 months). In addition, approximately one-third of the cohort consisted of small bowel or unknown primary NETs, entities known to undergo only marginal shrinkage under the pressure of temozolomide treatment.

Both TKIs and alkylating agents have an established place in the medical treatment of patients with NETs. At present, sunitinib is approved by both the FDA and the EMA for the treatment of pancreatic NETs based on the results of a phase 3 trial[6]. Cabozantinib has recently received regulatory approval for both pancreatic and extrapancreatic NETs by both the FDA and EMA[10]. Other TKIs including pazopanib[19], axitinib[20], lenvatinib[21], and surufatinib[22,23] have been evaluated in pancreatic and/or extrapancreatic NETs, but are not approved for treatment in the United States or Europe. With the exception of lenvatinib, which was found to be associated with an exceptionally high investigator-assessed ORR of 42% and 25% for pancreatic and

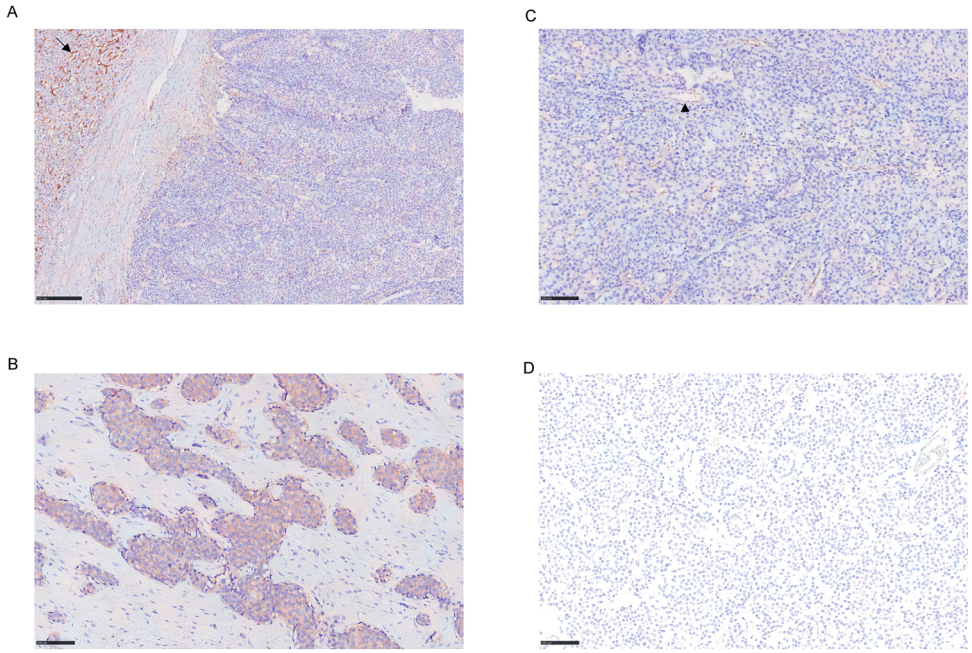

Fig. 5 | Immunohistochemical expression of AXL, VEGFR2 and c-MET in NET samples. Immunohistochemical staining was performed on samples from $n = 19$ independent tumors, and representative images illustrating recurrent staining patterns for AXL (**A**), VEGFR2 (**B**) and c-MET (**C**, positive; **D**, negative) are shown. The scale bar is 250 µm in (**A**), 100 µm in (**B**–**D**). Arrow: sinusoidal endothelial cells. Arrowhead: endothelial cells.

