

## Efficacy and safety of cabozantinib for advanced gastrointestinal (GI) neuroendocrine tumors (NET) after progression on prior therapy: Subgroup analysis of the phase 3 CABINET trial (Alliance A021602).

Jonathan R. Strosberg, Tyler J. Zemla, Susan Michelle Geyer, Michael V. Knopp, Spencer Behr, Sydney Pulsipher, Jared David Acoba, Ardaman Shergill, Edward M. Wolin, Thorvardur Ragnar Halfdanarson, Bhavana Konda, Nikolaos Trikalinos, Bernard Tawfik, Nitya Prabhakar Raj, Shagufta Shaheen, Namrata Vijayvergia, Arvind Dasari, Eileen M. O'Reilly, Jeffrey A. Meyerhardt, Jennifer A. Chan; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Alliance Statistics and Data Management Center and Mayo Clinic Rochester, Rochester, MN; Wright Center of Innovation & IROC, University of Cincinnati, Cincinnati, OH; Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA; Alliance Statistics and Data Management Center, Rochester, MN; University of Hawaii Cancer Center, Honolulu, HI; Alliance Protocol Operations Office, University of Chicago, Chicago, IL; Icahn Mount Sinai School of Medicine, New York, NY; Mayo Clinic Comprehensive Cancer Center, Rochester, MN; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Washington University School of Medicine in St. Louis, Siteman Cancer Center, St. Louis, MO; University of New Mexico Comprehensive Cancer Center, Albuquerque, NM; Memorial Sloan Kettering Cancer Center, New York, NY; Stanford Cancer Center, Stanford, CA; Fox Chase Cancer Center, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA

**Background:** In the phase 3 CABINET trial (NCT03375320), cabozantinib (CABO) significantly prolonged median progression-free survival (PFS) compared to placebo (PB) in patients with advanced, previously treated, progressive extrapancreatic NET (epNET) [HR 0.38 (95% CI, 0.25-0.59,  $P < 0.0001$ )] and pancreatic NET (pNET) [HR 0.23 (95% CI, 0.12-0.42,  $P < 0.0001$ )] (Chan et al., NEJM, 2024). In this analysis, we focus on outcomes of patients with epNET arising in the GI tract. **Methods:** Patients with locally advanced or metastatic epNET or pNET were randomized 2:1 in separate cohorts to receive CABO 60 mg daily vs PB. The epNET cohort included patients with tumors arising in the GI tract (not including pancreas), lung, unknown primary, and other rare primary sites. In this subgroup analysis of the epNET cohort, patients with GI NET were included. Eligibility included progression by RECIST within 12 months (mo) prior to registration,  $\geq 1$  prior systemic therapy. Primary endpoint: PFS by blinded independent central review (BICR). Secondary endpoints: objective response rate, overall survival, safety. **Results:** 116 of the 203 patients in the epNET cohort had GI NET (CABO,  $n=70$ ; PB,  $n=46$ ). Median age was 66 yrs; females: 46%; G1/G2/G3/unknown grade: 35%/57%/6%/2%. ECOG performance status: 0/1-2: 43%/57%. White race: 86%. The most common primary tumor locations were ileum/cecum (54%), small intestine with location not specified (20%); non-cecum colon or rectum (11%), stomach (4%); duodenum (3%); jejunum and nonspecified midgut site (3% each). Prior systemic therapies included somatostatin analogs (SSA) (100%), everolimus (59%); Lu-177 dotatate (77%); temozolomide +/- capecitabine (16%). In patients with GI NET, CABO was associated with improved PFS by BICR compared to PB (stratified HR, 0.50; 95% CI: 0.28-0.88, 1-sided stratified log-rank  $P=0.007$ ). Median PFS with cabozantinib was 8.5 mo (95% CI, 6.0-16.7) compared to 5.6 mo (95% CI, 3.9-11.0) with PB. CABO demonstrated potential benefit in patients with midgut GI NET and across clinical factors including grade, functional status related to hormone secretion, concurrent SSA use, and prior therapy with Lu-177 dotatate or everolimus. The most frequent grade 3/4 adverse events attributed to therapy with CABO included hypertension (19%), diarrhea (13%), fatigue (10%). **Conclusions:** CABO is associated with improvement in PFS compared to PB in patients with advanced GI NET. Potential benefit was observed across clinical factors including grade, functional status, concurrent SSA, and prior treatment. The safety profile for CABO in patients with GI NET is consistent with that previously reported. Support: U10CA180821, U10CA180882; U10CA180820 (ECOG-ACRIN), U10CA180868 (NRG Oncology), U10CA180888 (SWOG); Exelixis; <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT03375320. Research Sponsor: National Cancer Institute; U10CA180821, U10CA180882 (Alliance for Clinical Trials in Oncology); U10CA180820 (ECOG-ACRIN), U10CA180868 (NRG Oncology), U10CA180888 (SWOG); Exelixis.