

Selpercatinib in Patients With *RET* Fusion–Positive Non–Small-Cell Lung Cancer: Updated Safety and Efficacy From the Registrational LIBRETTO-001 Phase III Trial

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PURPOSE Selpercatinib, a first-in-class, highly selective, and potent CNS-active *RET* kinase inhibitor, is currently approved for the treatment of patients with *RET* fusion–positive non–small-cell lung cancer (NSCLC). We provide a registrational data set update in more than double ($n = 316$) of the original reported population ($n = 144$) and better characterization of long-term efficacy and safety.

METHODS Patients were enrolled to LIBRETTO-001, a phase III, single-arm, open-label study of selpercatinib in patients with *RET*-altered cancers. An analysis of patients with *RET* fusion–positive NSCLC, including 69 treatment-naïve and 247 with prior platinum-based chemotherapy, was performed. The primary end point was objective response rate (ORR; RECIST v1.1, independent review committee). Secondary end points included duration of response (DoR), progression-free survival (PFS), overall survival, and safety.

RESULTS In treatment-naïve patients, the ORR was 84% (95% CI, 73 to 92); 6% achieved complete responses (CRs). The median DoR was 20.2 months (95% CI, 13.0 to could not be evaluated); 40% of responses were ongoing at the data cutoff (median follow-up of 20.3 months). The median PFS was 22.0 months; 35% of patients were alive and progression-free at the data cutoff (median follow-up of 21.9 months). In platinum-based chemotherapy pretreated patients, the ORR was 61% (95% CI, 55 to 67); 7% achieved CRs. The median DoR was 28.6 months (95% CI, 20.4 to could not be evaluated); 49% of responses were ongoing (median follow-up of 21.2 months). The median PFS was 24.9 months; 38% of patients were alive and progression-free (median follow-up of 24.7 months). Of 26 patients with measurable baseline CNS metastasis by the independent review committee, the intracranial ORR was 85% (95% CI, 65 to 96); 27% were CRs. In the full safety population ($n = 796$), the median treatment duration was 36.1 months. The safety profile of selpercatinib was consistent with previous reports.

CONCLUSION In a large cohort with extended follow-up, selpercatinib continued to demonstrate durable and robust responses, including intracranial activity, in previously treated and treatment-naïve patients with *RET* fusion–positive NSCLC.

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INTRODUCTION

RET fusions are identified in 1%-2% of patients with non–small-cell lung cancer (NSCLC).¹⁻³ These fusions result in ligand-independent constitutive activation of the *RET* pathway and increased oncogenic signaling.⁴ Both selpercatinib⁴ and pralsetinib⁵ are selective *RET* inhibitors, which have demonstrated promising clinical activity in patients with *RET* fusion–positive NSCLCs. This underscores the benefit of including *RET* fusions as part of comprehensive oncogene driver testing in patients with NSCLCs.^{6,7}

On the basis of compelling and durable responses observed in the largest clinical study in *RET*-altered cancers, selpercatinib emerged as a new standard of care for patients with *RET*-altered lung and thyroid cancers.⁴ The drug was first approved in May 2020 by the US Food and Drug Administration for adult patients with *RET* fusion–positive NSCLCs and subsequently has gained regulatory approval in multiple geographies. Additional data regarding the drug's activity and safety, with increased patient numbers and longer follow-up, are valuable as more providers treat patients

CONTEXT

Key Objective

Selpercatinib is a first-in-class, highly selective, and potent CNS-active RET kinase inhibitor. An updated assessment of the efficacy and safety of selpercatinib in patients with *RET* fusion–positive non–small-cell lung cancer treated in the phase I/II LIBRETTO-001 trial was performed. The data cutoff date was June 15, 2021.

Knowledge Generated

With longer follow-up and additional patients, selpercatinib continued to demonstrate marked efficacy, with a high objective response rate, continued durability of response, and substantial CNS activity, as well as a consistent safety profile.

Relevance

Given the durable efficacy observed in patients with non–small-cell lung cancer, broad-based genomic profiling should be considered to identify patients with *RET* fusions who may benefit from selpercatinib (Ann Oncol 32:337-350, 2021).

with this first-in-class, highly selective, and potent RET inhibitor.

In LIBRETTO-001, a registrational, phase I/II, single-arm, open-label study, selpercatinib demonstrated durable antitumor activity, including intracranial efficacy.^{4,8,9} In the initial registrational analysis set (n = 144), high response rates and favorable tolerability were observed in both treatment-naïve (n = 39) and platinum-based chemotherapy pretreated (n = 105) patients with *RET* fusion–positive advanced NSCLC.⁴ However, since the majority of patients were alive and progression-free at the time of initial approval, the median duration of response (DoR) and progression-free survival (PFS) could not be accurately estimated.

