A021602

Randomized, Double-Blinded Phase III Study of CABozantinib Versus Placebo IN Patients With Advanced NEuroendocrine Tumors After Progression on Prior Therapy (CABINET)

ClinicalTrials.gov Identifier: NCT03375320

Study Background

Trial Description

This phase III trial studies cabozantinib to see how well it works compared with placebo in treating patients with neuroendocrine or carcinoid tumors that may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body (advanced). Cabozantinib is a chemotherapy drug known as a tyrosine kinase inhibitor, and it targets specific tyrosine kinase receptors, that when blocked, may slow tumor growth.

Arms:

Arm I (cabozantinib S-malate): (Experimental): Patients receive cabozantinib Smalate PO QD on days 1-28 of each cycle. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. Patients also undergo CT, MRI, and/or x-ray imaging during screening and on study.

Arm II (placebo): (Placebo Comparator): Patients receive placebo PO QD on days 128 of each cycle. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. Patients also undergo CT, MRI, and/or x-ray imaging during screening and on study. A protocol amendment activated in November 2020 permitted patients who were receiving placebo to cross over to open-label cabozantinib after real-time central confirmation of progressive disease.

Objectives:

PRIMARY OBJECTIVES:

I. To determine whether cabozantinib S-malate (cabozantinib) can significantly improve progression-free survival (PFS) compared to placebo in patients with advanced pancreatic neuroendocrine tumors (NET) whose disease has progressed after prior therapy.

II. To determine whether cabozantinib can significantly improve progression-free survival (PFS) compared to placebo in patients with advanced carcinoid tumors

whose disease has progressed after prior therapy. SECONDARY OBJECTIVES: I. To determine whether cabozantinib can significantly improve overall survival (OS) compared to placebo in patients with advanced pancreatic NET whose disease has progressed after prior therapy.

III. To determine whether cabozantinib can significantly improve overall survival (OS) compared to placebo in patients with advanced carcinoid tumors whose disease has progressed after prior therapy.

IV. To evaluate safety and tolerability of cabozantinib versus placebo in patients with advanced pancreatic NET using Common Terminology Criteria for Adverse Events (CTCAE) and Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

V. To evaluate safety and tolerability of cabozantinib versus placebo in patients with advanced carcinoid tumors using CTCAE and PRO-CTCAE. V. To evaluate the overall radiographic response rate of cabozantinib versus placebo in patients with advanced pancreatic NET whose disease has progressed after prior therapy.

VI. To evaluate the overall radiographic response rate of cabozantinib versus placebo in patients with advanced carcinoid tumors whose disease has progressed after prior therapy.

OTHER OBJECTIVE:

I. Results of the primary analysis will be examined for consistency, while considering the stratification factors and/or covariates of baseline quality of life (QOL) and fatigue.

QUALITY OF LIFE SUBSTUDY OBJECTIVE:

I. To compare overall quality of life, disease-related symptoms, and other domains between the two treatment groups (cabozantinib versus [vs.] placebo) within each cohort of patients (pancreatic NET vs. carcinoid tumor). (Quality of Life Substudy Objective - A021602-HO1)

POPULATION PHARMACOKINETICS SUBSTUDY OBJECTIVE:

I. To describe the population pharmacokinetic and exposure-response relationships of cabozantinib in patients with advanced neuroendocrine tumors. (Population Pharmacokinetics Substudy Objective - A021602-PP1)

OUTLINE: Patients are randomized to 1 of 2 arms.

ARM I: Patients receive cabozantinib S-malate orally (PO) once daily (QD) on days 128 of each cycle. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. Patients also undergo computed tomography (CT), magnetic resonance imaging (MRI), and/or x-ray imaging during screening and on study.

ARM II: Patients receive placebo PO QD on days 1-28 of each cycle.

Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. Patients also undergo CT, MRI, and/or x-ray imaging during screening and

on study. A protocol amendment activated in November 2020 permitted patients who were receiving placebo to cross over to open-label cabozantinib after real-time central confirmation of progressive disease. After completion of study treatment, patients are followed up every 12 weeks until disease progression or start of new anticancer therapy, and then every 6 months until 8 years after registration.

Study Milestones:

Start date: October 26, 2018

Primary Completion Date: August 23, 2023

Publication Information:

Analysis Type: Primary

PubMed ID: 39282913

Citation: Chan, Jennifer A et al. Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors. The New England journal of medicine, 10.1056/NEJMoa2403991. 16 Sep. 2024, doi:10.1056/NEJMoa2403991

Associated Datasets: NCT03375320-D1-Dataset.csv (pt_chars), NCT03375320-D2 Dataset.csv (txct), NCT03375320-D3-Dataset.csv (hrql), NCT03375320-D4-Dataset.csv (pfs_interim)

Dataset Information:

Dataset Name: NCT03375320-D1-Dataset.csv (pt_chars)

Description: Dataset NCT03375320-D1-Dataset.csv (pt_chars) is one of 4 datasets associated with PubMed ID 39282913. This dataset contains data presented in all tables and figures, excluding AE tables, health-related quality of life, and interim analysis.

Data can be used to approximate published study findings, but exact reproduction of previous manuscripts may not be possible in some cases (e.g., when data must be modified for de-identification purposes or have undergone further data cleaning).

