Selpercatinib in RET fusion-positive non-small-cell lung cancer (SIREN): a retrospective analysis of patients treated through an access program

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Abstract

Introduction: Rearranged during transfection (RET) gene fusions are rare genetic drivers in non-small cell lung cancer (NSCLC). Selective RET-inhibitors such as selpercatinib have shown therapeutic activity in early clinical trials; however, their efficacy in the real-world setting is unknown.

Methods: A retrospective efficacy and safety analysis was performed on data from RET fusion-positive NSCLC patients who participated in a selpercatinib access program (named patient protocol) between August 2019 and January 2021.

Results: Data from 50 patients with RET fusion-positive advanced NSCLC treated with selpercatinib at 27 centers in 12 countries was analyzed. Most patients were Non-Asian (90%), female (60%), never-smokers (74%), with a median age of 65 years (range, 38–89). 32% of the patients had known brain metastasis at the time of selpercatinib treatment. Overall, 13 patients were treatment-naïve, while 37 were pretreated with a median of three lines of therapy (range, 1–8). The objective response rate (ORR) was 68% [95% confidence interval (CI), 53–81] in the overall population. The disease control rate was 92%. The median progression-free survival was 15.6 months (95% CI, 8.8–22.4) after a median follow-up of 9 months. In patients with measurable brain metastases ($n = 8$) intracranial ORR reached 100%. In total, 88% of patients experienced treatment-related adverse events (TRAEs), a large majority of them being grade 1 or 2. The most common grade ⩾3 TRAEs were increased liver enzyme levels (in 10% of patients), prolonged QTc time (4%), abdominal pain (4%), hypertension (4%), and fatigue/asthenia (4%). None of patients discontinued selpercatinib treatment for safety reasons. No new safety concerns were observed, nor where there any treatment-related death.

Conclusions: In this real-world setting, the selective RET-inhibitor selpercatinib demonstrated durable systemic and intracranial antitumor activity in RET fusion-positive NSCLC and was well tolerated.

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Introduction

Rearranged during transfection (RET) gene fusions have been identified in approximately 10–20% of papillary thyroid cancers and in up to 1–2% of non-small cell lung cancers (NSCLCs), primarily in adenocarcinomas and less commonly in other tumor types.[1–5] The RET proto-oncogene codes for a transmembrane receptor-tyrosine kinase (RTK); the constitutive activation of the intracellular kinase domain through RET chimeric fusion proteins favours tumor cell growth and spread.[5,6] Moreover, as is the case with other oncogenic driven NSCLCs [e.g. epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)], brain metastases are frequently found in cases of advanced RET fusion-positive NSCLC.[7] In addition, RET gene fusions seem mutually exclusive with other major oncogenic drivers of lung cancer.[6,8]

Chemotherapy, immunotherapy, or the combination of both, as well as multiple kinase inhibitors (MKIs), exhibit modest efficacy in RET fusion-positive NSCLC.[9–11] Until recently, patients with RET fusion-positive cancers have experienced an unmet need for an efficient and safe targeted therapy. Indeed, potent and specific inhibition of RET may provide clinical benefits to patients with malignancies due to the presence of oncogenic alterations in RET.

Selpercatinib, formerly known as LOXO-292, is a highly selective next generation RET-inhibitor. This small molecule has been designed to competitively and selectively block the adenosine triphosphate binding site of the RET receptor tyrosine kinase. Selpercatinib was first conceived as a selective and alternative therapy option after resistance to MKIs.[12] The efficacy and safety data associated with selpercatinib on NSCLC and thyroid carcinoma solid tumors were first presented in 2018 at the World Conference on Lung Cancer, and the American Thyroid Association, respectively. The data concerned with the RET fusion-positive NSCLC part of the multicenter, global, open-labeled phase I/II LIBRETTO-001 trial (ClinicalTrials.gov identifier: NCT03157128) were subsequently published in August 2020.[13] This study described 105 consecutively-enrolled NSCLC patients who had previously received platinum-based chemotherapy; in those pretreated patients, a high objective response rate (ORR) [64%; 95% confidence interval (CI), 54–73], a sustained median duration of response (mDoR) (17 months; 95% CI, 12.0–NR), and a favorable

median progression-free survival (mPFS) were attained (16 months; 95% CI, 13.7–NR). Among 39 previously untreated patients, the ORR was higher, at 85% (95% CI, 70–94), while mDoR and mPFS have still not been reached at the time-point of the interim analysis (median follow-up of 16 months). Among the 96 patients presenting with CNS metastases at the start of the study, the intracranial ORR (icORR) reached 87% (95% CI, 66–97), and the intracranial mDoR was 9 months (95% CI, 3–24).

The U.S. Food and Drug Administration granted selpercatinib breakthrough therapy designation in August 2018 and US-approval in May 2020 for the first and following lines of treatment in metastatic RET fusion-positive NSCLC, advanced or metastatic RET-mutant medullary thyroid cancer, and RET fusion-positive thyroid cancer. In Europe, selpercatinib was approved in February 2021 for the same indications following prior treatment. In many countries worldwide, selpercatinib has been available since May 2019 through an Expanded Access Program (EAP) and the Named Patient Protocol (NPP) for the treatment of patients with locally-advanced and metastatic RET fusion-positive NSCLC who were not able to participate in a clinical trial and had no other treatment options.

To the best of our knowledge, only a few single retrospective analyses of patients treated with selpercatinib outside of clinical trials have been previously published.[10,14] The main objective of our analysis was to evaluate the efficacy and safety of this RET-inhibitor on participants in a selpercatinib NPP under real-world conditions. Considering that RET fusion-positive alterations in NSCLC are rare, here, we present retrospectively collected data from an international network of NSCLC-treating pneumologists and oncologists.

