6000 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

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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Background: Cabo extends progression-free survival (PFS) in patients (pts) with progressive, metastatic MTC (Schöffski, *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.