Lung Cancer 174 (2022) 118–124

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Pralsetinib in *RET* fusion-positive non-small-cell lung cancer: A real-world data (RWD) analysis from the Italian expanded access program (EAP)

Antonio Passaro [a,*], Giuseppe Lo Russo [b], Francesco Passiglia [c], Manolo D'Arcangelo [d], Andrea Sbrana [e], Marco Russano [f], Laura Bonanno [g], Raffaele Giusti [h], Giulio Metro [i], Federica Bertolini [j], Salvatore Grisanti [k], Annamaria Carta [l], Fabiana Cecere [m], Michele Montrone [n], Giacomo Massa [b], Fabiana Perrone [o], Francesca Simionato [p], Giorgia Guaitoli [q], Vieri Scotti [r], Carlo Genova [s,t], Antonio Lugini [u], Lucia Bonomi [v], Ilaria Attili [a], Filippo de Marinis [a]

[a] *Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milan, Italy*
[b] *Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[c] *Department of Oncology, University of Turin, S. Luigi Gonzaga Hospital, Orbassano (TO), Italy*
[d] *Oncology Department, Ospedale Santa Maria delle Croci, Ravenna, Italy*
[e] *Department of Surgical, Medical and Molecular Pathology and Critical Area Medicine, University of Pisa, Pisa, Italy*
[f] *Medical Oncology, Campus Bio-Medico University, Rome, Italy*
[g] *Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padua, Italy*
[h] *Medical Oncology Unit, Sant'Andrea Hospital, Rome, Italy*
[i] *Department of Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy*
[j] *Department of Oncology and Hematology, Modena University Hospital, Modena, Italy*
[k] *Department of Medical Oncology, ASST Spedali Civili di Brescia, University of Brescia, Brescia, Italy*
[l] *SC Oncologia Medica, Ospedale Businco - ARNAS G. Brotzu, Cagliari, Italy*
[m] *Oncology 1, Regina Elena National Cancer Institute - IRCCS, Roma, Italy*
[n] *Medical Thoracic Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari 70124, Italy*
[o] *Medical Oncology Unit, University Hospital of Parma, Parma, Italy*
[p] *Department of Oncology, San Bortolo General Hospital, Azienda ULSS8 Berica, Vicenza, Italy*
[q] *PhD Program Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy*
[r] *Azienda Ospedaliero-Universitaria Careggi, Florence, Italy*
[s] *Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italia*
[t] *Dipartimento di Medicina Interna e Specialità Mediche, Università degli Studi di Genova, Italia*
[u] *AO San Giovanni Addolorata, UOC Oncologia Medica, Roma, Italy*
[v] *Oncology, Department of Oncology and Hematology, ASST Papa Giovanni XXIII, Bergamo, Lombardia, Italy*

ARTICLE INFO

Keywords:
RET gene fusion
RET rearrangement
Tyrosine kinase inhibitor (TKI)
NSCLC
Targeted therapy
Personalized treatment

ABSTRACT

Objectives: The selective RET-inhibitor pralsetinib has shown therapeutic activity in early clinical trials in patients with non-small cell lung cancer (NSCLC) harboring rearranged during transfection (*RET*) gene fusions. To date, the real-world efficacy of pralsetinib in this population is unknown.

Materials and methods: A retrospective efficacy and safety analysis was performed on data from patients with *RET*-fusion positive NSCLC enrolled in the pralsetinib Italian expanded access program between July 2019 and October 2021.

Results: Overall, 62 patients with *RET*-fusion positive NSCLC received pralsetinib at 20 Italian centers. Next-generation sequencing was used to detect *RET* alterations in 44 patients (73 %). The most frequent gene fusion partner was *KIF5B* (75 % of 45 evaluable). Median age was 62 years (range, 36–90), most patients were female (57 %) and never smokers (53 %). Brain metastases were known in 18 patients (29.5 %) at the time of pralsetinib treatment. 13 patients were treatment naïve (unfit for chemotherapy), 48 were pretreated (median number of previous lines: 1, range, 1–4). The objective response rate (ORR) was 66 % [95 % confidence interval (CI), 53–81] in the evaluable population (n = 59). The disease control rate (DCR) was 79 %. After a median

* Corresponding author at: Division of Thoracic Oncology, European Institute of Oncology IRCCS, Via G. Ripamonti 435, Milan 20141, Italy.
E-mail address: antonio.passaro@ieo.it (A. Passaro).

https://doi.org/10.1016/j.lungcan.2022.11.005
Received 24 September 2022; Received in revised form 25 October 2022; Accepted 6 November 2022
Available online 9 November 2022

follow-up of 10.1 months, the median progression free survival was 8.9 months (95 %CI, 4.7–NA). In patients with measurable brain metastases (n = 6) intracranial ORR was 83 %, intracranial DCR was 100 %. Overall, 83.6 % of patients experienced any-grade treatment-related adverse events (TRAEs), 39 % grade 3 or greater (G ≥ 3). The most common G ≥ 3 TRAEs were neutropenia (9.8 %), dry mouth/oral mucositis (8.2 %), and thrombocytopenia (6.6 %). Seven patients (12 %) discontinued pralsetinib due to TRAEs, twenty-six had at least one dose level modification due to TRAEs. Two treatment-related deaths were observed (1 sepsis, 1 typhlitis).
Conclusions: In the real-world setting, pralsetinib confirmed durable systemic activity and intracranial response in *RET*-fusion positive NSCLC. Toxicity profile was consistent with previous reports.

