

FAST FACTS

A021602 - RANDOMIZED, DOUBLE-BLINDED PHASE III STUDY OF CABOZANTINIB VERSUS PLACEBO IN PATIENTS WITH ADVANCED NEUROENDOCRINE TUMORS AFTER PROGRESSION ON PRIOR THERAPY (CABINET)

Registration Eligibility Criteria (Step 1)

1. Documentation of Disease
 - a. Histologic Documentation: Well- or moderately-differentiated neuroendocrine tumors of pancreatic and non-pancreatic (i.e. carcinoid) origin by local pathology.
The pathology report must state ONE of the following: 1) well- or moderately-differentiated neuroendocrine tumor, 2) low- or intermediate-grade neuroendocrine tumor, or 3) carcinoid tumor or atypical carcinoid tumor.
Documentation of histology from a primary or metastatic site is allowed.
Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma without specification of differentiation status, adenocarcinoid tumor, or goblet cell carcinoid tumor are not eligible. Patients with *well-differentiated* grade 3 neuroendocrine tumor are eligible.
 - b. Stage: Locally advanced/unresectable or metastatic disease.
 - c. Tumor Site: Histological documentation of neuroendocrine tumor of pancreatic, gastrointestinal (GI), lung, thymus, other, or unknown primary site. GI, lung, thymus, other, and unknown primary NETs will enroll in the carcinoid tumor cohort of the study.
Functional (i.e. associated with symptoms or a clinical syndrome related to hormone secretion by tumor) or nonfunctional tumors are allowed.
 - d. Radiologic Evaluation: Target lesions must have shown evidence of disease progression by RECIST v1.1 criteria in the 12 months prior to registration. The radiologic images, imaging reports, and clinic notes indicating growth of existing lesions, development of new lesions, or treatment changes must be submitted per [Section 6.1.1](#).
2. Measurable Disease
 - a. Patients must have measurable disease per RECIST 1.1 by computer tomography (CT) scan or magnetic resonance imaging (MRI) (see Section 11.0).
Lesions must be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 1 cm with CT or MRI (or ≥ 1.5 cm for lymph nodes). Non-measurable disease includes disease smaller than these dimensions or lesions considered truly non-measurable including: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung. See Section 11.0 for additional details.
3. Prior Treatment
 - a. Patient must have experienced disease progression after receiving or intolerance leading to treatment discontinuation of at least one FDA-approved line of therapy (except somatostatin analogs). Prior lines of therapy must include one of the following: everolimus, sunitinib, or lutetium Lu 177 dotatate in patients with pancreatic NET; everolimus in patients with lung NET; everolimus or lutetium Lu 177 dotatate in patients with gastrointestinal NET.
Prior treatment (except somatostatin analogs) with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, and/or radiation must be completed at least 28 days prior to registration.
Prior treatment with somatostatin analogs is allowed, and continuation of treatment with somatostatin analogs while on cabozantinib/placebo is allowed provided that the patient has been on a stable dose for at least two months.

Prior systemic treatment with radionuclide therapy must be completed at least 6 weeks prior to registration.

Prior treatment with hepatic artery embolization (including bland embolization, chemoembolization, and selective internal radiation therapy) or ablative therapies is allowed if measurable disease remains outside of the treated area or if there is documented disease progression in a treated site. Prior liver-directed or other ablative treatment must be completed at least 28 days prior to registration.

Prior treatment with cabozantinib is not allowed.

Patients should have resolution of any toxic effects of prior therapy (except alopecia and fatigue) to NCI CTCAE, version 5.0, grade 1 or less.

Patients must have completed any major surgery at least 12 weeks prior to registration and any minor surgery (including uncomplicated tooth extractions) at least 28 days prior to registration. Complete wound healing from major surgery must have occurred at least 28 days prior to registration, and complete wound healing from minor surgery must have occurred at least 10 days prior to registration.

4. Patient History

- a. No class III or IV CHF within 6 months of registration.

No clinically significant cardiac arrhythmia within 6 months of registration.

No unstable angina or MI within 6 months of registration.

No thromboembolic events within 6 months of registration (incl. stroke, TIA, DVT, & PE).

No known history of congenital long QT syndrome.

No uncontrolled hypertension within 14 days of registration (defined as SBP \geq 150 mmHg and/or DBP \geq 90 mmHg despite optimal medical management).

No clinically significant GI bleeding within 6 months of registration.

No clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding within 6 months of registration including, but not limited to: active peptic ulcer, known endoluminal metastatic lesion(s) with history of bleeding, inflammatory bowel disease, or other gastrointestinal conditions with increased risk of perforation.

No GI perforation within 6 months of registration.

No known tumor with invasion into the GI tract from the outside causing increased risk of perforation or bleeding within 28 days of registration.

