CASE REPORT

Intracranial Response to Selpercatinib After Pralsetinib-Induced Disease Progression in Rearranged During Transfection Fusion-Positive Non-Small-Cell Lung Cancer: Case Report

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ABSTRACT

RET fusion-positive NSCLC accounts for 1% to 2% of lung carcinoma cases. Although two Food and Drug Administration–approved selective RET inhibitors, pralsetinib, and selpercatinib, have revealed efficacy in managing RET fusion-positive NSCLC, this case series is unique in its focus on the intracranial response to selpercatinib after disease progression during pralsetinib treatment. This report contributes to the literature by providing evidence of selpercatinib's potential as a treatment option in such refractory cases. The patients described in both cases were diagnosed with metastatic RET fusion-positive NSCLC and developed intracranial metastases during pralsetinib treatment. After switching to selpercatinib, both exhibited significant intracranial responses. The first patient reported a reduction in brain metastasis size and maintained a response for over 1.5 years. The second patient also responded intracranially to selpercatinib but unfortunately passed away 8 months later owing to pulmonary hemorrhage, possibly linked to prior radiation treatment. These cases highlight the potential efficacy of selpercatinib in treating intracranial metastases in RET fusion-positive patients with NSCLC after pralsetinib-refractory progression. The key takeaway is that selpercatinib may offer a viable treatment option in such scenarios, although more extensive studies are needed to determine its role as a monotherapy or in combination with other treatments.

Keywords: RET; Selpercatinib; Non–small-cell lung carcinoma; RET fusion; NSCLC; Case Report

Introduction

Rearranged during transfection (RET fusion-positive NSCLC accounts for 1% to 2% of lung carcinoma patients.[1] There are two Food and Drug Administration–approved selective RET inhibitors for the treatment of RET fusion-positive NSCLC: pralsetinib[2] and selpercatinib.[3]

According to findings from the ARROW trial,[2] a phase 1-2 study, an orally administered selective RET inhibitor, pralsetinib (400 mg once daily), reported efficacy in patients with locally advanced or metastatic RET fusion-positive NSCLC. The trial reported a median progression-free survival of 13.0 months (95% confidence interval [CI]: 9.1–not reached) in treatment-naive patients and 16.5 months (95% CI: 10.5–24.1) in those with prior platinum-based chemotherapy. Moreover, among patients with measurable intracranial metastases at baseline (n = 50/121; 41.3%), all of whom had previously received systemic platinum-based chemotherapy, the intracranial objective response rate was 70% (95% CI: 35%–93%). The median duration of intracranial response was 10.5 months (95% CI: 5.5–12.6). The most

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common grade III to IV treatment-related adverse events were neutropenia (18%) and hypertension (10%). Overall, 7% of the patients discontinued pralsetinib owing to treatment-related adverse events.

In the LIBRETTO-001 trial,[3] a phase 1-2 study, the efficacy of selpercatinib (160 mg twice daily), an orally administered selective inhibitor of the RET receptor tyrosine kinase, was evaluated in patients diagnosed with locally advanced or metastatic RET fusion-positive NSCLC. This study reported a median progression-free survival of 22.0 months (95% CI: 13.8–not estimable) in treatment-naive patients and 24.9 months (95% CI: 19.3–not estimable) in those who had previously undergone platinum-based chemotherapy. Among patients with measurable intracranial metastases at baseline (n = 106 of 316; 33.5%), the objective response rate was 85% (95% CI: 65%–96%) with 27% having a complete response. The median duration of intracranial response in treatment-naive patients was 9.4 months (95% CI: 7.4–15.3). Selpercatinib was also reported to have an acceptable safety profile, with only 8% of patients discontinuing selpercatinib owing to adverse events. The most common grade III to IV treatment-related adverse events were hypertension (19.7%), elevated alanine aminotransferase (11.4%), and aspartate aminotransferase (8.8%).

