Efficacy of cabozantinib (Cabo) in medullary thyroid cancer (MTC) patients with RAS or RET mutations: Results from a phase III study.

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Research Funding:

Background:

Cabo extends progression-free survival (PFS) in patients (pts) with progressive, metastatic MTC (Schö"ski, *J Clin Oncol* 30, 2012). Mutations in the *RET* oncogene are associated with most hereditary cases and ~half of sporadic cases of MTC. RAS gene mutations have recently been identified in subsets of *RET* wild type (wt) cases. Therefore, we investigated the association of *RET* (a prospectively defined endpoint) and RAS mutations (a post hoc analysis) with efficacy outcomes in the phase 3 study of cabo in MTC.

Methods:

Pts enrolled into the double-blind, placebo-controlled phase III trial were evaluated for the presence of somatic and germline *RET* mutations using Sanger and next generation methods. A subset of pts determined to be *RET* wt (44 pts) or *RET* unknown (41 pts) were then evaluated for tumor-associated mutations in *KRAS*, *NRAS*, and *HRAS* in codons 12, 13, and 61 by next generation sequencing. Impact of *RET* and RAS gene mutation status was evaluated with respect to PFS and tumor response rate (RR) according to RECIST.

Results:

RET status was determined in 65% of the study pts (215/330), of which 79% harbored an activating mutation, and 21% were RET wt. All RET mutational subgroups (RET mutated, RET wt, and RET unknown) showed hazard ratios indicating PFS benefit from cabo treatment, and demonstrated RRs between 22% and 32%. However pts harboring a RET mutation had longer median PFS on cabo (60 wks) than pts with wt RET (25 wks, PFS difference p=0.0001). Also, pts with the poor prognosis mutation RET M918T showed a longer median PFS on cabo treatment (61 wks) than pts with any other RET mutation (36 wks, PFS difference p=0.009). Patients with hereditary MTC had similar PFS to those with sporadic disease, and the presence of the common RET polymorphism G691S had no effect on either PFS or RR. Sixteen of 85 tested pts (5% of total study pts) with wt or unknown RET status were found to harbor a RAS gene mutation. The RAS-mutated pts showed a similar RR (31%) and PFS (47 wks) as RET mutated pts (32% and 60 wks).

Conclusions:

While hazard ratios indicate PFS improvement for all RET subgroups on cabo, the extent of benefit may depend in part on RET genotype. Cabo treatment benefit is also seen in pts harboring a RAS mutation. Clinical trial information: [NCT00704730](https://clinicaltrials.gov/ct2/show/study/NCT00704730).

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