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RESEARCH

Cabozantinib for advanced grade 3 neuroendocrine tumors: subgroup analysis of the phase 3 CABINET trial (Alliance A021602)

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Abstract

Well-differentiated grade 3 neuroendocrine tumors (NETs) have recently been described as a distinct category, and randomized data regarding efficacy of therapy for these patients are scarce. In the phase 3 CABINET trial, cabozantinib improved PFS compared with placebo in patients with advanced, previously treated, progressive extra-pancreatic NETs (epNETs) and pancreatic NETs (pNETs) of all grades. Here, we evaluate if these results remain consistent in a subgroup of patients with well-differentiated G3 NETs. Patients with locally advanced or metastatic epNETs or pNETs were randomized 2:1 in independent cohorts to receive cabozantinib 60 mg daily vs placebo. We analyzed outcomes of the subset of patients with G3 NETs (Ki-67 > 20%), combining patients in the pNET and epNET cohorts due to small sample sizes. Twenty-four patients had G3 NETs, 16 randomized to cabozantinib and 8 to placebo. Primary sites included pancreas (n = 12), GI tract (n = 7), unknown primary sites (n = 3), and lung/thymus (n = 2). Median PFS for patients with G3 NETs treated with cabozantinib was 7.9 vs 3 months with placebo (HR = 0.15, 95% CI: 0.04–0.57, 1-sided log-rank P = 0.0034). The confirmed overall radiographic response rate was 25% (4/16) with cabozantinib vs 0% (0/8) with placebo. Safety outcomes were consistent with published data for the trial as a whole. Subset analysis of the CABINET trial showed improved PFS associated with cabozantinib vs placebo for G3 NETs of pancreatic and extra-pancreatic origin. Despite limited numbers, these results suggest that cabozantinib can be an effective option for patients with advanced G3 NETs.

ClinicalTrials.gov Identifier: NCT03375320.

Keywords: cabozantinib; grade 3 neuroendocrine tumor; pancreatic neuroendocrine tumor; extra-pancreatic neuroendocrine tumor

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Introduction

Well-differentiated high-grade (grade 3) gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are a recently defined category, characterized by well-differentiated morphology and high-proliferative activity (mitotic rate > 20 per 2 mm^2 and/or Ki-67 index >20%) (1). Biologically, G3 NETs are similar to lower-grade NETs and distinct from poorly differentiated neuroendocrine carcinomas (NECs) in terms of mutational patterns and somatostatin receptor expression (2). The pancreas is the most common primary site for well-differentiated G3 NETs.

Thoracic NETs consist of lung and thymic primaries that are still categorized by World Health Organization (WHO) classifications as typical carcinoid (mitotic rate < 2) or atypical carcinoid (mitotic rate 2–10) (3). Similar to GEP-NETs, well-differentiated high-grade lung and thymic NETs have been described as morphologically well-differentiated and biologically similar to typical or atypical carcinoid tumor (4). These malignancies are distinct from poorly differentiated small cell or large cell thoracic NECs. Although not clearly defined in the pathology literature, these tumors can also be characterized as well-differentiated, G3 NETs.

The optimal treatment strategies for well-differentiated G3 NETs have not been well studied. Published phase 3 data on somatostatin analogs at standard doses have been confined to tumors with Ki-67 < 10% (5), and retrospective series suggest that median progression-free survival (PFS) is relatively short in G3 NETs when treated with octreotide or lanreotide (6). Data on targeted therapies, such as everolimus or sunitinib, are also primarily restricted to G1 and G2 NETs. In one retrospective series of pancreatic NET patients treated in Japan, 6 out of 10 patients with G3 tumors treated with the tyrosine kinase inhibitor (TKI) sunitinib achieved an objective radiographic response (ORR) (7). The phase 2 EVINEC trial of second-line everolimus enrolled 39 patients with various high-grade neuroendocrine neoplasms and included 13 patients with G3 NETs. The median PFS was 5.2 months in this subpopulation (8).

More robust data support the use of cytotoxic chemotherapy for G3 NETs, particularly in early lines of therapy (9, 10). A large retrospective study of NET patients treated with capecitabine and temozolomide included 38 patients with G3 NETs, primarily with pancreatic primary. The median PFS was 28 months, and ORR was 42% (11). A multicenter retrospective study included 64 patients with well-differentiated G3 GEP-NETs treated with temozolomide-based regimens, primarily capecitabine and temozolomide. ORR was 41% in this population (12). Other retrospective studies have demonstrated high response rates using temozolomide-based chemotherapy. Intravenous cytotoxic regimens, such as 5-fluorouracil plus oxaliplatin (FOLFOX), have demonstrated activity in well-differentiated G3 NETs, primarily originating in the pancreas (9, 13, 14). Platinum and etoposide combinations commonly used in poorly differentiated NECs are associated with relatively low response rates (2).

Peptide receptor radionuclide therapy (PRRT) has also demonstrated activity in patients with somatostatin-receptor expressing G3 GEP-NETs. Retrospective series of PRRT beyond first line have reported an ORR of approximately 30–40% and median PFS durations of approximately 12–16 months (15, 16). The phase 3 NETTER-2 trial randomized 226 patients with higher G2 and G3 NETs (Ki-67 10–55%) to receive ^{177}Lutetium(Lu)-Dotatate plus octreotide versus high-dose octreotide in the first-line setting (17). The trial met its primary endpoint with an improvement in median PFS from 9 to 23 months. Among 79 patients with G3 tumors (primarily pancreatic primary), the median PFS improved from 5.6 to 22.2 months (hazard ratio (HR) 0.27; 95% confidence interval (CI) 0.15–0.49). ORR was 48% with ^{177}Lu-Dotatate plus octreotide in the G3 population (16).

The NETTER-2 trial offers the only prospective, randomized data with a defined category of well-differentiated G3 NETs, indicating that ^{177}Lu-Dotatate is an appropriate therapy option in patients newly diagnosed with metastatic disease. While improvements have been shown in the upfront setting for these patients, prospective randomized studies enrolling these patients with progressive tumors are lacking.

The Alliance for Clinical Trials in Oncology double-blinded phase 3 CABINET trial (A021602, NCT00375320) randomized 298 patients with progressive well-differentiated NETs (grades 1–3) after at least one prior line of therapy (not including somatostatin analog) to receive cabozantinib or placebo (18). The trial enrolled patients in two separate cohorts, pancreatic (p) NETs and extra-pancreatic (ep) NETs, which consisted of gastrointestinal, lung thymic, and unknown primaries. Each participant signed an IRB-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines. To assess the role of cabozantinib for the treatment of well-differentiated G3 NETs, we performed an analysis of both cohorts, individually and combined.

Methods

Patients with locally advanced or metastatic epNETs (203 patients) or pNETs (95 patients) were randomized 2:1 in independent cohorts to receive cabozantinib 60 mg daily versus placebo. The protocol was approved by the National Cancer Institute (NCI) Central Institutional Review Board. The primary endpoint was PFS. This was defined as time from randomization to radiographic progression according to RECIST 1.1 (19)

(determined by blinded independent central review, BICR) or death and was evaluated by intent-to-treat analysis. Patients were scanned every 12 weeks. Key secondary endpoints included ORR and safety. Confirmed radiographic response was defined as two consecutive scans showing complete or partial response per RECIST 1.1. The severity of adverse events was graded according to the NCI Common Terminology Criteria for Adverse Events version 5.0 (20). A protocol amendment early during the course of the trial allowed for crossover from placebo to cabozantinib upon central confirmation of progression. A detailed methodology of the CABINET trial has been previously described (18). The data-cutoff date was August 24, 2023.

We analyzed outcomes of the subset of patients with G3 NETs (Ki-67 > 20%), combining patients in the pNET and epNET cohorts as the primary analysis due to small sample sizes. The median PFS (based on BICR) and the corresponding 95% CIs by arm were estimated using Kaplan–Meier methods. HRs along with the corresponding 95% CIs comparing cabozantinib versus placebo were calculated from Cox proportional hazards regression models. A one-sided *P*-value from a stratified log-rank test was also computed, with stratification by cohort, with a *P*-value lower than 0.05 considered significant. ORR was computed and compared between arms utilizing a Fisher's exact test. Similar methods were applied looking at the trends for PFS and ORR between cohorts (pNETs vs epNETs). OS was not analyzed due to the endpoint still maturing.

