

Supplementary Appendix

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Supplementary Table 1: Results of Interim Analyses of Progression-free Survival

Cohort	N (Cabozantinib and Placebo groups)	Number of events	Hazard Ratio for Progression-free Survival (95% CI)	p-value
Extra-pancreatic NET				
2 nd Interim Analysis of PFS by Investigator Assessment ^a	175	109	0.41 (0.27-0.62)	<0.001
PFS by Available Blinded Independent Central Review ^b	200	81	0.47 (0.29-0.78)	<0.001
Pancreatic NET				
1 st Interim Analysis of PFS by Investigator Assessment ^c	82	50	0.25 (0.12-0.49)	<0.001
PFS by Available Blinded Independent Central Review ^b	95	37	0.26 (0.12-0.57)	<0.001

Abbreviations: NET, Neuroendocrine Tumor; PFS, Progression-free survival; CI, confidence interval

^a Data cutoff date for 109 events by investigator assessment: December 13, 2022

^b Data cutoff date for DSMB interim analysis report: July 18, 2023

^c Data cutoff date for 50 events by investigator assessment: December 2, 2022

The table summarizes the results of interim analyses that were requested and reviewed by the Alliance Data and Safety Monitoring Board. Interim analyses of PFS per RECIST 1.1 criteria by investigator review were conducted after 109 events had occurred in the extra-pancreatic NET cohort (66% of the projected total number of events) and after 50 events had occurred in the pancreatic NET cohort (33% of the projected total number of events). In addition, PFS was assessed in both cohorts using the available blinded independent central radiology review results.

Supplementary Table 2A: Baseline demographic and clinical characteristics of all patients enrolled in the extra-pancreatic NET cohort

	Cabozantinib (n=134)	Placebo (n=69)
Time from diagnosis to randomization, months, median (range)	65 (10-489)	76 (13-340)
Age, years, median (range)	66 (28-86)	66 (30-82)
Race, n (%)		
Asian	3 (2)	1 (1)
Black or African American	9 (7)	7 (10)
White	115 (86)	55 (80)
Unknown	5 (4)	2 (3)
Not reported	2 (1)	4 (6)
Ethnicity, n (%)		
Hispanic or Latino	8 (6)	9 (13)
Not Hispanic or Latino	125 (93)	56 (81)
Unknown	1 (1)	3 (4)
Not reported	0 (0)	1 (1)
Sex, n (%)		
Female	74 (55)	31 (45)
Male	60 (44)	38 (55)
ECOG PS, n (%)		
0	49 (37)	32 (46)
1	84 (63)	36 (52)
2	1 (1)	1 (1)
Primary tumor site, n (%)*		
Gastrointestinal	70 (52)	46 (67)
Midgut ^a	59 (44)	34 (49)
Non-midgut ^b	11 (8)	12 (17)
Lung	27 (20)	12 (17)
Thymus	6 (5)	4 (6)
Unknown	22 (16)	2 (3)
Other ^c	5 (4)	2 (3)
Pancreas	4 (3)	3 (4)
Tumor differentiation, n (%)		
Well differentiated	118 (88)	61 (88)
Moderately differentiated	6 (5)	5 (7)
Not specified	10 (8)	3 (4)
Tumor grade, n (%)		
Grade 1	37 (28)	15 (22)
Grade 2	86 (64)	48 (70)
Grade 3	8 (6)	5 (7)
Unknown	3 (2)	1 (1)
Functional (hormone syndrome) status, n (%)		
Functional tumor	41 (31)	25 (36)
Non-functional tumor	75 (56)	34 (49)
Unknown	18 (13)	10 (15)
Sites of metastatic disease, n (%)		
Liver	119 (89)	63 (91)
Lymph nodes	92 (69)	50 (72)
Bone	67 (50)	33 (48)
Lungs	30 (22)	13 (19)
Abdominal wall	10 (7)	6 (9)
CNS/brain	4 (3)	3 (4)
Other ^d	48 (36)	23 (33)
Concurrent SSA, n (%)	92 (69)	48 (70)
Prior SSA n (%)	125 (93)	64 (93)

Number of prior systemic therapies, median (range)	2 (1-6)	2 (1-6)
Prior systemic therapy, n (%)		
Lu-177 dotatate	80 (60)	41 (59)
Everolimus	96 (72)	44 (64)
Temozolomide +/- Capecitabine	43 (32)	20 (29)
Cisplatin or carboplatin + etoposide	11 (8)	8 (12)
Prior locoregional therapy, n (%)	45 (34)	29 (42)
Prior surgery for metastatic site, n (%)	43 (32)	17 (25)
Prior radiation for metastatic site, n (%)	30 (22)	12 (17)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status

*The intent-to-treat cohort includes 7 patients with pancreatic neuroendocrine tumors who were misallocated to the extra-pancreatic neuroendocrine tumor cohort by the registering site.

^a Midgut primary sites: jejunum, ileum, appendix, cecum, small intestine not otherwise specified, midgut not otherwise specified

^b Non-midgut gastrointestinal primary sites: stomach, duodenum, ampullary, biliary tract, non-cecum colon, rectum

^c Other primary sites: presacral (n=3), kidney (n=2), larynx (n=1), ethmoid sinus (n=1)

[§]Common other metastatic sites included mesentery, peritoneum, omentum, ovary, pancreas, breast, adrenal gland.

