

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

RET fusions are oncogenic drivers in 1 to 2% of non–small-cell lung cancers (NSCLCs). In patients with *RET* fusion–positive NSCLC, the efficacy and safety of selective *RET* inhibition are unknown.

METHODS

We enrolled patients with advanced *RET* fusion–positive NSCLC who had previously received platinum-based chemotherapy and those who were previously untreated separately in a phase 1–2 trial of selpercatinib. The primary end point was an objective response (a complete or partial response) as determined by an independent review committee. Secondary end points included the duration of response, progression-free survival, and safety.

RESULTS

In the first 105 consecutively enrolled patients with *RET* fusion–positive NSCLC who had previously received at least platinum-based chemotherapy, the percentage with an objective response was 64% (95% confidence interval [CI], 54 to 73). The median duration of response was 17.5 months (95% CI, 12.0 to could not be evaluated), and 63% of the responses were ongoing at a median follow-up of 12.1 months. Among 39 previously untreated patients, the percentage with an objective response was 85% (95% CI, 70 to 94), and 90% of the responses were ongoing at 6 months. Among 11 patients with measurable central nervous system metastasis at enrollment, the percentage with an objective intracranial response was 91% (95% CI, 59 to 100). The most common adverse events of grade 3 or higher were hypertension (in 14% of the patients), an increased alanine aminotransferase level (in 12%), an increased aspartate aminotransferase level (in 10%), hyponatremia (in 6%), and lymphopenia (in 6%). A total of 12 of 531 patients (2%) discontinued selpercatinib because of a drug-related adverse event.

CONCLUSIONS

Selpercatinib had durable efficacy, including intracranial activity, with mainly low-grade toxic effects in patients with *RET* fusion–positive NSCLC who had previously received platinum-based chemotherapy and those who were previously untreated. (Funded by Loxo Oncology and others; LIBRETTO-001 ClinicalTrials.gov number, NCT03157128.)

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THE *RET* PROTO-ONCOGENE ENCODES A transmembrane receptor tyrosine kinase that is involved in normal embryonic development.¹ Fusions between sequences that encode the kinase domain containing the carboxy terminal region of *RET* and various upstream gene partners lead to abnormal expression and oligomerization of chimeric kinase fusion proteins. These fusions result in constitutively active, ligand-independent signaling and oncogenesis.² Activating *RET* fusions typically occur in a mutually exclusive fashion with other cancer drivers and lead to classic dependency of the tumor cells on the activated oncogenic kinase.²⁻⁴

RET fusions have been identified in 1 to 2% of patients with non-small-cell lung cancer (NSCLC),^{3,5,6} and they appear to be associated with a high risk of brain metastases.⁷ Multitargeted kinase inhibitors that were initially designed to target other kinases but that have some measure of *RET* inhibition have been evaluated in prospective clinical trials. The use of these drugs resulted in only limited clinical benefit,⁸⁻¹¹ perhaps because of poor anti-*RET* activity, poor pharmacokinetic characteristics, and dose-limiting off-target toxic effects that are associated with the concurrent inhibition of multiple non-*RET* kinases.^{2,12} These toxic effects lead to frequent dose reductions and even permanent drug discontinuation.

Selpercatinib (formerly known as LOXO-292) is a novel, ATP-competitive, highly selective small-molecule inhibitor of *RET* kinase. Experimental models showed that it has nanomolar potency against diverse *RET* alterations, including fusions, activating point mutations, and predicted acquired resistance mutations, while mainly sparing non-*RET* kinases and non-kinase targets.¹³ In addition, selpercatinib was designed to penetrate the central nervous system (CNS) and has been shown in preclinical models to have antitumor activity in the brain. We evaluated the efficacy of selpercatinib in a phase 1–2 clinical trial (LIBRETTO-001). Adolescent and adult patients with any type of solid tumor harboring an activating *RET* alteration (i.e., fusions or mutations) were eligible. Here, we report the efficacy and safety of selpercatinib in patients with *RET* fusion-positive NSCLC.