In this article, we provide an updated analysis of the activity of selpercatinib in *RET* fusion–positive NSCLC. This includes efficacy in a total of 316 patients (172 additional patients). Furthermore, we provide 18 more months of follow-up than that previously published.⁴

METHODS

Patients

The complete eligibility criteria are detailed in the Protocol (online only) as previously disclosed.⁴ Eligible patients were age ≥ 18 years or ≥ 12 years, if permitted by regulatory authorities, with measurable disease per RECIST Version 1.1. Local molecular testing in a certified laboratory was performed with next-generation sequencing, fluorescence in situ hybridization, or polymerase chain reaction to determine *RET* alteration status, and the result was reviewed and confirmed by the sponsor before enrollment. Patients were required to have an Eastern Cooperative Oncology Group Performance Score of 0-2 and adequate organ function. Patients with known brain metastases, either asymptomatic or neurologically stable for ≥ 2 weeks, were eligible. The trial was conducted in accordance with Good Clinical Practice guidelines, in line with principles of the Declaration of

Helsinki, and all applicable country and local regulations. Protocol was approved by the institutional review board or independent ethics committee at each investigative site. All patients provided written informed consent.

Trial Design and Treatment

This open-label phase I/II trial was conducted at approximately 85 sites in 16 countries. Selpercatinib was orally administered in a continuous 28-day cycle until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients enrolled in the phase I dose escalation portion received 20 mg once daily or 20-240 mg twice a day of selpercatinib. Inpatient dose escalation was permitted with sponsor approval. All patients in phase II received the recommended phase II dose of 160 mg twice a day. Patients who dose-reduced were permitted to re-escalate once the adverse events (AEs) had been resolved. Patients with progressive disease could continue treatment with selpercatinib per investigator discretion with sponsor approval. The phase II primary end point was objective response rate (ORR) by the independent review committee (IRC) per RECIST version 1.1. The secondary end points included ORR by the investigator, PFS, DoR, overall survival (OS), and safety. All responses required a confirmation of radiologic assessment > 4 weeks after first assessment.

Assessments

Radiologic tumor assessments were performed at baseline, every 8 weeks for 1 year, and then every 12 weeks thereafter. Tumor evaluations were performed using RECIST version 1.1. During phase I, brain imaging was obtained at baseline only if clinically indicated. By contrast, all phase II patients underwent brain imaging at baseline. Intracranial responses were assessed by IRC using RECIST version 1.1. AEs were assessed from first dose of study drug until safety follow-up visit 28 days after last selpercatinib dose. Unresolved serious adverse events (SAEs) were continued to be assessed after the safety follow-up visit. AEs were graded according to Common Terminology Criteria for Adverse Events version 4.03.

Oversight

The trial was designed by both the sponsor and the investigators. All the authors contributed to the writing and/or revisions of the manuscript. A medical writer, paid by the sponsor, provided writing support. All the authors approved the final version for completeness and accuracy of clinical data and analysis and protocol adherence.

Statistical Analysis

For this analysis, the primary efficacy-evaluable analysis populations included all patients with documented *RET* fusion–positive NSCLC previously treated with platinum-based chemotherapy ($n = 247$) or no prior therapy ($n = 69$) who had at least a 6-month follow-up from the first dose. CNS efficacy was assessed in 106 patients with NSCLC treated with selpercatinib who had documented baseline CNS metastases per investigator assessment, regardless of disease measurability or prior therapy. The full safety population ($N = 796$) was defined as all patients who had received at least one dose of selpercatinib as of the data cutoff date of June 15, 2021. The NSCLC safety population ($n = 356$) was defined as all patients with *RET* fusion–positive NSCLC who had received at least one dose of selpercatinib as of the data cutoff date. Database lock was performed on August 6, 2021. CIs for response rates were calculated using the Clopper-Pearson method. DoR, PFS, and OS were estimated using the Kaplan-Meier method. As the time-to-event data remain immature, median follow-up times were provided for each efficacy end point to provide appropriate context. Follow-up times were estimated using the reverse Kaplan-Meier method.¹⁰ Cumulative incidence rates were calculated using a competing risk model with CNS/systemic disease progression or death as competing risks. An exploratory ad hoc intrapatient analysis was performed to compare (McNemar's exact test) retrospective physician-reported best overall response (BOR), on the basis of patients' medical records, from last systemic therapy received before enrollment with investigator-assessed BOR on selpercatinib treatment per RECIST version 1.1, assessed prospectively, with each patient serving as their own control.