1. Introduction

Among the increasing list of targetable oncogenes in non-small cell lung cancer (NSCLC), the identification of rearranged during transfection (*RET*) gene fusions has rapidly modified the landscape of treatment options in patients harboring these rare gene alterations. *RET* gene rearrangements determining RET chimeric fusion proteins (transmembrane receptor-tyrosine kinase – RTK) with constitutively active intracellular kinase domain, are identified in approximately 1–2 % of NSCLCs, predominantly with adenocarcinoma histology[1].

RET fusion-positive NSCLCs frequently present with brain metastases at advanced stage diagnosis. Although chemotherapy has shown modest efficacy, the use of ICI-based therapies has shown limited benefit in treating advanced RET-positive tumors[2–4]. The use of multiple kinase inhibitors (MKIs – e.g., cabozantinib, lenvatinib, vandetanib), with modest activity in other tumors with RET gene fusions or RET point mutations (approximately 10 % of thyroid cancers), showed very limited activity in NSCLC histology[5–7].

The development of highly potent and specific RET inhibitors in the latest years, lead to the first evidence of treatment efficacy and prolonged clinical benefit in patients harboring *RET* gene alterations, across histologies[8].

Pralsetinib (formerly BLU-667) and selpercatinib (formerly LOXO-292) are highly selective small molecule inhibitors of RET.

In the multicenter, open-label phase I/II LIBRETTO-001 trial, selpercatinib showed high objective response rate (ORR) in 105 previously treated patients with advanced *RET* fusion-positive NSCLC (ORR 64 %, 95 %CI 54–73), with median progression free survival (PFS) of 19.3 months (95 % CI 13.9–NR) and prolonged median duration of response (DoR 17.5 months, 95 % CI 12.1–NR)[9,10]. In the same study, with updated follow up, ORR was 85 % (95 % CI 70–94) in previously untreated patients (n = 69), with median PFS 22 months and median DoR 20.2 months[11]. In addition, intracranial ORR (icORR) was 84.6 % (95 % CI 65.1–95.6), with a CNS mDoR of 9.4 months (95 %CI 7.4–15.3), among 26 patients with measurable CNS metastases at baseline.

The activity of pralsetinib in *RET* fusion-positive NSCLC was evaluated in the phase I/II ARROW trial. In this study, ORR was 61 % (95 % CI 50–71) in previously treated and 70 % (95 % CI 50–86) in treatment-naïve patients (ineligible for platinum-based chemotherapy), and median PFS was 17.1 (95 % CI 8.3–22.1) and 9.1 (95 % CI 6.1–13) months, respectively[12]. In updated results including treatment-naïve patients eligible for platinum-based chemotherapy, ORR was 79 % and median PFS was not reached (with 8.2 months of median follow up) in this cohort[13]. Overall, 33 % of patients had baseline CNS involvement in this study, and icORR was 70 % (95 % CI 35 – 93) among those with CNS measurable disease, with 10.5 months (95 % CI 5.5–12.6) median CNS DoR.

Following these results, both drugs received approval by Food and Drug Administration (FDA) and, more recently, by European Medicines Agency (EMA) for the treatment of advanced or metastatic *RET* fusion-positive NSCLC.

Awaiting the regulatory approvals, pralsetinib use was available in Italy through an Expanded Access Program (EAP) for the treatment of patients with advanced or metastatic *RET* fusion-positive NSCLC who were not candidate for clinical trial and had no other treatment options. We conducted a retrospective collection of efficacy and safety data from the Italian EAP pralsetinib use.

To date, a real-world (RW) experience has been published with selpercatinib, however, only few series have been presented on the use of pralsetinib in the real-world setting.

To our knowledge, the current work represents the largest retrospectively collected multicenter RWD on pralsetinib selectively in *RET* fusion-positive NSCLC patients.

2. Materials and methods

2.1. Patients and study design

We conducted a retrospective analysis of efficacy and safety of pralsetinib on data from patients with *RET*-fusion positive NSCLC enrolled in the pralsetinib Italian expanded access program (EAP) between July 2019 and October 2021.

Anonymized data about patient demographics, clinical characteristics, as well as pralsetinib treatment details, tumor responses and safety information, were extracted from available medical records by the treating physician, centrally collected, and analyzed at European Institute of Oncology (IEO), Milan, Italy.

Patients received an initial dose of pralsetinib 400 mg (four 100 mg capsules) orally, once daily. Some patients, based on clinical evaluation by treating physician, might have received a reduced initial dose as safety precaution. Pralsetinib administration was then carried on according to tolerance and safety as per EAP indications and following clinical practice at the treating physician's discretion.

Pralsetinib treatment was continued until disease progression, unacceptable toxicity, patient's withdrawal of consent or death.

This retrospective study was conducted in accordance with the principles of Good Clinical Practice and following the Declaration of Helsinki. All the study procedures were carried out by the general authorization to process personal data for scientific research purposes from "The Italian Data Protection Authority" (http://https://www.garanteprivacy.it/web/guest/home/docweb/-/docwebdisplay/export/2485392, accessed on 10 April 2022). The study protocol was approved by the ethics committee of the European Institute of Oncology, Milan (LUNG-013) and each participating center. All information regarding subjects was managed using anonymous numerical codes and handled in compliance with the Declaration of Helsinki.

2.2. Study endpoints

The primary endpoint of this study was ORR, defined as the proportion of patients with complete response (CR) and partial response (PR), according to RECIST v1.1 criteria.

