Selpercatinib in *RET* Fusion–Positive Non–Small Cell Lung Cancer: Final Safety and Efficacy, Including Overall Survival, From the LIBRETTO-001 Phase I/II Trial

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ABSTRACT

LIBRETTO-001 (ClinicalTrials.gov identifier: NCT03157128) is a registrational phase I/II, single-arm, open-label trial of selpercatinib in RET-dependent cancers. With 19 months of additional follow-up, we report the final efficacy and safety results of selpercatinib in patients with *RET* fusion–positive non–small cell lung cancer (NSCLC) who had previously received platinum-based chemotherapy (N = 247) or were treatment-naïve (N = 69). The objective response rate (ORR) was 62% for pretreated patients and 83% for treatment-naïve patients. Duration of response (DoR) was 31.6 months for pretreated and 20.3 months for treatment-naïve patients (median follow-up approximately 38 months). Median progression-free survival (PFS) was 26.2 months for pretreated and 22.0 months for treatment-naïve patients (median follow-up approximately 40 months). Median overall survival was 47.6 months in pretreated patients and was not reached in the treatment-naïve group (median follow-up approximately 43 months). At the 3-year landmark estimate, 57% of pretreated and 66% of treatment-naïve patients were alive. Among 26 patients with measurable CNS metastases at baseline, the CNS-ORR was 85% with a CNS-DoR of 9.4 months and CNS-PFS of 11.0 months. The safety profile of selpercatinib was consistent with previous reports. With substantial additional follow-up, selpercatinib continued to show durable responses and intracranial activity, with a manageable safety profile in patients with *RET* fusion–positive NSCLC.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

RET fusions are targetable alterations in non–small cell lung cancer (NSCLC). Selpercatinib, a highly selective RET kinase inhibitor with CNS penetration,[1-3] was approved for the treatment of *RET* fusion–positive NSCLC on the basis of the results of the single-arm phase I/II trial LIBRETTO-001 (ClinicalTrials.gov identifier: NCT03157128).[1,4] These results were confirmed in the recent randomized phase III trial LIBRETTO-431 (ClinicalTrials.gov identifier: NCT04194944); at an interim analysis, selpercatinib demonstrated superior progression-free survival (PFS) over platinum-based chemotherapy with or without pembrolizumab in first-line treatment.[2] On the basis of these data, current treatment guidelines recommend selpercatinib as first-line treatment for *RET* fusion–positive NSCLC.[5-7] Here, we report long-term efficacy and safety from the final analysis of selpercatinib in patients with *RET* fusion–positive NSCLC in the LIBRETTO-001 clinical trial, providing 3-year response outcomes, PFS and overall survival (OS), including the first reports of median OS in pretreated patients and median PFS in patients with measurable CNS metastasis at baseline. To our knowledge, this is the first mature estimation of median OS for selpercatinib and offers insights into how OS may mature in LIBRETTO-431.

METHODS

Study Design

Patients received selpercatinib in 28-day continuous cycles at doses of 20 mg once daily to 240 mg twice daily during the dose-escalation phase I. The recommended dose for phase II was 160 mg twice daily.[4] Treatment continued until disease progression, death, withdrawal of consent, or unacceptable toxicity. Patients with progressive disease could continue selpercatinib if they were deriving clinical benefit according to the investigator and with sponsor approval.

Patients with *RET* fusion–positive, locally advanced or metastatic NSCLC were enrolled. Key exclusion criteria included symptomatic primary CNS tumor, metastases,

TABLE 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristic	Previous Platinum Chemotherapy (n = 247)	Treatment-Naïve (n = 69)
Age, years		
Median (range)	61.0 (23-81)	63.0 (23-92)
Distribution, No. (%)		
<45	33 (13.4)	7 (10.1)
45 to <65	127 (51.4)	31 (44.9)
65 to <75	70 (28.3)	24 (34.8)
75 to <85	17 (6.9)	4 (5.8)
≥85	0	3 (4.3)
Sex, No. (%)		
Female	140 (56.7)	43 (62.3)
Male	107 (43.3)	26 (37.7)
Race, No. (%)[a]		
White	108 (43.7)	48 (69.6)
Asian	118 (47.8)	13 (18.8)
Black	12 (4.9)	4 (5.8)
Other	6 (2.4)	4 (5.8)
Missing	2 (0.8)	0
Smoking status, No. (%)		
Never	165 (66.8)	48 (69.6)
Former	78 (31.6)	19 (27.5)
Current	4 (1.6)	2 (2.9)
ECOG performance status score, No. (%)		
0	90 (36.4)	25 (36.2)
1	150 (60.7)	40 (58.0)
2	7 (2.8)	4 (5.8)
NSCLC histologic subtype, No. (%)		
Adenocarcinoma	221 (89.5)	62 (89.9)
Large cell neuroendocrine carcinoma	3 (1.2)	0
Squamous cell carcinoma	1 (0.4)	0
NSCLC-NOS	22 (8.9)	7 (10.1)
Stage of disease, No. (%)		
IIIB or IIIC	7 (2.8)	2 (2.9)
IV	157 (63.6)	50 (72.5)
IVA	29 (11.7)	4 (5.8)
IVB	27 (10.9)	8 (11.6)
IVC	15 (6.1)	1 (1.4)
Previous systemic lines, No. (%)		
Median	2	0
1-2	140 (56.7)	0
≥3	107 (43.3)	0
Previous regimen, No. (%)		
Platinum-based chemotherapy	247 (100)	NA
Anti–PD-1 or anti–PD-L1 therapy	144 (58.3)	NA
Multikinase inhibitor	78 (31.6)	NA
Cabozantinib	25 (10.1)	0
Vandetanib	12 (4.9)	0
Sorafenib	0	0
Lenvatinib	8 (3.2)	0
Other MKIs	52 (21.1)	0
Other[b]	102 (41.3)	NA
RET fusion, No. (%)[c]		
KIF5B-RET	153 (61.9)	48 (69.6)
CCDC6-RET	53 (21.5)	10 (14.5)
NCOA4-RET	5 (2.0)	1 (1.4)
Other	15 (6.1)	2 (2.9)
Molecular assay type, No. (%)[d]		
NGS on tumor	209 (84.6)	42 (60.9)
NGS on plasma or blood	23 (9.3)	21 (30.4)
PCR	4 (1.6)	1 (1.4)
FISH	10 (4.0)	5 (7.2)
CNS metastases at baseline[e]	77 (31.2)	16 (23.2)