RESULTS

A total of 356 patients with *RET* fusion–positive advanced NSCLC were enrolled and treated with selpercatinib from May 2017 to May 2020. The baseline demographic characteristics of the primary efficacy-evaluable patients are displayed in [Table 1](#). Additional information is provided in the Data Supplement (online only). Patients previously treated with platinum-based chemotherapy received a median of 2 previous lines of treatment (range, 1-15; ≥ 3 : 42.3% of patients); 58.3% had received prior anti–programmed cell death protein 1 or anti–programmed cell death ligand 1 therapies, and 34.4% had prior multikinase inhibitors. With

the exception of prior therapy, baseline characteristics were similar across patients who were previously treated or treatment-naïve. The majority of *RET* fusions were identified with next-generation sequencing. The most common fusion partners identified included *KIF5B* and *CCDC6* ([Table 1](#)).

Treatment-Naïve Patients

A total of 69 treatment-naïve patients were analyzed. The ORR by IRC was 84% (95% CI, 73 to 92); 6% of patients achieved a complete response (CR; [Table 2](#); [Fig 1A](#)). At a median follow-up of 20.3 months for 58 responders, the median DoR by IRC was 20.2 months (95% CI, 13.0 to could not be evaluated [NE]), with 40% of responses ongoing ([Table 2](#); [Fig 2A](#)). The median time to response was 1.8 (range, 0.7-10.8) months, with the longest response ongoing at 39.3 months. The median PFS was 22.0 months (95% CI, 13.8 to NE), with 35% of patients alive and progression-free at a median follow-up of 21.9 months ([Fig 2C](#)). The estimated proportion of patients who were alive and progression-free at 1 and 2 years was 70.6% (95% CI, 57.8 to 80.2) and 41.6% (95% CI, 26.8 to 55.8; [Table 2](#)), respectively. At a median follow-up of 25.2 months, the median OS was not estimable (71% censoring rate). The estimated proportion of patients alive at 2 years was 69% (95% CI, 55 to 80; Data Supplement). At the time of data analysis, 46% of patients remained on selpercatinib treatment including 7% who remained on treatment beyond progression. Overall, 32% of patients received selpercatinib beyond progression on the basis of continuous clinical benefit per the investigator with sponsor approval.

Chemotherapy Pretreated Patients

A total of 247 patients previously received platinum-based chemotherapy. The ORR by IRC was 61% (95% CI, 55 to 67); a CR was achieved in 7% of patients ([Table 2](#)). At a median follow-up of 21.2 months, the median DoR by IRC was 28.6 months (95% CI, 20.4 to NE), with 49% of responses ongoing ([Table 2](#) and [Fig 2B](#)). The median time to response was 1.9 (range, 0.7-21.9) months, with the longest response ongoing at 43.3 months.

The median PFS was 24.9 months (95% CI, 19.3 to NE), with 38% of patients alive and progression-free at a median follow-up of 24.7 months ([Table 2](#)). The estimated proportion of patients who were alive and progression-free at 1 and 2 years was 70.5% (95% CI, 64.1 to 76.0) and 51.4% (95% CI, 44.3 to 58.1; [Fig 2D](#)), respectively. At a median follow-up of 26.4 months, the median OS was not estimable (68% censoring rate). The estimated proportion of patients alive at 2 years was 69% (95% CI, 62 to 75; Data Supplement). The median duration of treatment was 24.9 months (95% CI, 20.5 to 32.2). At the time of data analysis, 47% of patients remained on selpercatinib treatment including 11% who remained on treatment beyond progression. Overall, 35% of patients received selpercatinib beyond progression with sponsor approval. Efficacy results were consistent with those observed in the registration

TABLE 1. Clinicopathologic Features

Characteristic	Treatment-Naive (n = 69)	Previous Platinum Chemotherapy (n = 247)
Age, years		
Median (range)	63.0 (23-92)	61.0 (23-81)
Sex, No. (%)		
Female	43 (62.3)	140 (56.7)
Male	26 (37.7)	107 (43.3)
Race, No. (%) ^a		
White	48 (69.6)	108 (43.7)
Asian	13 (18.8)	118 (47.8)
Black	4 (5.8)	12 (4.9)
Others	4 (5.8)	7 (2.8)
Missing	0	2 (0.8)
Smoking status, No. (%)		
Never smoker	48 (69.6)	165 (66.8)
Former smoker	19 (27.5)	78 (31.6)
Current smoker	2 (2.9)	4 (1.6)
ECOG PS score, No. (%)		
0	25 (36.2)	90 (36.4)
1	40 (58.0)	150 (60.7)
2	4 (5.8)	7 (2.8)
NSCLC histologic subtype, No. (%)		
Adenocarcinoma	62 (89.9)	221 (89.5)
Large cell neuroendocrine carcinoma	0	3 (1.2)
Squamous cell carcinoma	0	1 (0.4)
NSCLC-NOS	7 (10.1)	22 (8.9)
Median previous systemic lines, No. (range)		
1-2	0	140 (56.7)
≥ 3	0	107 (43.3)
Previous regimen, No. (%)		
Platinum-based chemotherapy	NA	247 (100)
Anti-PD-1 or anti-PD-L1 therapy	NA	144 (58.3)
Multikinase inhibitor ^b	NA	85 (34.4)
Others ^c	NA	97 (39.3)
RET fusion, No. (%)		
KIF5B-RET	48 (69.6)	153 (61.9)
CCDC6-RET	10 (14.5)	53 (21.5)
NCOA4-RET	1 (1.4)	5 (2.0)
Others	10 (14.5)	38 (15.4)
CNS metastases at baseline ^d	16 (23.2)	77 (31.2)

NOTE. Percentages may not total to 100 because of rounding.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; NOS, not otherwise specified; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

^aRace was reported by the patients. Other races included American Indian, Alaska Native, and Pacific Islander, among others.