Secondary endpoints were: DCR, defined as the summed percentage of CR, PR and stable disease (SD); intracranial ORR and DCR (icORR, icDCR); median PFS, defined as the time from first dose of pralsetinib and first occurrence of disease progression; median duration of treatment (mDoT), assessed as the time from first to last dose of pralsetinib received; median duration of response (mDoR), measured as the time from first response to pralsetinib and disease progression or death due to any cause; treatment-related adverse events (TRAEs) determined by the

treating physician.

OS, defined as the time between the start of pralsetinib treatment and the occurrence of death from any cause, was examined as an exploratory endpoint.

2.3. Assessments and statistical analysis

Tumor response and progression were assessed 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 and evaluated as per RECIST v1.1. CNS disease was assessed with brain CT or magnetic resonance imaging (MRI) evaluation, and follow-up brain scans were conducted according to local standards of care.

ORR, DCR, icORR, icDCR, DoT, DoR, PFS and OS were analyzed in the overall population, as well as separately for pretreated and treatment-naïve patients.

Median PFS, DoT, DoR and OS were estimated by using Kaplan–Meier methods. Median follow-up was calculated with the reverse Kaplan–Meier method.

The Cox regression model was used for subgroup analysis on survival outcomes; the Log-rank test was used to test comparison between subgroups (previous lines of systemic anticancer therapy, as well as pretreated patients versus treatment-naïve patients or different RET fusion partners).

Adverse events (AEs) were documented according to safety assessment performed at baseline and at every subsequent visit or clinical evaluation. AEs were judged treatment-related based on the assessment made by the local treating physician. Dose modifications or interruptions and treatment discontinuation due to TRAEs were reported. All reported TRAEs were graded as per the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Median values were used to describe continuous variables, percentages were used for categorical variables. Mann-Whitney test was used to compare continuous variables, whereas two-sided chi-squared or fisher exact test were used to compare categorical variables, as appropriate. Data were presented as hazard ratios (HR) or odds ratios (OR) and their 95 % confidence interval (CI), as appropriate. CIs for proportions, such as ORR and DCR, were calculated using the Clopper–Pearson method.

Statistical significance level was set at $p < 0.05$ for all tests. All statistical analyses were performed with R Studio version 4.1.2.

3. Results

3.1. Patients and treatment

Overall, 62 patients with advanced or metastatic NSCLC harboring *RET* gene fusions received pralsetinib treatment at 20 Centers in Italy. One patient was excluded due to incomplete data collection. Thirteen patients (21.3 %) received pralsetinib as their first-line treatment (treatment naïve) because they were assessed as unfit for any chemotherapy treatment. 48 patients (78.7) were previously treated and received pralsetinib as subsequent treatment (median number of previous lines: 1, range, 1–4).

Median age at pralsetinib start was 62 years (range, 36–90) in the overall population, and 66 years (range, 36–90) in treatment-naïve population (Table 1). Most patients were female (57.4 %), never (52.5 %) or former (34.4 %) smokers, with adenocarcinoma histology (91.8 %). The majority of patients (83.6 %) had ECOG PS 0–1 in the overall population. Of note, 30.8 % of patients in the treatment-naïve group had ECOG PS 2 or greater.

Next-generation sequencing was the most adopted testing method to detect *RET* alterations, performed in 44 patients (72.1 %). Fluorescent in situ hybridization (FISH) and real-time polymerase chain reaction (RT-PCR) were used in 12 (19.7 %) and 9 (14.8 %) cases, respectively. The most frequent gene fusion partner was *KIF5B* (75 % of 45 evaluable).

Brain metastases were known in 18 patients (29.5 %) at the time of pralsetinib treatment. Among them, 13 patients received CNS radiotherapy: 11 patients received radiotherapy previous to pralsetinib treatment, whereas 3 additional patients received radiotherapy (and one patient was reirradiated to the brain) during pralsetinib. Of note, 6 patients with CNS involvement were not previously treated (46.2 % among the treatment-naïve population).

Overall, 57 patients received pralsetinib at initial dose of 400 mg once daily, whereas four patients were administered a reduced initial dose of 300 mg once daily as safety precaution adopted by their treating

Table 1
Demographics and clinical characteristics of study population.