extrapancreatic NETs respectively[21], TKIs have shown thus far only marginal activity in terms of tumor shrinkage, with response rates <20% and <10% in pancreatic and extrapancreatic NETs respectively[6,10,19,20,22,23]. Temozolomide, alone or in combination with capecitabine, is currently considered a standard option in patients with advanced NETs, particularly of pancreatic origin. In phase 2, prospective ECOG-ACRIN E2211 trial[7], temozolomide monotherapy has been reported to induce responses in approximately 35% of patients with pancreatic NETs. However, response rates to temozolomide monotherapy are known to be inferior in extrapancreatic NETs, ranging from 4% in G1/G2 small intestine NETs[24] to 9–31% in lung NETs[25]. Non-conventional schedules of temozolomide have been recently investigated, and metronomic temozolomide has been associated with an ORR of 19% in a single-institution retrospective series of 26 patients with pancreatic or extrapancreatic, well or poorly differentiated neuroendocrine neoplasms (NENs)[26]. More recently, in a multicenter, single-arm, phase 2 study of 38 patients with poorly differentiated NENs, temozolomide one week on/one week off induced objective responses in 18% of the cohort and determined only mild toxicities[27], emerging as a possible candidate for combination therapies against NENs.

Metronomic alkylator therapy is known to exert anti-tumor effects not only through direct cytotoxicity, but also through sustained suppression of endothelial proliferation, reduction of circulating endothelial progenitor cells, and modulation of the immune microenvironment[14,15,28]. Antiangiogenic agents may in turn, normalize tumor vasculature, improve drug delivery, and thus enhance the activity of continuous, low-dose temozolomide[29]. Several clinical trials have investigated the activity and safety of metronomic temozolomide in combination with antiangiogenic drugs, including bevacizumab and thalidomide, in patients with advanced NENs[30–33]. Overall, these combination regimens yielded response rates ranging from 15% to 63%, with manageable toxicity profiles. As expected, chemosensitivity was greater in pancreatic NETs than in tumors arising from other primary sites.

Our study shows that combining cabozantinib with metronomic temozolomide fails to exert the expected synergistic activity in terms of tumor shrinkage, leading to an ORR of 15%, which appears comparable to that of cabozantinib or temozolomide in monotherapy. Specifically, the ORR observed across patients with panNETs in our study appears lower when compared with historical data[7] from conventional temozolomide dosing (200 mg/m^2 daily for 5 days every 28 days) in similar patient populations (ORR: 17% vs 34%, respectively), possibly reflecting differences in pharmacokinetics, cumulative dose intensity, or mechanisms of action of metronomic temozolomide. By producing more continuous, lower-peak alkylator exposure, metronomic temozolomide may indeed result in less overt cytoreduction, while potentially enhancing other clinically meaningful outcomes such as disease stabilization and duration of benefit, possibly through angiogenesis inhibition and immune modulation[14,15,28]. Consistent with this hypothesis, the proportion of patients globally benefitting from the investigational treatment in our trial (CBR: 100%) compares favorably to that observed in clinical trials of cabozantinib (CBR: 80% and 70% in pancreatic and extra-pancreatic NETs, respectively) or temozolomide alone (CBR: 74%)[7,10].

A delay in progression in the absence of radiographically defined tumor response is often observed in trials investigating active agents against NETs, and PFS is currently considered the standard efficacy endpoint in randomized studies of NET patients. The median PFS of 28.5 months (95% CI, 16.8–28.5 months) recorded in our study falls outside the upper confidence interval of the PFS seen in trials of cabozantinib and temozolomide monotherapies. Indeed, while cabozantinib was associated with a median PFS of 13.8 months (95% CI, 9.2–18.5 months) and 8.4 months (95% CI, 7.6–12.7 months) in pancreatic and extra-pancreatic NETs, respectively[7], temozolomide induced a median PFS of 15.1 months (95% CI, 10.5–21 months) in pancreatic NETs[10]. Although cross-trial comparisons should be drawn with caution, the magnitude of the PFS improvement seen in our study suggests that, although inactive in terms of objective responses, the combination of cabozantinib and metronomic temozolomide might exert synergistic activity in delaying progression in patients with pancreatic and extra-pancreatic NETs.

