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**Cabozantinib in Progressive Medullary Thyroid Cancer**

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**Abstract**

**Purpose** Cabozantinib, a tyrosine kinase inhibitor (TKI) of hepatocyte growth factor receptor (MET), vascular endothelial growth factor receptor 2, and rearranged during transfection (RET), demonstrated clinical activity in patients with medullary thyroid cancer (MTC) in phase I.

**Patients and Methods** We conducted a double-blind, phase III trial comparing cabozantinib with placebo in 330 patients with documented radiographic progression of metastatic MTC. Patients were randomly assigned (2:1) to cabozantinib (140 mg per day) or placebo. The primary end point was progression-free survival (PFS). Additional outcome measures included tumor response rate, overall survival, and safety.

**Results** The estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40;  $P < .001$ ). Prolonged PFS with cabozantinib was observed across all subgroups including by age, prior TKI treatment, and *RET* mutation status (hereditary or sporadic). Response rate was 28% for cabozantinib and 0% for placebo; responses were seen regardless of *RET* mutation status. Kaplan-Meier estimates of patients alive and progression-free at 1 year are 47.3% for cabozantinib and 7.2% for placebo. Common cabozantinib-associated adverse events included diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue and resulted in dose reductions in 79% and holds in 65% of patients. Adverse events led to treatment discontinuation in 16% of cabozantinib-treated patients and in 8% of placebo-treated patients.

**Conclusion** Cabozantinib (140 mg per day) achieved a statistically significant improvement of PFS in patients with progressive metastatic MTC and represents an important new treatment option for patients with this rare disease. This dose of cabozantinib was associated with significant but manageable toxicity.

**Footnotes**

See accompanying editorial doi: [10.1200/JCO.2013.51.5098](https://doi.org/10.1200/JCO.2013.51.5098)