Characteristic[§]	All patients (n = 61)	Pre-treated (n = 48)	Treatment naïve (n = 13)
Age, years	60	60	66
median[a] (range)	(35–90)62	(42–85)62	(35–90)66
median[b] (range)	(36–90)	(43–85)	(36–90)
Gender, n (%)	26	21	5
Male	(42.6)35	(43.7)27	(38.5)8
Female	(57.4)	(56.3)	(61.5)
Smoking status, n (%)	32	29	3
Never	(52.5)21	(60.4)13	(23.1)8
Former	(34.4)5	(27.1)4	(61.5)1
Current	(8.2)3	(8.3)2	(7.7)1
Unknown	(4.9)	(4.2)	(7.7)
ECOG PS, n (%)	23	19	4
0	(37.7)28	(39.6)23	(30.8)5
1	(45.9)10	(47.9)6	(38.5)4
≥2	(16.4)	(12.5)	(30.8)
Histology subtype, n (%)	56	45	11
Adenocarcinoma	(91.8)1	(93.8)0	(84.6)1
NSCLC NOS	(1.6)4	(0)3	(7.7)1
other	(6.6)	(6.2)	(7.7)
RET testing method, n (%)	5	4	1
RT-PCR	(8.2)43	(8.3)33	(7.7)10
NGS[c]	(70.5)	(68.9)	(76.9)
RT-PCR + NGS	1 (1.6)12	1 (2.1)10	0 (0
FISH	(19.7)	(20.8)	2 (15.4)
RET fusion partner, n (%)	34	27	7
KIF5B	(55.7)6	(56.3)5	(53.8)1
CCDC6	(9.8)2	(10.4)1	(7.7)1
NCOA4	(3.3)3	(2.1)2	(7.7)1
other	(4.9)16	(4.2)13	(7.7)3
ND	(26.2)	(27.1)	(23.1)
Site of metastasis, n (%)	18	12	6
Brain	(29.5)25	(25)19	(46.2)6
Lung	(41)21	(39.6)14	(46.2)7
Bone	(34.4)11	(29.8)9	(53.8)2
Liver	(18)24	(18.8)20	(15.4)4
Pleura	(39.3)27	(41.7)21	(30.8)6
Lymph nodes	(44.3)12	(43.8)10	(46.2)2
other	(19.7)	(20.8)	(15.4)
Previous treatments	1	1	
Median (range)	(0–4)	(1–4)	–
Previous treatment regimens[d], n (%)	–	43 (89.6)15	–
Platinum-based CTx[e]		(31.3)14	
Anti-PD-1/PD-L1 monotherapy		(29.2)11 (22.9)	
Other CTx regimens			
TKIs			
Brain radiotherapy, n (%)	14	11	3
Yes[f]	(23)7	(22.9)5	(23.1)2
For symptomatic mets	(14.9)7	(10.4)5	(15.4)1
For asymptomatic mets	(14.9)47	(10.4)37	(7.7)10
No	(77)	(77.1)	(76.9)

§Percentages may be not equal to 100% because of rounding.
[a] at advanced stage diagnosis.
[b] at pralsetinib start.
[c] 3 cases detected by NGS on liquid biopsy.
[d] cumulative across treatment lines.
[e] 11 patients received platinum-based chemotherapy in combination with anti-PD-1/anti-PD-L1.
[f] 11 patients received previous brain radiotherapy, 4 patients received brain radiotherapy during pralsetinib treatment.

physicians.

Median follow-up was 10.1 months (IQR 7.4– 13.8 months) for OS and 11 months (IQR 7.7–20.5 months) for PFS in the overall population. In the previously treated and in the treatment-naïve population, median follow up for PFS was 11.5 (IQR 8.4–20.5) and 7.5 months (IQR 6.6–15.4), respectively.

Median DoT in the overall cohort and in the previously treated population was 8 months (95 % CI 4 months – NA) (Fig. 1a–c). Median DoT was not estimable (95 %CI 3– NA) in the treatment-naïve cohort (Fig. 1b).

3.2. Efficacy

The ORR was 66.1 % (95 %CI 53–78) in the evaluable population (n = 59), n = 2 patients were excluded from ORR evaluation because no radiological assessment was available before the occurrence of death. ORR was higher in pretreated patients (68.8 %, 95 %CI 53.7–81.3) as compared to treatment naïve patients (46.2 %, 95 % CI 19.2–74.9). DCR was 79.7 % (95 % CI 67– 89), similar between the two groups (Table 2). Responses were not found to be affected by previous exposure to immune checkpoint inhibitors or gene fusion partner (p = 0.44, p = 0.89, respectively).

Median DoR in the overall cohort was not reached (95 % CI 9.3– NA) (Fig. 1d). Median DoR was 11.7 months (95 % CI 8.9– NA) in the previously treated population, and not estimable in the treatment-naïve cohort (Fig. 1e and f).

In patients with measurable brain metastases (n = 6), intracranial ORR was 66.7 % (95 % CI 22.3– 95.7 %), and intracranial DCR was 100 %.

After a median follow-up of 10.1 months, the median PFS was 8.9 months (95 %CI, 4.9–NA) (Fig. 1g).

Median PFS was 8.9 months (95 %CI, 4.6–NA) in the previously treated population, and 5.6 months (95 % CI 3.2– NA) in the treatment-naïve cohort (Fig. 1h and i). None of the evaluated clinical factors, including treatment line, previous immunotherapy regimens, gene fusion partner, were found to affect PFS (p = 0.08, p = 0.3, p = 0.9,

