**CLINICAL VIGNETTE**

# RET-Fusion Positive Advanced Non-Small-Cell Lung Cancer: A Case Report and Review of the Literature

Joshua Rosenberg, MD and Mahshid Mosallaei-Benjamin, MD

***Case***

A 52-year-old female without significant past medical history was seen by her primary care physician for a dry cough persistent for 2 months. Chest x-ray showed a 3 cm density in the left lower lung. Blood counts and a complete metabolic panel revealed elevated alkaline phosphatase of 143 U/L (upper limit of normal 113 U/L). All other results were within normal limits. The patient was empirically treated for a community acquired pneumonia with azithromycin

Given persistent cough, CT chest was obtained one month later. This demonstrated a 4 cm opacity in the left lower lung. Bronchoscopy with bronchoalveolar lavage revealed normal cell count, negative cultures, but some revealed some atypical cells on cytology. The patient was seen by Pulmonology who started ciprofloxacin and inhaled corticosteroids, and scheduled repeat CT chest in 8 weeks.

Within one month, the patient noted progressive shortness of breath, dry cough, unintentional weight loss and both back and pelvic pain. Blood counts and chemistries were, again within normal limits except alkaline phosphatase which increased to 193 U/L. Repeat CT chest demonstrated a 4.9 cm opacity in the left lower lung with bilateral ground glass changes in the lower lung lobes bilaterally.

CT guided lung biopsy was obtained revealing a low-grade adenocarcinoma, with immuno-histochemical staining and morphology consistent with lung primary. PET/CT confirmed an FDG-avid left lower lung 4.5 cm lesion in addition to FDG-avid bone lesions at the third lumbar vertebrae and bilateral pelvis. An MRI brain was benign. Labs again revealed a largely unremarkable blood count and metabolic panel, with only an elevated alkaline phosphatase of 203 U/L. Carcinoembryonic antigen (CEA) was elevated to 28.3 ng/mL, with upper limit of normal 3.1 ng/mL.

The patient received palliative radiotherapy to the lesion at L3 and the pelvis, resulting in modest pain relief within 1 week, while awaiting next generation sequencing results from both blood and tumor tissue. Soon after completing radiation, a CCDC6-RET fusion was detected in both blood and tumor. Selpercatinib was started at 160 mg po BID, and within 72 hours of drug initiation, the patient noted improved pulmonary symptoms and further pain relief. Narcotics were able to be discontinued within one week following Selpercatinib initiation. Appetite and weight improved within two weeks of starting Selpercatinib.

CT scans of the chest, abdomen and pelvis three months after starting Selpercatinib revealed a partial response, with the lung lesion now measured at 2 cm, and improved bilateral ground glass changes. The bone lesions were sclerotic, consistent with treatment related changes, and there was no evidence for any new metastatic lesions. Both the alkaline phosphatase and CEA had normalized. The patient continues on Selpercatinib and is doing well.

***Discussion***

RET fusions were first identified in lung cancer in 2012.[1] The RET proto-oncogene encodes a transmembrane receptor tyrosine kinase that is involved in the embryonic development of the nervous system and kidneys.[2] Fusions between sequences that encode the kinase domain containing the carboxy terminal region of RET and upstream gene partners result in abnormal expression of chimeric kinase fusion proteins, which result in constitutively active, ligand independent signaling and oncogenesis.[3] RET fusions are found in 1-2% of non-small-cell lung cancer (NSCLC) and most commonly occur in a mutually exclusive fashion to other oncogenic drivers in NSCLC such as EGFR, ROS and ALK alterations.[3] Some of the first clinical trials in RET positive patients with NSCLC looked at multi-targeted kinase inhibitors such as vandetanib,[4] cabozantinib[5] and lenvatinib.[6] The use of these agents resulted in limited clinical improvements, with high rates of drug related toxicities resulting in dose modifications and treatment discontinuation.