NOTE. Percentages may not total to 100 because of rounding.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent in situ hybridization; NA, not applicable; NGS, next generation sequencing; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; MKI, multikinase inhibitor; PCR, polymerase chain reaction; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.
[a]Patients reported race.
[b]In other, VEGF/VEGFR inhibitor was the most common (n = 80).
[c]Unknown *RET* fusion partners (n = 30) are not listed.
[d]Other molecular assays (n = 1) are not listed.
[e]CNS metastases at baseline by investigator assessment; includes both measurable and nonmeasurable CNS metastases.

leptomeningeal carcinomatosis, or untreated spinal cord compression. Patients with brain metastases were eligible if neurologic symptoms and CNS imaging were stable and their steroid dose was stable for 14 days before starting selpercatinib. For patients who had previous CNS radiation, intracranial lesions needed to show postradiation progression to be selected as a target lesion at baseline. Full criteria are in the protocol. This report includes treatment-naïve or previously treated patients with *RET* fusion–positive NSCLC. Pretreated patients could have received any number of previous therapies, including immune checkpoint inhibitors, multitargeted kinase inhibitors, and chemotherapy, but must have received previous platinum-based chemotherapy.

This trial followed the Good Clinical Practice guidelines, the Declaration of Helsinki, and all relevant regulations. The protocol was approved by the institutional review board or independent ethics committee at each site. Written informed consent was obtained from all patients or their guardians, if younger than 18 years.

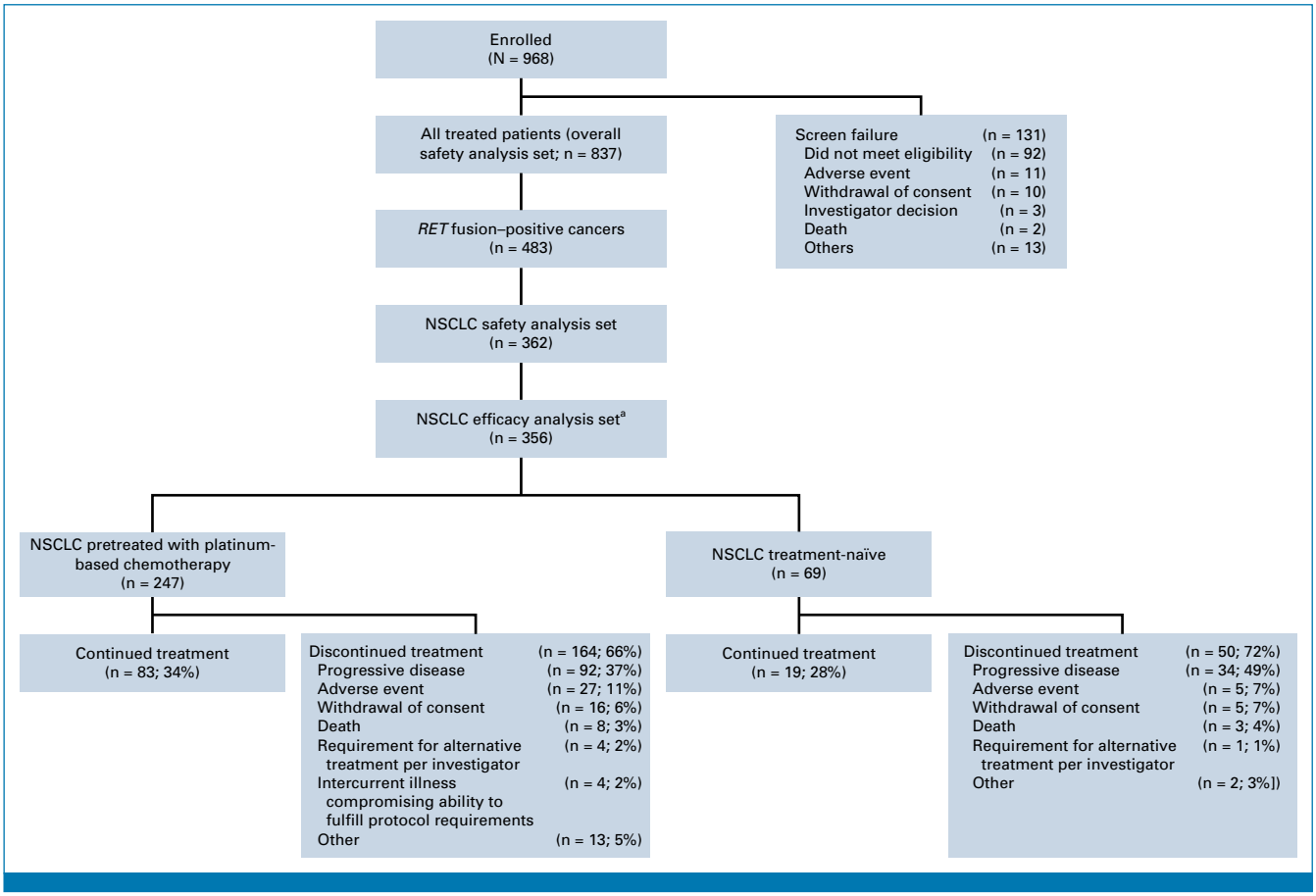

FIG 1. Flow diagram of patient disposition. Other cohorts included 19 patients who had received systemic therapies other than platinum-based chemotherapy and 21 patients with nonmeasurable disease. In total, 50 patients (72%) discontinued treatment in the treatment-naïve group and 164 (66%) in the pretreated group. [a]The safety analysis set included six patients who received previous treatment with a selective RET inhibitor; these patients were not included in the NSCLC efficacy analysis set. Patients who had received at least one dose of selpercatinib and achieved at least 6 months of potential follow-up time from the first dose of selpercatinib (or disease progression or death, whichever occurred first), as of 13 January 2023, were considered eligible for efficacy analyses. Of the 356 patients with *RET* fusion–positive NSCLC (independent of analysis set), 107 patients had investigator-identified CNS metastasis. Twenty-six had measurable and 81 had nonmeasurable CNS disease at baseline as assessed by an independent review committee. NSCLC, non–small cell lung cancer.