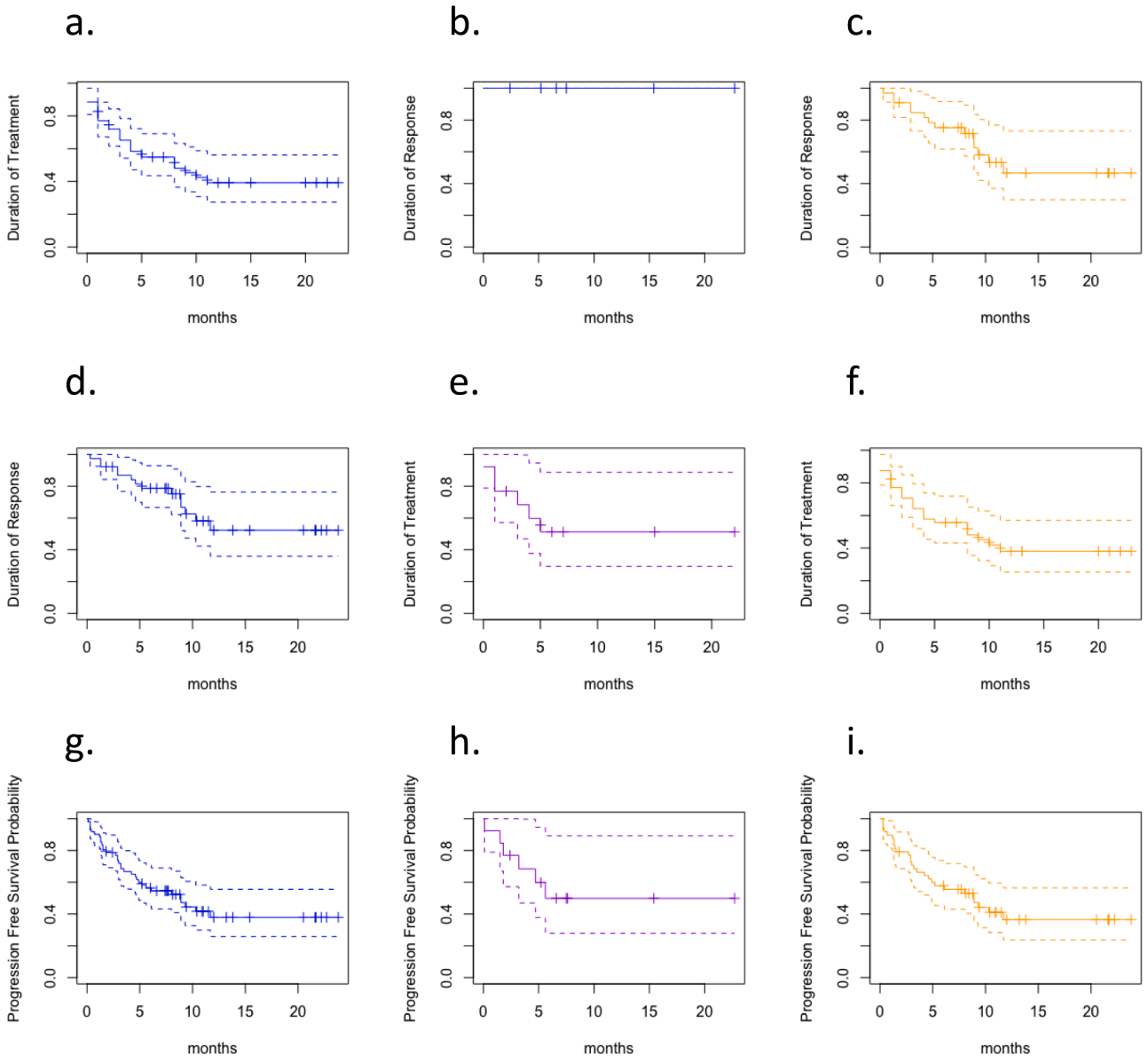

Fig. 1. Efficacy results with pralsetinib in the overall, treatment naïve, and pre-treated populations. Duration of treatment (DoT) in the overall (a), treatment naïve (b), and pre-treated patients (c); Duration of response (DoR) in the overall (d), treatment naïve (e), and pre-treated patients (f); Progression free survival (PFS) in the overall (g), treatment naïve (h), and pre-treated patients (i).

Table 2
Efficacy results with pralsetinib in patients with RET-fusion positive NSCLC.

Treatment responses	All patients (n = 61)	Pre-treated (n = 48)	Treatment naïve (n = 13)
Objective response rate (ORR), % (95 % CI)	66.1 (53–78)	68.8 (53.7–81.3)	46.2 (19.2–74.9)
Disease control rate (DCR), % (95 % CI)	79.7 (67–89)	77.1 (62.7–88.0)	76.9 (46.2–95.0)
Best response, n (%)	2	2	
Complete response (CR)	(3.3)37	(4.2)31	-6
Partial response (PR)	(60.7)8	(64.6)4	(46.2)4
Stable disease (SD)	(13.1)	(8.3)	(30.8)
Progressive disease (PD)	12 (19.7)2	9 (18.8)2	3 (23.1)
NA	(3.3)	(4.2)	-
Intracranial response[a], %	66.7	60	
(95 % CI)	(22.3–95.7)	(14.7–94.7)	100
Intracranial ORR	100	100	100
Intracranial DCR			
Intracranial best	3	2	1
response[a], n (%)	(50)1	(40)1	(1 0 0)
Complete response (CR)	(16.7)2	(20)2	-
Partial response (PR)	(33.3)	(40)	-
Stable disease (SD)	0	0	-
Progressive disease (PD)			
Median follow up	11	11.5	7.5
median, months (IQR)	(7.7– 20.5)	(8.4–20.5)	(6.6– 15.4)
PFS	8.9	8.9	5.6
median, months (95 % CI)	(4.9–NA)	(4.6–NA)	(3.2-NA)
Duration of treatment	8	8	NA
median, months (95 % CI)	(4–NA)	(4–NA)	(3-NA)
Treatment	19	15	4
discontinuation, n (%)	(31.1)7	(31.3)6	(30.8)1
PD	(11.5)2	(12.5)2	(7.7)
TRAE	(3.3)	(4.2)	0
Death			

[a] of 6 patients with measurable, non-radiated lesions.

respectively), with exception of female sex (HR 2.67, 95 % CI 1.24–5.78, p = 0.009) but this finding was not confirmed at multivariate analysis (data not shown).

Median OS was not estimable due to the limited follow-up (Fig. 2). OS rate at 12 months was 56.4 % (95 % CI 43.7– 72.8 %) in the overall cohort, 73.8 % (95 % CI 52.2– 100 %) and 53.6 % (95 % CI 39.9– 71.9 %) in the previously treated and untreated population, respectively.