Supplementary Table 2B: Baseline demographic and clinical characteristics of all patients enrolled in the pancreatic NET cohort

	Cabozantinib (n=64)	Placebo (n=31)
Time from diagnosis to randomization, months, median (range)	71 (18-213)	73 (18-230)
Age, years, median (range)	60 (29-79)	64 (39-79)
Race, n (%)		
American Indian/Alaskan Native	1 (2)	0 (0)
Asian	4 (6)	0 (0)
Black or African American	3 (5)	3 (10)
More than one race reported	1 (2)	0 (0)
Native Hawaiian/Pacific Islander	1 (2)	0 (0)
White	54 (84)	25 (81)
Unknown	0 (0)	1 (3)
Not reported	0 (0)	2 (6)
Ethnicity, n (%)		
Hispanic or Latino	2 (3)	2 (6)
Not Hispanic or Latino	61 (95)	26 (84)
Unknown	0 (0)	1 (3)
Not reported	1 (2)	2 (6)
Sex, n (%)		
Female	27 (42)	13 (42)
Male	37 (58)	18 (58)
ECOG PS, n (%)		
0	35 (55)	15 (48)
1	28 (44)	16 (52)
2	1 (2)	0
Primary site, n (%)*		
Pancreas	62 (97)	30 (97)
Ileum	1 (2)	0
Cecum	0	1 (3)
Stomach	1 (2)	0
Tumor differentiation, n (%)		
Well differentiated	59 (92)	30 (97)
Moderately differentiated	4 (6)	0
Not specified	1 (2)	1 (3)
Tumor grade, n (%)		
Grade 1	14 (22)	7 (23)
Grade 2	39 (61)	19 (61)
Grade 3	8 (13)	3 (10)
Unknown	3 (5)	2 (7)
Functional (hormone syndrome) status, n (%)		
Functional	11 (17)	5 (16)
Nonfunctional	48 (75)	22 (71)
Unknown	5 (8)	4 (13)
Sites of metastatic disease, n (%)		
Liver	63 (98)	29 (94)
Lymph nodes	29 (45)	17 (55)
Bone	19 (30)	7 (23)
Lungs	3 (5)	2 (6)
Abdominal wall	3 (5)	2 (6)
Other [§]	9 (14)	4 (13)
Concurrent SSA, n (%)	35 (55)	17 (55)
Prior SSA, n (%)	63 (98)	30 (97)

Number of prior systemic therapies, median (range)	3 (1-9)	2 (1-7)
Prior systemic therapy, n (%)		
Lu-177 dotatate	38 (59)	18 (58)
Everolimus	51 (80)	25 (81)
Sunitinib	18 (28)	7 (23)
Temozolomide +/- capecitabine	43 (67)	16 (52)
Prior locoregional therapy, n (%)	36 (56)	10 (32)
Prior surgery for metastatic site, n (%)	18 (29)	7 (24)
Prior radiation for metastatic site, n (%)	6 (10)	4 (14)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status

*The intent-to-treat cohort includes 3 patients with extra-pancreatic neuroendocrine tumors who were misallocated to the pancreatic neuroendocrine tumor cohort by the registering site.

§ Common other metastatic sites included peritoneum, ovary, spleen.

Supplementary Table 3: Background Information Regarding Patients with Neuroendocrine Tumors and Representativeness of Study Participants

Category	
Disease, problem, or condition under investigation	Advanced neuroendocrine tumors
Special considerations related to:	
Sex	Neuroendocrine tumors affect men and women equally (ratio of 1:1).
Age	The age at diagnosis of patients with neuroendocrine tumors has a wide range with median age at diagnosis of approximately 60 years. There is an increase in distant disease with advancing age.
Race or ethnic group	Most patients with neuroendocrine tumors in the United States according to population-based studies are White (~80%). Other races include Black (~15%), Asian/Pacific Islander (~5%), American Indian/Alaskan Native (<1%). Approximately 10% of patients are Hispanic.
Other considerations	Primary sites of disease for patients diagnosed with neuroendocrine tumors in the United States include lung (~25%), gastrointestinal tract (~50%), pancreas (~10%), other rare sites including thymus.

Overall representativeness of this trial	Information regarding patient birth date, sex, race and ethnicity were reported by investigators at the time of study enrollment. Patients enrolled in the CABINET trial are representative of patients with advanced neuroendocrine tumors in the United States. The breakdowns of age, sex, race, ethnicity, and primary tumor site of study participants are comparable to the general population of patients with NET in the United States. There is some heterogeneity in these factors worldwide, particularly with respect to the most prevalent primary tumor site in different regions. However, common primary sites of disease worldwide also include the gastrointestinal tract, pancreas, and lung.
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Sources:

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Supplementary Table 4: Subsequent Anti-cancer Therapy Received by Patients Enrolled in the Extra-pancreatic NET Cohort

	Cabozantinib (N=111)	Placebo (N=60)
	N (%)	N (%)
Crossover to cabozantinib	NA	20 (33)
Cytotoxic chemotherapy	15 (14)	6 (10)
Peptide receptor radionuclide therapy	13 (12)	3 (5)
Anti-VEGFR TKI	5 (5)	4 (7)
Everolimus	1 (1)	2 (3)
Radiation	4 (4)	0
Liver-directed therapy	3 (3)	4 (7)
Other	9 (8)	1 (2)
No additional therapy	61 (55)	20 (33)

The table lists the first anti-cancer treatment received by patients after discontinuing blinded study therapy. Twenty patients in the placebo group crossed over to receive cabozantinib on protocol after confirmation of progressive disease while receiving blinded therapy. Two patients in the cabozantinib group continued cabozantinib after stopping blinded therapy, and one patient in the placebo arm received cabozantinib off-protocol. Twenty-one patients in the cabozantinib group and seven patients in the placebo group were still receiving blinded therapy at the time of the study unblinding and data cutoff date. Additionally, two patients in the cabozantinib arm and two patients in the placebo arm never began blinded therapy.