Efficacy and Safety Measures

Efficacy and safety assessments were performed according to the protocol as previously described.[4] The primary end point was objective response rate (ORR) assessed by an independent review committee (IRC) using RECIST version 1.1. All responses required confirmation through a follow-up scan at least 4 weeks after the initial scan indicating a response. Secondary end points included duration of response (DoR), PFS, OS, CNS-ORR, CNS-DoR, and CNS-PFS. For patients with brain metastases, CNS-ORR was assessed by IRC according to RECIST 1.1. Safety was analyzed through adverse events (AEs), graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

The data cutoff for this analysis was January 13, 2023, adding 19 months of follow-up since the previous data cutoff of August 2021.[8] CIs for response rates were calculated using the Clopper-Pearson method. DoR, PFS, and OS were estimated using the Kaplan-Meier method, and median follow-up times for each efficacy end point using the reverse Kaplan-Meier method.

RESULTS

Patients

Between May 9, 2017, and January 13, 2023, 837 patients were enrolled. The *RET* fusion–positive NSCLC safety population included 362 patients, and the efficacy population included 356 patients, with 247 previously treated with platinum-based chemotherapy and 69 treatment-naïve (Table 1; Fig 1).

Efficacy

The ORR was 62% (95% CI, 55 to 68) in patients previously treated with platinum-based chemotherapy and 83% (95%

TABLE 2. Efficacy Results by IRC Assessment

Outcome	Previous Platinum Chemotherapy (n = 247)	Treatment-Naïve (n = 69)
ORR[a]		
No. (%)	152 (61.5)	57 (82.6)
95% CI	55.2 to 67.6	71.6 to 90.7
Best overall response, No. (%)		
Complete response	20 (8.1)	5 (7.2)
Partial response	132 (53.4)	52 (75.4)
Stable disease	80 (32.4)	7 (10.1)
Progressive disease	7 (2.8)	3 (4.3)
Not evaluable	8 (3.2)	2 (2.9)
Time to response, months		
Median (range)	1.9 (0.7-44.2)	1.8 (0.7-10.8)
DoR[b]		
Patients with a response, No.	152	57
Patients with censored data, No. (%)	75 (49.3)	25 (43.9)
DoR, months, median (95% CI)	31.6 (20.4 to 42.3)	20.3 (15.4 to 29.5)
Duration of follow-up, months, median (Q1-Q3)	39.5 (24.6-45.0)	37.1 (24.0-45.1)
1-year DoR, % (95% CI)	73.0 (65.0 to 79.5)	66.7 (52.4 to 77.6)
2-year DoR, % (95% CI)	55.1 (46.4 to 62.9)	38.1 (24.5 to 51.6)
3-year DoR, % (95% CI)	44.7 (35.7 to 53.4)	35.4 (22.0 to 49.0)
PFS		
Patients with censored data, No. (%)	114 (46.2)	31 (44.9)
PFS, months, median (95% CI)	26.2 (19.3 to 35.7)	22.0 (16.5 to 24.9)
Duration of follow-up, months, median (Q1-Q3)	41.2 (24.9-46.9)	38.9 (19.4-46.9)
1-year PFS, % (95% CI)	70.6 (64.2 to 76.1)	70.8 (58.0 to 80.3)
2-year PFS, % (95% CI)	52.3 (45.4 to 58.7)	44.9 (31.8 to 57.3)
3-year PFS, % (95% CI)	41.1 (34.2 to 47.9)	34.6 (22.3 to 47.3)
OS		
Patients with censored data, No. (%)	137 (55.5)	43 (62.3)
OS, months, median (95% CI)	47.6 (35.9 to NE)	NE (37.8 to NE)
Duration of follow-up, months, median (Q1-Q3)	44.6 (37.6-49.8)	41.9 (34.3-47.6)
1-year OS, % (95% CI)	87.9 (83.1 to 91.5)	94.1 (85.1 to 97.8)
2-year OS, % (95% CI)	67.9 (61.5 to 73.5)	74.3 (61.9 to 83.1)
3-year OS, % (95% CI)	56.6 (49.8 to 62.8)	65.6 (52.4 to 75.9)

Abbreviations: DoR, duration of response; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q1, first quartile; Q3, third quartile.

[a]ORR was defined as the proportion of patients with best overall response of confirmed complete response or partial response. Response was confirmed by a repeat assessment ≥28 days.

[b]Censored patients are represented as a percentage of responders by IRC assessment, treatment-naïve (n = 57) and pretreated patients (n = 152).

CI, 72 to 91) in treatment-naïve patients, with 8% and 7% achieving a complete response, respectively (Table 2; Appendix Fig A1, online only). Appendix Tables A1 and A2 show efficacy summaries from previous data cutoffs. Median PFS in pretreated patients was 26.2 months (95% CI, 19.3 to 35.7) with a median follow-up of 41.2 months. In treatment-naïve patients, median PFS was 22.0 months (95% CI, 16.5 to 24.9) with a median follow-up of 38.9 months (Table 2; Fig 2).

Median OS was 47.6 months (95% CI, 35.9 to not evaluable [NE]) for pretreated patients with a median follow-up of 44.6 months and 56% of patients censored. In the treatment-naïve group, median OS was not reached (95% CI, 37.8 to NE) with a median follow-up of 41.9 months and 62% of patients censored. 3-year OS rates were 57% (95% CI, 50 to 63) for pretreated patients and 66% (95% CI, 52 to 76) for treatment-naïve (Table 2; Fig 2).

