

## Selective inhibitor shows early promise in patients with RET-altered cancers

April 16 2018

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BLU-667, a next-generation inhibitor that selectively targets the oncogenic receptor tyrosine kinase RET, was well tolerated and had broad clinical benefit in patients with advanced cancer that had progressed on previous therapies including multikinase inhibitor therapy. Proof-of-concept data will be presented from an ongoing phase I clinical trial at the AACR Annual Meeting 2018, April 14-18, in Chicago.

"RET-altered cancers across multiple tumor types represent a high medical need, as there are no approved agents that selectively target this oncogene," said Vivek Subbiah, MD, assistant professor, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, and Associate Medical Director, The Clinical Center for Targeted Therapy, The University of Texas MD Anderson Cancer Center, Houston.

"Current therapies for RET-altered cancers are restricted to multikinase inhibitors and chemotherapy, which are nonspecific and display significant off-target toxicity. In an effort to revolutionize treatment for these cancers, BLU-667 was designed to specifically target oncogenic RET fusions and activating mutations."

Prior preclinical work found that BLU-667 potently inhibits oncogenic RET and displays anti-tumor activity in a variety of RET-driven cancers, Subbiah noted. In addition, the inhibitor was 100 times more selective for the RET kinase relative to more than 350 human kinases tested, and it potently inhibited gatekeeper mutations shown to confer resistance to multikinase therapies, he explained.

Subbiah and colleagues tested BLU-667 in an open-label, first-in-human study. As of Feb. 13, 2018, they had enrolled 43 patients with unresectable, advanced solid tumors, with 26 patients having RET-mutant medullary thyroid [cancer](#) (MTC), 15 patients having non-small cell lung cancer (NSCLC) with RET fusion, and two patients with non-RET cancers. Patients had a median of one prior anti-neoplastic [therapy](#); prior therapies ranged from zero to eight treatments.

BLU-667 doses ranging from 30 to 400 mg were administered orally every day. The maximum tolerated dose (MTD) was not reached.

BLU-667 demonstrated broad antitumor activity with a best overall response rate of 37 percent in the 30 patients with RET alterations who received doses  $\geq 60$ mg and had at least one post-baseline response assessment. Patients with NSCLC and MTC had a best overall response rate of 45 and 32 percent, respectively. As of the data cutoff, 33 of 43 enrolled patients remained on study.

BLU-667 was well-tolerated; grade 1 constipation was the most commonly reported adverse event (23 percent). Three dose-limiting toxicities (DLTs) were documented, and there were no grade 4-5 adverse events. The dose escalation portion of the trial is still underway.

Additional data are expected to be presented at the AACR Annual Meeting 2018.

"This ongoing phase I study has shown proof-of-concept of this selective RET inhibitor," said Subbiah. "Although it's very early in clinical testing, we observed promising antitumor activity in NSCLC and MTC.

"Precision targeted therapy with RET inhibition can have a powerful impact in patients whose cancer is induced by these oncogenic drivers, even in early clinical trial testing," noted Subbiah. "I encourage all

cancer [patients](#) to undergo genomic testing, as tumors with rare genomic aberrations may have effective drugs that are in clinical trials that could be beneficial to them."

Provided by American Association for Cancer Research

Citation: Selective inhibitor shows early promise in patients with RET-altered cancers (2018, April 16) retrieved 2 May 2024 from <https://medicalxpress.com/news/2018-04-inhibitor-early-patients-ret-altered-cancers.html>

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