Lung Cancer: Targets and Therapy

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COMMENTARY

LIBRETTO-431: Confirming the Superiority of Selpercatinib to Chemotherapy and the Lack of Efficacy of Immune Checkpoint Inhibitors in Advanced *RET* Fusion-Positive (*RET*+) NSCLC, Another Unique Never-Smoker Predominant Molecular Subtype of NSCLC

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Abstract: Selpercatinib, a potent and highly selective RET kinase inhibitor with significant CNS activity, has recently gained US approval for the treatment of NSCLC harboring *RET* fusions (*RET*+) based on a large-scale single-arm study. The LIBRETTO-431 trial was the global pivotal registration phase 3 trial comparing selpercatinib to platinum-based chemotherapy with or without pembrolizumab as the first-line treatment of patients with advanced *RET*+ NSCLC. Never-smokers constituted 67.4% of the *RET*+ NSCLC patients enrolled. *KIF5B-RET* made up the vast majority (77%) of the *RET*+ fusion variant with known fusion partner. The results of this study demonstrated significant improvement in progression-free survival (PFS) benefit as well as impressive intracranial disease response in participants treated with selpercatinib as compared to those treated with chemotherapy, with a HR [hazard ratio] of 0.46 (95% CI 0.33–0.70; $P < 0.001$) for the intention-to-treat (ITT)-pembrolizumab group and HR of 0.46 (95% CI 0.31–0.70, $P < 0.001$) for the overall ITT-group of patients. The addition of pembrolizumab to platinum/pemetrexed chemotherapy resulted in numerically identical PFS (11.2 months). These results point to selpercatinib's superiority to traditional chemotherapy regimens in the treatment of NSCLC harboring *RET* fusions and add to literature on the salience of targeted precision oncology and lack of efficacy of immune checkpoint inhibitor in NSCLC patients with never-smoker predominant actionable driver mutations. *RET*+ NSCLC should be added to the list of molecular subtypes (*EGFR*+, *ALK*+, *ROS1*+) of NSCLC to be excluded in chemoimmunotherapy trial.

Keywords: LIBRETTO-431, selpercatinib, RET fusion positive NSCLC, pralsetinib, immunotherapy in never-smokers, relative dose intensity

Introduction

There are 58 human receptor tyrosine kinases (RTKs) that can be categorized into 20 sub-families.[1] The identification of multiple modes of oncogenic alterations in many of these RTKs (single amino acid substitutions, insertions and deletions, gene amplification, protein over-expression, and chromosomal rearrangement) and the subsequent development of targeted therapies has transformed the treatment landscape of non-small cell lung cancer (NSCLC) over the past 20 years. Following the discovery of *ALK* and *ROS1* fusions in NSCLC in 2007,[2,3] fusions in the rearranged during transfection (*RET*) proto-oncogene in NSCLC were reported in 2011 by four groups nearly simultaneously.[4–7] Overall, *RET* fusions have

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been observed in approximately 1–2% of patients with NSCLC.[8] As with all RTK fusion-positive NSCLC, there is a high cumulative incidence of the development of brain metastasis during the natural disease course of *RET*+ NSCLC.[9]

Selpercatinib

Selpercatinib, a potent and specific RET TKI, received US FDA accelerated approval on May 8, 2020 based on the single-arm phase 2 LIBRETTO-001 study. For full approval, the US FDA required the sponsor of selpercatinib to perform a randomized phase 3 trial to confirm selpercatinib's clinical benefit.[10,11] Furthermore, given its high CNS potency, selpercatinib can effectively prevent or delay the emergence of CNS metastasis in patients with baseline CNS metastasis when treated with selpercatinib in the advanced disease state.[12]

The LIBRETTO-431 Trial Design

The design of LIBRETTO-431 has been described in detail.[13] The goal of the trial was to demonstrate the superiority of selpercatinib to chemotherapy with or without an immune checkpoint inhibitor (ICI) as first-line treatment of advanced *RET*+ NSCLC. Importantly, the role of chemotherapy with the addition of an ICI has remained an unanswered question in the never-smoker predominant actionable driver mutation-positive NSCLC population, outside of those harboring *EGFR* and *ALK* mutations. Hence, the standard of care arm in the LIBRETTO-431 trial consisted of the KEYNOTE-189 regimen,[14] currently the most popular first-line treatment regimen in NSCLC.