Among 107 of 356 (30%) patients with brain metastases at baseline as assessed by the investigator, 26 had measurable CNS disease as deemed by the IRC. These patients had on-treatment serial brain imaging, which the IRC reviewed to determine CNS-ORR, CNS-DoR, and CNS-PFS. Objective intracranial responses were observed regardless of whether

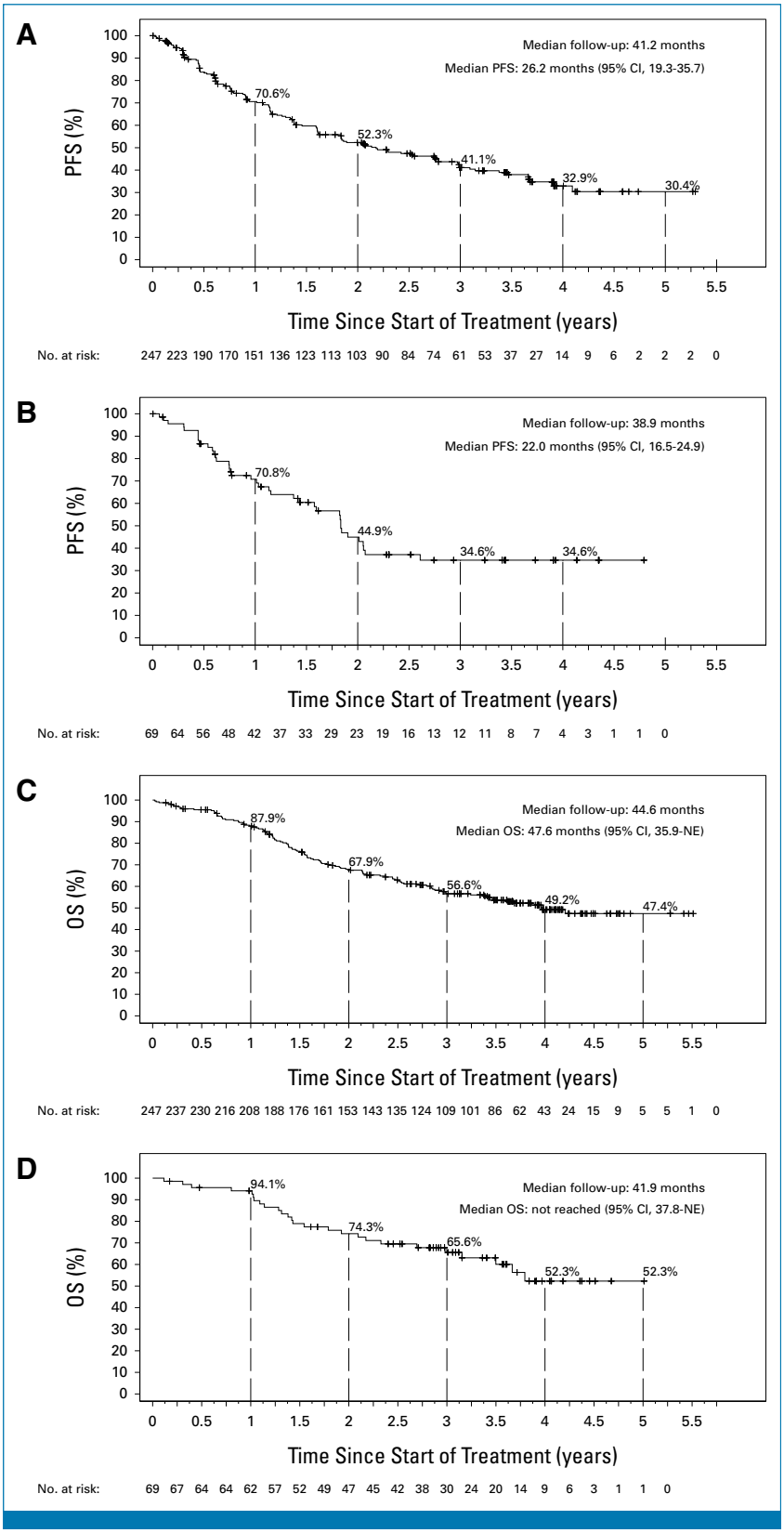

FIG 2. Long-term PFS and OS with selpercatinib. Kaplan-Meier plots show PFS on the basis of IRC assessment for patients with *RET* fusion–positive NSCLC who (A) received previous platinum-based chemotherapy (n = 247) or (B) were treatment-naïve (n = 69). Kaplan-Meier plots show OS for patients with *RET* fusion–positive NSCLC who (C) received previous platinum-based chemotherapy (n = 247) or (D) were treatment-naïve (n = 69). Tick marks indicate censored data. Eligible patients are defined (continued on following page)

FIG 2. (Continued). as treated patients. Patients enrolled in phase II who discontinued selective RET inhibitor(s) due to intolerance are excluded. IRC, independent review committee; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival.

patients received previous radiation therapy or the timing of the previous radiation therapy, including in 8 of 10 patients who received previous brain radiation (Appendix Tables A3-A4; Appendix Fig A2). Among the patients with measurable CNS metastasis at baseline, CNS-ORR was 85% (95% CI, 65 to 96), with 27% achieving a complete response. Median CNS-DoR was 9.4 months (95% CI, 7.4 to 15.3) with a median follow-up of 25.8 months (Appendix Fig A3). Median CNS-PFS was 11.0 months (95% CI, 9.2 to 17.1) with a median follow-up of 33.1 months (Appendix Table A4).

Safety

In the safety analysis population (N = 362; all patients with *RET* fusion–positive NSCLC who received at least one dose of selpercatinib, including six previously treated with a selective RET inhibitor and excluded from the efficacy analysis set), the median time on treatment was 24.6 months. The most common (≥10%) grade ≥3 treatment-emergent AEs were hypertension (19%) and aspartate and ALT elevation (10%/15%; Appendix Table A5).