Materials and methods

Study design
A retrospective, non-interventional, international, multicenter study: 'selpercatinib in RET fusion-positive NSCLC' (SIREN) aimed to collect data on RET fusion-positive NSCLC patients treated with selpercatinib within a NPP. The primary outcome of this real-world data analysis was the systemic ORR defined according to RECIST v1.1 criteria. The secondary outcomes were the

following: (i) the evaluation of treatment-related adverse events (TRAEs) determined by the treating physician; (ii) a disease control rate (DCR) defined as the proportion of patients with complete response, partial response, or stable disease; (iii) the icORR; (iv) the median duration of treatment (mDoT) defined as the time between selpercatinib start to last dose received; (v) the mDoR assessed as the time between the initial response to therapy and subsequent disease progression or death due to any cause; and (vi) the mPFS measured as the time from first dose of selpercatinib to first progression event according to RECIST v1.1 criteria.

This retrospective study was conducted in accordance with the principles of Good Clinical Practice and following the Declaration of Helsinki. The study protocol was approved by the ethics committee of the city of Vienna, Austria (EK 20-330-VK). The study participants' privacy and confidentiality was guaranteed according to Austrian law (Austrian Data Protection Act, version: 25 May 2018; BGBl. I Nr. 165/1999).

Study population and treatment

Twenty-seven centers in twelve different countries contributed to this dataset: Australia (1 center), Austria (8), Canada (2), Finland (1), France (2), Germany (4), Italy (2), Netherlands (2), Spain (1), Slovenia, (1), Sweden (2), and Switzerland (1). The data of all eligible patients treated by the physicians who participated in the selpercatinib NPP [selpercatinib treatment plan in a Named Patient Program for adult and pediatric patients with locally advanced or metastatic solid tumors or malignancy with RET activation (Study Alias: J2G-OX-Y049)] were included. Eligible adult patients had to fulfill the following criteria: (i) NSCLC with RET activation, who are not eligible for an ongoing selpercatinib clinical trial and are medically-suitable for treatment with selpercatinib; (ii) have progressed or are intolerant to standard therapy, or no standard therapy option exists, or in the opinion of the investigator, are unlikely to derive significant clinical benefit from standard therapy; (iii) have adequate organ function and (iv) have received at least one follow-up assessment of treatment response (CT scan).

Patients typically received an oral dose of 160 mg (two 80 mg capsules) twice a day (BID). Based on their individual clinical profile, some patients might have been assigned a reduced initial dose, which was subsequently scalable at the treating physician's discretion, following clinical tolerance and safety. Selpercatinib treatment was continued until disease progression, lack of clinical benefit, unacceptable toxicity, patient's withdrawal of consent, or the treating physician's decision to withdraw the patient from the NPP.

Data collection

The data covered RET-positive NSCLC patients treated with selpercatinib through the NPP between August 2019 and January 2021. Predefined data about patient demographics and clinical characteristics (age, gender, race, smoking and performance status, disease stage, metastases, histology, previous regimens, RET fusion partner), selpercatinib treatment (duration and dose, best response, as well as date, type, and location of progression), and safety information have been extracted from available medical records and anonymized by the treating physicians.

Efficacy and safety assessments

Scheduled efficacy assessment of tumor response and progression per RECIST v1.1 protocol was based on a computer tomography (CT) scan of the chest and abdomen performed every 6–12 weeks, according to the clinical practice of each institution.[15] Brain CT or magnetic resonance imaging (MRI) evaluation and follow-up brain scans were conducted according to local standards of care. In addition, laboratory tests and a physical examination, as well as the monitoring of vital signs, serum pregnancy tests, and electrocardiograms were systematically collected every 6 weeks.

The following efficacy parameters were analyzed for the overall population, as well as separately for two subgroups (pretreated and treatment-naïve patients): ORR, DCR, DoT, DoR and PFS. In patients with measurable disease at baseline, tumor response (maximum change in tumor size) was assessed by comparing pretreatment lesions measurements at baseline to at least one post-treatment imaging evaluation.

The assessment of if an adverse event (AE) was treatment-related was made by the treating physician. All reported TRAEs were graded as per the Common Terminology Criteria for Adverse Events

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(CTCAE, version 5.0). Safety was monitored at baseline, at every subsequent assessment visit, or as clinically indicated. Each dose modification or interruption and treatment discontinuation due to TRAEs were documented. Some dose modifications or interruptions were based on treating physician's discretion only and would have not been required by the NPP-treatment-protocol.

Statistical analysis

All anonymized data were centrally-collected and analyzed at the Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology in Vienna (Austria). Descriptive data and categorical data were expressed as frequencies and proportions, while continuous data were reported as mean ± standard deviation (SD). Median DoR, DoT, and PFS were analyzed using the Kaplan–Meier methodology with median presented along with 95% Cis. CIs for proportions, such as ORR and DCR, were calculated using the Clopper–Pearson method. Comparison between subgroups (previous lines of systemic anticancer therapy, as well as pretreated patients *versus* treatment-naïve patients or different RET fusion partners) were performed by Log-rank test with a level of significance of 5% (Chi square $p = 0.05$). All statistical analyses were conducted using SPSS software (v.26.0, IBM SPSS Statistics).

Results

Patients

A total of 50 patients with locally-advanced or metastatic RET fusion-positive NSCLC were retrospectively documented (for demographics and clinical characteristics, see Table 1). Overall, 37 patients were pretreated and received a median of three treatment lines (range, 1–8) before selpercatinib, while 13 patients were treatment-naïve and received selpercatinib as a first-line therapy. Most patients were women (60%), Non-Asian (90%), and never-smokers (74%). All patients except one (stage IIIc) had stage IV disease before selpercatinib first-dose administration, with a median of two different locations of metastases per patient (range, 1–5). Among the 16 patients with known brain lesions at the time of selpercatinib initiation as assessed by the treating physician, six (38%) were asymptomatic; in the treatment-naïve subgroup, all patients with intracranial metastases ($n = 3$) had related symptoms, whereas six pretreated patients (46%) did not present with any neurological symptoms. Due to the presence of cerebral lesions, three patients (19%) had received prior whole-brain radiation therapy (WBRT) and two patients (12%) had received prior brain-surgery. In addition, four patients (25%) received brain radiation [three had WBRT, one had stereotactic radiotherapy (SRT)] concomitant to selpercatinib treatment. Lung adenocarcinoma was the predominant histology (90%). Among all patients, the RET fusion-partner was identified in 45 patients (90%). Kinesin-1 heavy chain (KIF5B) was the most common upstream RET-fusion partner (66%), followed by coiled-coil domain-containing protein 6 (CCDC6) (20%). Molecular RET testing was performed locally, mainly *via* next-generation sequencing (NGS) (86%) or fluorescence *in situ* hybridization (FISH) (6%).