Case Presentations

Here, we present two cases of patients with RET fusion-positive NSCLC with intracranial response to selpercatinib after intracranial disease progression during pralsetinib treatment.

Case 1

A 59-year-old woman, initially diagnosed with stage III NSCLC (adenocarcinoma and high programmed death-ligand 1 expression of more than 50%, next-generation sequencing was not performed) underwent a left-sided pneumonectomy followed by four cycles of adjuvant chemotherapy (carboplatin-pemetrexed). On disease progression (on the basis of the growth of intrapulmonary nodules in the remaining lung) she was treated with nivolumab (programmed cell death protein 1 binding immune checkpoint inhibitor), resulting in stable disease. After a year, there was evidence of disease progression on the basis of new intrapulmonary nodules. Next-generation sequencing was performed on the pneumonectomy specimen for, revealing a KIF5B–RET fusion. The KIF5B rearrangement is the most frequently observed fusion partner in RET fusion-positive NSCLC, occurring in approximately 70% of RET-positive cases.[4] The patient was enrolled in the ALERT-lung trial,[5] a single-arm trial exploring alectinib (600 mg twice daily) activity in RET fusion-positive advanced NSCLC. After five months of alectinib treatment, disease progression necessitated a switch to pralsetinib 400 mg once daily (compassionate use program). Treatment with pralsetinib resulted in a partial response on the computed tomography scan obtained after six weeks of treatment (Fig. 1).

The patient presented with loss of vision in her left eye after 18 months of treatment with pralsetinib, for which she was referred to an ophthalmologist. Because of suspicion of a left eye metastasis, brain magnetic resonance imaging (MRI) was performed, revealing a solitary cerebellar metastasis on the left side measuring a maximum of 7 mm; no radiological abnormalities were observed in the left eye. There were no indications of extracranial progression.

The patient switched to selpercatinib (160 mg twice daily). After three weeks the visual symptoms improved, and the brain MRI reported a decrease in the size of the brain metastasis from 7 mm to 3 mm (Fig. 2*A–C*). The patient has been treated with selpercatinib for 1.5 years now, with ongoing response at the time of writing.

Ophthalmologic examination revealed a macular scar in the left eye, suggestive of residual scarring from an eye metastasis that was too small to be assessable on the brain MRI, but which also responded well to selpercatinib.

Case 2

A 45-year-old female patient, initially diagnosed with stage III NSCLC (adenocarcinoma, RET fusion-positive), underwent treatment with chemoradiotherapy (carboplatin-pemetrexed). Information about the RET fusion partner was not available because the diagnosis was made using fluorescence in situ hybridization. Unfortunately, after four years, there was disease progression owing to lymphogenic progression. Subsequent treatment lines (cisplatin-pemetrexed and carboplatin-paclitaxel) rendered insufficient effect with progressive disease as the best response, prompting a switch to fourth-line nivolumab. Because of suspicion of pneumonitis, nivolumab was discontinued, and the patient was referred to our hospital for inclusion in the ALERT trial[5] for treatment with alectinib. After five months, disease progression occurred, leading to discontinuation of alectinib and initiation of sixth-line pralsetinib (compassionate use program).

The duration of response was eight months, after which the patient developed extensive intracranial progression, for which she was treated with whole-brain radiotherapy. Three months after radiotherapy, there was again extensive intracranial disease progression. Pralsetinib was discontinued, and treatment with seventh-line selpercatinib was initiated under compassionate use.