Dose withholding occurred in 254 patients (70%), dose reduction in 177 (49%), and discontinuation in 40 (11%), with only 16 (4%) due to a selpercatinib-related treatment-emergent AE (Appendix Table A6). Fatal treatment-emergent AEs occurred in 26 patients (7%), none considered related to selpercatinib.

DISCUSSION

We report final efficacy and safety analyses from the LIBRETTO-001 trial in patients with *RET* fusion–positive NSCLC with over 3 years of follow-up. In line with previous reports, selpercatinib showed substantial and durable antitumor activity in patients who received selpercatinib as first-line therapy, in those who had received previous platinum-based chemotherapy, and in those with CNS metastases at baseline.[1,2,4]

With 3.5 years of follow-up, median OS was 47.6 months in pretreated patients and not reached in treatment-naïve patients. This was substantially better than the median OS in the GLORY real-world study where *RET* fusion–positive patients were treated with nonselective RET inhibitors,[9] and better or comparable to OS benefit of other selective agents targeting driver alterations.[10-12] For comparison, the median OS for pretreated patients receiving other targeted therapies has been 25.1-51.4 months.[12,13] For treatment-naïve patients, the LIBRETTO-001 OS between 2 and 3 years appears comparable to that reported with selective ALK inhibitors.[14] Median CNS-PFS for patients with measurable brain metastases at baseline was 11.0 months, marking the first report for *RET* fusion–positive NSCLC and showing comparable PFS benefit to other selective agents targeting driver alterations.[15] With an additional 19 months of follow-up, the safety profile of selpercatinib continues to be characterized by toxicities that are manageable by dose modifications and standard clinical care. Although dose reductions were seen in 49% of patients to manage AEs, only 4% discontinued due to selpercatinib-related toxicity, suggesting dose reduction effectively allows patients to continue treatment. Previous exposure-response analyses have suggested no PFS detriment at lower exposures, suggesting selpercatinib dose reduction may allow ongoing clinical benefit.[16,17]

Recently, the randomized phase III trial LIBRETTO-431 confirmed the clinical benefit of selpercatinib, with median OS not yet reached.[2] To our knowledge, the data from LIBRETTO-001 constitute the first mature estimation of median OS for selpercatinib and provide insights into OS maturation in LIBRETTO-431. Finally, these results reinforce the importance of testing for *RET* fusions in NSCLC to identify patients who may benefit from first-line selpercatinib treatment.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-24-02076. 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 the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently 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

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APPENDIX

TABLE A1. Efficacy Comparison of Previous Data Cutoffs in the Previous Platinum Chemotherapy Population

Data Cutoff Date	December 16, 2019	March 30, 2020	June 15, 2021	January 13, 2023
No.	184	218	247	247
ORR by IRC, % (95% CI)	57 (49 to 64)	57 (50 to 64)	61 (55 to 67)	62 (55 to 68)
DoR				
Patients with censored data, No. (%)	79 (76.0)	86 (69.4)	92 (60.9)	75 (49.3)
DoR, median (95% CI), months	17.5 (12.1 to NE)	17.5 (12.1 to NE)	28.6 (20.4 to NE)	31.6 (20.4 to 42.3)
Duration of follow-up, months, median	9.2	12.0	21.2	39.5
1-year DoR, % (95% CI)	71.9 (58.4 to 81.7)	69.1 (58.1 to 77.8)	73.1 (64.9 to 79.7)	73.0 (65.0 to 79.5)
2-year DoR, % (95% CI)	NR	NR	55.8 (46.4 to 64.2)	55.1 (46.4 to 62.9)
3-year DoR, % (95% CI)	NR	NR	NR	44.7 (35.7 to 53.4)
PFS				
Patients with censored data, No. (%)	128 (69.6)	144 (66.1)	138 (55.9)	114 (46.2)
PFS, months, median (95% CI)	19.3 (14 to NE)	19.3 (16.5 to NE)	24.9 (19.3 to NE)	26.2 (19.3 to 35.7)
Duration of follow-up, months, median	11.0	13.6	24.7	41.2
1-year PFS, % (95% CI)	69.1 (60.6 to 76.1)	69.7 (62.2 to 75.9)	70.5 (64.1 to 76.0)	70.6 (64.2 to 76.1)
2-year PFS, % (95% CI)	NR	NR	51.4 (44.3 to 58.1)	52.3 (45.4 to 58.7)
3-year PFS, % (95% CI)	NR	NR	NR	41.1 (34.2 to 47.9)

Abbreviations: DoR, duration of response; IRC, independent review committee; NE, not estimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

TABLE A2. Efficacy Comparison of Previous Data Cutoffs in the Treatment-Naïve Population

Data Cutoff Date	December 16, 2019	March 30, 2020	June 15, 2021	January 13, 2023
No.	39	48	69	69
ORR by IRC, % (95% CI)	85 (70 to 94)	85 (72 to 94)	84 (73 to 92)	83 (72 to 91)
DoR				
Patients with censored data, No. (%)	26 (78.8)	31 (75.6)	32 (55.2)	25 (43.9)
DoR, months, median (95% CI)	NE (12.0 to NE)	NE (12.0 to NE)	20.2 (13.0 to NE)	20.3 (15.4 to 29.5)
Duration of follow-up, months, median	7.4	9.8	20.3	37.1
1-year DoR, % (95% CI)	63.5 (34.0 to 82.6)	65.0 (42.8 to 80.3)	66.1 (51.6 to 77.3)	66.7 (52.4 to 77.6)
2-year DoR, % (95% CI)	NR	NR	41.6 (25.6 to 56.8)	38.1 (24.5 to 51.6)
3-year DoR, % (95% CI)	NR	NR	NR	35.4 (22.0 to 49.0)
PFS				
Patients with censored data, No. (%)	30 (76.9)	34 (70.8)	37 (53.6)	31 (44.9)
PFS, months, median (95% CI)	NE (13.8 to NE)	NE (13.8 to NE)	22.0 (13.8 to NE)	22.0 (16.5 to 24.9)
Duration of follow-up, months, median	9.2	10.8	21.9	38.9
1-year PFS, % (95% CI)	75 (56 to 87)	67.6 (49.5 to 80.3)	70.6 (57.8 to 80.2)	70.8 (58.0 to 80.3)
2-year PFS, % (95% CI)	NR	NR	41.6 (26.8 to 55.8)	44.9 (31.8 to 57.3)
3-year PFS, % (95% CI)	NR	NR	NR	34.6 (22.3 to 47.3)

