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TITLE: Real-world outcomes of RET inhibitor switching in RET fusion–positive NSCLC patients

AUTHORS: Katherine E Smith (presenting author)[1], Parth A Desai[2], Alexander Drilon[3], Christine Garcia[4], Aaron S. Mansfield[1], Aaron Sheppard[5], Amber Thomassen[5], Vivek Subbiah[6]

1. Department of Oncology, Mayo Clinic, Rochester, MN, USA
2. Department of Hematology & Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA.
3. Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA
4. Weill Cornell Medicine / New York Presbyterian Hospital, New York, NY, USA
5. Rigel Pharmaceuticals, Inc., South San Francisco, CA, USA
6. Sarah Cannon Research Institute, Nashville, TN, USA

BACKGROUND

The receptor tyrosine kinase RET (REarranged during Transfection) inhibitors (RETi) pralsetinib and selpercatinib are approved for metastatic RET fusion positive NSCLC. Treatment-related adverse events (AEs) may lead to switching between RETis; however, evidence guiding management after RETi intolerance is limited. We evaluated real-world outcomes of patients with RET fusion–positive NSCLC who switched RET inhibitors, with a focus on those that switched due to AE related events.

METHODS

A retrospective chart review was conducted via a standardized web-based form among US oncologists treating RET fusion positive advanced NSCLC. Eligible patients initiated pralsetinib or selpercatinib for RET fusion-positive NSCLC between October 2020 and December 2024, with collection balanced across treatments. Data gathered included baseline characteristics, reasons for choosing treatments, and efficacy outcomes.

RESULTS

A total of 162 patient charts were collected from 58 physicians; 82 treated with pralsetinib as their first RETi and 80 initially treated with selpercatinib (Figure 1). Among them, 17/82 (20.7%) patients treated with pralsetinib and 25/80 (31.3%) patients treated with

selpercatinib patients switched RETi therapy. Reasons for switching from pralsetinib were loss/lack of response (n=14), insurance (n=2), and AE (n=1). Reasons for switching from selpercatinib were loss/lack of response (n=13), insurance (n=4), AE (n=7) and unspecified (n=1). Of the 7 patients on selpercatinib who switched due to AEs, the AEs included fatigue (n=3;43%), transaminitis (n=1;14%), hypertension (n=1;14%), QT prolongation (n=1;14%), and neuropathy (n=1;14%). The patient on pralsetinib who switched due to AE experienced edema.

Of the 8 patients who switched RETi due to AEs, the mean age was 66.3 (SD=9.3) and 50% (n=4) were male. 75% (n=6) were initially diagnosed with stage IIIb or higher NSCLC. At RETi initiation, 75% (n=6) had an ECOG ≤1 and 37.5% (n=3) had CNS metastasis. Fifty percent (n=4) received RETi as first-line therapy.

After switching RET inhibitors due to an AE, the ORR was 62.5% (2 CR, 3 PR). Of the 7 switching to pralsetinib, the ORR was 57.1% (2 CR, 2 PR). The patient who switched to selpercatinib achieved a PR. Median post-switch treatment duration was 99.5 days (100 days for pralsetinib, 29 days for selpercatinib).

## CONCLUSION

Among patients who switched RETi's due to an AE, response rates exceeded 60%, aligning with the 50% response rate observed in the RET MAP registry. Collectively, these results underscore that switching from one RET inhibitor to another can be efficacious, particularly for patients who must discontinue initial therapy because of adverse events.

Figure 1: