

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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