Patients who received a previous therapy ($n = 37$) were heavily pretreated with a median of three (range, 1–8) lines of therapies: 60% of patients received a platinum-based chemotherapy, 50% an anti-programed cell death protein 1 (anti-PD-1) or programmed death-ligand 1 (PD-L1) therapy, and 24% a tyrosine kinase inhibitor (TKI). For more details, see the legend of Table 1.

Fifteen patients received pretreatment chemotherapy (10 patients as monotherapy and five patients in combination with an anti-angiogenic agent), ten patients had immunotherapy [one patient in combination with a vascular endothelial growth factor (VEGF)/angiopoietin-2 (Ang2)-blocking nanobody], five patients received a chemo-immunotherapy, and seven patients were solely-treated with one or more TKIs. Before selpercatinib, two patients had previously been treated with another selective RET-inhibitor (pralsetinib), which was discontinued in both cases because of toxicity.

Efficacy

Response. Table 2 presents the efficacy outcome of selpercatinib therapy in this population. In the overall population, the ORR was 68% (95% CI, 53–81), with four patients (8%) showing a complete response (CR), 30 patients (60%) a partial response (PR), 12 patients (24%) a stable disease (SD) and two patients (4%) progressive diease (PD). Two patients (4%) were not evaluable (no measurable lesions). The median time to best response was 2.6 months in the overall population and in pretreated patients (95% CI, 2.4–3.6 and 2.5–4.0, respectively) and 1.7 months in treatment-naïve

Table 1. Demographics and clinical characteristics of patients prior to selpercatinib administration[a].

Characteristic	All patients (n = 50)	Treatment-naive patients (n = 13)	Pretreated patients (n = 37)
Age, years			
Median (range)	65 (38–89)	69 (48–89)	58 (38–80)
Age groups, *n* (%)			
<65	25 (50)	5 (38)	20 (54)
≥65	25 (50)	8 (62)	17 (46)
Gender, *n* (%)			
Male	20 (40)	5 (39)	15 (41)
Female	30 (60)	8 (62)	22 (60)
Race, *n* (%)			
Asian	5 (10)	2 (15)	3 (8)
Non-Asian	45 (90)	11 (85)	34 (92)
Smoking status, *n* (%)			
Never smoker	37 (74)	9 (69)	28 (76)
Former smoker	13 (26)	4 (31)	9 (24)
Smoker (<30 py)	8 (16)	3 (23)	5 (14)
Heavy smoker (≥30 py)	4 (8)	0	4 (11)
Unknown	1 (2)	1 (8)	0
Current smoker	0	0	0
Performance status (ECOG)[b], *n* (%)			
0	22 (44)	8 (62)	14 (38)
1	14 (28)	1 (8)	13 (35)
≥2	14 (28)	4 (31)	10 (27)
Location of metastasis, *n* (%)			
Brain	16 (32)	3 (23)	13 (35)
Bones	18 (34)	2 (15)	16 (43)
Lungs	16 (32)	4 (31)	15 (41)
Liver	15 (30)	4 (31)	11 (30)
Lymph nodes	14 (28)	1 (8)	13 (35)
Pleural	11 (22)	2 (15)	9 (24)
Other	15 (30)	5 (38)	10 (27)
Brain metastasis, *n* (%)	N = 16	N = 3	N = 13

(continued)

Table 1. (continued)

Characteristic	All patients (*n* = 50)	Treatment-naive patients (*n* = 13)	Pretreated patients (*n* = 37)
Asymptomatic	6 (38)	0	6 (46)
Symptomatic	10 (63)	3 (100)	7 (54)
Histology subtype, *n* (%)			
Adenocarcinoma	45 (90)	12 (92)	33 (90)
NSCLC NOS	3 (6)	1 (8)	2 (5)
Other	2 (4)	0	2 (5)
RET fusion partner, *n* (%)			
KIF5B	33 (66)	10 (77)	23 (62)
CCDC6	10 (20)	2 (15)	8 (22)
TRIM27	1 (2)	0	1 (3)
NCOA	1 (2)	1 (3)	0
Not determined	5 (10)	0	5 (14)
Previous regimens[c]			
Median (range)	3 (1–8)	NA	3 (1–8)
Type of regimen, *n* (%)			
Platinum-based chemotherapy	30 (60)	NA	30 (81)
Anti-PD-1 or PD-L1 therapy	25 (50)	NA	25 (68)
TKI[d]	12 (24)	NA	12 (32)

[a]Percentage may not equal to 100 because of rounding.
[b]ECOG performance status, with higher numbers indicating worse daily living capability.
[c]Previous regimens defined as at least one dose of chemotherapy and/or immunotherapy and one dose of TKI.
[d]TKIs administered include alectinib (eight patients), brigatinib (2), cabozantinib (1), crizotinib (1), and pralsetinib (2). Some patients have received more than one prior TKI.
Anti-PD-1; anti-cell death protein 1; CCDC6, coiled-coil domain-containing protein 6; ECOG, Eastern Coooperative Oncology Group; KIF5B, kinesin-1 heavy chain; NA, not applicable; NCOA, nuclear receptor coactivator-1; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; py, pack years; RET; rearranged during transfection; TRIM27, zinc finger protein RFP.

patients (95% CI, 1.2–3.6). Similar ORR values were obtained for pretreated patients (68%; 95% CI, 50–82) or treatment-naïve patients (69%; 95% CI, 39–91). Pretreated patients showed 11% of CR and 58% of PR; all complete responses were observed in pretreated patients.

