Case Report

RET-mutated non-small cell lung cancer treated with pralsetinib: a case series

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Background: Targeted therapies significantly changed the treatment scenario of non-small cell lung cancer (NSCLC) and improved prognosis of patients harbouring oncogenic drivers. Among these, REarranged during Transfection (RET) fusions are rare, occurring in 1% to 2% of NSCLC. Recent trials revealed the efficacy of novel inhibitors such as pralsetinib and selpercatinib. Due to rarity of RET fusion and novelty of these target therapies, observational and "real world" evidence are missing. The purpose of this series is to point out the impact of treatment with pralsetinib in the clinical setting.

Case Description: We report the clinical cases of four patients with metastatic RET-positive NSCLC, who achieved clinical benefit and objective response upon treatment with pralsetinib (400 mg/die). All patients received target therapy after failure of chemotherapy or immunotherapy. Three patients experienced adverse events leading to dose reduction (200 mg/die), but none permanently discontinued treatment.

Conclusions: To our knowledge this is the first clinical series about pralsetinib treatment for metastatic RET positive NSCLC in a "real world" setting. It proves the importance of investigating and targeting RET fusions in NSCLC patients. According to the literature, patients receiving RET inhibitor appear to have significant and lasting responses.

Keywords: Non-small cell lung cancer (NSCLC); REarranged during Transfection (RET); target therapy; case report

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Introduction

The advent of targeted therapies has radically changed the treatment landscape of non-small cell lung cancer (NSCLC) with oncogenic driver alterations (1,2). Several studies showed improved quality of like and significant survival benefit compared to chemotherapy. Thus, tyrosine kinase inhibitors (TKI) have become the standard of care for patients harbouring actionable mutations on *EGFR*, *ALK*, *BRAF* and *ROS-1* (3-6).

Novel molecular diagnostics tools such as the next generation sequencing (NGS) have contributed to the discovery of further oncogenic drivers. Fusion of REarranged during Transfection (RET), HER2, c-MET exon 14 skipping mutation, KRASG12C mutation and NTRK have been identified as additional molecular targets in NSCLC patients (7-11).

RET gene rearrangements occur in 1–2% of lung adenocarcinomas, especially in young and non-smoking patients (12-14). Pralsetinib is an oral TKI with potent anti-RET activity. A multicenter and multi-cohort trial showed overall responses in 61% of patients previously treated with platinum-based chemotherapy, and in 70% of treatment-naive patients (15). Based on these results, Food and Drug Administration (FDA) granted accelerated approval to pralsetinib for metastatic RET fusion-positive NSCLC in September 2020. Panel and international guidelines recommends pralsetinib as a first-line or subsequent

Table 1 Summary of clinical characteristics

Clinical case	Age, years	Sex	Smoking habitus	Previous therapeutic line	RET fusion	Best response to pralsetinib
Case 1	78	Female	Former smoker	1	RET-KIF5B	PR
Case 2	59	Male	Former smoker	2	RET-C10orf118	PR
Case 3	63	Female	Never smoker	1	RET-NCOA4	PR
Case 4	54	Female	Never smoker	2	RET-KIF5B	PR

RET, REarranged during Transfection; PR, partial response.

therapy option for patients with metastatic NSCLC who are positive for RET rearrangements (16). Additionally, the efficacy of selpercatinib, an ATP-competitive, highly selective small-molecule inhibitor of RET kinase, was also demonstrated in both pre-treated and naïve patient, with an objective response of 64% and 85% respectively (17).

In Italy, the compassionate use of pralsetinib allowed to target pretreated NSCLC patients harboring RET fusions. Ongoing trials are evaluating pralsetinib as front-line treatment for metastatic or unresectable locally advanced disease (18,19). As described in a recent report, pralsetinib was also successfully ad neoadjuvant therapy (20).

Due to rarity of RET fusion and novelty of these target therapies, observational and "real world" evidence are missing. We report four clinical cases of RET-mutated NSCLC patients treated with pralsetinib. To our knowledge this is the first clinical series on metastatic RET positive NSCLC treated with pralsetinib.

Clinical characteristics are summarized in *Table 1*. Radiological response is represented in *Figure 1*, treatment timeline and molecular asset are represented in *Figure 2*. We present the following cases in accordance with the CARE reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-50/rc).