3.3. Safety

Overall, 51 out of 61 (83.6 %) patients experienced any-grade treatment-related adverse events (TRAEs). The most common TRAEs were fatigue (49.2 %), dry mouth/oral mucositis (39.3 %), increased liver enzymes (24.6 %) and nausea (23 %) (Fig. 3).

Twenty-four patients (39.3 %) had grade 3 or greater (G ≥ 3) TRAEs. The most common G ≥ 3 TRAEs were neutropenia (9.8 %), dry mouth/oral mucositis (8.2 %), thrombocytopenia (6.6 %), increased liver enzyme levels (4.9 %), anemia (4.9 %), and fatigue (4.9 %). Seven patients (11.5 %) discontinued pralsetinib due to TRAEs, twenty-seven (44.3 %) had at least one dose level modification due to TRAEs. The most frequent adverse events leading to dose reduction were dry mouth/oral mucositis (n = 5) and hematological toxicities (n = 5). Two deaths were observed due to severe systemic infection (1 sepsis, 1 typhlitis), judged as treatment-related by the investigators.

No statistically significant differences were observed in the occurrence of any grade or G ≥ 3 TRAEs according to previous exposure to immune checkpoint inhibitors (OR 1.12, 95 % CI 0.28–5.07 and OR 0.90, 95 % CI 0.29–2.77, respectively).

4. Discussion

In our real-world data analysis, sixty-one patients with NSCLC harboring RET-gene fusions were treated with pralsetinib (48 previously treated and 13 treatment-naïve). This number is more than half the first presented efficacy population of the phase I/II ARROW (92 pre-treated and 29 treatment-naïve among total 233 patients included)[12]. Median age of patients included was similar compared to the pivotal trial, in particular treatment-naïve patients were older compared to those who were previously treated (66 vs 62 in our experience, and 65 vs 60 in the ARROW trial). This is possibly related to the definition of patients unfit for any treatment options in those receiving pralsetinib in the treatment-naïve setting, consistent with the initial inclusion criteria of phase I/II trial.

The ORR was 66 % in our cohort, 68.8 % in previously treated, whereas numerically lower in treatment naïve patients, although DCR was similar in the two groups (77 %). Of note, treatment naïve patients were older and had twice the incidence of PS ECOG 2 (30.8 % vs 12.5 %) compared to previously treated patients, thus potentially justifying the lower ORR in this subgroup. Baseline CNS involvement was 29.5 % in our real-world population, similar to 33 % in the ARROW trial. icORR was 66.7 % among 6 evaluable patients, with icDCR 100 %. In the ARROW trial, updated icORR was 70 % (10 patients evaluable), and icDCR was 100 %[8,13].

The median PFS was 8.9 months (4.6–NA) with a median follow up of 11.5 months in the previously treated population. In the ARROW trial, the median follow up was longer, 14.7 months in the pre-treated patients, with longer median PFS of 17.1 months[12]. In our treatment-naïve cohort, median PFS was 5.6 months (3.2-NA) with median follow up of 7.5 months. The ARROW trial had longer follow up of 11.5 months in the treatment-naïve population, with median PFS of 9.1 months. Of note, results of the treatment-naïve population in the ARROW trial notably improved in the updated publication including the patients enrolled after an amendment allowing front-line pralsetinib also in patients who were not unfit for other treatments[13]. Notably, this population is not comparable to our real-world data.

In our experience, treatment with pralsetinib lead to TRAEs in 83.6 % of patients, and G ≥ 3 TRAEs in 39.3 %, and 44.3 % of TRAEs leading to dose reduction. Overall TRAEs occurred in 93 % of patients in the ARROW trial, 48 % G ≥ 3, and 38 % dose reductions. Similar discontinuation rates due to TRAEs were observed in our cohort (11.5 %) and in the pivotal trial (7 %). Two deaths (3 %) in our population were ascribed to TRAEs according to their treating physicians. In the overall population of the ARROW trial (N = 281), 1 death (<1%) was reported to be related to TRAE (pneumonia).

Clinical evidence with selpercatinib showed comparable efficacy results than those obtained with pralsetinib, both in clinical trial and in real-world setting[9,14]. Indeed, the phase I/II.

LIBRETTO-001 [9] study enrolled patients with similar clinical and biological features as compared to those of the ARROW trial, with exception of younger median age (61) and no limitations for the definition of previously untreated patients. Of note, numerically lower incidence of G ≥ 3 TRAEs was reported both in the LIBRETTO-001 (28 %) and the selpercatinib (24 %) real-world data analysis, but a direct comparison of safety profile between the two compounds is lacking, to date [5,14]. A correlation between the incidence of TRAEs and previous exposure to ICIs was observed with selpercatinib. However, we investigated the potential role of previous ICIs on pralsetinib outcomes, and found no correlation with treatment response, nor with the incidence of TRAEs.

5. Conclusions

In conclusion, we are reporting on the largest real-world experience with pralsetinib in RET-positive NSCLC. Despite retrospective and limited to Italian experience, our data robustly confirm efficacy results reported in the phase I/II ARROW trial, reflecting a similar patients' population and comparable safety outcomes.