Patients were randomized 1:1 initially and then 2:1 to selpercatinib (160 mg twice daily) or to pemetrexed (500 mg/m^2) and either carboplatin (AUC 5) or cisplatin (75 mg/m^2), with or without pembrolizumab (200 mg every 3 weeks). Upon progression confirmed by blinded independent central review (BICR), patients in the chemotherapy arm were allowed to cross over to the selpercatinib arm. To achieve the predefined statistical power, the maximum percentage of patients who would not receive pembrolizumab in the chemotherapy arm was set at 20%.

The primary endpoint was BICR-assessed progression-free survival (PFS). Secondary endpoints included efficacy overall (overall survival, objective response rate, and duration of response), CNS efficacy (objective response rate, duration of response, time to progression), safety, and patient-reported outcomes. Stratification factors included geography (East Asian vs non-East Asian), brain metastases (present vs absent or unknown), and investigator's choice of treatment with pembrolizumab. Patients with symptomatic CNS metastases were excluded. Regular imaging of the brain was performed only in patients with baseline brain metastasis.

RET fusions were identified via next-generation sequencing (NGS) or polymerase chain reaction (PCR) using a sponsor-enabled or locally qualified test, an excellent addition to the design of this study. If available, an archived tumor sample was also required for retrospective central confirmation of *RET* fusion status, but the exact platform for this confirmation was not reported. Importantly, patients were excluded from the trial if they harbored additional validated oncogenic driver mutations in NSCLC, as secondary acquired *RET* fusions could act as resistance mechanisms to EGFR TKIs.[15]

Sample size calculations assumed a median PFS of 9 months in the chemotherapy and pembrolizumab arm, based on the KEYNOTE-189 results.[14] The trial strived to increase median PFS from approximately 7 months with selpercatinib compared to chemotherapy (9 vs 16). To achieve a hazard ratio (HR) of 0.56, it was estimated a minimum of 200 patients would be enrolled in the intent-to-treat (ITT) pembrolizumab population, for the ITT pembrolizumab population to yield 89% statistical power with a one-sided type I error rate of 0.025.[13,16]

The LIBRETTO-431 Trial Conduct

LIBRETTO-431 trial enrolled 261 patients from 23 countries who had treatment-naïve advanced (unresectable stage IIIB/C and stage IV) non-squamous NSCLC. Fifty-eight percent of the *RET*+ NSCLC patients were identified by next-generation sequencing (NGS). The median age of the patients was 61–62 years of age, 55.2% (144/261) were Asians, 54.8% (143/261) were females, and 19.5% (51/261) presented with known brain metastasis. Importantly 67.4% (176/261) of the *RET*+ NSCLC patients were never-smokers. The vast majority, 77% (120/156), of *RET*+ NSCLC with known fusion partners was the *KIF5B-RET* variant. Among the 171 patients with known PD-L1 expression status, 43.9% (75/171) had expression >1%, 29.2% (50/171) between 1–49%, and 26.9% (46/171) ≥50%.

Among the overall ITT population, selpercatinib demonstrated a PFS of 24.8 months (95% CI 17.3–NE [not evaluable]), whereas the chemotherapy group demonstrated a PFS of 11.2 months (95% CI 8.8–16.8) with a HR of 0.48 (95% CI 0.33–0.70; $P < 0.001$). Identical results were observed in the ITT-pembrolizumab population where selpercatinib achieved an identifical PFS of 24.8 months (95% CI 16.9–NE) compared to 11.2 months (95% CI 8.8–16.8) in the chemotherapy group with a HR of 0.46 (95% CI 0.31–0.70; $P < 0.001$). The median PFS in the chemotherapy arm of 11.2 months was numerically identical with or without the addition of pembrolizumab. Median duration of response (DOR) was also higher in the selpercatinib group (24.2 months; 95% CI 17.9–NE) compared to the chemotherapy group (11.5 months; 95% CI 9.7–23.3).