Case presentation

Clinical case 1

A 78-year-old Caucasian woman, former smoker, was diagnosed with metastatic lung adenocarcinoma in July 2020. PD-L1 immunohistochemistry (IHC) expression on tumor sample was 70%. No actionable mutations on *EGFR*, *ALK* and *ROS1* genes were detected. The patient received first-line treatment with immunotherapy, pembrolizumab 200 mg every 3 weeks. After three months, a full-body computed tomography (CT) scan showed pleural disease progression. Comprehensive molecular profiling using NGS panel (Foundation Medicine, Cambridge, MA, USA) revealed *RET-KIF5B* fusion. Therefore, in January 2021 the patient started pralsetinib 400 mg/die. Mild hypertension and dysgeusia occurred during treatment but no discontinuation or dose reduction was required. We observed a rapid improvement of respiratory symptoms. In March 2021, CT scan showed a significant partial response in both nodes and pleural disease (*Figure 1A*). In September 2021 dose reduction (200 mg/die) was needed due recurrent mucositis and fatigue. Last CT scan performed in January 2022 showed stable disease. Patient died in February 2022 for cardiovascular event, not directly related to the disease and pralsetinib treatment.

Clinical case 2

In August 2019, a 59-year-old Caucasian man, former smoker, was diagnosed with lung adenocarcinoma with lung, nodes, adrenal and peritoneum metastases. The patient experienced progressive disease after four cycles of first-line platinum-based doublet chemotherapy. In November 2019, he started a second-line chemotherapy with Nintedanib plus docetaxel, achieving long-lasting control of disease. *RET-C10orf118* fusion was detecting thanks NGS panel on tissue biopsy (Foundation Medicine). In March 2021, CT scan showed progressive disease and, then, the patient started treatment with pralsetinib 400 mg/die. CT scan performed after 3 month of treatment showed partial response (*Figure 1B*). To this date (April 2022), the patient is receiving this treatment reporting clinical benefit and no relevant adverse events.

Clinical case 3

A 63-year-old Caucasian woman, never smoker, was diagnosed with lung adenocarcinoma and multiple bone metastases in August 2019. No druggable mutations were found, PD-L1 IHC expression was 3% on tumor cells. In November 2019, the patient started a chemotherapy

