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Targeted therapy pralsetinib safely effectively treats lung and thyroid cancers with RET alterations

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Results from the multi-cohort Phase I/II ARROW clinical trial, conducted by The University of Texas MD Anderson Cancer Center researchers, showed that a once-daily dose of pralsetinib, a highly selective RET inhibitor, was safe and effective in treating patients with advanced RET fusion-positive non-small cell lung cancer (NSCLC) and RET-altered thyroid cancer. The findings for each cohort were published today in *The Lancet Oncology* and *The Lancet Diabetes & Endocrinology,* respectively.

"Targeted therapies have dramatically improved care for patients with NSCLC and thyroid cancer driven by oncogenes, and the rapid clinical translation of selective RET inhibitor pralsetinib marks another milestone in a paradigm shift toward precision medicine," said principal investigator Vivek Subbiah, M.D., associate professor of Investigational Cancer Therapeutics.

The Food and Drug Administration approved pralsetinib for metastatic RET fusion-positive NSCLC in September 2020 and advanced RET-altered thyroid cancers in December 2020.

RET fusions occur when part of the DNA containing the RET gene breaks off and fuses with a different gene, which activates the kinase enzyme that continuously sends growth signals to the cell and drives cancer development. RET alterations are caused by a mutation in the

DNA sequence and are oncogenic drivers in a variety of tumor types, most commonly in medullary thyroid cancers (approximately 90% of advanced cases), papillary thyroid cancers (approximately 10-20% of cases) and NSCLC (approximately 1-2% of cases).

Because standard cancer treatments—including surgery, radiation, chemotherapy and immunotherapy—have shown limited efficacy in patients with RET fusion-positive solid tumors, RET fusions have become an emerging target for novel therapies.

"Patients with RET-altered cancer are in need of personalized therapies," Subbiah said. "Based on this published data, pralsetinib shows durable responses in both the treatment-naïve and treatment-refractory settings in RET-positive NSCLC and thyroid cancer, providing evidence that this drug can be an option as a new standard of care for patients with this rare cancer."

In the NSCLC cohort, the analysis included 233 patients with RET fusion-positive NSCLC, as of a data cutoff of May 22, 2020. Ninety-two patients previously received platinum-based chemotherapy and 29 had no prior systemic treatment. The findings showed that pralsetinib achieved an overall response rate (ORR) of 70% and a complete response rate of 11% in patients with no prior systemic treatment, and a 61% ORR and 6% complete response rate in patients who previously received platinum-based chemotherapy.

In the thyroid arm of the study, researchers enrolled patients with RET-altered locally advanced/metastatic solid tumors, including 122 patients with RET-mutant medullary thyroid cancer and 20 patients with RET fusion-positive thyroid cancers, as of a data cutoff of May 22, 2020. The ORR was 71% in patients with treatment-naïve RET-mutant medullary thyroid cancer, 60% in patients previously treated with cabozantinib and/or vandetanib and 89% in patients with RET fusion-positive thyroid

cancer.

"Until 2020, standard approved therapies for advanced thyroid cancer included multikinase inhibitors, which are effective but associated with a broad spectrum of potentially dose-limiting adverse effects," said trial co-investigator Mimi Hu, M.D., professor of Endocrine Neoplasia and Hormonal Disorders. "The highly potent RET-inhibitors, such as pralsetinib, led to a high response rate and have a more tolerable side-effect profile, thus improving patient satisfaction. Development of novel precision therapies is essential for our patients with this rare disease."

Five thyroid cancer patients (4%) discontinued therapy due to treatment-related adverse events (TRAEs), one patient died due to a TRAE and 14 NSCLC patients (6%) discontinued treatment due to TRAEs. Ultimately, the results showed that pralsetinib was a potent yet well-tolerated treatment for patients with RET fusion-positive NSCLC and RET-altered thyroid cancer.

"These data reiterate the importance of continued clinical implementation of genomic testing to identify actionable oncogenic drivers that include RET alterations," Subbiah said.

Blueprint Medicines Corporation funded the ARROW study. A full list of co-authors and their disclosures can be found in The Lancet Oncology and The Lancet Diabetes & Endocrinology papers.

Provided by University of Texas M. D. Anderson Cancer Center

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