Several factors, including informative censoring[34] may have confounded our analysis of PFS, leading to an overestimation of the

treatment effect. Indeed, a relatively high rate of patients withdrew from the study prior to progression due to toxicity. This may explain the discrepancy between the PFS and the observed TTF of 16.8 months (95% CI, 5.2–22.2 months). However, informative censoring and its effects on survival outcomes have been observed in many positive trials in the NET field[35]. As TTF measures are not reported in trials of cabozantinib[10] or temozolomide[7], no inter-study comparisons can be performed. The lack of separate patient cohorts for pancreatic and extra-pancreatic NETs is another factor potentially confounding the PFS results observed in our study.

The toxicities arising in patients receiving the combination of cabozantinib and metronomic temozolomide were largely consistent with the known side effect profile of the two individual agents. No unanticipated or new toxicities related to study treatment were identified. Most frequent grade ≥3 toxicities included thrombocytopenia (11%), diarrhea (8%) and colitis (8%). The frequency of grade ≥3 thrombocytopenia and diarrhea compared similarly to that reported in previous trials of cabozantinib[10] or temozolomide monotherapies[7], whereas the rates of colitis appeared higher, possibly showing an additive effect of the two agents. A deeper understanding of the underlying pathogenesis of colitis development in patients treated with cabozantinib and temozolomide is needed to maximize the risk/benefit ratio associated with the drug combination. Overall, dose reductions and interruptions were more frequently required to manage adverse events associated with cabozantinib rather than temozolomide. The treatment discontinuation rates due to toxicities observed in our study were similar to those reported in previous studies of cabozantinib[10], but higher than those recorded in the ECOG-ACRIN E2211 trial for temozolomide alone[7]. It is conceivable that the dose and schedule of treatment could be further optimized so as to limit toxicity while preserving efficacy. No study drug-related deaths or second-primary cancers were recorded in our trial.

Several biomarkers were investigated in our study to identify predictors of clinical benefit from cabozantinib plus temozolomide. When assessed by methylation-specific PCR, MGMT deficiency was associated with improved tumor response ($p = 0.002$). Along these lines, MGMT deficiency, as defined by either low IHC or positive promoter methylation, was also significantly associated with longer PFS ($p = 0.03$). Our findings align with prior clinical evidence[7,36] and, despite the limitations imposed by the small sample size and the absence of a non-temozolomide-containing comparator arm, suggest that MGMT testing may have clinical relevance even in combination regimens. Whether MGMT promoter methylation should be preferred over IHC assessment remains a conundrum.

Among receptor tyrosine kinases primarily targeted by cabozantinib (AXL, VEGFR, and c-MET), only c-MET was expressed by NET cells in our study. In particular, the proportion of cases that tested positive for c-MET (29%) falls within the range of positivity (21–100%) observed in previous studies[37–39]. Notably, patients whose tumors expressed c-MET exhibited better ORR and PFS compared with those whose tumors tested negative for the biomarker. Future research is needed to validate this finding in appropriately powered patient cohorts. The uniform negativity of the VEGFR2 and AXL staining in tumor cells observed in our study stands in stark contrast with prior reports[19,40–42], which demonstrated expression of these biomarkers in approximately two-thirds of the investigated tumors. Differences in antibodies, antigen retrieval protocols, and detection systems, as well as the inherent heterogeneity of NET biology, can explain the discrepancy between our findings and the available literature, at least in part. Given the uniform expression of VEGFR2 and AXL in non-neoplastic microenvironment cells, the possibility that cabozantinib activity in NETs may rely on both tumor-intrinsic and off-tumor effects cannot be excluded.

Our study has several limitations. First, its non-randomized nature hinders direct comparisons of treatment outcomes with a standard arm. Second, the study sample size limits the statistical power to conduct exploratory analyses and identify subgroups of patients that may obtain a greater benefit with the investigational drug combination. This is of particular relevance for biomarker correlative analyses, whose results should be interpreted with caution. The wide 95% CIs surrounding estimates of association between biological and clinical variables reflect indeed considerable uncertainty around the true effect sizes. Third, heterogeneity in the location and grading of primary tumors adds another layer of complexity to data interpretation. Fourth, no MGMT testing was performed to preselect the patients most likely to derive a benefit from temozolomide. Nevertheless, this would have skewed the enrollment towards a patient population mostly comprised of pancreatic primaries. Lastly, response evaluation by the investigators rather than by an independent committee represents an additional limitation, introducing potential bias in the evaluation of treatment efficacy.

