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#6 in a Series

## FOCUS:

## Thyroid Cancer

*Treatment & Research Updates*

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# Combination of BRAF Inhibitor Plus MEK Inhibitor Promising for PTC and Other Solid Tumors

BY MARK FUERST

CHICAGO—A combination of the oral BRAF inhibitor LGX818 and the oral MEK 1/2 inhibitor MEK162 shows promising clinical activity in BRAF V600-dependent advanced solid tumors, including papillary thyroid cancer, according to preliminary results from a Phase Ib/II open-label, dose-escalation study reported here at the American Society of Clinical Oncology Annual Meeting (***Abstract 9029***).

Three types of cancers—melanoma as well as thyroid and colon cancers—are commonly driven by mutations in the BRAF gene, explained Richard Kefford, MD, Professor of Medicine at the University of Sydney Westmead Institute of Cancer Research, speaking in an interview at the meeting. Combining BRAF and MEK inhibitors in BRAF V600 mutant tumors may prevent or overcome resistance to monotherapy and potentially improve the safety profile of single-agent therapy,


"These two drugs are easy to use and very active in all cohorts," he said. "We were able to rescue a proportion of patients who had failed on BRAF inhibitor therapy."

LGX818 is a potent, highly selective BRAF inhibitor that has shown signs of efficacy in a Phase I study in advanced tumors, including melanoma and metastatic colorectal cancer. MEK162 is a potent, highly selective inhibitor of MEK1/2. Promising data have been reported in trials in advanced solid tumors, including *NRAS* or BRAF V600 mutant melanoma, said Kefford.

"This is a very active MEK kinase combination," he said. "Early data are similar in activity to other similar combinations. The main advantage of these two drugs is that they have a favorable pharmacokinetic profile. It is a very clean combination, with no effective target side effects, such as the fever, photosensitivity, and liver toxicity seen with other combinations."

## Study Details

As of the time the data were compiled for the meeting, 30 patients (9 BRAF inhibitor-naive melanoma; 14 BRAF inhibitor-pretreated melanoma; 2 BRAF inhibitor-naive thyroid cancer and 1 BRAF inhibitor-pretreated papillary thyroid cancer; 2 BRAF inhibitor-naive metastatic colorectal cancer and 2 BRAF inhibitor-pretreated colorectal cancer) were treated with LGX818 daily plus MEK162 twice daily at the following dose levels (50 mg plus 45 mg, 100 mg plus 45 mg, 200 mg plus 45 mg, 400 mg plus 45 mg, 450 mg plus 45 mg, and 600 mg plus 45 mg).

There was no dose-limiting toxicity in the first five dose levels, although one was seen at the 600 mg + 45 mg level.

The maximum tolerated dose (MTD) has not yet been determined, Kefford said. The Phase II part of the study was initiated at doses of 450 mg for LGX818 and 45 mg for MEK162, with no drug-drug interaction seen. "Drug exposures were similar in combination compared with single-agent studies of MEK162 and LGX818," he said.

The disease control rate was 100 percent for all BRAF inhibitor-naïve patients and among the BRAF-inhibitor-pretreated patients, 100 percent for the thyroid cancer patients, 64 percent for melanoma patients, and 33 percent for metastatic colorectal cancer patients. The overall response rates were 88 percent for BRAF inhibitor-naïve and 18 percent for BRAF inhibitor-pretreated melanoma patients and 67 percent for thyroid cancer patients.

At the time of data cutoff, 18 of 30 patients continued on trial, including eight of the nine with BRAF inhibitor-naive melanoma, seven of 14 patients with BRAF inhibitor-pretreated melanoma, and three of the seven patients with thyroid cancer or metastatic colorectal cancer.

Kefford said he and his colleagues considered the combination to be well tolerated with no substantial increase in adverse events for the combination versus single-agent therapy. "The combination may mitigate some on-target adverse events common with BRAF inhibitor monotherapy, including cutaneous toxicities, myalgia, and arthralgia, and no febrile or photosensitivity events have been reported to date."

RICHARD KEFFORD, MD: "These two drugs are easy to use and very active in all cohorts. We were able to rescue a proportion of patients who had failed on BRAF-inhibitor therapy."

The most common adverse events were grade 1/2 GI toxicities, visual disturbances, headache, and fatigue. Five patients had grade 3 adverse events suspected to be treatment related, two transaminase increases, two lipase increases, and one with retinal vein occlusion, and one with maculopapular rash. One patient had a dose reduction of MEK162 and LGX818. Two patients discontinued treatment due to an adverse event (one due to elevated transaminases and one due to retinal vein occlusion).

In conclusion, Kefford said, "We saw good clinical pharmacokinetics with this combination. Preliminary data from this study indicate that LGX818 plus MEK162 can be safely combined with promising clinical benefit. The combination may mitigate some on-target adverse events common with single BRAF inhibitor therapy."

He added that the combination has a distinct safety profile compared with other treatments and that there have been no febrile events or photosensitivity reported to date and there was low incidence of rash (only one patient had acneiform dermatitis).

"Clinical activity was reported in patients with BRAF V600 mutant

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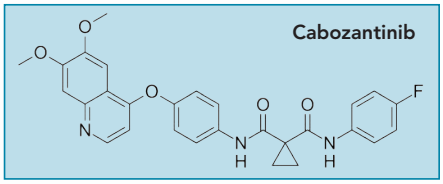
# Medullary Thyroid Cancer: Cabozantinib Extends PFS in Patients with RET or RAS Mutations

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.

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## →LGX818 & MEK162

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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.