Importantly among patients with baseline brain metastasis, the intracranial (IC) ORR was 82.4% for selpercatinib with complete IC-response rate of 35.3% compared to 58.3% in the chemotherapy group and a complete IC-response rate of 16.7%. The median intracranial PFS was 16.1 months (95% CI 8.8–not reached) in the selpercatinib group compared to 10.4 months (95% CI 3.8–not reached) in the chemotherapy group. In patients without baseline CNS disease, the 12-month cumulative incidence rate (CIR) of CNS progression was astonishingly low at 1.1% in the selpercatinib group (95% CI 0.1–5.2) compared to 14.7% (95% CI 5.7–27.6) in the chemotherapy group, favoring selpercatinib with a HR of 0.17 (95% CI 0.04–0.69) although these patients did not have to undergo regular brain imaging. In patients with baseline CNS disease, the 12-month CIR was 25.7% in the selpercatinib group (95% CI 8.8–46.7) compared to 33.3% (95% CI 14.3–53.8) in the chemotherapy group, favoring selpercatinib, albeit with a non-significant HR of 0.61 (95% CI 0.19–1.92).[16]

Given cross-over from chemotherapy to selpercatinib was allowed, overall survival (OS) was not significant among the ITT population with a HR of 1.04 (95% CI 0.58–1.88; $P = 0.89$) nor among the ITT-pembrolizumab population with a HR of 0.96 (95% CI 0.50–1.84; $P = 0.90$).

Quality of Life Improvement

Fewer selpercatinib-treated patients (23%) compared to chemotherapy-treated patients (36%) reported worsening quality of life: the median time to confirmed worsening of pulmonary symptoms was 1.9 months (95% CI 0.7–6.6) among all chemotherapy-treated patients compared to not reached for selpercatinib-treated patients (HR = 0.34; 95% CI 0.22–0.55).

Tolerability of Selpercatinib

Adverse events led to dose reduction in 51% and permanent discontinuation in 10% of selpercatinib-treated patients. The median relative dose intensity (RDI) of selpercatinib was 88%, which was lower than expected. Ideally the median RDI should be >90%. The more informative data of mean RDI of selpercatinib was not reported. The four most common grade 3 or higher adverse events were alanine aminotransferase (ALT) increase (22%), hypertension (20%), aspartate aminotransferase (AST) elevation (13%), and QTc prolongation (9%).

The Superiority of Selpercatinib Over Chemotherapy in *RET*+ NSCLC

The LIBRETTO-431 trial provides convincing evidence of selpercatinib's efficacy in the first-line treatment of patients with advanced NSCLC harboring *RET* fusions. Treatment with selpercatinib conferred a formidable and clinically meaningful PFS benefit of 24.8 months, more than doubling the 11.2 months seen in both chemotherapy-backbone groups. Furthermore, selpercatinib, already known to possess impressive CNS activity, has proven to be incredibly effective in the prevention of CNS disease in *RET*+ NSCLC patients, in particular. Selpercatinib-treated patients demonstrated an impressive improvement in intracranial response rate and delay in CNS progression, with a 12-month cumulative incidence rate of only 1.1% in the selpercatinib group compared to 14.7% in the control group. Importantly, this population is estimated to possess a 46% lifetime prevalence of brain metastasis, rendering selpercatinib's promise of CNS penetrance even more enticing. Therefore, selpercatinib is the first-line treatment of choice of stage 4 *RET*+ NSCLC.