The maximum change in tumor size related to baseline is shown in Figure 1 for both subgroups. Two patients were excluded from this analysis as they did not have measurable lesions at baseline.

Two patients (4%) who showed at least a 20% tumor size increase (PD) and twelve patients (24%) showing a tumor decrease less than 30% (SD) were defined as non-responders. Most of the treated patients (*n* = 34, 68%) experienced a tumor shrinkage, with a median maximum change in tumor size of −45% (95% CI, −53 to −36) in the overall population, −53% (95% CI, −65 to −34) in the treatment-naïve patients, and −43% (95% CI, −54 to −33) in the pretreated patients (Figure 1a).

Table 2. Efficacy of selpercatinib in RET fusion-positive patients[a].

Treatment response	All patients (*n* = 50)	Treatment-naive patients (*n* = 13)	Pretreated patients (*n* = 37)
Objective response rate (ORR)[b], % (95% CI)	68 (53–81)	69 (39–91)	68 (50–82)
Disease control rate (DCR)[c], % (95% CI)	92 (81–98)	92 (64–100)	92 (78–98)
Best response, *n* (%)			
Complete response (CR)	4 (8)	0	4 (11)
Partial response (PR)	30 (60)	9 (69)	21 (58)
Stable disease (SD)	12 (24)	3 (23)	9 (24)
Progressive disease (PD)	2 (4)	0	2 (5)
Not evaluable	2 (4)	1 (8)	1 (3)
Progression-free survival (PFS)			
Patients with progression or death, *n* (%)	15 (30)	4 (31)	11 (30)
Median, months (95% CI)	15.6 (8.8–22.4)	15.6 (NR)	12.2 (NR)
Median follow-up, months	9.4	9.4	9.2
Type of progression, *n* (%)	*N* = 15	*N* = 4	*N* = 11
Systemic	9 (60)	3 (75)	6 (55)
Oligo	5 (33)	0	5 (45)
Singular	1 (7)	1 (25)	0
Duration of treatment[d]			
Median, months (95% CI)	16.9 (10.7–23.1)	16.9 (NR)	12.1 (11.9–12.5)
Discontinued	13 (26)	3 (23)	10 (27)
Primary reason for discontinuation			
Progressive disease	10 (77)	2 (67)	8 (80)
TRAEs	0	0	0
Death	3 (23)	1 (33)	2 (20)
Intracranial response[e]	All patients (*n* = 8)	Treatment-naive patients (*n* = 1)	Pretreated patients (*n* = 7)
Intracranial ORR (icORR), %	100	100	100
Best intracranial response, *n* (%)			
Complete response (CR)	0	0	0
Partial response (PR)	8 (100)	1 (100)	7 (100)
Stable disease (SD)	0	0	0
Progressive disease (PD)	0	0	0

Data-cutoff date: January 27, 2021; ORR, PFS assessed according to RECIST v1.1 for patients with measurable disease.
[a]Percentage may not equal to 100 because of rounding.
[b]ORR was defined as complete or partial response.
[c]DCR was including complete response, partial response, or stable disease.
[d]DoT was defined as the time between selpercatinib start to last dose received.
[e]Only patients with untreated or previously progressed and measurable brain lesions were included. Measurable disease was defined as ⩾5 mm measurable lesion at baseline.
CI, confidence interval; DCR, disease control rate; NR, not reached; icORR, intracranial ORR; ORR, objective response rate; TRAEs, treatment-related adverse events.
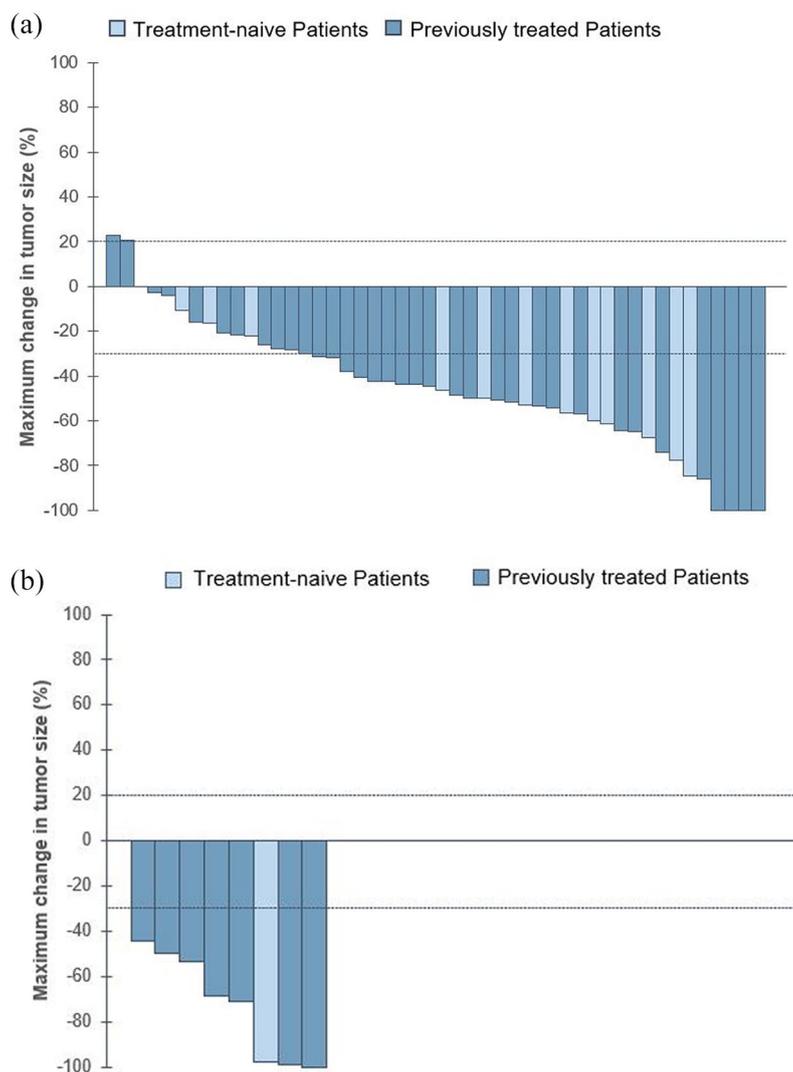
Figure 1. Efficacy: maximum change in tumor size. Waterfall plots of maximum change in tumor size measured according to RECIST v1.1 in all target lesions between baseline and follow-up imaging in previously treated and untreated patients in the overall population (A) and in intracranial lesions in patients with measurable baseline intracranial target lesions (B). Both growth (+20%) and shrinkage (-30%) of tumor size are indicated by the dashed lines. On Figure 1B, data for two patients having measurable lesions (≥5 mm, <10 mm) were included in this analysis. To note, data for patients who underwent brain surgery and/ or radiotherapy because of cerebral lesions concomitant or directly before selpercatinib treatment, as well as one patient with baseline lesion <5 mm (also showed shrinkage), were not shown on this figure.