Data collection and statistical analysis were conducted by the Alliance Statistics and Data Management Center. Data quality was ensured by review of data by the Alliance Statistics and Data Management Center and by the study chairperson following Alliance policies.

Results

Of the 298 patients randomized between October 2018 and August 2023 across both cohorts of the CABINET trial, 24 patients (8.1%) had G3 NETs (arm A (cabozantinib): 16; arm B (placebo): 8). In the G3 NET cohort, there were an equal number of pNET and epNET patients (*n* = 12 each). The subset of epNET patients included 2 ileal, 2 rectal, 1 duodenal, 1 gastric, 1 lung, 1 thymic, 1 small intestine, and 3 unknown primaries. Median Ki-67% was similar in the cabozantinib and placebo groups (33 and 30%, respectively). Patients were heavily pretreated with the majority in both arms of the study having received at least 4 lines of prior treatment. The baseline patient characteristics are summarized in Table 1.

Similar to the effects observed in the overall cohort, G3 NET patients treated with cabozantinib had significantly better PFS compared to those treated with placebo (HR = 0.15, 95% CI: 0.04–0.57; *P* = 0.0034; Fig. 1). The median PFS for patients with G3 NETs treated with cabozantinib was 7.9 months (95% CI: 5.6-not estimable (NE)) vs 3.0 months (1.5-NE) with placebo. The confirmed ORR was 25% (4/16) with cabozantinib vs 0% (0/8) with placebo (Fisher's exact *P* = 0.26; Fig. 2). Safety outcomes were consistent with published data for the trial as a whole (Table 2).

Table 1 Baseline demographic and clinical characteristics of patients with grade 3 NETs enrolled in the extra-pancreatic and pancreatic NET cohorts of the CABINET trial.

	Cabozantinib (*n* = 16)	Placebo (*n* = 8)
Age, years, median (range)	63 (38–80)	67 (47–82)
Female, *n* (%)	7 (44)	3 (38)
ECOG PS 0/1, %	56/44	50/50
Primary tumor site, *n* (%)		
Pancreas	9 (56)	3 (38)
Gastrointestinal tract	3 (19)	4 (50)
Unknown	3 (19)	0 (0)
Lung or thymus	1 (6)	1 (13)
Ki-67%, median (range)	33 (15–56)	30 (23–40)
Functional tumor, %	19	13
Concurrent SSA, %	56	50
Prior systemic therapies, *n* (%)		
SSA	15 (94)	7 (88)
Temozolomide + capecitabine	13 (81)	6 (75)
^{177}Lu-Dotatate	11 (69)	5 (63)
Everolimus	11 (69)	6 (75)
5-Fluorouracil + oxaliplatin	4 (25)	2 (25)
Sunitinib	3 (19)	1 (13)

Although numbers were limited, the benefit of cabozantinib in the G3 population was observed predominantly in the subset with pNETs, where the median PFS for those treated with cabozantinib was 13.5 months (95% CI: 7.6-NE) vs only 1.5 months for those in the placebo arm (*P* = 0.0004). In the subset of G3 epNET patients, the differences were attenuated with median PFS of 6.5 months (95% CI: 3.0-NE) with cabozantinib vs 4.2 months (95% CI 3.0-NE) with placebo (*P* = 0.15). For the 4 confirmed responses observed in the overall G3 NET group treated with cabozantinib, 3 were in the pNET subgroup and 1 was in the epNET subgroup.