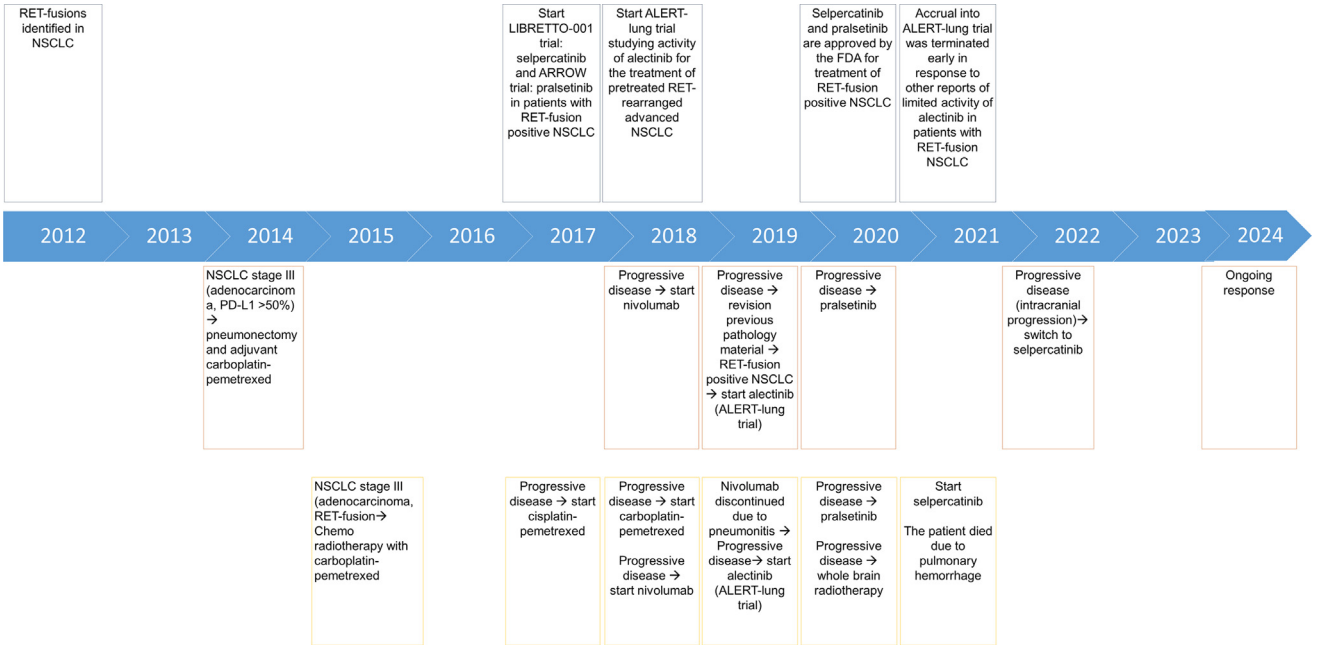

Figure 1. Timeline of patients' treatment (case 1: orange, case 2: yellow) and events. FDA, Food and Drug Administration; PD-L1, programmed death-ligand 1.

The first brain MRI, six weeks after the start of selpercatinib, reported a response (Fig. 2*D–F*). Unfortunately, the patient passed away eight months after the start of selpercatinib owing to pulmonary hemorrhage, possibly originating from the previously irradiated areas in her lungs.

Discussion

These cases highlight the intracranial efficacy of selpercatinib after intracranial disease progression on pralsetinib in patients with RET fusion-positive NSCLC. Both pralsetinib and selpercatinib proved to have intracranial efficacy, with an objective response rate of 70% (95% CI: 35%–93%)[2] and 85% (95% CI: 65%–96%)[3] respectively. Because of the small sample size, we cannot generalize the findings of this case series to a broader population. Nevertheless, we believe these cases reveal that selpercatinib could be a promising option for managing intracranial disease progression in RET-altered NSCLC patients previously treated with pralsetinib.