^bMultikinase inhibitors administered included cabozantinib, vandetanib, lenvatinib, and others. Patients might have received more than one multikinase inhibitor.

^cOther prior systemic therapies included radioactive iodine, mammalian target of rapamycin inhibitor, epidermal growth factor receptor inhibitor, vascular endothelial growth factor/vascular endothelial growth factor receptor inhibitor, and selective RET inhibitor.

^dIncludes both measurable and nonmeasurable CNS metastases.

TABLE 2. Efficacy

Response	Treatment-Naive (n = 69)	Previous Platinum Chemotherapy (n = 247)
Objective response by IRC, % (95% CI)	84 (73 to 92)	61 (55 to 67)
Best response, No. (%)		
CR	4 (6)	18 (7)
Partial response	54 (78)	133 (54)
Stable disease	6 (9)	81 (33)
Progressive disease	3 (4)	7 (3)
NE	2 (3)	8 (3)
DoR		
Median (95% CI), months	20.2 (13.0 to NE)	28.6 (20.4 to NE)
Censoring rate (%)	55.2	60.9
Median duration of follow-up, months	20.3	21.2
1-year DoR, % (95% CI)	66.1 (51.6 to 77.3)	73.1 (64.9 to 79.7)
2-year DoR, % (95% CI)	41.6 (25.6 to 56.8)	55.8 (46.4 to 64.2)
PFS		
Disease progression, No. (%)	29 (42.0)	89 (36.0)
Median (95% CI), months	22.0 (13.8 to NE)	24.9 (19.3 to NE)
Censoring rate, No. (%)	37 (53.6)	138 (55.9)
Median duration of follow-up, months	21.9	24.7
1-year PFS, % (95% CI)	70.6 (57.8 to 80.2)	70.5 (64.1 to 76.0)
2-year PFS, % (95% CI)	41.6 (26.8 to 55.8)	51.4 (44.3 to 58.1)
OS		
Patients with censored data, No. (%)	49 (71.0)	169 (68.4)
Median duration of follow-up, months	25.2	26.4
1-year OS, % (95% CI)	92.7 (83.3 to 96.9)	87.9 (83.0 to 91.4)
2-year OS, % (95% CI)	69.3 (55.2 to 79.7)	68.9 (62.2 to 74.7)
3-year OS, % (95% CI)	57.1 (35.9 to 73.6)	58.5 (49.7 to 66.3)

Abbreviations: CR, complete response; DoR, duration of response; IRC, independent review committee; NE, could not be evaluated; OS, overall survival; PFS, progression-free survival.

analysis set (Data Supplement) and previous data cutoffs, December 2019 and March 2020 (Data Supplement).

An exploratory ad hoc analysis was performed in the patients who were previously treated to compare physician-

reported BOR from last systemic therapy (received before enrollment) with selpercatinib BOR (RECIST version 1.1 per investigator). This analysis allowed each patient to serve as their own control (Data Supplement). Overall, responses were observed in 64% of patients with selpercatinib compared with a response rate of 15% to the last prior therapy received before enrollment ($P < .0001$, McNemar's exact test). The percentage of patients who responded to selpercatinib by response to prior therapy is shown in the Data Supplement. A similar analysis in a subgroup of patients who received selpercatinib in the second-line setting was conducted. This showed a response rate of 73% with second-line selpercatinib treatment compared with 18% with first-line platinum-based chemotherapy that these patients received before enrollment. Furthermore, improvements in ORR were observed regardless of the type of prior therapy received (Data Supplement).

Patients With CNS Metastases

In the 106 patients with brain metastases at baseline, the median intracranial PFS was 19.4 months (95% CI, 13.8 to NE) at a median follow-up of 22.1 months. In the subset of patients with measurable CNS metastasis at baseline ($n = 26$), the intracranial ORR by IRC was 85% (95% CI, 65 to 96), including 27% intracranial CRs (Data Supplement and Fig 1C). None of these 26 patients had primary intracranial progression as their best response. Objective responses were observed regardless of whether patients had received prior systemic therapy and/or radiotherapy. In the 22 responders with measurable CNS metastases, the median duration of CNS response was 9.4 months (95% CI, 7.4 to 15.3). In the 178 phase II patients with baseline confirmation that no CNS metastasis was present, the estimated probability of observing intracranial progression at 2 years was 0.7% (Data Supplement).