No radiologic or clinical evidence of pancreatitis.

No known cavitory lung lesions.

No known endobronchial lesions involving the main or lobar bronchi and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. (CT with contrast is recommended to evaluate such lesions.)

No hemoptysis greater than ½ teaspoon (2.5 mL) or any other signs of pulmonary hemorrhage within the 3 months prior to registration.

No known tumor invading or encasing any major blood vessels.

No history of non-healing wounds or ulcers within 28 days of registration.

No history of fracture within 28 days of registration.

No brain metastases or cranial epidural disease unless adequately treated, stable, and off steroid support for at least 4 weeks prior to registration.

No known medical condition causing an inability to swallow oral formulations of agents.

No history of allergic reaction attributed to compounds of similar chemical or biological composition to cabozantinib/placebo.

No “currently active” second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for \geq 3 years.

5. Concomitant Medications

- a. Other planned concurrent investigational agents or other tumor directed therapies (chemotherapy, radiation) are not allowed while on this study.

Concurrent use of somatostatin analogs while on cabozantinib/placebo is allowed provided that the patient has been on a stable dose for at least two months.

Full dose oral anticoagulation/antiplatelet therapy is not permitted. Low dose aspirin ≤ 81 mg/day is allowed. Anticoagulation with therapeutic doses of LMWH is allowed in patients who are on a stable dose of LMWH for at least 6 weeks prior to registration. Treatment with warfarin is not allowed. Anticoagulation in patients with brain metastases is not permitted.

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed. Patients must discontinue the drug at least 14 days prior to registration on the study. See Section 8.1.12 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug at least 14 days prior to the registration on the study. See Section 8.1.13 for more information.

6. Not pregnant and not nursing
 - a. Women of childbearing potential must have a negative pregnancy test done ≤ 14 days prior to registration.
A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).
7. Age ≥ 18 years
8. ECOG Performance Status: 0-2
9. Required Initial Laboratory Values:
 - a. Absolute Neutrophil Count (ANC) $\geq 1,500/\text{mm}^3$
Hemoglobin ≥ 9 g/dL
Platelet Count $\geq 100,000/\text{mm}^3$
PT/INR, PTT < 1.3 x upper limit of normal (ULN)
AST/ALT ≤ 3 x ULN
Total Bilirubin ≤ 1.5 x ULN*
Creatinine ≤ 1.5 mg/dL OR Creatinine Clearance ≥ 45 mL/min
Albumin ≥ 2.8 g/dL
Potassium within normal limits (WNL)**
Phosphorus WNL**
Calcium WNL**
Magnesium WNL**
Urine Protein to Creatinine (UPC) Ratio ≤ 1
QTcF ≤ 500 msec
TSH WNL**
*Except in the case of Gilbert disease, in which case Total Bilirubin must be ≤ 3 x ULN
**Supplementation is acceptable to achieve a value WNL. In patients with low albumin levels, a corrected calcium value WNL is acceptable. In patients with abnormal TSH, if Free T4 is normal and patient is clinically euthyroid, patient is eligible.

Re-Registration Eligibility Criteria (Step 2)

1. Documentation of Disease
 - a. Patients must have centrally-confirmed radiographic disease progression per RECIST v1.1.
2. Not pregnant and not nursing
 - a. Women of childbearing potential must have a negative pregnancy test done ≤ 14 days prior to registration.
A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).
3. Required Laboratory Values:

- a. Absolute Neutrophil Count (ANC) $\geq 1,500/\text{mm}^3$
- Hemoglobin $\geq 9 \text{ g/dL}$
- Platelet Count $\geq 100,000/\text{mm}^3$
- PT/INR, PTT $< 1.3 \times$ upper limit of normal (ULN)
- AST/ALT $\leq 3 \times$ ULN
- Total Bilirubin $\leq 1.5 \times$ ULN*
- Creatinine $\leq 1.5 \text{ mg/dL}$ OR Creatinine Clearance $\geq 45 \text{ mL/min}$
- Albumin $\geq 2.8 \text{ g/dL}$
- Potassium within normal limits (WNL)**
- Phosphorus WNL**
- Calcium WNL**
- Magnesium WNL**
- Urine Protein to Creatinine (UPC) Ratio ≤ 1
- QTcF $\leq 500 \text{ msec}$
- TSH WNL**

*Except in the case of Gilbert disease, in which case Total Bilirubin must be $\leq 3 \times$ ULN

**Supplementation is acceptable to achieve a value WNL. In patients with low albumin levels, a corrected calcium value WNL is acceptable. In patients with abnormal TSH, if Free T4 is normal and patient is clinically euthyroid, patient is eligible.

Schema

1 Cycle = 28 Days