Three cases have been previously reported describing the intracranial efficacy of selpercatinib after leptomeningeal metastases in patients treated with pralsetinib. D'Arienzo et al.[6] reported a case of a 64-year-old man with RET fusion-positive NSCLC 12 months after initiation of pralsetinib. During the treatment period, pralsetinib was interrupted several times owing to pralsetinib-induced pneumonitis. After the leptomeningeal disease was confirmed, pralsetinib was discontinued, and treatment with selpercatinib was initiated. Clinical improvement was seen within 72 hours. Because of the concurrent presence of pneumonitis, the patient was simultaneously treated with a high dosage of prednisone. It is unclear whether the rapid neurologic improvement can be attributed to either selpercatinib, prednisone, or a combination of both. A complete radiologic intracranial response and resolution of the pralsetinib-induced pneumonitis was seen three months after switching treatment to selpercatinib. Unfortunately, the patient died two months later owing to an extracranial progression of the disease. Cognigni et al.[7] reported a similar case of a RET fusion-positive NSCLC patient treated with pralsetinib who developed recurrent pralsetinib-induced pneumonitis 13 months after the start of treatment, requiring interruptions and dose reductions of pralsetinib. This ultimately resulted in the intracranial progression of the disease and necessitated a switch to treatment with selpercatinib, leading to intracranial disease control.

Tsui et al.[8] describe a case of a 63-year-old woman with RET fusion-positive NSCLC. After 16 months of pralsetinib treatment, the patient experienced intracranial disease progression. Pralsetinib was discontinued, and the patient was initially treated with stereotactic radiotherapy. Because of symptomatic intracranial disease progression with leptomeningeal metastasis, selpercatinib and a high dosage of dexamethasone were initiated. A neurologic response was observed within 72 hours after the start of selpercatinib. Radiological intracranial response was seen on the brain MRI six weeks after treatment initiation, along with reduction of leptomeningeal contrast enhancement.