Safety

In the full safety population ($n = 796$), selpercatinib's AE profile was consistent with previous reports. With longer follow-up and larger patient number, this updated full safety population reflects a near doubling of total exposure time from data cutoff used in the previous report (16,098 months versus 8,692 months). Importantly, the profile observed in patients with NSCLC is consistent with that of the full safety patient population (Data Supplement).

Treatment-emergent AEs, regardless of causality, in addition to AEs that were deemed related to selpercatinib per the investigator, are shown in Table 3. The most common grade ≥ 3 treatment-emergent AEs were hypertension (19.7%), ALT increased (11.4%), AST increased (8.8%), diarrhea (5.0%), and electrocardiogram QT prolonged (4.8%). The most common grade ≥ 3 treatment-related AEs included hypertension (13.2%) and AST/ALT elevations (6.3%/9.0%).

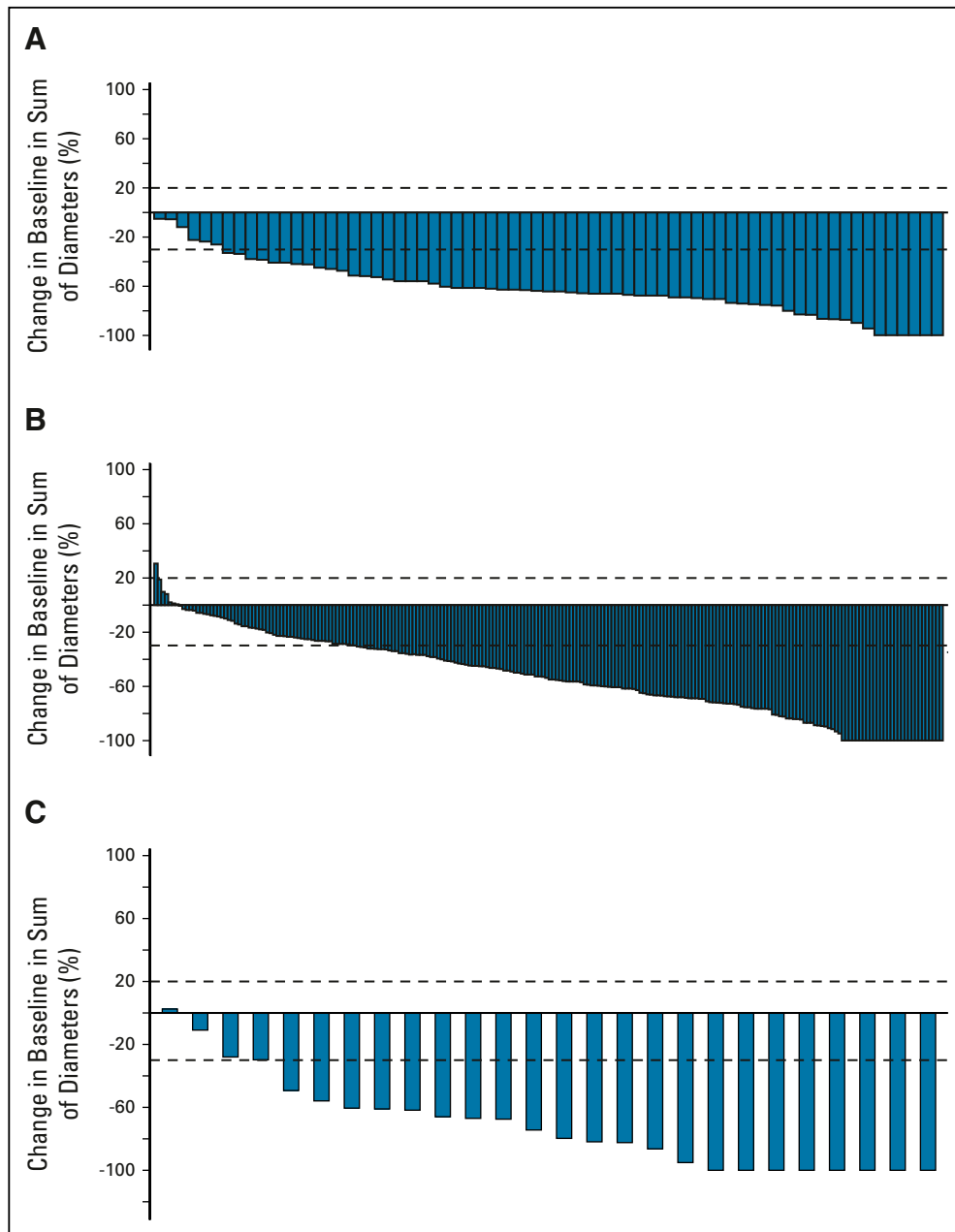


FIG 1. Response to selpercatinib. The waterfall plots of maximum change in tumor size are shown in (A) for the 69 patients who were treatment-naive and (B) for 226 with prior platinum chemotherapy and (C) the change in intracranial tumor size for the 26 patients with measurable CNS disease at baseline. Vertical bars represent the best percent change from baseline in the sum of diameters for all target lesions. Progressive disease (+20%) and partial response (−30%) are indicated with the dashed lines.

