[News * Analysis * Commentary * Controversy]

SPECIAL EDITION supplement to
November 25, 2013 issue

ONCOLOGY TIMES

Lippincott Williams & Wilkins
Wolters Kluwer Health

Celebrating 35 Years of Publishing 35

The Independent Hem/Onc News Source

Shutterstock.com/Sebastian Kaulitzki

#6 in a Series

FOCUS:

Thyroid Cancer

Treatment & Research Updates

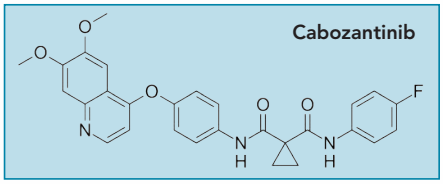
[INSIDE]

Medullary Thyroid Cancer: Cabozantinib Extends PFS in Patients with RET or RAS Mutations

BY MARK FUERST

CHICAGO—Treatment with the tyrosine kinase inhibitor (TKI) cabozantinib can significantly extend progression-free survival (PFS) in patients with progressive, metastatic medullary thyroid cancer, especially in patients who harbor RET or RAS mutations, according to the results of a study presented at the American Society of Clinical Oncology Annual Meeting (***Abstract 6000***).

Cabozantinib is a potent inhibitor of the receptor tyrosine kinases MET, RET, and vascular endothelial growth factor receptor 2 (VEGFR), which have all been implicated in the pathogenesis of thyroid cancer, explained Steven I. Sherman, MD, Chair of the Department of Endocrine Neoplasia and Hormonal Disorders at the University of Texas MD Anderson Cancer Center.



As had been shown in a Phase III study presented at the 2012 ASCO Annual Meeting, treatment with cabozantinib resulted in significant prolongation of PFS in patients with progressive, metastatic medullary thyroid cancer. That study showed that cabozantinib led to a significant improvement in median PFS (11.2 months) compared with placebo (4.0 months) and a one-year progression-free survival rate of 47.3 percent in the cabozantinib arm compared with 7.2 percent in the placebo arm.

There was no difference in overall survival, but long-term follow-up for survival is still ongoing, Sherman said.

At the 2013 meeting, Sherman presented a more detailed analysis of RET and RAS mutations from that study.

"Medullary thyroid cancer is a rare form of thyroid cancer, and patients with distant metastases have a median survival of about two years," he noted. "One-quarter of cases are hereditary, and three-quarters of cases occur sporadically. Mutations in the RET oncogene are associated with most hereditary cases and about half of sporadic cases of medullary thyroid cancer. One particular mutation, the RET M918T mutation, is associated with poor prognosis.

"RAS gene mutations have recently been identified in subsets of RET wild-type cases," he continued. "We therefore investigated the association of RET—a prospectively defined endpoint—and RAS mutations—a post-hoc analysis—with efficacy outcomes in the Phase III study of cabozantinib in medullary thyroid cancer."

Patients were evaluated for the presence of somatic and germ-line RET mutations. A subset of patients determined to have RET wild-type (44 patients) or RET mutation-unknown (41 patients) cancers were then evaluated for tumor-associated mutations in KRAS, NRAS, and HRAS in codons 12, 13, and 61 by next generation sequencing.

The impact of RET and RAS gene mutation status was evaluated with respect to PFS and tumor response rate according to Response Evaluation Criteria in Solid Tumors.

continued on page 12

→LGX818 & MEK162

continued from page 10

melanoma and thyroid cancer, with the majority of patients ongoing," Kefford said. Based on the promising data from this study, a Phase III trial combining LGX818 and MEK162 is planned.

Discussant Remarks

The Discussant for the study, Ahmad Tarhini, MD, PhD, Associate Professor of Medicine and Translational Science at the University of Pittsburgh, commented that the clinical activity for the combination of LGX818 and MEK162 is consistent with prior results of a BRAF inhibitor plus a MEK inhibitor in melanoma, and that preliminary adverse event data show a low incidence of squamous cell carcinoma, keratoacanthomas, and no pyrexia.

"It is likely that this combination will provide additional options for patients with BRAF-mutant or NRAS-mutation tumors," he said.

Based on the promising data from this study, a Phase III trial combining LGX818 and MEK162 is now planned.

He noted that there remain open questions for the field of BRAF inhibitors, including overcoming subsequent resistance with combination therapy, dose interruption, and sequencing with immunotherapy.

"BRAF-MEK combinations appear to be very promising studies in Phase III studies," he said, adding that the pathways to BRAF-inhibitor resistance have now been recognized.

Tarhini mentioned a human melanoma xenograft model of vermurafenib-resistant tumors that become drug dependent for continued proliferation. In one study, cessation of the drug led to regression of established drug-resistant tumors. A discontinuous dosing strategy forestalled the onset of drug-resistant disease.

In a cohort of patients with vermurafenib-resistant tumors following cessation of treatment, 14 of 19 patients had radiologic evidence of reduced tumor growth velocity.

"These types of studies offer support for sequencing trials of immunotherapy and BRAF/MEK inhibitors with crossover to determine the ideal sequence of therapies," he said.