In conclusion, the combination of cabozantinib and metronomic temozolomide did not show synergistic activity in terms of tumor shrinkage in patients with advanced, progressive, pancreatic and extrapancreatic NETs. However, the proportion of patients benefitting from the treatment and the median PFS observed in our trial appear encouraging and justify larger, controlled studies to further investigate the added value of combining cabozantinib with metronomic temozolomide. Determining the magnitude of PFS improvement achievable with combination therapy compared with cabozantinib monotherapy in a phase 3 randomized setting appears of critical importance. Whether combining cabozantinib and temozolomide may result in superior survival outcomes as compared with sequencing strategies involving the two agents is unknown.

Methods

Ethics statement

This study was an open-label, single-arm, multicenter, phase 2 study of cabozantinib and temozolomide in patients with well-differentiated NETs of lung or GEP origin. The protocol (NCT04893785; available as Supplementary Note) was approved by the Ethics Committee at each participating center and was conducted in accordance with the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent prior to any study-related procedures. No compensation was provided to study participants.

Patient selection and eligibility

Subjects were eligible if they were adults (age ≥18 years) with metastatic well-differentiated (grade 1 to 3 per WHO 2019 and 2021 classifications[43,44]) NETs of lung, GEP or unknown primary origin. Patients were required to have evidence of radiologically documented progressive disease within 12 months of study entry. Any number of prior systemic treatments was allowed, and concurrent therapy with SSAs was permitted as long as patients remained on a stable dose for at least 2 months. Other key eligibility criteria were measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[45], Eastern Cooperative Oncology Group (ECOG) performance status ≤2, absolute neutrophil count ≥1500 cells/μl, platelets ≥ 100,000 cells/μl, haemoglobin ≥9 g/dl, total bilirubin ≤1.5 times the upper limit of normal (ULN), AST and ALT ≤ 2.5 times ULN (≤ 5 times ULN if liver metastases were present), creatinine clearance ≥60 mL/min (calculated using the Cockcroft-Gault formula). Key exclusion criteria included a history of uncontrolled congestive heart failure (NYHA II, III, IV), baseline prolongation of QTcF (>450 ms for males, >470 ms for females), concurrent systemic use of anticoagulants, platelet inhibitors, corticosteroids or immunosuppressive agents, presence of conditions increasing the risk of bleeding or bowel perforation (i.e., cavitating pulmonary lesions, endobronchial masses, lesions invading major blood vessels, active peptic ulcer disease, abdominal abscess or

fistula, inflammatory bowel disease, bowel obstruction/perforation, diverticulitis, pancreatitis, cholecystitis, cholangitis, evidence of serious non-healing wound or ulcer or bone fracture). Patients with HBV or HIV infection (active or not), as well as patients requiring dialysis or with uncontrolled thyroid dysfunction were also excluded. Patients with known brain metastases could be enrolled only if the brain disease had been stable for at least 3 months after radiotherapy and/or surgery. Neither sex nor gender were considered to design the study. Participant gender was recorded based on self-report.

Treatment and evaluation

Cycles were defined as 28-days (±3 days). Cabozantinib was orally administered at a dose of 40 mg once daily while temozolomide was administered at 100 mg/m^2/day 1 week on/1 week off. One dose reduction of cabozantinib (20 mg/day) and two dose reductions of temozolomide (75 mg/m^2 and 50 mg/m^2 in a stepwise fashion) were allowed in case of ≥grade 2 intolerable toxicities. Treatment interruptions for up to 14 days were permitted to allow resolution of study drug-related toxicities. Patients were eligible to continue monotherapy with cabozantinib should they experience unacceptable adverse events (AEs) requiring the discontinuation of temozolomide. The study treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent.