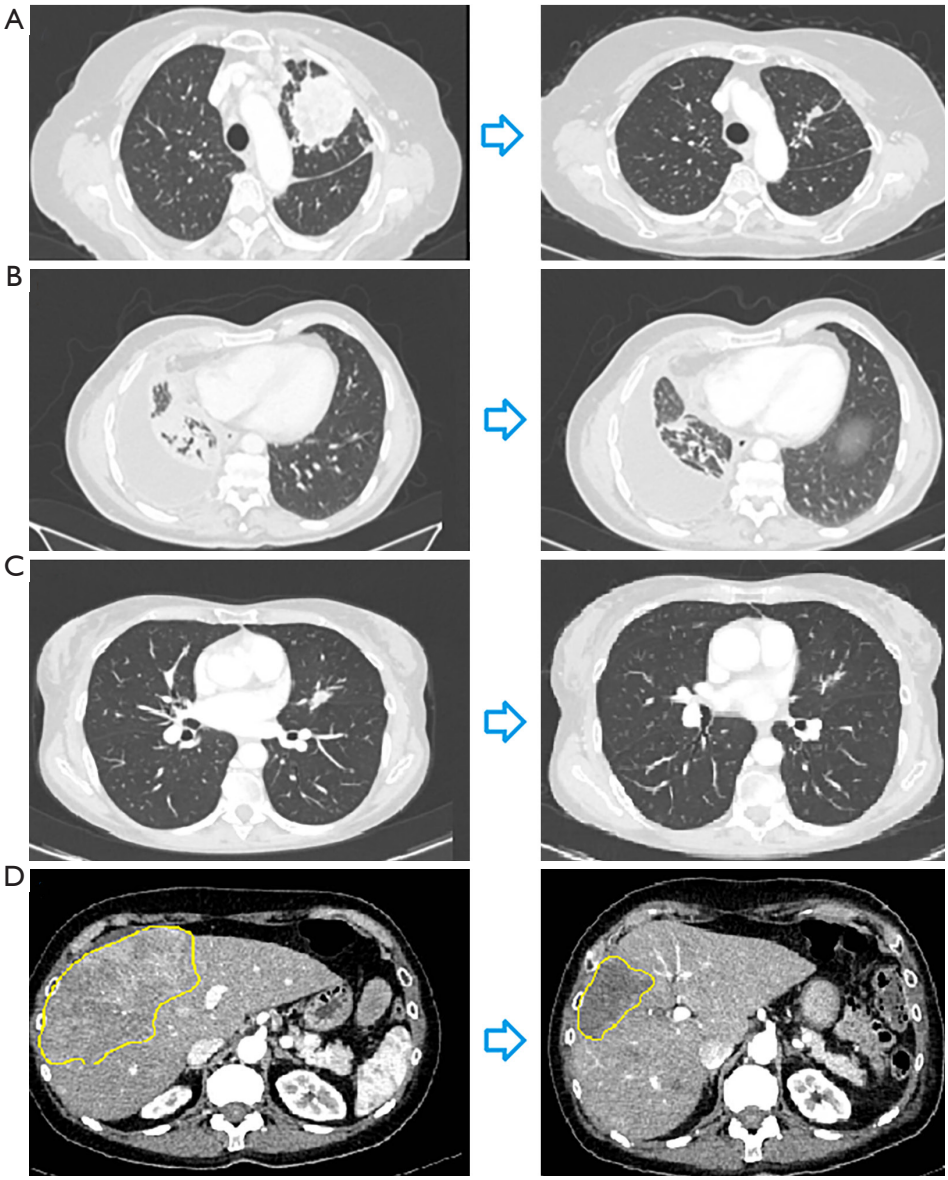

Figure 1 First CT revaluation during treatment with Pralsetinib. (A-C) CT scan shows side reduction of lung cancer of the first three cases. (D) CT scan shows necrosis and significant reduction of liver metastases in the last cases of this series. CT, computed tomography.

treatment with Cisplatin plus Pemetrexed. CT scan, performed after IV cycles of chemotherapy, showed partial response and the patient continued maintenance therapy with pemetrexed until September 2020, when a skeletal scintigraphy showed a progressive disease. NGS analysis (Foundation Medicine), performed with liquid biopsy, revealed a *RET-NCOA4* fusion. Therefore, the patient started pralsetinib 400 mg/die. The first radiological re-assessment, performed in December 2020, showed partial response. After 5 months of treatment, the patient experienced olecranon bursitis, mucositis and grade 4 neutropenia [according to Common Terminology Criteria for Adverse Events (CTCAE) v5]. For this reason, patients stopped treatment and resumed it after recovery with reduced pralsetinib dosage to 200 mg/die. In April 2022, patient has had no other significant toxicities and continues treatment with pralsetinib while maintaining clinical benefit and stable radiological disease (*Figure 1C*).

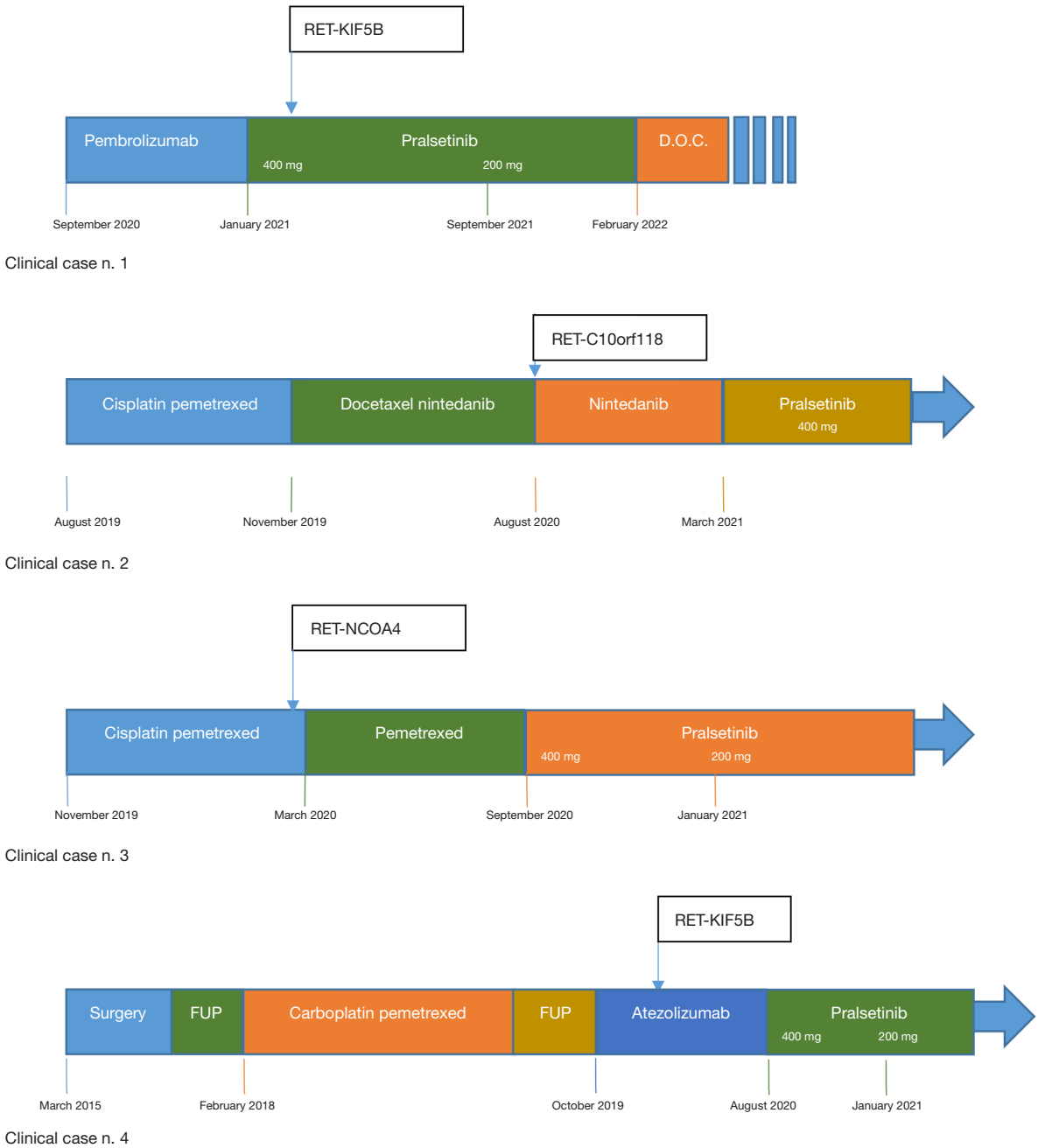

Figure 2 Timeline and month duration of each treatment. RET, REarranged during Transfection; D.O.C., deceased of other causes; FUP, follow-up.

Clinical case 4

A 54-year-old Caucasian woman, underwent left superior lobectomy for lung adenocarcinoma in march 2015. She received adjuvant chemotherapy with Cisplatin plus Gemcitabine and subsequent radiotherapy. In December 2017, a PET CT scan showed pulmonary relapse, multiple nodes and bone metastases. *PD-L1* IHC expression was 10%. Tumor sample resulted wild type for *EGFR*, *ALK* and *ROS1* mutations. The patient received first-line chemotherapy with Carboplatin plus pemetrexed, and needed bone radiotherapy with palliative intent. After chemotherapy failure, the patient started immunotherapy

with atezolizumab. In June 2020, NGS on liquid biopsy (Foundation Medicine) detected *RET-KIF5B* fusion. In August 2020, CT scan showed ubiquitous progressive disease and the patient started pralsetinib. During treatment, the patient developed grade 3 neutropenia, grade 2 anemia and asthenia, leading to reduce dosage at 200 mg/die. CT scan showed partial response (*Figure 1D*). Patient in April 2022 is still receiving treatment maintaining clinical benefit and objective response.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Informed consents were obtained from the patients' relatives/parents. A copy of the written consent is available for review by the editorial office of this journal. Local ethics committee approval was not required due to non-experimental content of the manuscript.

Discussion

In last decades, targeted therapies have dramatically changed the treatment landscape of NSCLC treatment. The advent of novel molecular profiling tools such as NCS led to discovery of new oncogene drivers. Among these, RET fusions, albeit rare, are amenable targets for TKIs. According recent evidence, selpercatinib and pralsetinib have a strong antitumor effect, similar to the more well-known target therapies used against *EGFR*, *ALK* and *ROS-1* aberrations (3,4,6,15,17). However, NSG is not routinely used in current clinical practice and only a few centers can benefit from it. Similarly, in several countries, pralsetinib and selpercatinib are not yet standard of care in patients with RET-positive NSCLC. Consequently, the impact of these treatments has not been adequately investigated in "real-world" studies.

These clinical series proved the significance of looking for RET fusions in order properly tailor patient's treatment. Indeed, all patients received pralsetinib achieving significant clinical benefit and radiological response after failure of chemotherapy or immunotherapy. Three patients experienced adverse events leading to dose reduction, but none permanently discontinued treatment. Further and large-scale studies are needed in order to explore and evaluate the clinical outcomes of RET-positive NSCLC treated with TKIs.

Our real word experience is consistent in terms of clinical benefit and progression free survival with results from clinical trials (21).

Conclusions

Despite being only a small case report, this report points out the significance of investigating and targeting RET fusions in NSCLC. Patients receiving pralsetinib had significant clinical benefit and lasting objective responses. Further and large-scale studies are needed in order to explore and evaluate the clinical outcomes of RET-positive NSCLC treated with TKIs.

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