So far, the mDoR was still immature due to the short follow-up of patients; DoR for individual pretreated and treatment-naïve patients are presented on supplemental Figure 1.

Selpercatinib led to a higher ORR than the last prior line of treatment (68% *versus* 41%): 66% *versus* 40% in patients who received a prior platinum-based chemotherapy; 50% *versus* 10% in patients who received prior immunotherapy; 80% *versus* 40% in patients who previously had combined

chemo-immunotherapy; and 86% *versus* 43% in patients who received a prior TKI (supplemental Table 1). Similar results in favor of selpercatinib were also observed for DCR (92% *versus* 83%). In patients with KIF5B as a RET-fusion partner, the ORR was 64%, while in patients with CCDC6 it was 70%.

Progression-free survival and duration of treatment. After a median follow-up of 9 months the median PFS reached 15.6 months in the overall

population (95% CI, 8.8–22.4) and in patients who had not received treatment previously (95% CI, NR). The median PFS of the pretreated group was 12.2 months (95% CI, NR) (Table 2, Figure 2b). Based on Kaplan–Meier analysis, the PFS rate was 87% at 6 months and 58% at 1 year. Among patients presenting with KIF5B or CCDC6 as a RET-fusion partner, no statistically significant difference in mPFS was observed ($p = 0.8$, data not shown).

The median DoT was 16.9 months, both in the overall population and in treatment-naïve patients (95% CI, 10.7–23.1 and NR, respectively), while the mDoT reached 12.1 months (95% CI, 11.9–12.5) in pretreated patients (see Figure 2a). A total of 37 patients (35 of them progression-free and two treated beyond progression) remained on treatment after a median follow-up of 9 months.

Three patients with disease progression have been re-biopsied. All cases showed the known RET-fusion, no additional mutation, or specific resistance mechanism detected by local NGS.

Intracranial response. At baseline, 16 patients had known brain metastases. For the assessment of intracranial response, only patients with untreated or previously-progressed and measurable brain lesions were included ($n = 8$). Seven of those patients were assessed with a MRI and one with a CT scan of the brain. All eight patients showed an intracranial response (icORR, 100%). (Table 2, Figure 1b).

Imaging assessments from two Austrian patients are presented in Figure 3 (a–d). As shown, the first patient experienced a complete remission of the extensive pleural effusion and the massive thoracic tumor, while the second patient became neurologically completely asymptomatic within a week after selpercatinib first dose and showed a partial intracranial response after 3 months therapy.

Safety. The median duration of exposure to selpercatinib was 8 months (range, 1–17). All TRAEs are listed in supplemental Table 2, while Figure 4 presents the most common TRAEs that occurred in ≥10% of patients. In total, 43 of 50 patients (88%) experienced TRAEs of any grade, a large majority of them being of grade 1 or 2 and reversible; the most frequent TRAEs were fatigue/asthenia (in 40% of patients), increased liver enzyme levels (34%), dry mouth (26%), hypertension (26%), and peripheral edema (20%). TRAEs of grade ≥3 were reported in twelve patients (24%), and included increased liver enzyme levels (10%), prolonged QTc time (4%), abdominal pain (4%), hypertension (4%), and fatigue/asthenia (4%). At data-cutoff date, three patients had died (two had a myocardial infarction and the third experienced oncologic progression); these events were classified as unrelated to selpercatinib treatment by the treating physicians.

Most of the patients had a BID starting dose of 160 mg ($n = 41/50$; 82%), while the other patients received a reduced starting dose (120 mg by 4% for two patients and 80 mg by 14% for seven patients) because of their age, weight, and/or comorbidities; in three of these latter patients, due to good tolerability, a dose escalation occurred during the treatment course. The best-tolerated dose was 160 mg BID (in 50% of patients), 120 mg BID (10%), 80 mg BID (30%), or 40 mg BID/80 mg per day (4%). In the 50 patients who received selpercatinib, dose reduction was warranted in 20 patients (40%) because of TRAEs (supplemental Table 2, Figure 4); the most common TRAEs leading to dose reduction were fatigue/asthenia (14%) and increased liver enzyme levels (12%). In two patients, their selpercatinib dose was later increased to the starting dose, while the other patients remained on treatment at the reduced dose. TRAEs lead to dose interruption in 13 patients (26%). No patient discontinued from treatment because of TRAEs.