→CABOZANTINIB

continued from page 11

In general, the magnitude of benefit with cabozantinib therapy was similar for those with hereditary disease and sporadic disease, he reported. "In RET mutation-positive patients, the median PFS was three times longer with cabozantinib—60 weeks—than with placebo—20 weeks. In contrast, in the small subset of patients with RET mutation-negative tumors, there was no significant improvement in PFS, and the median PFS was essentially identical—25 weeks for patients receiving cabozantinib and 20 weeks for those on placebo."

He added that heterogeneity in the RET mutation-negative group may play a role in the results.

RET M918T Mutation

Patients with the RET M918T mutation had prolonged PFS relative to patients with other RET mutations.

"There was highly significant improvement of PFS with cabozantinib therapy—61 weeks—compared with placebo—17 weeks—among those with the RET M918T mutation," he said.

For other mutations, the difference was not statistically significant (cabozantinib at 36 weeks vs. placebo at 24 weeks).

STEVEN I. SHERMAN, MD: "RAS gene mutations have recently been identified in subsets of RET wild-type cases. We therefore investigated the association of RET—a prospectively defined endpoint—and RAS mutations—a post-hoc analysis—with efficacy outcomes in the Phase III study of cabozantinib in medullary thyroid cancer."

Similar to the situation with patients in the RET mutation-positive subgroup, those with unknown RET mutation status showed prolongation of PFS on cabozantinib—median PFS of 48 weeks—versus placebo—13 weeks.

Sherman said that somatic RAS mutations have recently been found in medullary thyroid cancer patients who lacked RET mutations. In a post-hoc analysis, RAS mutations were evaluated in a subset of tumor samples, including RET mutation-negative (41) and RET mutation-unknown (44) samples. Sixteen patients had RAS mutations.

"Despite the small number of patients, they also had a significant improvement in PFS with cabozantinib (47 weeks) compared with placebo (8 weeks)," he said.

In a subgroup of 33 RET mutation-negative patients without known RAS mutations, there was no difference in median PFS between the two arms (cabozantinib at 24 weeks, placebo at 22 weeks). "Despite a clear difference in PFS, the objective response rate ranged only from 18 to 34 percent across varying mutation subgroups in the cabozantinib arm of the study," he said.

The highest response rates were seen in those with the RET M918T mutation or RAS mutations, and the lowest in RET mutation negative/no RAS mutation group.

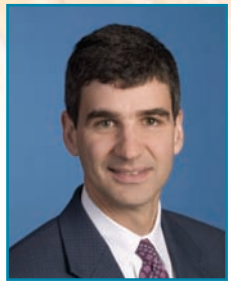
In conclusion, Sherman said, "the greatest degree of benefit in PFS and objective response was seen in patients with activating RET or RAS mutations, both of which are upstream kinases in signaling pathways. The RET mutation-unknown patients experienced outcomes similar to those in the RET mutation-positive group, which may be due to less common RET or RAS mutations or other abnormalities that could contribute to sensitivity to VEGFR or MET inhibition."

One limitation of the study, he added, is that in most cases only primary tumors were available: "Therefore, the presence of additional mutations and or genetic heterogeneity or metastatic lesions could not be assessed. This may partially explain why objective responses were still observed in patients whose tumors were RET and RAS mutation negative."

Discussant

The Discussant for the study, A. Dimitrios Colevas, MD, Associate Professor of Medicine and Oncology at Stanford School of Medicine, commented: "A lot of drugs have been studied in small trials of medullary thyroid cancer. They all have common signal transduction and similar activity. Cabozantinib and vandetanib share binding to MET and VEGFR. How do we know which targets are relevant? It is worth looking at relevant mutations. [This study] outlined that RET M918T is a relevant mutation."

Does it matter that cabozantinib has lower IC_{50s} than vandetanib in the RET M918T mutation of medullary thyroid cancer patients? he asked. "We don't know the answer. We do know that cabozantinib works better in patients who have RET or RAS mutations."



A. DIMITRIOS COLEVAS, MD: "If we test for RET M918T it, we could tell patients that their prognosis is worse but that they are more likely to have a meaningful response to cabozantinib. That alone is a reason to test, but not a reason to exclude people from therapy."

Knowing that the RET M918T mutation is relevant, the question remains whether it is worth it to test for this mutation. "If we test for it, we could tell patients their prognosis is worse but that they are more likely to have a meaningful response to cabozantinib. That alone is a reason to test, but not a reason to exclude people from therapy."

Why does the drug work in RAS-mutant medullary thyroid cancer? "The answer is because things are more complicated than we think. It's likely the disease does not proceed down one pathway. Other targets may make a difference." He noted that there may be synergy of PI3K and RAF inhibition.

A good response by patients with RET mutation-positive disease is not unique to cabozantinib. For those with sporadic medullary thyroid cancer, "if patients are RET mutation-positive, they are more likely to respond to vandetanib. There is a suggestion of improved PFS and overall response. This seems to cluster with the specific RET M918T mutation. This is a consistent story for these two TKIs."

In conclusion, Colevas said, "we get better activity if these medullary thyroid cancer patients have a RET or RAS mutation. Response rates and PFS are better in patients with the RET M918T mutation. It is unclear that testing for either RET or RAS mutations guides therapy with cabozantinib, but this does have prognostic significance. Cabozantinib and vandetanib show the same trends with respect to anti-cancer activity and RET status."