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COMMENT

An early look at selective RET inhibitor resistance: new challenges and opportunities

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Two RET inhibitors, selpercatinib and pralsetinib, recently received approval for the treatment of advanced *RET* fusion-positive lung cancer. Acquired resistance to these inhibitors will be a major challenge. We have shown that resistance can emerge due to recurrent *RET* kinase domain mutations and, in most cases, due to RET-independent mechanisms.

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MAIN

Lung cancer remains one of the most common cancers worldwide afflicting over two million persons a year, and is the leading cause of cancer mortality.[1] Efforts to develop new treatment strategies in lung cancer have evolved at a rapid pace. In 2020 alone, eleven therapies received approvals by the US Food and Drug Administration (FDA) for new indications in lung cancer. Two of these, selpercatinib and pralsetinib, were novel tyrosine kinase inhibitors (TKIs) selectively targeting RET proto-oncogene (RET).

RET gene fusions are the driver oncogene identified in approximately 1–2% of non-small cell lung cancer (NSCLC).[2] Previously, targeted therapy options for patients with advanced *RET* fusion-positive NSCLC were limited, with no approved RET-targeted therapies prior to 2020; the standard treatment remained chemotherapy with or without immunotherapy. The recent FDA approvals for selpercatinib and pralsetinib were granted on the basis of results from the registrational LIBRETTO-001 and ARROW Phase 1/2 trials, respectively. In these studies, both TKIs demonstrated robust efficacy with objective response rates ranging from 55–64% among platinum chemotherapy-pre-treated and 66–85% among treatment-naïve patients with *RET* fusion-positive NSCLC.[3,4]

While these advances are encouraging, prior experiences with targeted therapies in NSCLC and other solid tumours collectively teach us that acquired resistance to RET-selective TKIs will inevitably emerge as a major hurdle, hindering durable benefit in patients and causing disease relapse.[5] Thus, endeavours to understand and overcome mechanisms of resistance to these RET inhibitors are a major focus.

Our recent study[6] is one of the few published to date that offers early insights into selective RET inhibitor resistance. This multi-institutional study included patients with advanced *RET* fusion-positive lung cancer who were treated with selpercatinib or pralsetinib and underwent post-treatment biopsies (tumour or plasma). The re-biopsies were analysed by next-generation sequencing to identify mechanisms of resistance. While the sample size was small (18 patients with a total of 23 biopsies), it is the largest series to date given the recent development of these inhibitors. We found that *RET* resistance mutations were detected in two of 20 distinct resistant cases (as three cases had paired tissue/plasma at the same timepoint). In both cases, the mutation affected *RET* G810 in the solvent front. Solomon and colleagues previously reported that *RET* G810 mutations confer selpercatinib resistance in *RET* fusion-positive NSCLC and *RET*-mutant medullary thyroid cancer (MTC) through steric hindrance with drug binding.[7] In the remaining 18 cases (90%) in our series, a *RET* mutation was not identified, suggestive of the tumours harbouring a RET-independent mechanism of resistance.

Our findings have now been replicated in other series. For example, in a preliminary analysis of pralsetinib resistance from the ongoing ARROW trial, RET-mediated resistance appeared similarly uncommon, with *RET* mutations—at the G810 and L730 (in the roof region of the ATP-binding site) residues—detected in approximately 10% of circulating tumour DNA biopsies.[8] The inhibitor's mode of binding and interaction with the target kinase will influence the spectrum of kinase mutations that can confer resistance. Indeed, using X-ray crystal structures of RET–selpercatinib and RET–pralsetinib complexes, Subbiah and colleagues recently demonstrated that these inhibitors are not susceptible to *RET* gatekeeper (V804) mutations because of their mode of binding, while remaining susceptible to non-gatekeeper mutations.[9] They identified *RET* solvent front (G810) mutations as well as hinge region (Y806) mutations in a patient with *RET*-mutant MTC resistant to selpercatinib.[9] These findings are intriguing in the context of the known mechanisms of resistance to epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors in *EGFR*-mutant or *ALK* fusion-positive NSCLC, where the reported frequency of on-target resistance mutations has been higher.[10,11] In addition, gatekeeper mutations have been more readily identified after progression on approved TKIs in *EGFR*-mutant or *ALK* fusion-positive NSCLC as compared with *RET* fusion-positive NSCLC, suggesting either fundamental differences in biology and/or that the lessons learned from EGFR and ALK TKI drug development may have informed the optimisation of selective RET inhibitors.[5]

It is premature to draw conclusions regarding the true frequency of RET-dependent versus RET-independent resistance and the full spectrum of resistance mutations. We await larger sample sizes

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and longer follow-up. Nevertheless, our study, together with additional recent studies evaluating RET inhibitor resistance,[6–8,12] provide early guidance on the existing gaps and opportunities in the treatment of advanced *RET* fusion-positive lung cancer.

First, while not overwhelmingly dominant, *RET* resistance mutations are recurrent in patients treated with selpercatinib or pralsetinib. For these patients, novel RET inhibitors harbouring potency against the resistance mutations are needed. Drug development efforts are ongoing in this space. As an example, TPX-0046 is a potent RET/SRC inhibitor which has demonstrated preclinical potency against *RET* G810 solvent front mutations, and is currently in Phase 1 testing in patients with advanced *RET*-altered solid tumours (clinicaltrials.gov identifier NCT04161391).[13]

Second, further investigation of RET-independent mechanisms of resistance becomes paramount given the relatively low frequency of *RET* mutations identified thus far. In our study, acquired *MET* amplification was identified in three cases and acquired *KRAS* amplification in one case resistant to selpercatinib or pralsetinib. In all of these cases, concomitant *RET* resistance mutations were not detected.[6,14] Importantly, resistance mediated by *MET* amplification is potentially clinically actionable in lung cancer, as exemplified by responses to osimertinib (EGFR TKI) plus savolitinib (MET TKI) in patients with *EGFR*-mutant NSCLC harbouring *MET* amplification.[15] Similarly, Rosen and colleagues recently published their experience treating four patients with NSCLC and concurrent *RET* fusions and *MET* amplification, wherein the combination regimen of selpercatinib plus crizotinib (MET/ALK/ROS1 TKI) demonstrated clinical activity albeit of variable depth and duration.[12]

Optimal combinatorial strategies to target known actionable resistance gene alterations such as *MET* amplification remain undetermined, awaiting prospective trials. Moreover, in most cases with pralsetinib or selpercatinib resistance, the putative mechanism of resistance is not yet known. This gap calls for further genetic and non-genetic studies using clinical samples and preclinical models in order to comprehensively capture the landscape of RET inhibitor resistance mechanisms and ultimately to advance treatment options in patients. As these studies mature, the lessons learned will probably be relevant to a diverse array of solid tumours harbouring oncogenic *RET* alterations.

The identification of each novel target like RET and the successful development, and approval, of target-selective inhibitors bring tremendous hope. Our study and others investigating mechanisms of resistance will be an important part of the collective efforts geared towards further extending that hope.

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J.J.L. and J.F.G. contributed to the writing and review of this manuscript.

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