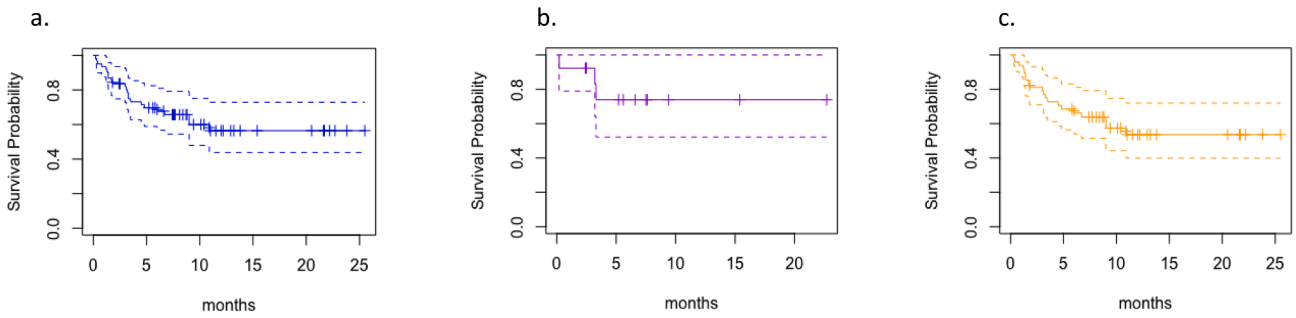

Fig. 2. Overall survival. Overall survival with pralsetinib in the overall (a), treatment naïve (b), and pre-treated (c) populations.

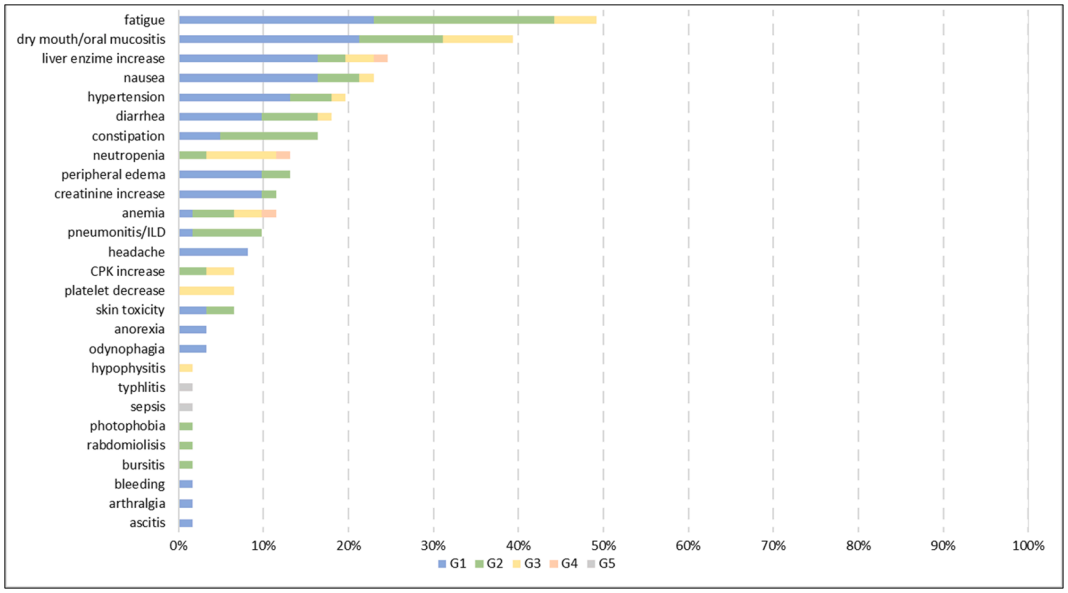

Fig. 3. Treatment related adverse events (AEs). The incidence of treatment-related adverse events (according to treating physicians) in the overall population is reported in percentages. Grading of AEs is indicated by different colors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was partially supported by the Italian Ministry of Health with “Ricerca Corrente” and “5×1000” funds, FIRSTt (Fondazione Italiana per la Ricerca e lo Studio nei Tumori del torace), and MIUR Dipartimenti Eccellenti 2017.

References

[1] C. Belli, F. Penault-Llorca, M. Ladanyi, N. Normanno, J.Y. Scoazec, L. Lacroix, J. S. Reis-Filho, V. Subbiah, J.F. Gainor, V. Endris, M. Repetto, A. Drilon, A. Scarpa, F. André, J.Y. Douillard, G. Curigliano, ESMO recommendations on the standard methods to detect RET fusions and mutations in daily practice and clinical research, Ann Oncol 32 (3) (2021) 337–350.

[2] J. Mazieres, A. Drilon, A. Lusque, L. Mhanna, A.B. Cortot, L. Mezquita, A.A. Thai, C. Mascaux, S. Couraud, R. Veillon, M. Van den Heuvel, J. Neal, N. Peled, M. Früh, T.L. Ng, V. Gounant, S. Popat, J. Diebold, J. Sabari, V.W. Zhu, S.I. Rothschild, P. Bironzo, A. Martinez-Marti, A. Curioni-Fontecedro, R. Rosell, M. Lattuca-Truc, M. Wiesweg, B. Besse, B. Solomon, F. Barlesi, R.D. Schouten, H. Wakelee, D. R. Camidge, G. Zalcman, S. Novello, S.I. Ou, J. Milia, O. Gautschi, Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry, Ann Oncol 30 (8) (2019) 1321–1328.

[3] A. Hegde, A.Y. Andreev-Drakhlin, J. Roszik, L. Huang, S. Liu, K. Hess, M. Cabanillas, M.I. Hu, N.L. Busaidy, S.I. Sherman, R. Dadu, E.G. Grubbs, S.M. Ali, J. Lee, Y.Y. Elamin, G.R. Simon, G.R. Blumenschein, V.A. Papadimitrakopoulou, D. Hong, F. Meric-Bernstam, J. Heymach, V. Subbiah, Responsiveness to immune checkpoint inhibitors versus other systemic therapies in RET-aberrant malignancies, ESMO open 5 (5) (2020) e000799.