The Limited Role of Immunotherapy in *RET*+ NSCLC

Unsurprisingly, the addition of pembrolizumab to platinum/pemetrexed chemotherapy did not result in any numerical increase in PFS when compared to platinum/pemetrexed chemotherapy, with both demonstrating a PFS of 11.2 months

(95% CI 8.8–16.8). There was also no difference in ORR with chemotherapy and ICI (65%) versus chemotherapy alone (63%). This result is consistent with the lack of benefit seen with ICIs in the never-smoker predominant actionable driver mutation-positive NSCLC population, given that 67.4% of the enrolled patients were never smokers. Similarly, the CHECKMATE-722[17] and KEYNOTE-789 trials[18] also did not report improvement in PFS in the post first-generation or third-generation EGFR TKI settings, albeit in the second-line rather than first-line space. Importantly, the pivotal DESTINY-Lung-04 trial (clinical trial information: NCT05048797) compares pembrolizumab plus chemotherapy to trastuzumab deruxtecan (HER2-DXd) in a 1:1 ratio. All patients who are randomized to the chemotherapy arm will receive pembrolizumab also which may represent a potential missed opportunity in assessing the contribution if any with the addition of pembrolizumab to platinum-based chemotherapy in another unique subset of never-smoker predominant actionable driver mutation positive NSCLC. We beleive if DESTINY-Lung04 was designed like LIBRETTO-431, the role of pembrolizumab would be neglible regardless if the chemotherapy arm will be superior to HER2-DXd or not.

The lack of additional benefit seen with the addition of ICI to chemotherapy is likely due, in part, to the biology that *RET*+ NSCLC patients are mostly never-smokers, with potentially lower tumor mutation burden. Never-smokers are known to have reduced response to immunotherapy, as smoking is known to increase tumor mutational burden, especially neo-antigens, which are known to be important factors in response to immunotherapy.[19]

Moreover, among the 12 first-line chemotherapy plus ICI or dual ICI regimens approved in the US, only the indicated use of cemiplimab further excluded *ROS1*+ NSCLC patients, as well as *EGFR*+ and *ALK*+ NSCLC patients.[20] The results of the LIBRETTO-431 trial should provide the clinical evidence to include *RET*+ NSCLC as additional exclusion criterion for the use of immunotherapy in the first-line treatment of advanced NSCLC.

The Other Selective RET TKI, Pralsetinib

Pralsetinib is another highly potent and specific RET TKI that received accelerated US FDA approval on September 4, 2020 based on a single-arm phase 2 study.[21] Interestingly, on August 29, 2023, the US FDA converted the accelerated to full approval of pralsetinib in *RET*+ NSCLC based on the updated ARROW trial, including data on an additional 123 patients with an additional 25 months of follow-up to assess durability of response.[22,23] The randomized phase 3 AcceleRET Lung trial (NCT04222972) was still ongoing (as of December 15, 2023).[24] The full approval of pralsetinib was based on BICR-assessed ORR, DOR, and PFS. Among 107 treatment-naïve patients, the ORR was 78% (95% CI 68–85) with a median DOR of 13.4 months (95% CI 9.4–23.1). Among 130 patients previously treated with platinum-based chemotherapy, the ORR was 63% (95% CI 54–71) with a median DOR of 38.8 months (95% CI 14.6–NE). The most common adverse reactions (≥25%) were musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, edema, pyrexia, and cough.[22] It will be important to see results of the AcceleRET Lung trial.

Concluding Thought

First, the results of the LIBRETTO-431 are a compelling addition to an ever-growing body of literature that likens *RET*+ NSCLC to *EGFR*+, *ALK*+, and *ROS1*+ NSCLC, which seem to predominantly afflict never-smokers. Importantly, 67.4% of the *RET*+ NSCLC patients enrolled into LIBRETTO-431 were never-smokers. The likely expected success of the LIBRETTO-432 trial comparing adjuvant selpercatinib to placebo in resected early-stage (stage IB to IIIA) *RET*+ NSCLC, together with the results of the ADAURA in resected early-stage *EGFR*+ NSCLC (PFS and overall survival benefit)[25,26] and ALINA in resected early-stage *ALK*+ NSCLC[27] trials, points to the importance of lung cancer screening among never-smokers.