Baseline radiographic assessments of tumor burden (multiphasic CT or MRI scans) were completed within 28 days of initiation of study treatment and repeated every 8 weeks from start of treatment for the first 6 months, then every 12 weeks. The RECIST version 1.1 was used for the evaluation of tumor response. Toxicities were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Health-related quality of life was evaluated before the start of the treatment period and then monthly thereafter using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and QLQ-GINET21[46,47].

Sample size calculation

The primary endpoint of the trial was ORR. Secondary endpoints included PFS, OS, CBR, duration of response (DOR) per RECIST 1.1 as well as safety and tolerability of the combination in this patient population.

The sample size calculation was based on the assumption that a true ORR of >50% would generate interest in a larger randomized study, whereas a response rate of ≤25% would not yield any further interest in this drug combination for this disease. The sample size was chosen based on a one-sided α level of 10% and a power of 90%. Taking into account a 15% drop-out rate, a final sample size of 35 patients was determined for the study. According to this statistical design, the regimen would have been considered promising if ≥13 of 35 evaluable patients achieved an objective response. A 12-month follow-up period was planned.

Correlative biomarker assessments

Both tumor tissue and blood samples were collected to evaluate biological predictors of response to the investigational treatment. Immunohistochemistry (IHC) was used to evaluate the expression of MGMT, c-MET, AXL, and VEGFR2. Sections of 4 µm in thickness were cut from archival paraffin-embedded pathology specimens. For antigen retrieval, sections were subjected to pretreatment in an EDTA buffer pH 9 at high temperature. IHC was done using a Bond-III autostainer (Leica). Antibody clones, dilutions, and incubation times are detailed in Supplementary Table 1. In all cases, the reaction product was revealed with the diaminobenzidine (DAB) chromogen. Tumors without an internal control (i.e., positive staining on endothelial cells for MGMT and VEGFR2, inflammatory or sinusoidal endothelial cells for AXL, bile duct epithelium or alveolar macrophages for c-MET) were not evaluated. For MGMT, nuclear expression was assessed on whole slides as previously described[7]. Briefly, a score based on nuclear staining intensity (0–3) multiplied by the percentage of stained cells (0–100%) was used. This H-score[48] ranged from 0 (no staining in the tumor) to 300 (diffuse intense staining of the tumor). Scoring was performed independently by two pathologists (GI and JS). H-scores were grouped into three standard categories: category 1 = <50, category 2 = 51–100, category 3 = >100. Categories 1 and 2 were combined for downstream analysis as there were only 3 patients with category 2. A semi-quantitative, 4-tier scoring system (0 = no staining; 1 = weak; 2 = moderate; 3 = strong) was applied to evaluate the expression of c-MET, AXL, and VEGFR2 in tumor cells.

A methylation-specific PCR analysis was used to assess MGMT promoter methylation status, as previously described[49]. Briefly, DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue samples using the FFPE DNA Extraction Kit (Qiagen). After bisulfite conversion of the purified DNA using the EZ DNA Methylation Gold Kit (Zymo Research), two PCR reactions were performed using two specific primer pairs designed to amplify methylated and unmethylated regions of the MGMT promoter, respectively. PCR products were resolved on agarose gel electrophoresis and visualized under UV illumination. A tumor sample was considered positive for MGMT promoter methylation if an 80-bp band was detected in the methylated PCR reaction.

Plasma VEGF-A levels were measured using study samples collected at study entry, at the time of best response and study termination for all accrued patients. Samples were stored at −80 °C until analysis. VEGF-A concentrations were determined using the Human VEGF ELISA kit (Invitrogen, Cat. #KHG0111) following the manufacturer's instructions. Optical density was measured at 450 nm using an iMark microplate reader (Bio-Rad), and VEGF-A concentrations were calculated from a standard curve generated with known VEGF-A concentrations. All samples were assayed in duplicate, and the mean value was used for analysis.