[4] S. Popat, S.V. Liu, N. Scheuer, G.G. Hsu, A. Lockhart, S.V. Ramagopalan, F. Griesinger, V. Subbiah, Addressing challenges with real-world synthetic control arms to demonstrate the comparative effectiveness of Pralsetinib in non-small cell lung cancer, Nature Communications 13 (1) (2022) 3500.

[5] A. Drilon, N. Rekhtman, M. Arcila, L. Wang, A. Ni, M. Albano, M. Van Voorthuysen, R. Somwar, R.S. Smith, J. Montecalvo, A. Plodkowski, M.S. Ginsberg, G.J. Riely, C. M. Rudin, M. Ladanyi, M.G. Kris, Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial, Lancet Oncol 17 (12) (2016) 1653–1660.

[6] S.H. Lee, J.K. Lee, M.J. Ahn, D.W. Kim, J.M. Sun, B. Keam, T.M. Kim, D.S. Heo, J. S. Ahn, Y.L. Choi, H.S. Min, Y.K. Jeon, K. Park, Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial, Ann Oncol 28 (2) (2017) 292–297.

[7] T. Hida, V. Velcheti, K.L. Reckamp, H. Nokihara, P. Sachdev, T. Kubota, T. Nakada, C.E. Dutcus, M. Ren, T. Tamura, A phase 2 study of lenvatinib in patients with RET fusion-positive lung adenocarcinoma, Lung cancer (Amsterdam, Netherlands) 138 (2019) 124–130.

[8] V. Subbiah, P.A. Cassier, S. Siena, E. Garralda, L. Paz-Ares, P. Garrido, E. Nadal, J. Vuky, G. Lopes, G.P. Kalemkerian, D.W. Bowles, M. Seetharam, J. Chang, H. Zhang, J. Green, A. Zalutskaya, M. Schuler, Y. Fan, G. Curigliano, Pan-cancer efficacy of pralsetinib in patients with RET fusion–positive solid tumors from the phase 1/2 ARROW trial, Nature Medicine 28 (8) (2022) 1640–1645.

[9] A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C. E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P. A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.

M. Rothenberg, K. Goto, V. Subbiah, Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer, N Engl J Med 383 (9) (2020) 813–824.

[10] B. Besse, A.E. Drilon, B.J. Solomon, V. Subbiah, D.S.-W. Tan, K. Park, F.G.D. Braud, G. Alonso, J. Wolf, V. Soldatenkova, A.K. Lin, P.P. French, K. Goto, O. Gautschi, Updated overall efficacy and safety of selpercatinib in patients (pts) with RET fusion+ non-small cell lung cancer (NSCLC), Journal of Clinical Oncology 39(15_suppl) (2021) 9065-9065.

[11] A. Drilon, V. Subbiah, O. Gautschi, P. Tomasini, F.G.M. De Braud, B. Solomon, D. Shao-Weng Tan, G. Alonso, J. Wolf, K. Park, K. Goto, V. Soldatenkova, S. Szymczak, S. Barker, T. Puri, A.B. Lin, H.H.F. Loong, B. Besse, 27P Durability of efficacy and safety with selpercatinib in patients (pts) with RET fusion+ non-small cell lung cancer (NSCLC), Annals of Oncology 33 (2022) S43.

[12] J.F. Gainor, G. Curigliano, D.W. Kim, D.H. Lee, B. Besse, C.S. Baik, R.C. Doebele, P. A. Cassier, G. Lopes, D.S.W. Tan, E. Garralda, L.G. Paz-Ares, B.C. Cho, S. M. Gadgeel, M. Thomas, S.V. Liu, M.H. Taylor, A.S. Mansfield, V.W. Zhu, C. Clifford, H. Zhang, M. Palmer, J. Green, C.D. Turner, V. Subbiah, Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study, Lancet Oncol 22 (7) (2021) 959–969.

[13] F. Griesinger, G. Curigliano, M. Thomas, V. Subbiah, C.S. Baik, D.S.W. Tan, D. H. Lee, D. Misch, E. Garralda, D.W. Kim, A.J. van der Wekken, J.F. Gainor, L. Paz-Ares, S.V. Liu, G.P. Kalemkerian, Y. Houvras, D.W. Bowles, A.S. Mansfield, J.J. Lin, V. Smoljanovic, A. Rahman, S. Kong, A. Zalutskaya, M. Louie-Gao, A.L. Boral, J. Mazieres, Safety and efficacy of pralsetinib in RET fusion–positive non-small cell lung cancer including as first-line therapy: update from the ARROW trial, Annals of Oncology (2022).

[14] O. Illini, M.J. Hochmair, H. Fabikan, C. Weinlinger, A. Tufman, A. Swalduz, K. Lamberg, S.M.S. Hashemi, F. Huemer, A. Vikström, M. Wermke, G. Absenger, A. Addeo, S. Banerji, A. Calles, S. Clarke, M. Di Maio, A. Durand, M. Duruisseaux, M. Itchins, O.S. Kääränien, F. Krenn, E. Laack, A.J. de Langen, K. Mohorcic, G. Pall, A. Passaro, G. Prager, A. Rittmeyer, J. Rothenstein, M. Schumacher, E. Wöll, A. Valipour, Selpercatinib in RET fusion-positive non-small-cell lung cancer (SIREN): a retrospective analysis of patients treated through an access program, Therapeutic advances in medical oncology 13 (2021) 17588359211019675.