Treatment-emergent SAEs occurred in 44% of patients, including 11% related to selpercatinib. Pneumonia (4%) was the most common SAE, and drug hypersensitivity (1%) was the most common treatment-related SAE. There was one fatal AE that was considered related to selpercatinib per the investigator in a patient with *RET*-mutant medullary thyroid cancer who died because of acute respiratory failure. Dose reductions occurred in 41% of patients. In total, 64 of 796 patients (8%) discontinued treatment

because of AEs, with 25 (3%) considered by the investigator to be related to selpercatinib.

DISCUSSION

Selpercatinib is currently approved for the treatment of patients with *RET* fusion–positive NSCLC in multiple countries. This update to the regulatory data set provided more than double the previously reported number of patients with an

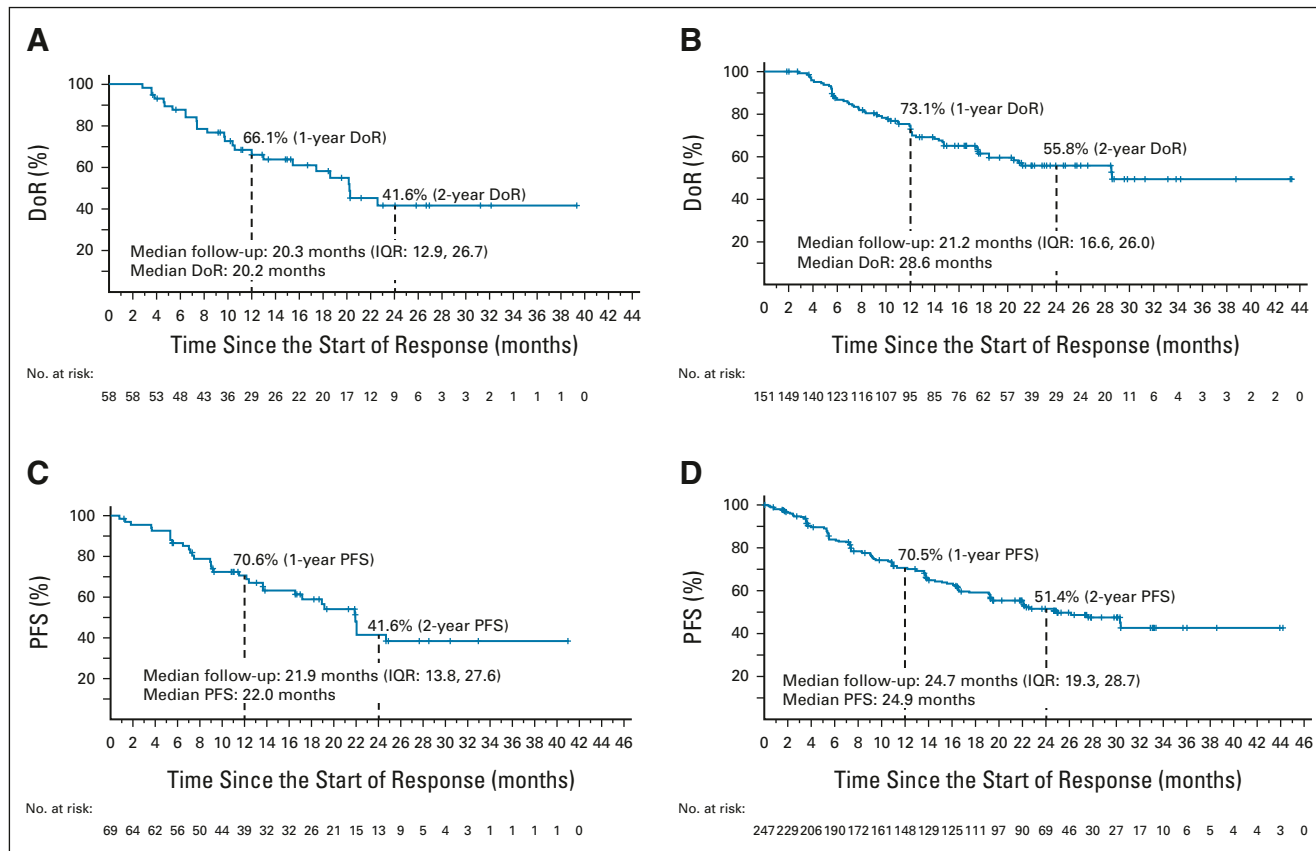


FIG 2. Long-term outcomes with selpercatinib. Kaplan-Meier (KM) plots depict PFS for patients who (A) were treatment-naïve or (B) had previous platinum chemotherapy. KM plots depict DoR for patients who (C) were treatment-naïve or (D) had previous platinum chemotherapy. Median PFS is displayed in the Table inset. Tick marks indicate censored data. DoR, duration of response; IQR, interquartile range; PFS, progression-free survival.

additional follow-up of 18 months.⁴ Several observations have emerged.