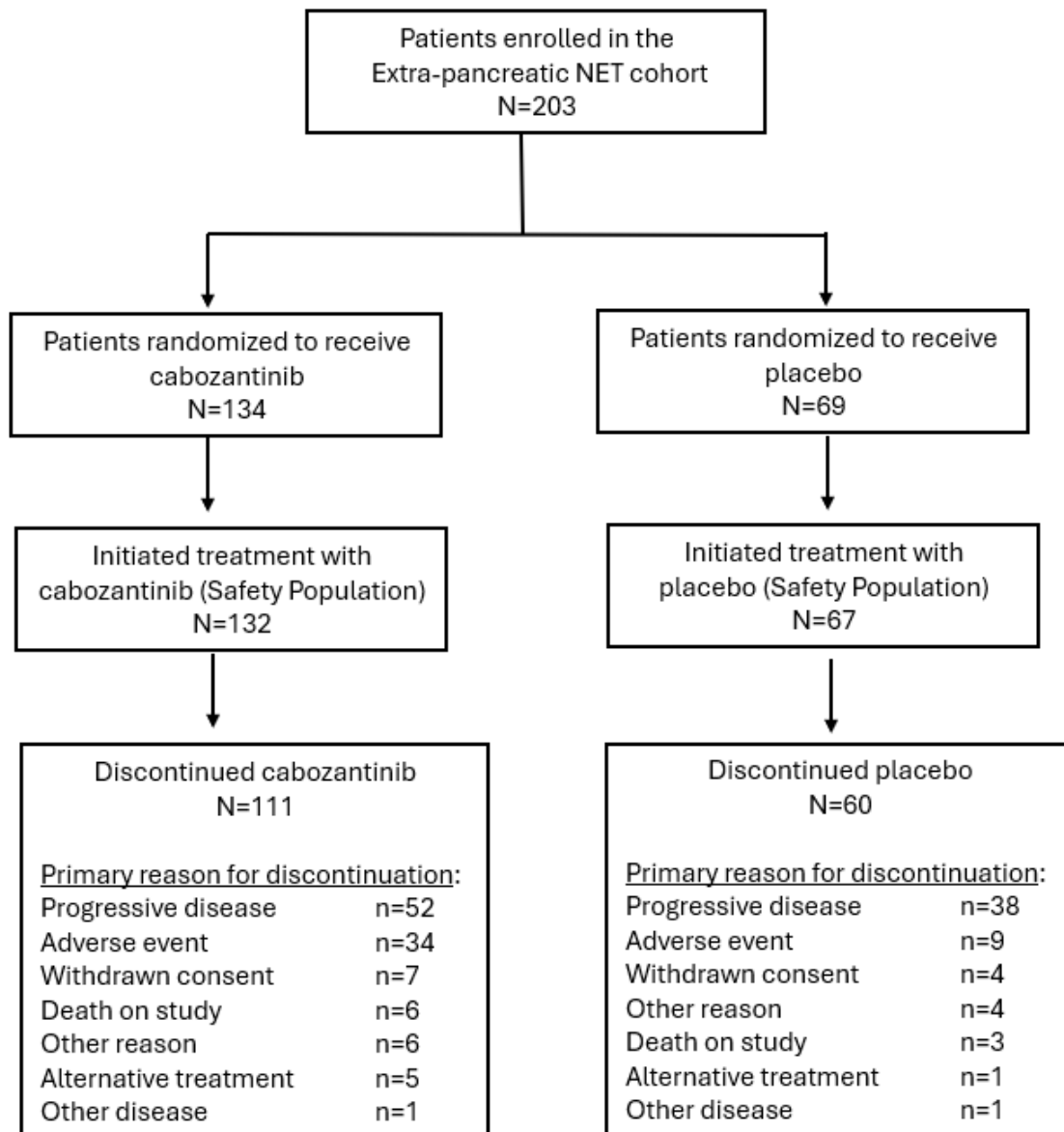
Supplementary Table 5: Subsequent Anti-cancer Therapy Received by Patients Enrolled in the Pancreatic NET Cohort

	Cabozantinib (N=49)	Placebo (N=29)
	N (%)	N (%)
Crossover to cabozantinib	NA	12 (41)
Cytotoxic chemotherapy	10 (20)	0
Peptide receptor radionuclide therapy	6 (12)	2 (7)
Anti-VEGFR TKI	4 (8)	3 (10)
Liver-directed therapy	2 (4)	0
Radiation	1 (2)	0
Other	2 (4)	1 (3)
No additional therapy	24 (49)	11 (38)

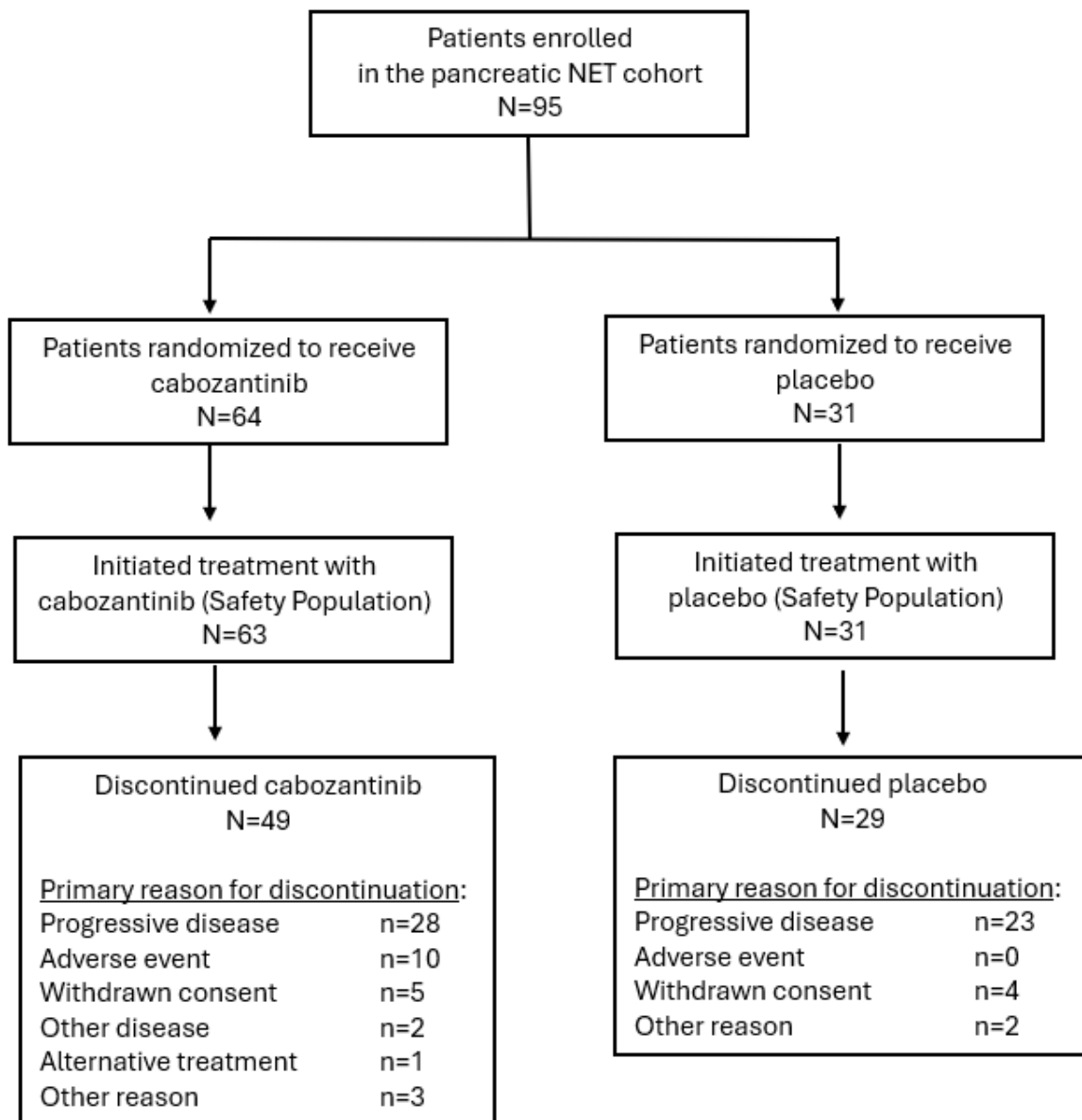
Abbreviations: VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor

The table lists the first anti-cancer treatment received by patients after discontinuing blinded study therapy. Twelve patients in the placebo group crossed over to receive cabozantinib on protocol after confirmation of progressive disease while receiving blinded therapy. Two patients in the cabozantinib group continued cabozantinib after stopping blinded therapy, and one patient in the placebo arm received cabozantinib off-protocol. Fourteen patients in the cabozantinib group and two patients in the placebo group were still receiving blinded therapy at the time of the study unblinding and data cutoff date. Additionally, one patient in the cabozantinib arm never began blinded therapy.

Supplementary Figure 1A: Enrollment, Randomization, and Disposition of Patients Enrolled in the Extra-pancreatic NET Cohort



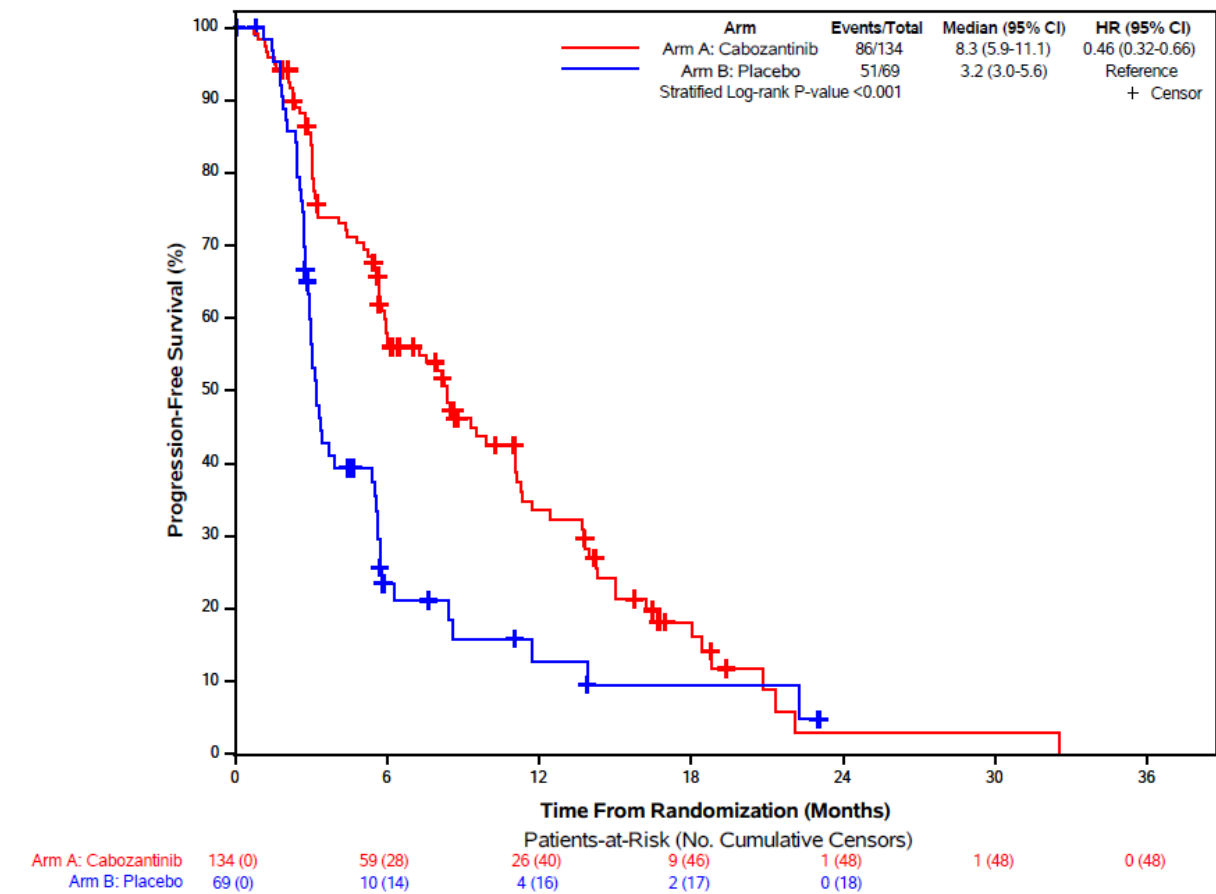
Supplementary Figure 1B: Enrollment, Randomization, and Disposition of Patients Enrolled in Pancreatic NET Cohort