Selpercatinib is a novel, ATP-competitive, highly selective small-molecule inhibitor of RET kinase, designed to penetrate the central nervous system and result in anti-tumor activity within the brain.[7] This drug has nanomolar potency against diverse RET alterations, fusions, activating point mutations and predicted acquired resistance mutations while largely sparing non-RET kinases and off kinase targets.[8] The FDA granted accelerated approval of Selpercatinib in May 2020 for those with advanced, RET-fusion positive NSCLC based on data coming out of the LIBRETTO-001 trial, a phase 1-2 study whose main outcome measures were overall response rate and response duration. All patients enrolled in the phase 2 compo-

nent of this trial received the recommended dose of Selpercatinib 160 mg by mouth twice daily.[7]

A total of 105 patients with RET positive NSCLC who previously received platinum-based chemotherapy and 39 previously untreated patients with advanced RET addicted NSCLC were enrolled on LIBRETTO-001.[7] The overall response rate for those previously treated with chemotherapy was 64%, with a median response duration of 17.5 months, while the intra cranial response was 91%.[7] Of note, these responses were noted regardless of the specific RET fusion partner, prior checkpoint inhibition receipt or multi targeted kinase inhibitors. The overall response rate for those previously untreated patients was 85%, with neither the median duration of response or medial progression free survival reached at the time of publication.[7] The most common Selpercatinib adverse event was diarrhea, dry mouth and hypertension. The most common grade 3-4 adverse events were hypertension in 14%, increased alanine aminotransferase (ALT) in 13%, and increased aspartate aminotransferase (AST) in 10%. Dose reductions were required in 30% of patients on study, while 2% had drug discontinuation, the most common reason being elevated ALT and drug hypersensitivity.[7]

In December 2020, the FDA approved Pralsetinib, an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic RET fusions and mutations based on data coming out of the ARROW clinical trial.[9] Pralsetinib resulted in a 61% overall response rate in those patients who previously received platinum-based chemotherapy with a median progression free survival of just over 17 months, while those without prior chemotherapy (poor chemotherapy candidates) had a 70% response rate.[9] The overall frequency of adverse events was manageable and generally similar to Selpercatinib, with a slightly different profile, including more neutropenia, but less transaminitis.

We present a patient with metastatic RET-fusion positive non-small-cell lung cancer who derived a significant radiographic and clinical benefit on Selpercatinib in the front-line setting. To date, trials suggest similar response rates for RET selective small molecular inhibitors when compared to other targeted therapies in oncogene drive lung cancers such as Osimertinib in EGFR-mutant NSCLC (80%),[10] Crizotinib in ROS1 fusion-positive NSCLC (72%)[11] or Alectinib in ALK-positive NSCLC (83%).[12] These data continue to support the use of earlier line, targeted therapies in driver mutation positive, or oncogene driven advanced NSCLC. This case further demonstrates the importance of next generation sequencing, whether via the blood, tumor tissue, or both, at diagnosis of advanced NSCLC to ensure no therapeutic option is missed.