Abbreviations: DoR, duration of response; IRC, independent review committee; NE, not estimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

TABLE A3. CNS-ORR and CNS-DoR by Previous Radiotherapy Date on the Basis of IRC Assessment in Patients With Measurable CNS Lesions

Outcome	With Brain RT			Without Brain RT (n = 16)	All Patients With Measurable CNS Lesions (n = 26)
	Brain RT ≤2 Months Before First Dose (n = 3)	Brain RT >2 Months Before First Dose (n = 7)	All With Previous Brain RT (n = 10)		
CNS-ORR					
No. (%)	3 (100.0)	5 (71.4)	8 (80.0)	14 (87.5)	22 (84.6)
95% CI	29.2 to 100.0	29.0 to 96.3	44.4 to 97.5	61.7 to 98.4	65.1 to 95.6
CNS best overall response, No. (%) [a]					
Complete response	1 (33.3)	1 (14.3)	2 (20.0)	5 (31.3)	7 (26.9)
Partial response	2 (66.7)	4 (57.1)	6 (60.0)	9 (56.3)	15 (57.7)
Stable disease	0 (0.0)	2 (28.6)	2 (20.0)	2 (12.5)	4 (15.4)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CNS-DoR					
Patients with censored data, No. (%)[a]	1 (33.3)	2 (40.0)	3 (37.5)	1 (7.1)	4 (18.2)
CNS-DoR, months, median (95% CI)	8.3 (5.1 to 8.3)	12.1 (3.7 to NE)	8.3 (3.7 to NE)	9.4 (6.7 to 15.3)	9.4 (7.4 to 15.3)
Duration of follow-up, months, median (Q1-Q3)	NR (7.4-NE)	24.8 (23.9-25.8)	23.9 (23.9-25.8)	NR (NE-NE)	25.8 (23.9-NE)
1-year DoR, % (95% CI)	0 (NE to NE)	60.0 (12.6 to 88.2)	45.0 (10.8 to 75.1)	31.2 (9.7 to 55.9)	36.1 (16.4 to 56.4)
2-year DoR, % (95% CI)	0 (NE to NE)	40.0 (5.2 to 75.3)	30.0 (4.4 to 62.8)	15.6 (2.5 to 39.1)	20.6 (6.5 to 40.2)

NOTE. Efficacy for patients with *RET* fusion–positive NSCLC and measurable CNS disease at baseline (N = 26). CNS-ORR is defined as the proportion of patients with best overall response of complete response or partial response. Response was confirmed by a repeat assessment no <28 days.

Abbreviations: DoR, duration of response; NE, not estimable; NR, not reached; NSCLC, non–small cell lung cancer; ORR, objective response rate; Q1, first quartile; Q3, third quartile; RT, radiation therapy.

[a]Percentage is calculated based on the number of patients with CNS best response of CR or PR as denominator (n = 22) per IRC using RECIST 1.1.

TABLE A4. CNS-PFS on the Basis of IRC Assessment in Patients With Measurable CNS Lesions

Outcome	All Patients With Measurable CNS Lesions (n = 26)
CNS-PFS	
Patients with censored data, No. (%)	7 (26.9)
Median (95% CI), months	11.0 (9.2 to 17.1)
Duration of follow-up, months, median (Q1-Q3)	33.1 (24.6-NE)
1-year CNS-PFS, % (95% CI)	41.8 (21.5 to 60.9)
2-year CNS-PFS, % (95% CI)	23.2 (8.5 to 42.1)
3-year CNS-PFS, % (95% CI)	23.2 (8.5 to 42.1)

Abbreviations: PFS, progression-free survival; Q1, first quartile; Q3, third quartile.

TABLE A5. Treatment-Emergent Adverse Events in ≥20% of Patients

	NSCLC Safety Population (n = 362)			
	Any Causality		Related to Treatment	
Preferred or *Composite Term*	Any Grade, No. (%)	Grade ≥3, No. (%)	Any Grade, No. (%)	Grade ≥3, No. (%)
Patients with ≥1 TEAE	362 (100.0)	283 (78.2)	347 (95.9)	152 (42.0)
Oedema	200 (55.2)	4 (1.1)	139 (38.4)	3 (0.8)
Diarrhea	197 (54.4)	19 (5.2)	126 (34.8)	11 (3.0)
Fatigue	167 (46.1)	9 (2.5)	85 (23.5)	3 (0.8)
Dry mouth	167 (46.1)	0	155 (42.8)	0
Hypertension (AESI)	149 (41.2)	70 (19.3)	102 (28.2)	51 (14.1)
AST increased (AESI)	155 (42.8)	37 (10.2)	124 (34.3)	24 (6.6)
Rash	154 (42.5)	4 (1.1)	99 (27.3)	4 (1.1)
ALT increased (AESI)	151 (41.7)	54 (14.9)	122 (33.7)	42 (11.6)
Nausea	122 (33.7)	5 (1.4)	45 (12.4)	2 (0.6)
Constipation	109 (30.1)	6 (1.7)	40 (11.0)	3 (0.8)
Abdominal pain	108 (29.8)	4 (1.1)	28 (7.7)	1 (0.3)
Headache	105 (29.0)	4 (1.1)	25 (6.9)	0
Cough	102 (28.2)	0	11 (3.0)	0
Dyspnea	100 (27.6)	21 (5.8)	14 (3.9)	0
Blood creatinine increased	97 (26.8)	9 (2.5)	51 (14.1)	0
Vomiting	92 (25.4)	7 (1.9)	23 (6.4)	2 (0.6)
Decreased appetite	88 (24.3)	4 (1.1)	40 (11.0)	1 (0.3)
Pyrexia	85 (23.5)	1 (0.3)	23 (6.4)	1 (0.3)
Thrombocytopenia	84 (23.2)	22 (6.1)	57 (15.7)	15 (4.1)
Dizziness	80 (22.1)	2 (0.6)	29 (8.0)	0
ECG QT prolonged (AESI)	77 (21.3)	23 (6.4)	59 (16.3)	16 (4.4)
Back pain	76 (21.0)	5 (1.4)	1 (0.3)	0
Urinary tract infection	73 (20.2)	9 (2.5)	2 (0.6)	0