The proportion of patients experiencing TRAEs in the subgroup who received an immunotherapy +/− chemotherapy ($n = 15$) as last treatment prior to selpercatinib was 100%, compared with 80% in other patients (treatment-naïve, chemotherapy, or TKI as last line of therapy, $n = 35$). TRAEs of grade ≥3 were observed in four patients (40%) in the immunotherapy-subgroup and in four patients (11%) in the other subgroup; the number of grade ≥3 events was eight in both subgroups. Of note, no grade 4 TRAEs occurred in the immunotherapy-subgroup (data not shown).

Discussion

We report on a relatively large sample of NSCLC patients with RET-fusion-positive alterations from a selpercatinib NPP in a real-world setting. The current manuscript confirms previously published data, with the study population being mainly young (50% under 65 years), female

(a)

(b)
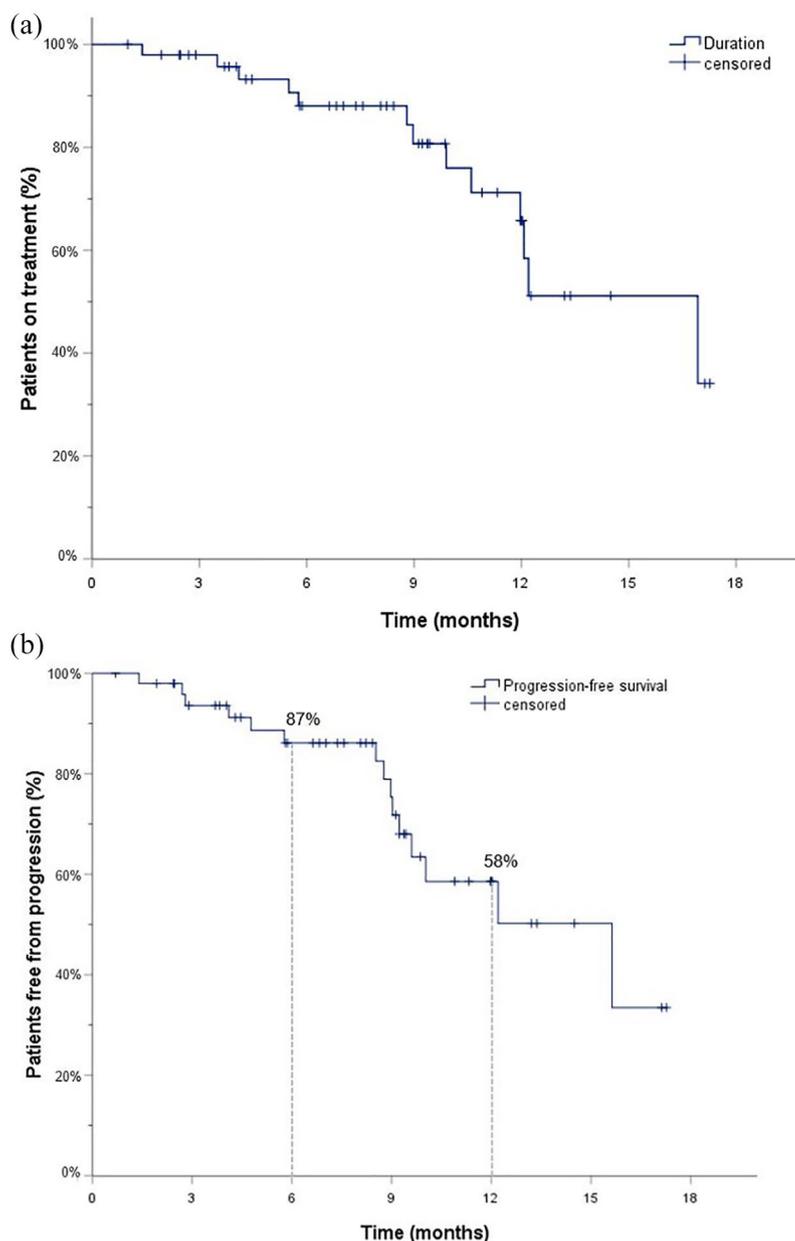
Figure 2. Duration of treatment (DoT) and progression free survival (PFS). Kaplan-Meier plots of (a) median DoT and (b) median PFS.

(60%), never-smokers (74%), and a large majority of them having adenocarcinoma (90%) and frequently brain lesions (32%) at the time RET alteration was diagnosed.[13,16] In addition, the proportion of the different RET-fusion partners identified in our analysis was similar to previously reported data.[17–19] Although the majority of patients documented had late stage disease (stage IV) and were heavily pretreated (median of 3 prior therapies), high response rates were obtained with selpercatinib therapy, including patients with baseline cerebral lesions. Given the high incidence of cerebral lesions among patients with RET-fusion-positive NSCLC, intracerebral anti-tumoral activity seems essential. Among the patients with baseline cerebral lesions, 100% of evaluable patients achieved an intracranial ORR; these data are also in agreement with those previously published (icORR, 91%).[13]