Discussion

High-level data on treatment for well-differentiated G3 NETs are scarce, especially in patients with progressive disease after front-line treatment. Results from the phase 3 NETTER-2 study indicate that ^{177}Lu-Dotatate plus octreotide improves outcomes when administered in the first-line metastatic setting; however, approval by the European Medicines Agency (EMA) remains restricted to grade 1 and grade 2 tumors (21). To our knowledge, the CABINET trial is the only other published

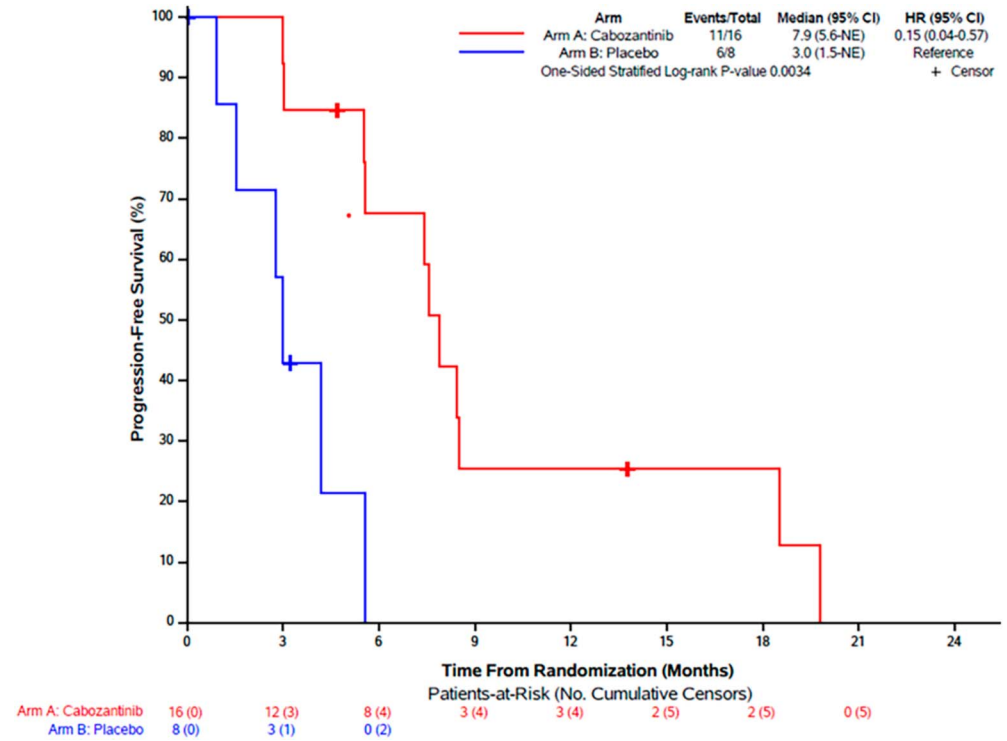

Figure 1

PFS: cabozantinib versus placebo. A full color version of this figure is available at https://doi.org/10.1530/ERC-25-0415.

randomized study that allowed for analysis of a G3 NET cohort since older randomized trials predated modern pathological classifications and routine use of Ki-67 for grading.

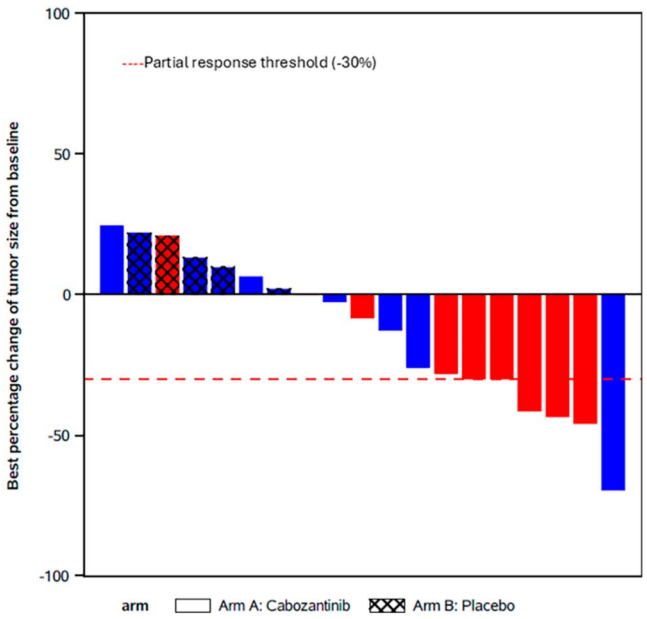

Figure 2

Waterfall plot illustrating best radiographic response of 19 evaluable patients: pNET patients (red) on cabozantinib (solid box) or placebo (checkered box). epNET patients (blue) on cabozantinib (solid box) or placebo (checkered box). A full color version of this figure is available at https://doi.org/10.1530/ERC-25-0415.