NOTE. AEs that occurred during treatment in ≥20% of patients, regardless of causality, and treatment-related per the investigator assessment. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v 21.0. Composite terms are shown in italics. The most common (≥5%) grade ≥3 TEAEs were hypertension (in 19.3% of the patients) and aspartate and ALT elevation (10.2%/14.9%), hyponatremia (9.9%), prolonged ECG QT interval (6.4%), thrombocytopenia (6.1%), pleural effusion (5.8%), dyspnea (5.8%), pneumonia (5.5%), and diarrhea (5.2%).
Abbreviations: AESI, adverse event of special interest; NSCLC, non–small cell lung cancer.

TABLE A6. Summary of Safety

Variable	NSCLC Safety Population (n = 362)	
	Any Causality	Related to Treatment
Any grade TEAE, No. (%)	362 (100.0)	347 (95.9)
Grade ≥3 TEAE, No. (%)	283 (78.2)	152 (42.0)
Serious TEAE, No. (%)	199 (55.0)	59 (16.3)
TEAE leading to dose withheld, No. (%)	254 (70.2)	189 (52.2)
TEAE leading to dose reduction, No. (%)[a]	177 (48.9)	166 (45.9)
TEAE leading to permanent treatment discontinuation, No. (%)[b]	40 (11.0)	16 (4.4)
Fatal TEAE, No. (%)[c]	26 (7.2)	0 (0.0)

Abbreviations: NSCLC, non–small cell lung cancer; TEAE, treatment-emergent adverse event.

[a]When related to treatment, most commonly because of elevation of AST (n = 29 patients [8.0%]) and ALT (n = 38 patients [10.5%]) and drug hypersensitivity (5.0%).

[b]When related to treatment, most commonly because of AST/ALT elevation, fatigue, drug hypersensitivity, proteinuria, and thrombocytopenia (each occurring in two patients [0.6%]).

[c]Most commonly because of respiratory failure (n = 6 patients [1.7%]) and cardiac arrest (n = 4 patients [1.1]).

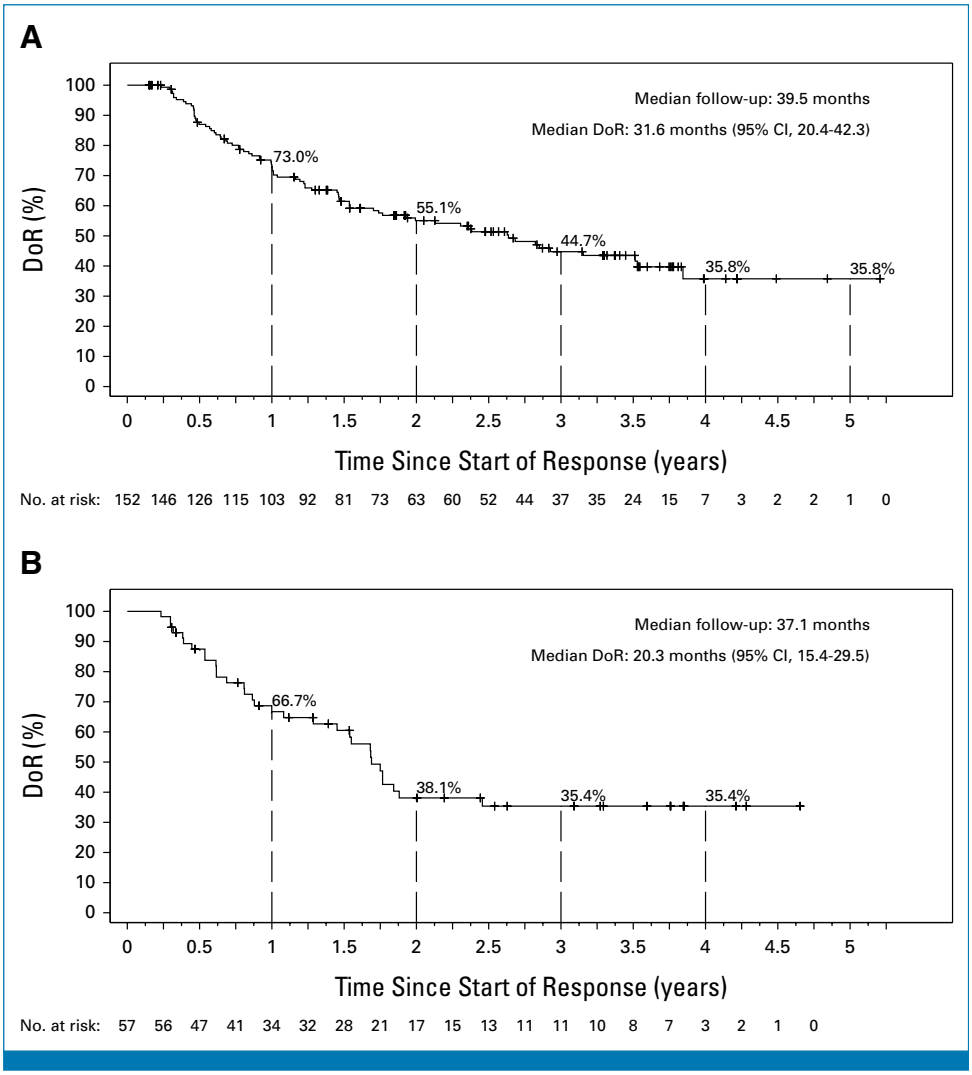

FIG A1. Long-term DoR with selpercatinib. Kaplan-Meier plots show DoR for patients with RET fusion–positive NSCLC who (A) received previous platinum-based chemotherapy (n = 247) or (B) were treatment-naïve (n = 69). Tick marks indicate censored data. DoR, duration of response; NSCLC, non–small cell lung cancer.