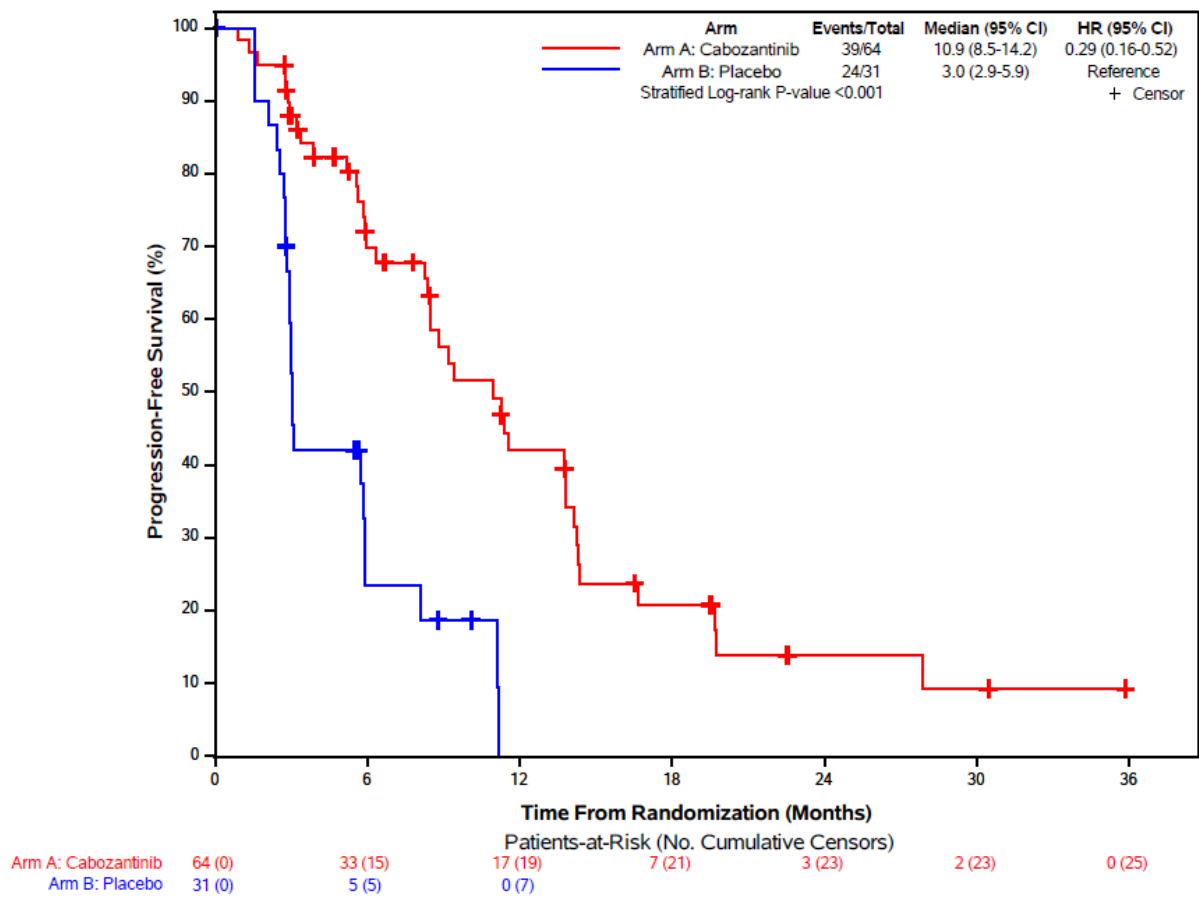
Supplementary Figure 2. Progression-free Survival by Investigator Review per RECIST 1.1 Criteria

Panel A demonstrates the results of progression-free survival (PFS), as assessed per RECIST 1.1 criteria by investigator review, for patients enrolled in the epNET cohort. **Panel B** demonstrates the results of PFS, as assessed by RECIST 1.1 criteria by investigator review, for patients enrolled in the pNET cohort. For the comparison between treatment groups in both cohorts, two-sided stratified log-rank P-value <0.001.