In this real-world setting, the median ORR obtained for pretreated patients was very similar
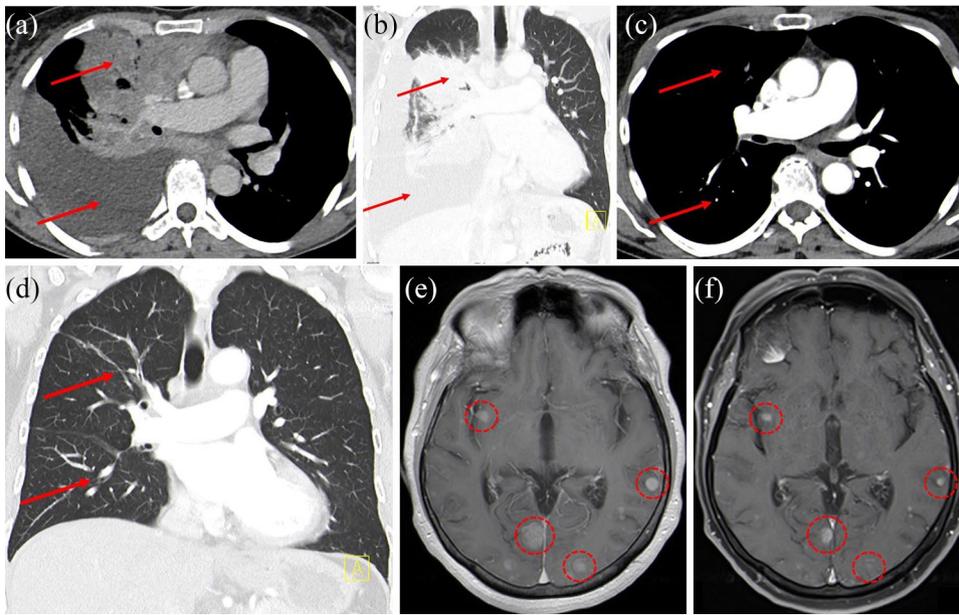
Figure 3. Systemic treatment response to selpercatinib in a pretreated patient and intracranial response in a treatment-naïve patient. (A-D) A 69-year-old male, never smoker, showing low performance status (ECOG 2 caused by oncological disease) and stage IV (T4 N3 M1a) RET fusion-positive NSCLC was enrolled in selpercatinib Named Patient Protocol (NPP) program in January 2020 in Vienna (Austria) after disease progression on chemo-immunotherapy (2 cycles carboplatin-pemetrexed/pembrolizumab). Contrast enhanced computed tomographic (CT) scans of the chest in January 2020 (A/C) and December 2020 (B/D). (E-F) A 68-year-old woman with stage IV (T4 N2 M1c) RET fusion-positive NSCLC and notable neurologic disorders (headache, dizziness, strabismus) due to several brain metastases started selpercatinib through NPP as first-line treatment in October 2020 in Vienna. Contrast enhanced T1-weighted images of the brain in October 2020 (E) and in January 2021 (F). Lesions are indicated by red arrows and dotted circles.
ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; PD-L1, Programmed cell death 1 ligand 1.

to the data from the LIBRETTO-001 phase I/II clinical study (68 *versus* 64%, respectively). Compared with the data presented by Drilon *et al.*, in our cohort, the median ORR among treatment-naïve patients was lower (69 *versus* 85%), while the median PFS in pretreated patients was shorter (12 *versus* 17 months).[13] Overall, our results might be explained by our less-selected real-world study population compared with the carefully chosen pool of patients included in the phase I/II study. Indeed, compared with the NSCLC population of the LIBRETTO-1 study, our patients were older (65 *versus* 61 years) and were presenting with a worse ECOG performance status (ECOG ≥2 in 28% *versus* ≤2%).[13] In the absence of available selective therapy outside of clinical trials for the treatment of this rare disease, any patient with confirmed RET gene fusions were enrolled in the NPP as compassionate use.

As is the case with other highly-selective TKIs, the genetic-driven disease response to selpercatinib treatment was fast, with a median time to best response of 3 months in the overall population and 2 months in treatment-naïve patients.

Even if patient selection criteria for participation in a selpercatinib NPP were much less strict than in a clinical trial, safety follow-up of participating patients performed every 6 weeks was quite extensive, including laboratory tests, physical examination, and other monitoring procedures (vital signs, serum pregnancy test, electrocardiogram). Outside highly-selected clinical study population, real-world data analyses are generating meaningful data about the efficacy and safety information on treatment in routine clinical practice; such data are helpful in terms of guiding therapy decisions, patient selection, and AE management. Real-world data are especially relevant in infrequent diseases, like in RET-fusion-positive NSCLC, and the provided confirmatory evidence from single-arm non-comparative trials might also be used for regulatory approvals.[20]

Moreover, this selective RET-inhibitor therapy showed a manageable safety profile, as most
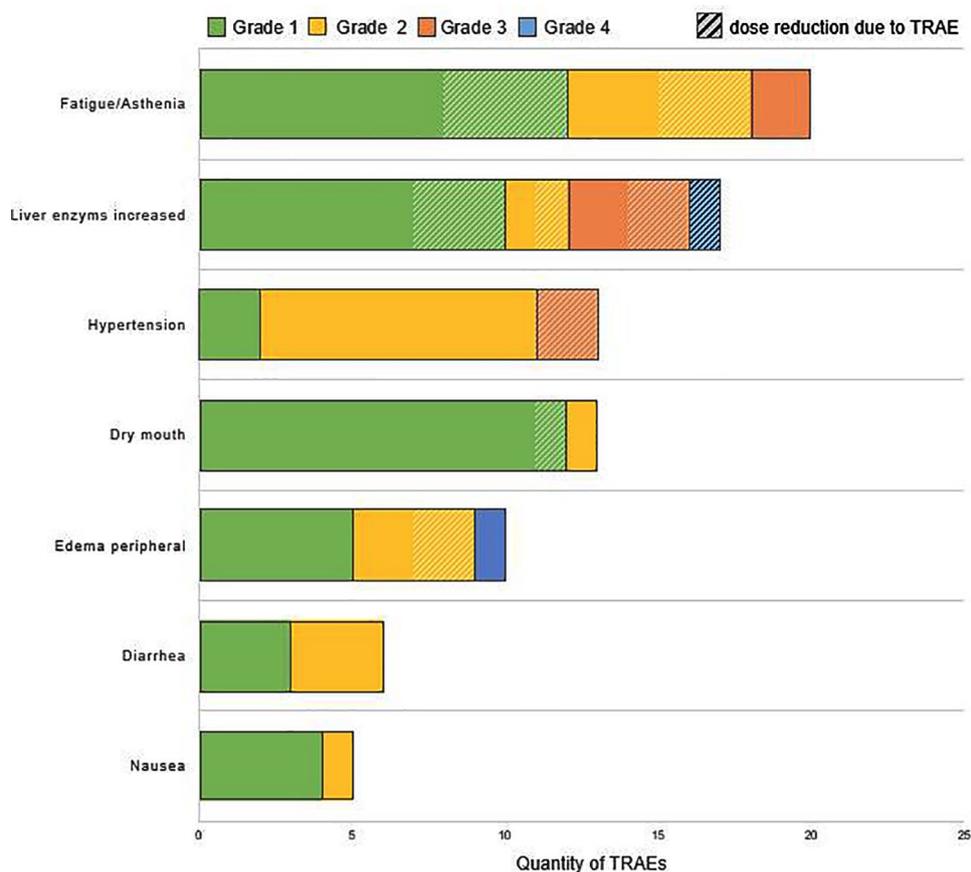
Figure 4. Treatment-related adverse events (TRAEs). Data-cutoff date: January 27, 2021; treatment-related adverse events (TRAEs) that occurred at any grade in at least 10% of treated patients. The analysis included all patients who received at least one dose of selpercatinib; TRAEs were graded as per Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) as determined by the treating physician. Percentage may not equal to 100 because of rounding; liver enzymes were including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and gamma-glutamyl transferase (GGT).