First, with increased patient numbers and longer follow-up, ORRs remained comparable with prior data cutoffs. The ORR was 84% (previously 85%⁴) for treatment-naïve patients and 61% (previously 57%⁴) for platinum pretreated patients, many of whom received other systemic therapies including immunotherapy and multikinase inhibitor therapy. This substantial antitumor activity is further underscored in this article by our exploratory ad hoc analysis of response to systemic therapy received immediately before selpercatinib. In this inpatient analysis, response to selpercatinib was significantly higher ($P < .0001$) than that to prior therapy including comparisons with response rates from prior treatment with chemotherapy or multikinase inhibitor therapy. Response rates were also higher with selpercatinib compared with immunotherapy or chem-immunotherapy, consistent with previous reports, showing poor outcomes with immunomodulatory therapy in *RET* fusion-positive NSCLCs.¹¹⁻¹³ Thus, as is supported by current guidelines,¹⁴ the administration of selpercatinib is recommended in patients with advanced NSCLC upon identification of a *RET* fusion, either in treatment-naïve or systemic therapy pretreated patients.

Second, this article highlights the durability of selpercatinib benefit. In treatment-naïve patients, our update demonstrates that the median DoR and median PFS are 20.2 months and 22.0 months, respectively (previously not estimable for both⁴). In platinum pretreated patients, the median DoR and median PFS were 28.6 months (previously 17.5 months⁴) and 24.9 months (previously 18.4 months⁴), respectively. Note that additional follow-up will be needed to characterize fully the durability of benefit for treatment-naïve patients, as these medians remain immature. Regardless, these outcomes compare favorably with the durability of platinum-based therapy with or without the addition of checkpoint inhibitors (median PFS 7-9 months)¹⁵⁻¹⁷ or other standard-of-care therapies,^{18,19} recognizing the limits of cross-trial comparisons. We await the readout of an ongoing randomized trial of selpercatinib versus chemotherapy in *RET* fusion-positive NSCLCs (LIBRETTO-431, ClinicalTrials.gov identifier: [NCT04194944](https://clinicaltrials.gov/ct2/show/study/NCT04194944)).²⁰

Third, compelling treatment outcomes were attained in both treatment-naïve and previously treated patients with pre-existing measurable CNS metastases. A previous report highlighted how the lifetime prevalence of brain metastases in advanced *RET* fusion-positive lung cancers

TABLE 3. AEs in the Full Safety Population

Preferred or Composite Terms	Any Causality (N = 796)		Related to Treatment (N = 796)	
	Any Grade ^a	Grade ≥ 3	Any Grade	Grade ≥ 3 ^b
Patients with ≥ 1 AE	795 (99.9)	572 (71.9)	756 (95.0)	307 (38.6)
<i>Edema</i>	386 (48.5)	6 (0.7)	246 (30.9)	5 (0.6)
<i>Diarrhea</i>	374 (47.0)	40 (5.0)	217 (27.3)	16 (2.0)
<i>Fatigue</i>	365 (45.9)	25 (3.1)	221 (27.8)	17 (2.1)
<i>Dry mouth</i>	344 (43.2)	0	304 (38.2)	0
<i>Hypertension (AESI)</i>	326 (41.0)	157 (19.7)	224 (28.1)	105 (13.2)
<i>AST increased</i>	292 (36.7)	70 (8.8)	229 (28.8)	50 (6.3)
<i>ALT increased</i>	284 (35.7)	91 (11.4)	227 (28.5)	72 (9.0)
<i>Abdominal pain</i>	268 (33.7)	20 (2.5)	88 (11.1)	3 (0.4)
<i>Constipation</i>	261 (32.8)	6 (0.8)	115 (14.4)	2 (0.3)
<i>Rash</i>	261 (32.8)	5 (0.6)	159 (20.0)	5 (0.6)
<i>Nausea</i>	248 (31.2)	9 (1.1)	98 (12.3)	3 (0.4)
<i>Blood creatinine increased</i>	227 (28.5)	15 (1.9)	123 (15.4)	2 (0.3)
<i>Headache</i>	220 (27.6)	11 (1.4)	76 (9.5)	3 (0.4)
<i>Cough</i>	184 (23.1)	0	19 (2.4)	0
<i>Dyspnea</i>	179 (22.5)	25 (3.1)	26 (3.3)	1 (0.1)
<i>Vomiting</i>	178 (22.4)	14 (1.8)	54 (6.8)	3 (0.4)
<i>ECG QT prolongation (AESI)</i>	168 (21.1)	38 (4.8)	130 (16.3)	27 (3.4)
<i>Arthralgia</i>	165 (20.7)	2 (0.3)	43 (5.4)	1 (0.1)

NOTE. Data are represented as No. (%). Table includes AEs that occurred in ≥ 20% of patients. Composite terms that are composed of preferred terms are shown in italics and are further defined in the Data Supplement.