Supplementary Figure 2A



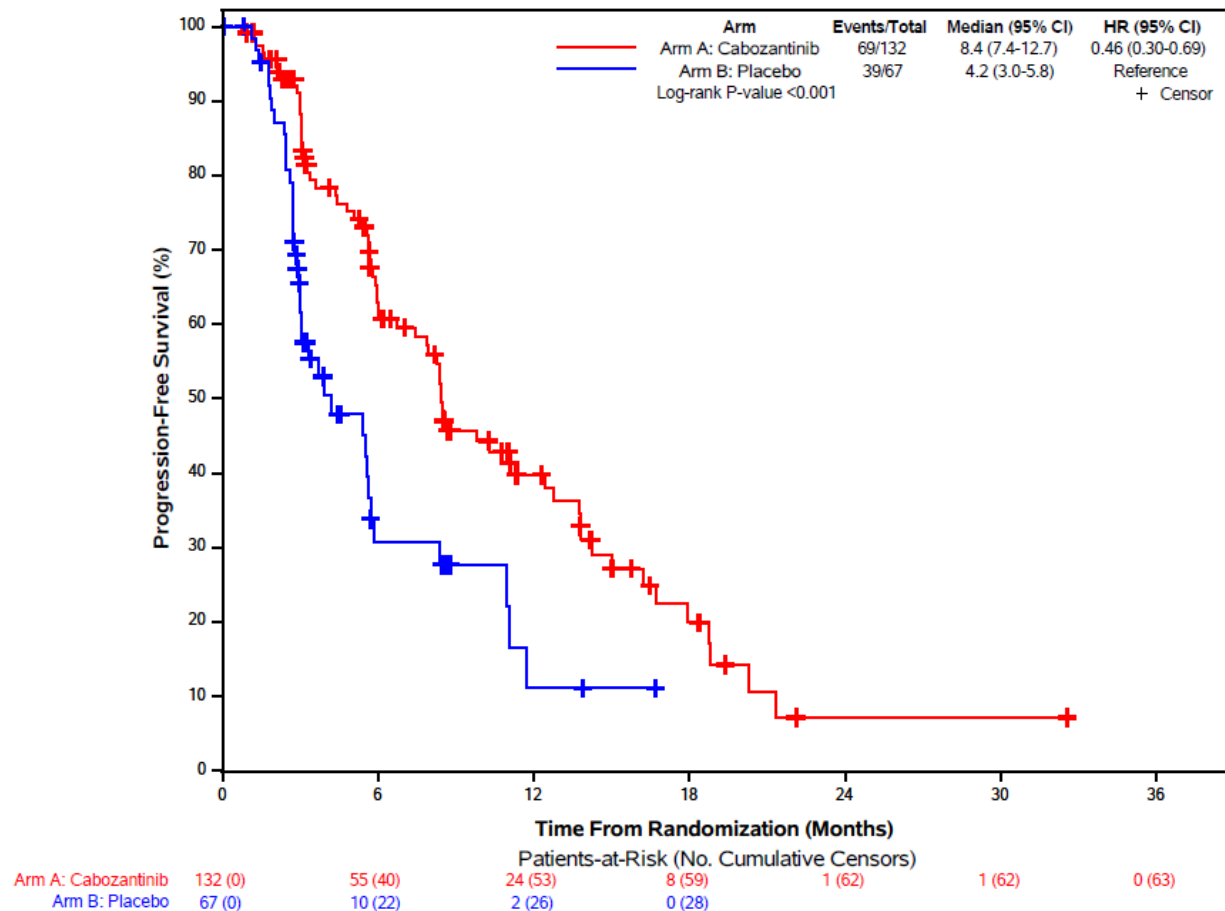
Supplementary Figure 2B



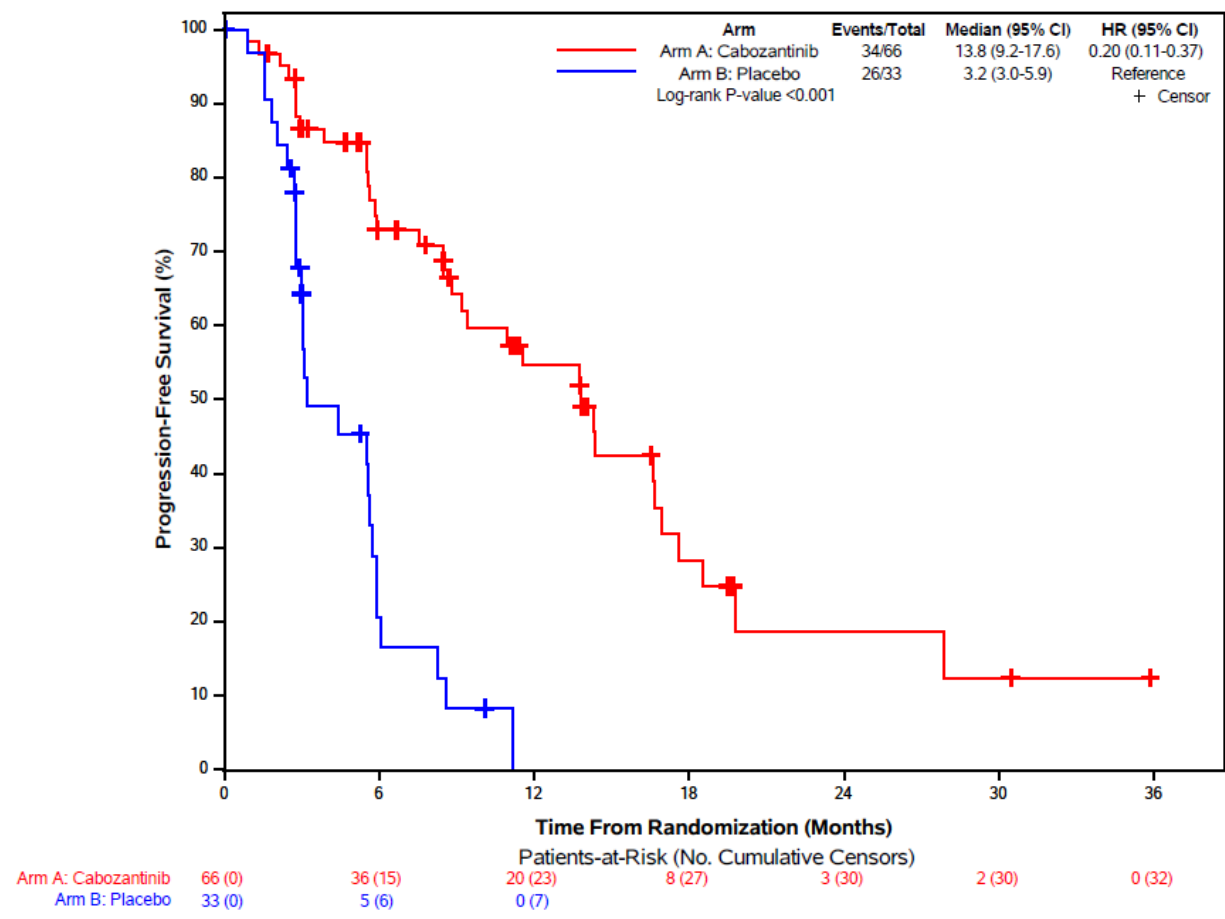
Supplementary Figure 3. Progression-free Survival by Blinded Independent Central Review Accounting for Cohort Misallocation

During the registration process, 7 patients with pancreatic NET were misallocated to the extra-pancreatic NET cohort and 3 patients with extra-pancreatic NET were misallocated to the pancreatic NET cohort by the registering site. Sensitivity analyses for progression-free survival (PFS) were conducted to account for misallocation of patients into the incorrect disease cohort. **Panel A** demonstrates the results of PFS, as assessed by blinded independent central review (BICR) per RECIST 1.1 criteria, for patients with a diagnosis of extra-pancreatic NET. **Panel B** demonstrates the results of PFS, as assessed by BICR per RECIST 1.1 criteria, for patients with a diagnosis of pancreatic NET. For the comparison between treatment groups in both cohorts, two-sided log-rank P-value <0.001.