Our analysis indicates that cabozantinib is active in this specific NET population and is associated with a statistically significant improvement in PFS, the standard endpoint for assessment of efficacy in the field of neuroendocrine tumors. Activity compared to placebo was observed predominantly in the pNET cohort, which seemed to drive the differential in these clinical outcomes between the treatment arms. However, given the very limited numbers of patients in the pNET and epNET subsets (12 patients each), it is uncertain whether primary site is a true predictive factor.

This post hoc analysis of a small trial subgroup has several important limitations. Because analysis of G3 NETs was not pre-specified in the statistical analysis plan, the findings should be considered exploratory and hypothesis-generating rather than confirmatory. The small sample size further limits the statistical power of the analysis and increases the risk of type I (false-positive) error, potentially overestimating the benefit of cabozantinib in this population.

Despite these limitations, cabozantinib can be considered a preferred option over other TKIs and everolimus in the G3 NET population. For somatostatin receptor-positive tumors, ^{177}Lu-Dotatate remains a standard early-line option based on the outcomes of the NETTER 2 study. Cytotoxic regimens, such as capecitabine and temozolomide, are also considered active based on robust retrospective data and may be selected for more aggressive presentations. Results from the ongoing phase 3 COMPOSE trial (NCT 04919226) will provide additional

Table 2 Treatment-related adverse events.

	Cabozantinib (*n* = 16)		Placebo (*n* = 7)	
	Any grade	Grade 3	Any grade	Grade 3
	Number of patients (%)			
Palmar-plantar erythrodysesthesia	11 (69)	2 (13)	0	0
Diarrhea	10 (63)	2 (13)	0	0
Fatigue	10 (63)	2 (13)	0	0
AST increase	9 (56)	0	1 (14)	0
ALT increase	9 (56)	0	1 (14)	0
Hypertension	8 (50)	3 (19)	3 (42)	0
Thrombocytopenia	8 (50)	0	0	0
Oral mucositis	7 (44)	2 (13)	2 (29)	0
Dysgeusia	6 (38)	0	0	0
Anorexia	5 (31)	1 (6)	0	0
Hypothyroidism	5 (31)	0	0	0
Nausea	5 (31)	0	0	0
Neutropenia	5 (31)	0	0	0
Maculopapular rash	4 (25)	0	1 (14)	0
Anemia	4 (25)	0	0	0
Weight loss	4 (25)	1 (6)	0	0
Leukopenia	4 (25)	0	0	0
Hair color changes	4 (25)	0	0	0
Lymphopenia	3 (19)	0	1 (14)	0
Creatinine increase	3 (19)	0	0	0
Hypomagnesemia	3 (19)	0	0	0
Hypophosphatemia	3 (19)	0	0	0
Hypoxia	2 (13)	2 (13)	0	0

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.
The safety population included all patients who underwent randomization and received at least one dose of study treatment. Shown are adverse events across all grades reported in 15% or more patients in the cabozantinib group with an attribution of being at least possibly related to study treatment and grade 3 treatment-related adverse events that were reported in at least 2 patients in the cabozantinib group. No patients experienced grade 4 or 5 treatment-related adverse events.

prospective evidence regarding the efficacy of PRRT with ^{177}Lu-edotreotide compared with cytotoxic chemotherapy or everolimus.

Conclusions

Subset analysis of the CABINET trial demonstrated improved PFS associated with cabozantinib versus placebo for well-differentiated G3 gastroenteropancreatic and thoracic NETs, consistent with the results for the overall study. Despite limited numbers, these subset results suggest that cabozantinib can be an effective option for patients with advanced G3 NETs.

Declaration of interest

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Author contribution statement

Strosberg and Chan conceived the study. Strosberg, Zemla, Geyer, Pulsipher, Ou, and Chan analyzed the data. Strosberg and Chan wrote the original draft of the manuscript. Strosberg, Zemla, Geyer, Pulsipher, Ou, Behr, Raj, Vijayvergia, Dasari, O'Reilly, Meyerhardt, Wolin, Halfdanason, and Chan reviewed and edited the manuscript.

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