EDITORIALS

Selpercatinib Aimed at *RET*-Altered Cancers

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A remarkable increase has occurred in the number of highly targeted drugs that have efficacy in patients with advanced cancers that harbor specific genomic alterations. Prime examples are the NTRK inhibitors that target *NTRK* fusions, which are found in only approximately 0.3% of cancers.[1,2] As many as 75% of the patients with tumors that bear NTRK fusions and who have received these agents have had a response. These results have led to the Food and Drug Administration (FDA) approval of the use of the NTRK inhibitors larotrectinib and entrectinib in adult and pediatric patients with *NTRK* fusion–positive solid tumors, regardless of the tissue of origin. Similarly, pembrolizumab, an immune checkpoint blockade antibody that targets programmed cell death protein 1, has been approved by the FDA for the treatment of all solid tumors with one of two specific molecular markers — microsatellite instability that derives from a defect in mismatch-repair genes and a high tumor mutational burden. Both of these markers have been associated with durable responses to pembrolizumab in a large subgroup of patients with advanced cancers.[3,4] In this issue of the *Journal*, Wirth et al.[5] and Drilon et al.[6] report that the potent RET inhibitor selpercatinib (LOXO-292) is now poised to alter the landscape of another genomic subgroup — *RET*-altered cancers.

The *RET* proto-oncogene encodes a transmembrane receptor tyrosine kinase that is composed of an intracellular kinase, a large extracellular domain, and a transmembrane domain.[1-4] RET functions as the receptor for the glial-cell line–derived neurotropic factor family of growth factors. Subsequent to ligand binding, autophosphorylation on intracellular tyrosine residues of RET generates docking sites for downstream signaling adaptors, activating multiple key cancer effectors.

RET aberrations can result in gain-of-function (ligand-independent) kinase activation through mutations, fusions or rearrangements, or amplifications. Overall, among diverse cancers, *RET* aberrations have been identified in approximately 2% of cases, with mutations being the most common alteration. Mutations constitute approximately 37% of *RET* alterations, followed by fusions (approximately 31%) and amplifications (approximately 25%).[7] *RET* missense mutations, which have been described in various types of cancers and in hereditary conditions, can occur in extracellular cysteine residues, triggering aberrant receptor dimerization or, in the intracellular kinase domain, promoting ligand-independent kinase activation.[7,8]

Activating *RET* germline mutations are associated with familial medullary thyroid cancer alone or as part of multiple endocrine neoplasia type 2. More than 50% of sporadic medullary thyroid cancers also harbor activating *RET* mutations. Alternatively, RET activation can occur through gene rearrangements that create an activated fusion protein. *RET* fusions are observed in 10 to 20% of papillary thyroid cancers as well as in small subgroups of non–small-cell lung cancers (NSCLCs) and colorectal, breast, and other cancers.[7,8] RET is thus an attractive therapeutic target.

Previously approved multikinase inhibitors such as vandetanib and cabozantinib, which have ancillary RET inhibitor activity, also have activity

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against RET-driven cancers. However, the use of these drugs is limited by their off-target side effects. In contrast, next-generation, highly potent, and selective RET inhibitors such as selpercatinib offer the potential for improved efficacy and a more satisfactory side-effect profile. The early-phase clinical trial of selpercatinib described in this issue of the *Journal* included a cohort of patients with thyroid cancer and a cohort of patients with NSCLC. In both the part of the trial involving patients with *RET*-altered thyroid cancer (reported by Wirth et al.) and the part of the trial involving patients with *RET*-altered NSCLCs (reported by Drilon et al.), selpercatinib produced durable responses in a majority of patients, and only approximately 3% of the patients discontinued selpercatinib because of drug-related adverse events.

Wirth and colleagues report that among 55 patients with *RET*-mutated medullary thyroid cancer that was previously treated with other RET inhibitors such as vandetanib, cabozantinib, or both, 69% had a response to selpercatinib, and 82% had progression-free survival at 1 year. Among 88 patients with *RET*-mutated medullary thyroid cancer who had not previously received vandetanib or cabozantinib, 73% had a response to selpercatinib, and 92% had progression-free survival at 1 year. Finally, 15 of 19 patients (79%) with previously treated *RET* fusion–positive thyroid cancer had a response.

RET fusions are oncogenic drivers in 1 to 2% of NSCLCs.[7,8] Drilon and colleagues report that among 105 patients with *RET* fusion–positive NSCLC who had previously received at least platinum-based chemotherapy, 64% had a response, and the median duration of response was 17.5 months. Furthermore, among 39 previously untreated patients, 85% had a response, and 90% of the responses were ongoing at 6 months. Finally, 10 of 11 patients (91%) with central nervous system metastasis had an intracranial response.

Taken together, these results show that selpercatinib had marked and durable antitumor activity in most patients with *RET*-altered thyroid cancer or NSCLC. *RET* abnormalities now join other genomic alterations such as *NTRK* fusions, tumor mutational burden, and deficient mismatch-repair genes across cancers and *ALK*, *BRAF*, *EGFR*, *MET*, and *ROS1* alterations in NSCLC that warrant molecular screening strategies. Next steps may include introducing these agents earlier in the course of the disease, addressing genomic co-alterations with customized combination-therapy strategies, and using additional techniques such as transcriptome analysis in order to fully understand the molecular landscape of cancer.[9,10]

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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