TRAEs were reversible and resolved with dose reduction or interruption. In contrast to the clinical data previously published, in our real-world population, no treatment discontinuation occurred due to TRAEs.[13] In these documented patients, few moderate to severe AEs were related to selpercatinib treatment; most of the patients were able to stay on treatment under a reduced dose until resolution of the safety issue; indeed, some patients were even able to resume at the starting dose. Compared with data from the phase I/II LIBRETTO-001 study, no new safety concerns have been raised in this real-world population.[13] Selpercatinib is a potent RET-inhibitor, which shows activity as well against VEGFR1 and VEGFR3; the lower activity against VEGFR2 may explain the reduced toxicity associated with selpercatinib compared with unspecific MKIs.[21]

With some exceptions, checkpoint-inhibitor therapy against PD-L1/PD-1 has shown low efficiency in patients with RET-alterations.[9,22] In general, platinum-based chemotherapy seems to achieve only modest response rates in patients presenting with specific gene alterations and results in off-target toxicity;[23] however, platinum-based chemotherapy was described as being effective in a small population (18 patients) presenting with RET fusion-positive NSCLC and analyzed retrospectively.[24] MKIs, such as cabozantinib, and vandetanib, which are showing moderate efficacy and substantial side effects in patients with RET-rearrangements, are leading to development of resistance mutations.[23] Selpercatinib is a RET-inhibitor with high target specificity associated with a low side-effects rate leading to fewer dose reduction or interruption compared with

unspecific MKIs. In this real-world data analysis, selpercatinib was more efficacious than any other systemic treatment.

In addition, our data show a trend toward more TRAEs occurring when immunotherapy (alone, or combined with a chemotherapy) was the last treatment line received before selpercatinib; similar observations have been previously reported when the TKI osimertinib was administered following nivolumab or pembrolizumab.[25,26] However, because of the small sample size of the subgroups analyzed, these results must be interpreted with caution. Data from the LIBRETTO-001 study previously has been analyzed regarding an increased number of treatment-emergent hypersensitivity reactions in the subgroup of patients previously treated with immunotherapy prior to selpercatinib. Treatment-emergent AEs of hypersensitivity related to selpercatinib of any grade were seen in 11.2% ($n = 17$) of patients who received immunotherapy prior to selpercatinib and 2.8% ($n = 5$) in immunotherapy-naïve patients; serious treatment-emergent AEs of hypersensitivity related to selpercatinib occurred in eight (5.3%) *versus* four (2.3%) patients, respectively.[27]

As selpercatinib therapy is now available for RET-fusion-positive NSCLC in Europe and the USA, the challenge will be to identify all patients presenting with RET gene fusions by systematic screening in ensure they benefit from this new targeted therapy. Based on international guidelines, the ESMO Translational Research and Precision Medicine Working Group recommends that NGS be used as the preferred RET oncogene testing method in each patient with defined cancer diseases, including NSCLC.[28,29]

This retrospective analysis has several limitations, including reporting bias, selection bias, and/or information bias. Moreover, the efficacy outcomes were described within the limitation of the small sample size of each subgroup and therefore only descriptively. Limitations include the variable clinical routine practices performed in the participating centers world-wide, in terms of RET-testing, intervals of follow-up visits, or therapy algorithms like treating beyond progression or not. Despite these limitations, our real-world observations were in many instances consistent with those previously reported from a RET phase I/II clinical study.[13]

Upfront targeted therapy using selective inhibitors against oncogenic drivers may be the ultimate goal of research and development in the cancer field. Second-line approval of selpercatinib in Europe in February 2021 is a first step toward a targeted efficacious and safe option for NSCLC patients with RET-alterations. It is the hope that selpercatinib will be established as a first-line targeted therapy in patients with RET-altered NSCLC to spare patients the side effects of chemotherapy.[23] Therefore, an ongoing multicentric, randomized, open-label phase III LIBRETTO-431 (NCT04194944) study in patients with locally-advanced or metastatic RET-fusion-positive NSCLC of non-squamous histology is currently evaluating the efficacy and safety of selpercatinib *versus* chemo-immunotherapy (platinum-based pemetrexed, with or without pembrolizumab) as a first-line therapy.

Authors' contributions
Oliver Illini; Conceptualization; analysis and interpretation data; data acquisition; investigation; methodology; project administration; supervision; validation; manuscript drafting; revision and final approval.

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Ewald Wöll; Data acquisition; manuscript drafting, revision and final approval.

Arschang Valipour; Conceptualization; methodology; supervision; validation; manuscript drafting, revision and final approval.

All authors contributed substantially to this work. Moreover, all of them revised it critically for important intellectual content and approved the final manuscript.

Conflict of interest statement

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Ethics approval and informed consent

The study protocol was approved by the ethics committee of the city of Vienna, Austria (EK 20-330-VK). According to Austrian laws, informed consent for each patient was not necessary for this retrospective analysis.

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Supplemental material

Supplemental material for this article is available online.

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