Statistical analysis

Continuous variables were summarized using descriptive statistics. Frequency counts and the percentage of subjects within each category were provided for categorical data. The association between categorical variables was assessed using a two-sided Fisher's exact test. The Mann-Whitney U test or the Kruskal-Wallis test with Dunn's post hoc test were used to evaluate inter-group differences for non-normally distributed data, as appropriate. ORs were calculated for comparisons of interest; the Haldane–Anscombe correction was applied when needed to permit stable estimation. Differences between paired measurements were assessed using the Wilcoxon matched-pairs signed-rank test. Longitudinal changes across timepoints were assessed using a linear mixed-effects model with time as a fixed effect and subject as a random intercept to account for repeated measurements. The Kaplan-Meier method was used to estimate all time-to-event functions. PFS was calculated from the date of first study treatment until the date of first progressive disease or death due to any cause. Time to treatment failure (TTF) was defined as the time from administration of the initial dose of the investigational treatment until study discontinuation for any reason. OS was defined as the time from start of treatment until death as a result of any cause, with patients censored at the date of last follow-up if still alive. ORR was defined as the percentage of patients who achieved a complete (CR) or partial response (PR) throughout the study period. CBR was defined as the percentage of patients achieving CR, PR or stable disease (SD). DOR was defined as the time elapsed from the date of the first documentation of an objective response (CR or PR) to the date of progressive disease (PD). Per protocol, efficacy analyses were conducted on all patients who received ≥1 cycle of the investigational treatment and underwent a post-treatment assessment of response. Safety was based on the assessment of AEs, clinical laboratory test results, vital signs, and physical examinations. Subgroup analyses were performed to explore potential signs of differential activity by the most relevant clinical-pathological features.

However, the study was not powered for formal comparisons, and findings were considered exploratory in nature. Variables assessed in univariate subgroup analyses included the following: age, gender, primary tumor site, grade, ECOG performance status at study entry, baseline Chromogranin-A (CgA) levels. Multivariable regression models utilizing a stepwise approach assessed the same variables to analyze their potential relationship with efficacy endpoints. Exact 95% confidence intervals (CIs) were calculated for each proportion of interest. All tests were two-sided and statistical significance was declared at $p < 0.05$. No data were excluded from the analyses. The investigators were not blinded to treatment allocation during the study and outcome assessment. Statistical analysis was performed using MedCalc statistical software 12.7 (MedCalc Software bvba, Ostend, Belgium) and Jamovi version 2.3.28 (The Jamovi Project, retrieved from https://www.jamovi.org, Sydney, Australia).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The study protocol is available as Supplementary Note in the Supplementary Information file. The clinical raw data are protected and are not available due to data privacy laws. The data that support the findings of this study are available from the corresponding author (Salvatore Tafuto; s.tafuto@istitutotumori.na.it) upon reasonable request (equivalent purposes to those for which the patients grant their consent to use the data). Data sharing requests will be considered on a case-by-case basis in a timely manner. Response to access requests will be provided within 4 weeks and data will be available for 6 months once access has been granted. Data will be provided anonymized, with no personal identifiable data. Source data of all figures are provided with this paper. Source data are provided with this paper.

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Author contributions

S.T. and D.V.S.G. were responsible for the study design and coordination. M.C. and E.L. drafted the manuscript. All authors (M.C., G.D.V.S., O.C., E.L., A.B., G.B., P.D., L.C., C.P., A.R., N.C., R.D.M., A.D.M., A.P., J.S., M.B., G.I., F.P, P.P, F.G., C.P., and S.T.) made substantial contributions to data acquisition, interpretation of study results, critical manuscript revision for important intellectual content, provided approval to the final version to be published and agreed to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Competing interests

Prof. Cives has performed a consultation for Ipsen. Prof. Badalamenti has performed a consultation for Ipsen and has received speaker's fees from Ipsen. Prof. Porta has performed consultations for Ipsen and Exelixis and has received speaker's fees from Exelixis. Dr. Tafuto has received grants or consulting fees from Ipsen. All remaining authors have declared no conflicts of interest.

Additional information

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