## REFERENCES


1. **Lipson D, Capelletti M, Yelensky R, Otto G, Parker A, Jarosz M, Curran JA, Balasubramanian S, Bloom T, Brennan KW, Donahue A, Downing SR, Frampton GM, Garcia L, Juhn F, Mitchell KC, White E, White J, Zwirko Z, Peretz T, Nechushtan H, Soussan-Gutman L, Kim J, Sasaki H, Kim HR, Park SI, Ercan D, Sheehan CE, Ross JS, Cronin MT, Jänne PA, Stephens PJ**. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med*. 2012 Feb 12;18(3):382-4. doi: 10.1038/nm.2673. PMID: 22327622; PMCID: PMC3916180.
2. **Subbiah V, Yang D, Velcheti V, Drilon A, Meric-Bernstam F**. State-of-the-Art Strategies for Targeting *RET*-Dependent Cancers. *J Clin Oncol*. 2020 Apr 10;38(11):1209-1221. doi: 10.1200/JCO.19.02551. Epub 2020 Feb 21. PMID: 32083997; PMCID: PMC7145587.
3. **Drilon A, Hu ZI, Lai GGY, Tan DSW**. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. *Nat Rev Clin Oncol*. 2018 Mar;15(3):151-167. doi: 10.1038/nrclinonc.2017.175. Epub 2017 Nov 14. Erratum in: *Nat Rev Clin Oncol*. 2017 Nov 28;: PMID: 29134959; PMCID: PMC7938338.
4. **Yoh K, Seto T, Satouchi M, Nishio M, Yamamoto N, Murakami H, Nogami N, Matsumoto S, Kohno T, Tsuta K, Tsuchihara K, Ishii G, Nomura S, Sato A, Ohtsu A, Ohe Y, Goto K**. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *Lancet Respir Med*. 2017 Jan;5(1):42-50. doi: 10.1016/S2213-2600(16)30322-8. Epub 2016 Nov 4. PMID: 27825616.
5. **Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M, Van Voorthuysen M, Somwar R, Smith RS, Montecalvo J, Plodkowski A, Ginsberg MS, Riely GJ, Rudin CM, Ladanyi M, Kris MG**. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016 Dec;17(12):1653-1660. doi: 10.1016/S1470-2045(16)30562-9. Epub 2016 Nov 4. PMID: 27825636; PMCID: PMC5143197.
6. **Hida T, Velcheti V, Reckamp KL, Nokihara H, Sachdev P, Kubota T, Nakada T, Dutcus CE, Ren M, Tamura T**. A phase 2 study of lenvatinib in patients with RET fusion-positive lung adenocarcinoma. *Lung Cancer*. 2019 Dec;138:124-130. doi: 10.1016/j.lungcan.2019.09.011. Epub 2019 Sep 16. PMID: 31710864.
7. **Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, McCoach CE, Gautschi O, Besse B, Cho BC, Peled N, Weiss J, Kim YJ, Ohe Y, Nishio M, Park K, Patel J, Seto T, Sakamoto T, Rosen E, Shah MH, Barlesi F, Cassier PA, Bazhenova L, De Braud F, Garralda E, Velcheti V, Satouchi M, Ohashi K, Pennell NA, Reckamp KL, Dy GK, Wolf J, Solomon B, Falchook G, Ebata K, Nguyen M, Nair B, Zhu EY, Yang L, Huang X, Olek E, Rothenberg SM, Goto K, Subbiah V**. Efficacy of Selpercatinib in *RET* Fusion-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020 Aug 27;383(9):813-824. doi: 10.1056/NEJMoa2005653. PMID: 32846060; PMCID: PMC7506467.
8. **Subbiah V, Velcheti V, Tuch BB, Ebata K, Busaidy NL, Cabanillas ME, Wirth LJ, Stock S, Smith S, Lauriault V, Corsi-Travali S, Henry D, Burkard M, Hamor R,**

**Bouhana K, Winski S, Wallace RD, Hartley D, Rhodes S, Reddy M, Brandhuber BJ, Andrews S, Rothenberg SM, Drilon A**. Selective RET kinase inhibition for patients with RET-altered cancers. *Ann Oncol*. 2018 Aug 1;29(8):1869-1876. doi: 10.1093/annonc/mdy137. PMID: 29912274; PMCID: PMC6096733.

9. **Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier PA, Lopes G, Tan DSW, Garralda E, Paz-Ares LG, Cho BC, Gadgeel SM, Thomas M, Liu SV, Taylor MH, Mansfield AS, Zhu VW, Clifford C, Zhang H, Palmer M, Green J, Turner CD, Subbiah V**. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol*. 2021 Jul;22(7):959-969. doi: 10.1016/S1470-2045(21)00247-3. Epub 2021 Jun 9. Erratum in: *Lancet Oncol*. 2021 Aug;22(8):e347. PMID: 34118197.
10. **Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS; FLAURA Investigators**. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa 1713137. Epub 2017 Nov 18. PMID: 29151359.
11. **Wu YL, Yang JC, Kim DW, Lu S, Zhou J, Seto T, Yang JJ, Yamamoto N, Ahn MJ, Takahashi T, Yamanaka T, Kemner A, Roychowdhury D, Paolini J, Usari T, Wilner KD, Goto K**. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2018 May 10;36(14): 1405-1411. doi: 10.1200/JCO.2017.75.5587. Epub 2018 Mar 29. PMID: 29596029.
12. **Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Pérol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T; ALEX Trial Investigators**. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017 Aug 31;377(9):829-838. doi: 10.1056/NEJMoa1704795. Epub 2017 Jun 6. PMID: 28586279.