Blank values indicate data not applicable or missing, except where otherwise noted.

NCT03375320-D1-Dataset.csv (pt_chars) Data Dictionary:

LABEL	NAME	ELEMENTS	COMMENTS
Data Center ID	SUBJECT		
Concurrent Somatostatin Analog Use	cc_sa	No | Yes	
Prior Sunitinib Therapy (OPEN)	pri_suni	No | Yes	Stratification factor for Pancreatic NET population.
Tumor Type (Intent to Treat)	tutype	Extra-Pancreatic NET | Pancreatic NET	
Tumor Type (Accounts for Cohort Misallocation)	gf_tutyp	Extra-Pancreatic NET | Pancreatic NET	
Sex	sex	Female | Male	
Ethnicity	ethnicity	Hispanic or Latino | Not Hispanic or Latino | Not reported | Unknown	
Race	race	Asian | Black or African American | Not Reported | Other | Unknown | White	

LABEL	NAME	ELEMENTS	COMMENTS
Functional (hormone secretion) status	hormf	Functional tumor | Nonfunctional tumor | Unknown	
Primary Site (OPEN)	site_trim	Midgut | Non-mi	
Tumor grade	TUGRADE	Grade 1 | Grade 2 | Grade 3 | Unknown	
Histologic differentiation	HISTGRADE	Moderately differentiated | Not specified | Well differentiated	
Prior locoregional therapy (for this tumor)	TULRT	1=Yes | 2=No	
Prior somatostatin analog use	SA	1=Yes | 2=No	
ECOG Performance Status	ECOGPSBSL	0 | 1 | 2	
End of Treatment Reason	endinitrsn	2=Patient Withdrawal/Refusal After Beginning Protocol Therapy | 3=Adverse Event | 4=Disease Progression Relapse During Active Treatment | 5=Alternative Therapy | 6=Patient Off Treatment For Other Complicating Disease | 7=Death On Study | 8=Other | 24=Patient Withdrawal/Refusal Prior to Beginning Protocol Therapy	
Arm Name	arm	A=Arm A: Cabozantinib | B=Arm B: Placebo	

LABEL	NAME	ELEMENTS	COMMENTS
Age (Years)	age		
Time from Diagnosis to Randomization (Months)	diag_to_random		
Number of lines of prior therapy	count_lines_prisystx	1 | 2 | 3 | 4 | 5 | 6 | 7 | 9	
Primary Site	psite_manu	Cecum | Ethmoid Sinus | GI (Midgut) | GI (Non-Midgut) | Ileum| Kidney | Larynx | Lung | Pancreas | Presacral | Stomach | Thymus | Unknown	
Metastatic Site - Nodal	METSITENOD	1=Yes | 2=No	
Metastatic Site - Liver	METSITELIV	1=Yes | 2=No	
Metastatic Site - Abdominal Wall	METSITEABD	1=Yes | 2=No	
Metastatic Site - Bone	METSITEBONE	1=Yes | 2=No	
Metastatic Site - CNS/Brain	METSITEBRAIN	1=Yes | 2=No	
Metastatic Site - Lung	METSITELUNG	1=Yes | 2=No	
Metastatic Site - Other	METSITEOTH	1=Yes | 2=No	

LABEL	NAME	ELEMENTS	COMMENTS
Prior surgery for metastatic site	METRESECT	No | Yes	
Prior radiation for metastatic site	METRA	1=Yes | 2=No	
Dose Reduction	reduction	No | Yes	
Initiated Treatment	safe	0=No | 1=Yes	
Prior Everolimus therapy	ever_rec	N=No | Y=Yes	
Prior Sunitinib Therapy (Rave)	suni_rec	N=No | Y=Yes	Derived from the On-Study: Prior Systemic Therapy form.
Prior Temozolomide +/- Cape. therapy	tmz_rec	N=No | Y=Yes	
Prior Lu-177 dotatate therapy	lu177_rec	N=No | Y=Yes	
Prior Cisplatin or Carboplatin + Etoposide	cis_carbo_rec	N=No | Y=Yes	
First Non-Protocol Treatment	first_nptx_grp	1=Crossover to cabozantinib | 2=Cytotoxic Chemotherapy | 3=Peptide receptor radionucleotide therapy |	

LABEL	NAME	ELEMENTS	COMMENTS
		4=Anti-VEGFR TKI | 5=Everolimus | 6=Radiation | 7=Liver-directed therapy | 8=Other | 9=No additional therapy	
IROC PFS Status	pfs_stat_iroc	0=Censor | 1=Event	Central Review. IROC = Imaging and Radiation Oncology Core
IROC PFS Time (Days)	pfs_time_iroc		Central Review.
Min Change from BSL (BICR)	min_p_chg_bsl		
Overall Survival Status	fu_stat_nocut	0=Censor | 1=Event	
Overall Survival Time (Days)	fu_time_nocut		
Local PFS Status	pfs_stat0	0=Censor | 1=Event	
Local PFS Time (Days)	pfs_time0		
Best Overall Response (BICR)	best_response_confirmed	PR | SD | PD	
Average Daily Dose (mg)	ave_daily_dose		
Treatment Duration (Months)	tx_months		