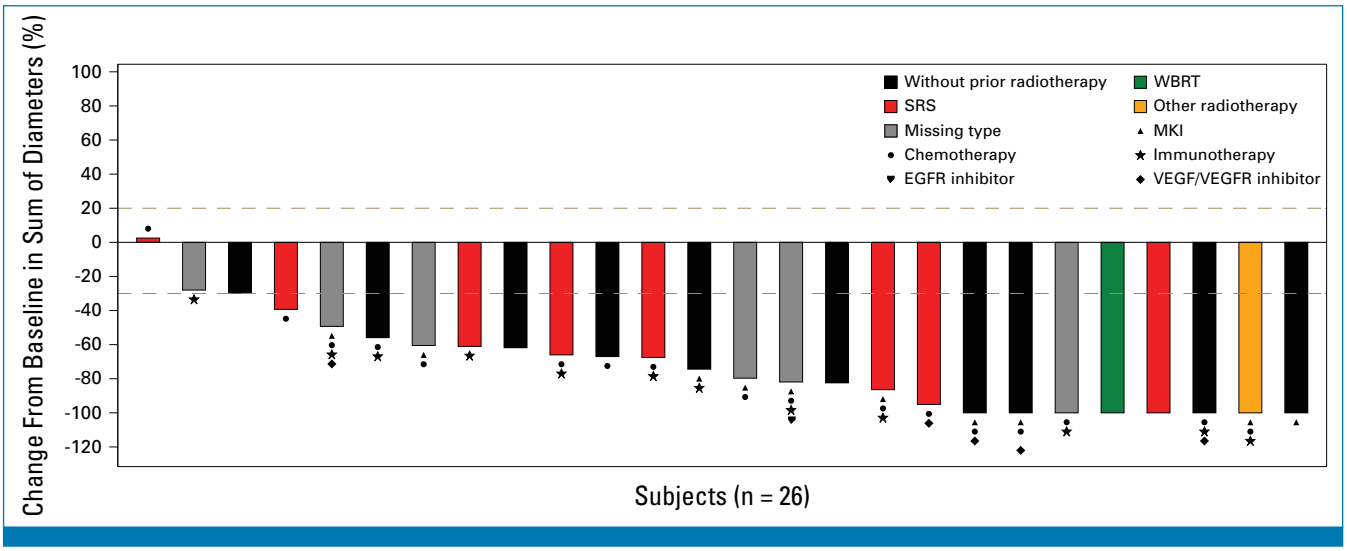

FIG A2. Best change in CNS tumor burden by previous therapy on the basis of IRC assessment in patients with measurable CNS Disease. Waterfall plot shows maximum change in tumor size on the basis of IRC assessment for patients with *RET* fusion–positive NSCLC with measurable CNS disease at baseline (n = 26). Vertical bars represent the best percent change from baseline in the sum of diameters for all target CNS lesions. Dashed lines indicate progressive disease (+20%) and partial response (−30%). SRS includes all patients reported to receive SRT, SBRT, GKS, and/or SRS. WBRT includes all patients reported to receive radiation of any kind to the whole brain, including conventional external beam, IMRT, and 3DCRT. DCRT, definitive chemoradiotherapy; EGFR, epidermal growth factor receptor; GKS, gamma knife surgery; IMRT, intensity modulated radiotherapy; IRC, Independent Review Committee; MKI, multikinase inhibitor; NSCLC, non–small cell lung cancer; SBRT, stereotactic body radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; WBRT, whole brain radiotherapy.

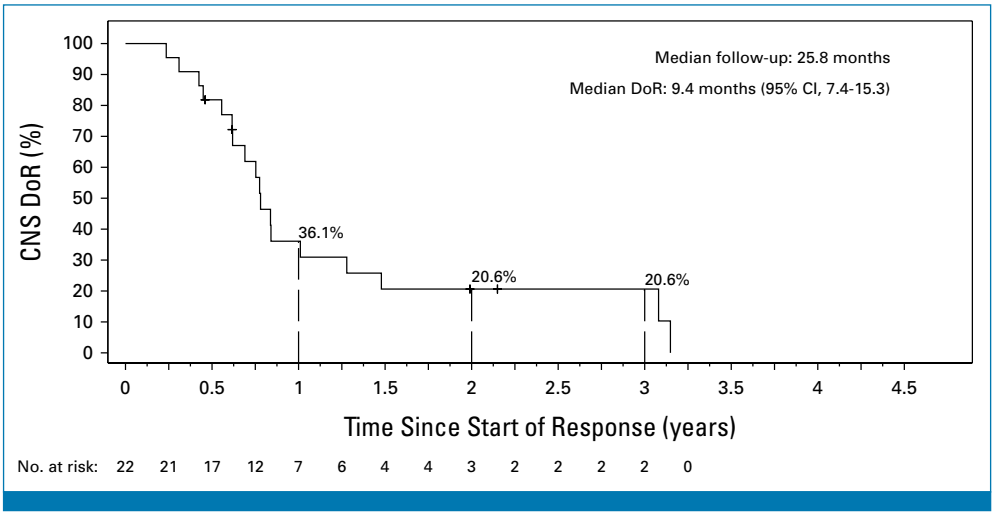

FIG A3. CNS DoR on the basis of IRC assessments in patients with measurable CNS disease. Kaplan-Meier plot shows DoR based on IRC assessment for patients with *RET* fusion–positive NSCLC with measurable CNS disease at baseline (n = 26). Tick marks indicate censored data. DoR, duration of response; IRC, independent review committee; NSCLC, non–small cell lung cancer.