Abbreviations: AE, adverse event; AESI, adverse events of special interest.

^aIn total, 45 patients had grade 5 treatment-emergent adverse events, including respiratory failure (in seven); sepsis and cardiac arrest (in five each), pneumonia and acute respiratory failure (in three each); dyspnea, cerebral hemorrhage, and cardiorespiratory arrest (in two each); pneumonitis, somnolence, aspiration, cardiac failure, bronchitis, chronic obstructive pulmonary disease, encephalopathy, small intestinal obstruction, brain herniation, multiple organ dysfunction syndrome, neoplasm progression, septic shock, general physical health deterioration, hemoptysis, hypoxia, corona virus infection, obstruction gastric, postprocedural hemorrhage, and sudden death (in one each).

^bOne grade 5 treatment-related adverse event (pneumonitis) was observed.

was 46%.²¹ In patients with measurable CNS disease, the intracranial ORR with selpercatinib was 85% and the median duration of intracranial response was 9.4 months. Furthermore, in the 106 patients with brain metastases at baseline, the median intracranial PFS was 19.4 months (95% CI, 13.8 to NE) at a median follow-up of 22.1 months. A response to selpercatinib in leptomeningeal metastases has also been reported in a patient with *RET* fusion–positive NSCLC.²² In addition to the activity observed in patients with brain metastases at baseline, in the 178 phase II patients with no CNS involvement at baseline, the estimated probability of observing intracranial progression at 2 years was 0.7%, suggesting that selpercatinib may also prevent the acquisition of metastases in the brain. As a brain-penetrant tyrosine kinase inhibitor,²³ selpercatinib's capacity to reduce CNS tumor burden, as a poor prognostic factor and significant source of clinical morbidity, represents a significant advantage over many standard chemotherapy approaches.²⁴

Finally, extended monitoring for safety analysis demonstrated consistency in the AE profile compared with

previous data cutoffs. This profile was also similar between the full safety population (all cancers treated with selpercatinib) and the NSCLC safety population. Providers should carefully monitor notable AEs such as liver enzyme elevation, hypertension, QTc prolongation, and hypersensitivity. The risk of hypersensitivity has previously been observed with increased frequency in patients with prior immunotherapy,²⁵ but has been manageable with the recommended guidance and supportive care.²⁶ The median duration of treatment exceeded 3 years (36.1 months [95% CI, 30.9 to NE]) across the full safety population of 796 patients, the majority of whom were pretreated.

In conclusion, selpercatinib continues to demonstrate marked efficacy and a consistent safety profile in this global, multicenter data set with longer follow-up and additional patients. Data will continue to mature and be augmented by the ongoing phase III LIBRETTO-431 trial, which will assess the PFS of selpercatinib compared with pemetrexed-inclusive platinum-based chemotherapy

and investigator's choice of pembrolizumab in treatment-naïve patients with *RET* fusion–positive advanced or metastatic lung cancers (ClinicalTrials.gov identifier: [NCT04194944](https://clinicaltrials.gov/ct2/show/study/NCT04194944)).^{20,27} LIBRETTO-431 is designed to explore the ability of selpercatinib to not only treat existing CNS metastases but also to prevent or delay the occurrence of new CNS metastases.

The LIBRETTO-001 study (ClinicalTrials.gov identifier: [NCT03157128](https://clinicaltrials.gov/ct2/show/study/NCT03157128)) continues to enroll patients with *RET*-

altered cancers. Selpercatinib has demonstrated potent and durable antitumor activity in *RET*-mutant cancers with medullary thyroid cancer, *RET* fusion–positive thyroid cancers,²⁸ and a variety of cancer types other than lung or thyroid cancer (tissue-agnostic analyses).²⁷ Given the durable efficacy observed in patients with lung cancer, broad-based genomic profiling should be considered across other cancer types to identify patients whose tumors harbor activating *RET* alterations.²⁹

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

Eli Lilly and Company provides access to all individual data collected during the trial, after anonymization, with the exception of pharmacokinetic, genomic, or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set and will be set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Selpercatinib in Patients With *RET* Fusion–Positive Non–Small-Cell Lung Cancer: Updated Safety and Efficacy From the Registrational LIBRETTO-001 Phase I/II Trial**

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