Supplementary Figure 3A



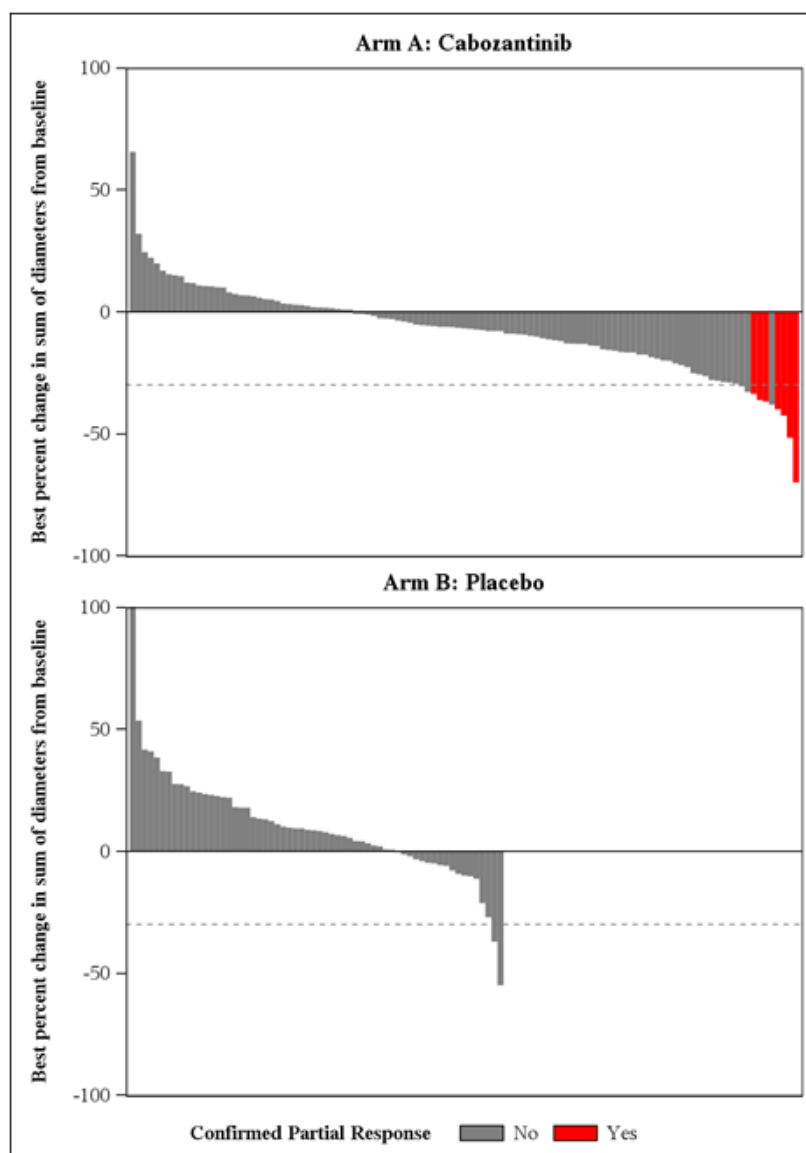
Supplementary Figure 3B



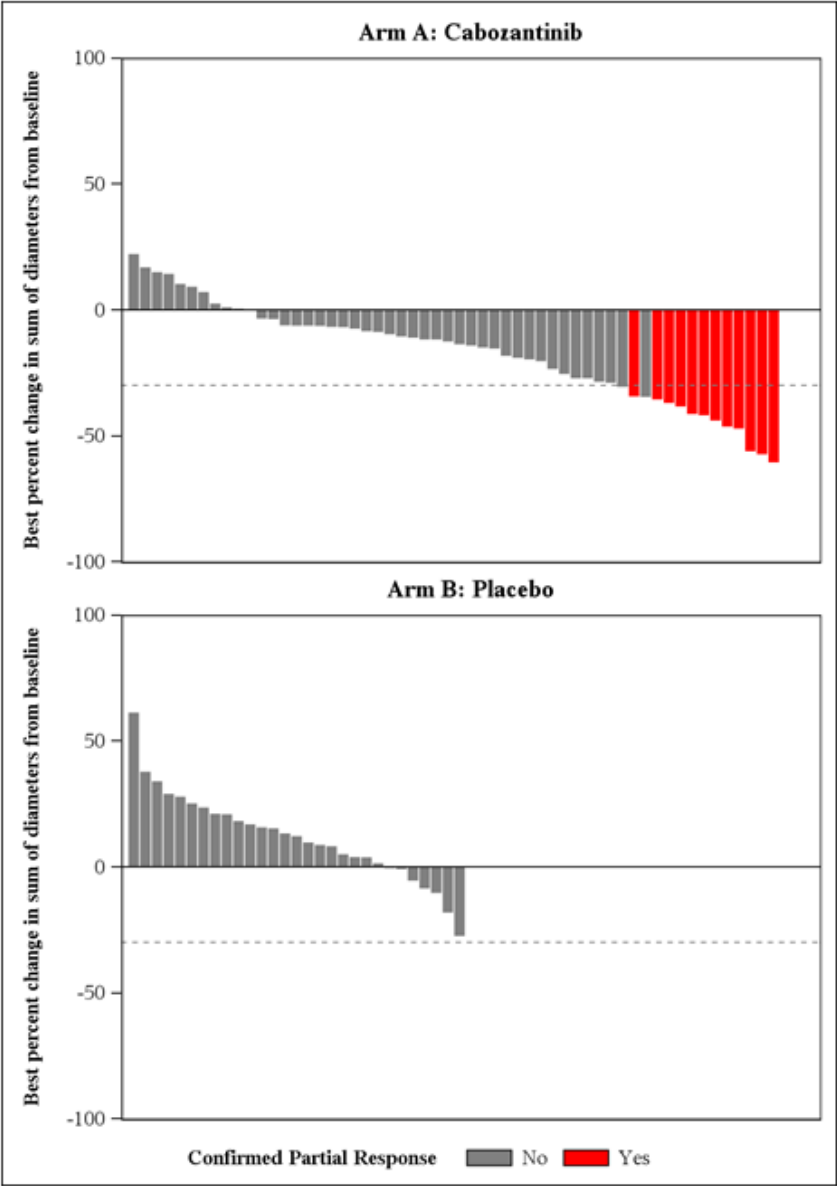
Supplementary Figure 4. Radiographic Response by Blinded Independent Central Review

The waterfall plots show the best percentage decrease from baseline in the sum of diameters of the target lesions in patients randomized to treatment with cabozantinib or placebo in the extra-pancreatic NET cohort (**Panel A**) and pancreatic NET cohort (**Panel B**). Each bar represents one patient who had at least one restaging scan. The horizontal dashed lines indicate a 30% reduction in sum of the diameters of the target lesions compared with baseline. In the epNET cohort, any reduction in target lesions was observed for 67% (74/111) and 29% (18/62) of the cabozantinib and placebo groups, respectively. In the pNET cohort, any reduction in target lesions was observed for 80% (45/56) and 24% (7/29) of the cabozantinib and placebo groups, respectively.

