



## Alliance A021602: Randomized, Double-blinded Phase III Study of Cabozantinib Versus Placebo in Patients with Advanced Neuroendocrine Tumors After Progression on Everolimus

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Dana-Farber Cancer Institute

TAP TO  
RETURN TO  
KIOSK MENU

### Rationale

#### Rationale

Objective

Study Schema

Treatment Plan

Key Eligibility Criteria

Follow Up

Effective treatments are needed for patients with advanced neuroendocrine tumors (NET) whose disease has progressed after therapy with everolimus. VEGF pathway inhibitors have activity in advanced NET. [1,2,3] Studies suggest that MET activation may also play a role in NET growth [4]. Cabozantinib is an inhibitor of tyrosine kinase receptors, including MET, VEGFR-2, AXL, and RET, known to influence tumor growth, metastasis, and angiogenesis. Preclinical and phase II clinical trial data have demonstrated evidence of activity of cabozantinib in patients with advanced pancreatic NET and carcinoid tumors. [5,6,7]

If this phase III study reveals significant improvement in PFS with cabozantinib compared with placebo, it could change clinical practice by establishing an effective line therapy for patients with pancreatic NET and carcinoid tumors.

#### References

1. Raymond et al., NEJM 2011; 364: 501-13.
2. Grande et al., Ann Oncol 2015; 26: 1987-93.
3. Phan et al., Lancet Oncol 2015; 16: 695-703.
4. Krampitz et al., PNAS 2016; 113: 4464-69.
5. Reuther et al., Neuroendocrinology; 103: 383-401.
6. Sennino et al., Cancer Discovery 2012; 2: 270-287.
7. Chan et al., ASCO GI, 2017

Please use the headings above to navigate through the different sections of the poster



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TAP TO  
RETURN TO  
KIOSK MENU

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Objective

Study Schema

Treatment Plan

Key Eligibility Criteria

Follow Up

Please use the headings above to navigate through the different sections of the poster

### Objective

#### Primary

- To determine whether cabozantinib can significantly improve progression-free survival (PFS) compared to placebo in patients with advanced pancreatic NET or carcinoid tumors whose disease has progressed after treatment with everolimus.

#### Secondary

- To determine whether cabozantinib can significantly improve overall survival (OS) compared to placebo in patients with advanced pancreatic NET or carcinoid tumors whose disease has progressed after treatment with everolimus.
- To evaluate safety and tolerability of cabozantinib versus placebo in patients with advanced pancreatic NET and carcinoid tumors.
- To evaluate overall radiographic response rate of cabozantinib versus placebo in patients with advanced pancreatic NET and carcinoid tumors.



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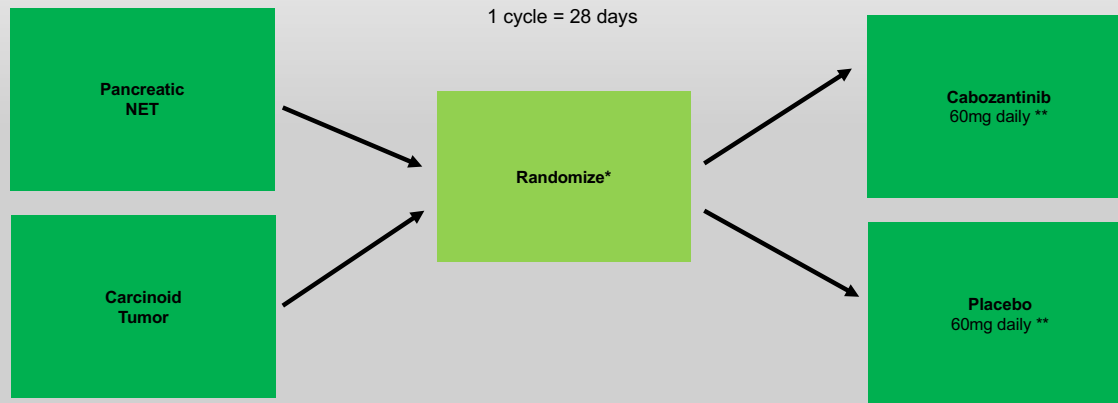
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TAP TO  
RETURN TO  
KIOSK MENU

- Rationale
- Objective
- Study Schema**
- Treatment Plan
- Key Eligibility Criteria
- Follow Up

## Study Schema



\* Randomization will be done separately for the pancreatic NET and carcinoid tumor cohorts.