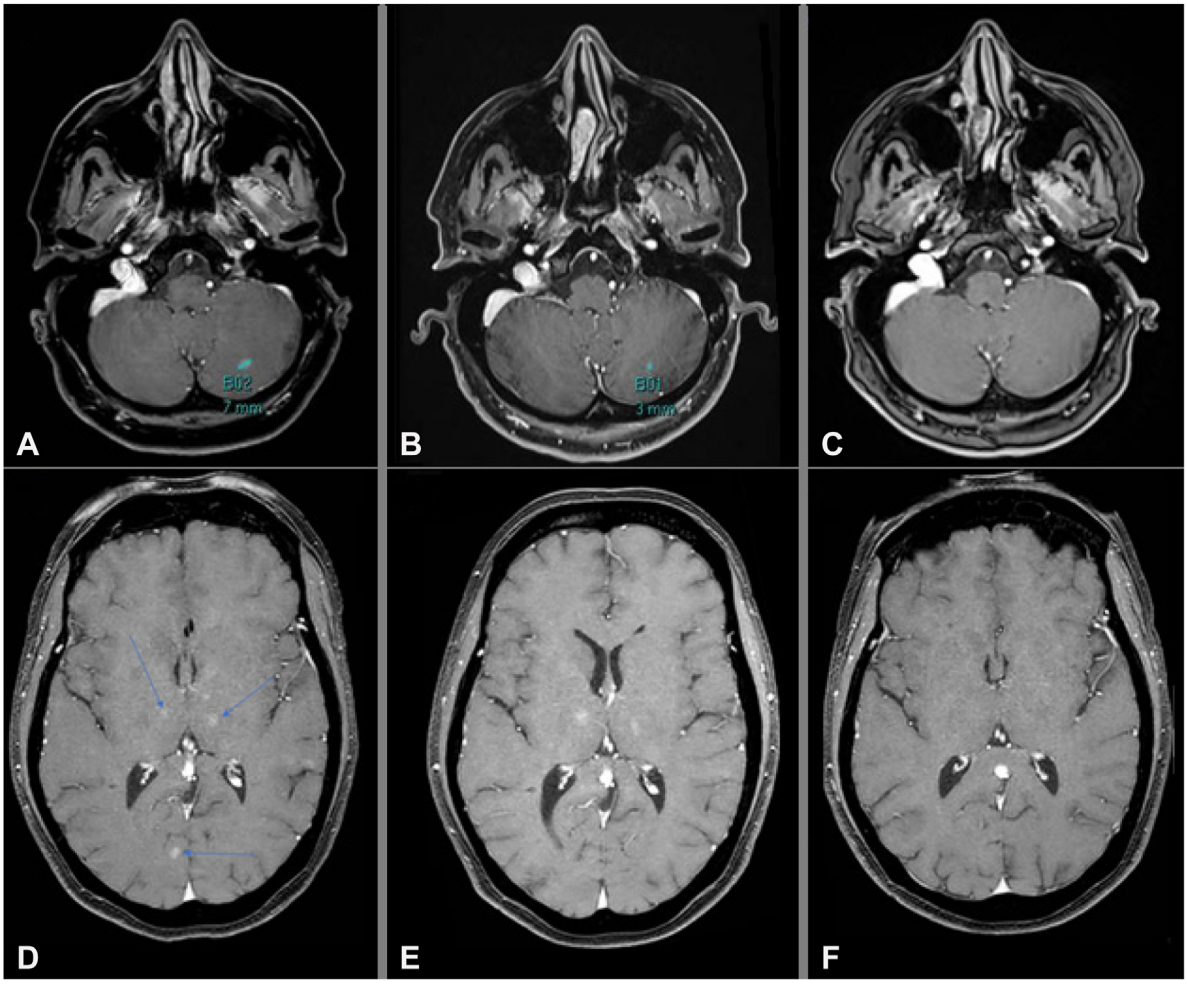

Figure 2. Magnetic resonance imaging of the brain. Case 1: *(A)* Intracranial disease progression on pralsetinib, *(B)* Intracranial disease response 3 weeks after selpercatinib treatment with a decrease in size of the brain metastasis from 7 mm to 3 mm, *(C)* Complete intracranial response 18 months after selpercatinib treatment. Case 2: *(D)* Intracranial disease progression on pralsetinib and 3 months after whole brain radiotherapy, *(E)* Intracranial disease response 6 weeks after selpercatinib treatment, *(F)* Intracranial disease response 5 months after selpercatinib treatment.

Approximately four months after initiating selpercatinib, dexamethasone was tapered and discontinued. Unfortunately, the patient developed neurologic symptoms and was found to have leptomeningeal disease progression. Consequently, the treating team decided to increase the dosage of selpercatinib to 240 mg twice daily, resulting in symptom improvement.

Our first patient had intracranial disease progression under pralsetinib and was only treated with selpercatinib. In contrast to the previously reported case reports,[6,8] we refrained from treatment with radiotherapy or corticosteroids. Therefore, the intracranial response of the first patient is attributable to selpercatinib alone. Our second patient was also treated with selpercatinib without corticosteroids, after intracranial disease progression. We expect that the intracranial response is entirely attributable to selpercatinib in this case as well.

Conclusion

Collectively, we have reported two cases of patients with RET fusion-positive NSCLC with intracranial response to selpercatinib after pralsetinib-refractory intracranial disease progression. These cases highlight selpercatinib's superior intracranial efficacy. Nevertheless, we cannot rule out the emergence of a mechanism conferring resistance to pralsetinib but not to selpercatinib, as we were unable to obtain pathology specimens when our patient had intracranial progression. To assess whether selpercatinib is a promising option for managing intracranial disease progression in patients with RET-altered NSCLC on pralsetinib, large randomized controlled trials need to be conducted. As earlier publications often combine selpercatinib with radiotherapy or corticosteroids, further research is also required to determine whether selpercatinib should be used as a monotherapy or in combination with other treatments.

Because of the small sample size and lack of control groups, the cases presented here offer insufficient evidence to support any specific treatment regimen.

CRediT Authorship Contribution Statement

Illaa Smesseim: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - original draft, Visualization, Project administration.

Tijmen van der Wel: Investigation, Resources, Data Curation, Writing - original draft, Visualization.

Sushil Badrising: Investigation, Resources, Data Curation, Writing - original draft, Visualization, Supervision.

Disclosure

Dr. Badrising reports receiving a speaker's fee and holding an advisory role at Janssen and Pfizer. The remaining authors declare no conflict of interest.

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