Supplementary Figure 4A



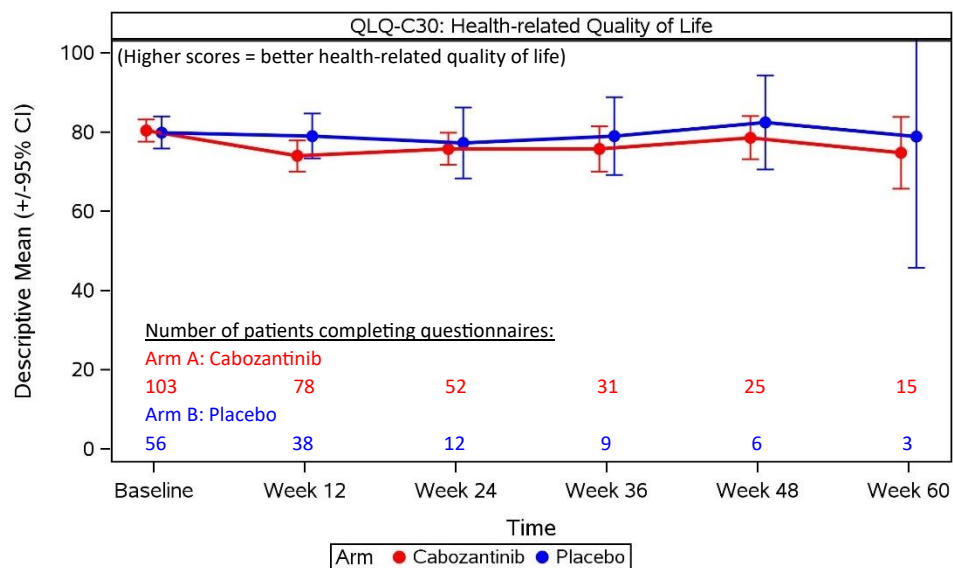
Supplementary Figure 4B



Supplementary Figure 5: Mean Health-Related Quality of Life Summary Scores and 95% Confidence Intervals by EORTC QLQ-C30

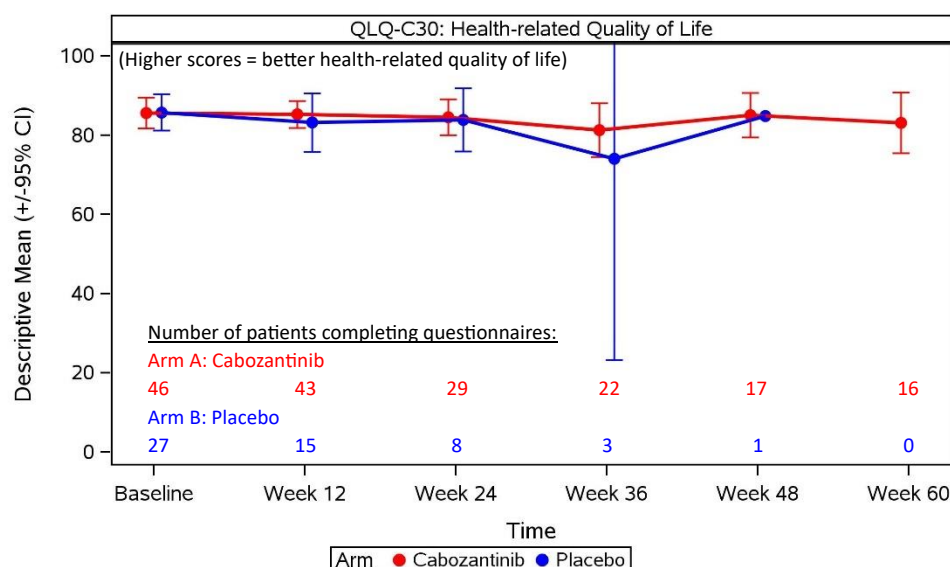
The figures demonstrate mean health-related quality of life summary scores and 95% confidence intervals by EORTC QLQ-C30 by treatment group and by time in the extra-pancreatic NET cohort (**Panel A**) and pancreatic NET cohort (**Panel B**). The number of patients in each treatment group who completed the questionnaire at each time point is also shown.

Supplementary Figure 5A



CI = confidence interval

Supplementary Figure 5B



CI = confidence interval

Additional health-related quality of life correlative study methods: The A021602-HO1 correlative study assessed health-related quality of life and disease-related symptoms in patients with extra-pancreatic and pancreatic NET tumors treated with cabozantinib versus placebo. For patients who consented to participate in this optional correlative study, patients completed the EORTC QLQ-C30 and EORTC QLQ-GINET21 questionnaires prior to treatment and every 12 weeks until disease progression or the start of a new anticancer therapy. Patient-reported treatment-related toxicities were also captured in the main body of the protocol using the National Cancer Institute's Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) prior to treatment and once per cycle. Finally, patients completed two LASA items assessing overall quality of life and fatigue (two items found to be important baseline measures and prognostic indicators) prior to treatment, and a Patient Global Impression of Change (PGIC) item at time points after starting treatment to facilitate analyses to estimate meaningful change.

Patients completed questionnaires on paper during planned clinic visits and prior to any discussion of their status with healthcare personnel. For assessments after cessation of protocol-treatment but prior to disease progression or the start of a new anticancer therapy, a member of the site study staff could administer the booklet over the phone if no clinic visit is available for in-person completion. EORTC QLQ-C30, GINET21, and PGIC were available in English; baseline LASA items and PRO-CTCAE were available in English and Spanish. The main endpoint of this correlative study was the health-related quality of life summary score of the EORTC QLQ-C30 measured after treatment initiation and before disease progression or start of

new anticancer therapy. Results of this correlative will be fully reported in a separate publication. Additional details of this study can be found in Section 14.1 of the protocol.