\*\* Treatment is to continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be followed for survival and progression every 12 weeks until progression or start of new anticancer therapy, and then for survival every 6 months until 8 years after registration or until death, whichever comes first.

Imaging after cessation of therapy may be performed at a non-registering institution. If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply. All protocol conduct must be followed, and the registering institution is responsible for ensuring all data is reported per protocol.

Please use the headings above to navigate through the different sections of the poster



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TAP TO  
RETURN TO  
KIOSK MENU

Rationale

Objective

Study Schema

Treatment Plan

Key Eligibility Criteria

Follow Up

Please use the headings above to navigate through the different sections of the poster

### Treatment Plan

#### Cabozantinib/Placebo

- Protocol treatment is to begin  $\leq$  14 days of registration.
- This is a 2:1 randomized, double-blind trial. The initial blinded, patient-specific clinical supplies of cabozantinib/placebo will be requested by the Alliance Statistical and Data Center at the time of randomization and should arrive at the clinical site  $\leq$  approximately 7-10 days after randomization.
- Protocol therapy will consist of 60 mg oral cabozantinib/placebo (three 20 mg tablets) taken once daily during each 28-day treatment cycle. Patients should not eat for at least 2 hours before and for at least 1 hour after taking cabozantinib/placebo.
- Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Crossover from placebo to cabozantinib at the time of disease progression will not occur. Patients will be monitored for treatment response and toxicity.

#### Imaging

Collection of CT or MRI and CXR (or MRI and non-contrast CT chest) images is required for all patients consented on A021602. Quality images will be collected digitally for archival and retrospective purposes. The same imaging modality (i.e. multiphase CT or MRI [and CXR or non-contrast chest CT]) used at baseline for each patient should be used for all subsequent evaluations to ensure accurate comparison. Images and local interpretation reports will be collected digitally at the following time points:

- Prior-to-baseline (scan within the 12 months prior to registration that was used to determine progression for eligibility)
- Baseline (completed within 28 days prior to patient registration)
- Restaging\* (performed every 12 weeks until progression)
- Progression

*\* For patients who discontinue protocol treatment prior to disease progression, continue to submit every 12 weeks until disease progression (or start of new anticancer therapy).*

- Images submitted for the progression time point (i.e., local determination of progressive disease) will be reviewed by the A021602 Imaging Central Review Panel in real time.
- Images submitted for the baseline time point and the restaging time points will be reviewed by the A021602 Imaging Central Review Panel retrospectively in batches.
- Images submitted for the prior-to-baseline time point are being collected for documentation purposes and will not be reviewed by the A021602 Imaging Central Review Panel at this time.
- Protocol has instructions for digital image submission.



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TAP TO  
RETURN TO  
KIOSK MENU

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Rationale

Objective

Study Schema

Treatment Plan

Key Eligibility Criteria

Follow Up

Please use the headings above to navigate through the different sections of the poster

- Histologic documentation of well- or moderately-differentiated neuroendocrine tumor of pancreatic or non-pancreatic origin
- Locally advanced/unresectable tumor(s) or metastatic disease
- Target lesion disease progression by RECIST v1.1 within 12 months
- Patients must have measurable disease per RECIST 1.1
- Prior treatment must be completed >28 days prior to registration
- Prior use (and concurrent use at stable dose) of somatostatin analogs is allowed
- Prior treatment with cabozantinib is not allowed
- Resolution of toxic effects from prior therapy to grade 1 or less
- Major surgery must be completed days prior to registration
- No class III or IV CHF, clinically significant cardiac arrhythmia, unstable angina, MI, or thromboembolic events (incl. stroke, TIA, DVT, and PE) within 6 months of registration
- No known history of congenital long QT syndrome
- No uncontrolled hypertension within 14 days of registration
- No clinically significant GI bleeding or GI abnormalities that may increase risk for GI bleeding or GI perforation within 6 months of registration



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TAP TO  
RETURN TO  
KIOSK MENU

- Rationale
- Objective
- Study Schema
- Treatment Plan
- Key Eligibility Criteria
- Follow Up

### Funding Support

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