Second, the LIBRETTO-431 trial enrolled patients with *RET* fusions detected via RT-PCR or NGS but not fluorescence in situ hybridization (FISH), which represents a significant leap in the utilization of diagnostic tests to detect RTK fusions in NSCLC. Among all the RTK fusions, FISH was only approved as compendium diagnostics in *ALK* + NSCLC. The criteria for using FISH to diagnose *ALK*+ NSCLC were based on at least 15% split signals defined as >2 split diameters identified in a minimum of 50 distinct tumor cells.[28] The criteria for *ROS1* or *RET* fusion using FISH were never established and validated. Moreover, FISH could not identify the fusion partners, the fusion breakpoints on the fusion partners, and any co-genomic alterations that may affect response to TKI such as *TP53* mutations. The use of NGS is a welcome shift to more molecularly based diagnostic methods to detect RTK fusions and represents further

evolution from the legacy companion diagnostic tests (primarily FISH) approved by the US FDA in the early development of ALK TKIs that have persisted even into the development of third-generation of ALK TKIs. It is gratifying to note that NGS was used to enroll 58% of the patients in LIBRETTO-431. Furthermore, plasma NGS genotyping accounts for ~5.8% (10% of NGS) of the patients enrolled. The inclusion of plasma genotyping alone as an eligible detection method represents validation of an easier diagnosis test with a faster turn-around time method and another huge step forward in advancing future development of TKIs against actionable driver mutations in NSCLC by "streamlining" the companion diagnosis test.

Third, the addition of pembrolizumab to platinum/pemetrexed chemotherapy, the KEYNOTE-189 regimen, did not provide any numerical increase to the overall response rate nor median PFS in *RET*+ NSCLC patients when compared to platinum/pemetrexed chemotherapy. These results from this phase 3 trial expands upon growing evidence of the lack of efficacy of immune checkpoint inhibitors in never-smoker predominant actionable driver mutation positive NSCLC. Going forward, future immunotherapy trials in NSCLC should exclude *RET*+ NSCLC patients in addition to *EGFR*+, *ALK*+, and *ROS1*+ NSCLC patients.[20]

Fourth, selpercatinib as a brain-penetrant RET TKI was highly potent in suppressing the emergence of brain metastasis in patients without baseline brain metastasis. Ideally, the protocol should have required regular brain imaging concurrently and regardless the presence or absence of baseline CNS metastasis at the time of surveillance scans so a more precise estimate on how potently selpercatinib can suppress the emergence of especially asymptomatic brain metastasis in patients without baseline CNS metastasis and how selpercatinib may change the natural histort of advanced *RET*+ NSCLC patients without brain metastasis.

Fifth, we eagerly await the AcceleRET trial to report their data, given that pralsetinib is the other next-generation RET TKI that is also approved for treatment of *RET*+ NSCLC. The inevitable cross-trial comparison of patient characteristics, diagnostic tests, ORR, PFS, intra-cranial efficacies, and adverse events between LIBRETTO-431 and AcceleRET will eventually allow us a better understanding of the natural history of *RET*+ NSCLC.

Lastly, selpercatinib is the first of the next-generation RET-specific TKIs. On-target resistance mutations[29,30] and off-target resistance mutations have been described.[30] Hence, we urgently need next-generation RET TKIs that can overcome gatekeeper and solvent-front mutations, given that the US FDA has granted selpercatinib tumor-agnostic approval for treatment of all *RET*+ solid tumors.[31] With time we anticipate more and more incidences of on-target resustance mutations will emerge creating an unmet medical need for next-generation RET TKIs.

Disclosure

Dr Sai-Hong Ou reports grants and personal fees from Pfizer, JNJ/Janssen, Daiichi Sankyo, DAVA oncology LLP, OncLive; personal fees from Bayer, BMS; grants from Mirati and Revolution Medicine; stock ownership from Nuvalent, MBrace Therapeutics, BlossomHill Therapeutics, Turning Point Therapeutics; grants, personal fees, and stock ownership from Elevation Oncology, outside the submitted work. The authors report no other conflicts of interest in this work.

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