METHODS

PATIENTS

Full eligibility criteria for the trial are detailed in the protocol, available with the full text of this article at NEJM.org. Eligible patients were 12 years of age or older (in areas where this criterion was allowed by regulatory authorities and institutional review boards; otherwise, the patients were 18 years of age or older) and had received a diagnosis of advanced or metastatic solid tumor. Patients were required to have a prospectively identified *RET* alteration (fusion or mutation) after they had reached dose level 2 (20 mg of selpercatinib twice daily), the dose at which steady-state selpercatinib pharmacokinetic exposures were predicted to be efficacious as defined by a trough level that exceeded the 50% inhibitory concentration for *RET* kinase activity. *RET* alteration status was determined by local molecular testing performed in a certified laboratory with the use of next-generation sequencing, fluorescence in situ hybridization (FISH), or polymerase-chain-reaction (PCR) assay. Central confirmation of the locally identified *RET* alteration was not required.

Other inclusion criteria included an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a scale from 0 to 5, with higher scores indicating greater disability), adequate organ function, and a corrected QT interval of 470 msec or less. Any number of previous therapies, including immune checkpoint inhibitors, multitargeted kinase inhibitors, and chemotherapy, were allowed. Patients with previously treated or untreated brain metastases who were either asymptomatic or had been in neurologically stable condition for at least 2 weeks were also eligible. Patients had to have a *RET* fusion-positive NSCLC to be included in the current analysis.

This trial was conducted in accordance with the Good Clinical Practice guidelines, the principles expressed in the Declaration of Helsinki, and all applicable country and local regulations. The protocol was approved by the institutional review board or independent ethics committee at each investigative site. All the patients, or guardians of patients younger than 18 years of age, provided written informed consent.

TRIAL DESIGN AND TREATMENT

This open-label phase 1–2 trial was conducted at 65 centers in 12 countries (Table S1 in the Supplementary Appendix, available at NEJM.org). Selpercatinib was administered orally (in capsule or liquid formulation), continuously, in 28-day cycles, until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients who were enrolled in the phase 1 dose-escalation portion of the trial received selpercatinib at doses ranging from 20 mg once daily to 240 mg twice daily. Inpatient dose escalation to higher doses that were determined by the investigators to be safe was permitted after a minimum of one cycle of treatment. All patients who were enrolled in the phase 2 portion of the trial received the recommended dose of 160 mg twice daily. Patients with documented disease progression could continue to receive selpercatinib if, in the opinion of the site investigator, they were deriving clinical benefit from this agent.

The primary end point was an objective response (a complete or partial response), as determined by an independent review committee of expert radiologists, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.¹⁴ Secondary end points included an objective intracranial response, progression-free survival, the duration of response, and safety. All responses required confirmation by a second consecutive radiologic assessment performed at least 4 weeks after the first assessment showed a response.

TRIAL ASSESSMENTS

Radiologic tumor assessments were conducted at baseline, every 8 weeks for 1 year, and every 12 weeks thereafter. Brain imaging during screening was mandated for all patients who were enrolled in the phase 2 portion of the trial. Patients with brain metastases that were identified at baseline underwent repeated brain imaging with each response assessment. Adverse events were assessed from the first dose of selpercatinib (or from the date that informed consent was obtained in patients with serious adverse events) until the safety follow-up visit 28 days after the last dose of selpercatinib was administered. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

TRIAL OVERSIGHT

This trial was designed jointly by the sponsor (Loxo Oncology, a wholly owned subsidiary of Eli Lilly) and the investigators. The sponsor collected, analyzed, and interpreted the trial data in collaboration with the authors. The first draft of the manuscript was written by the first author and last author in collaboration with the sponsor. All the authors provided input to revise the manuscript. A medical writer paid by the sponsor provided writing assistance. All the authors vouch for the completeness and accuracy of the clinical data and analyses and for the adherence of the trial to the protocol.

STATISTICAL ANALYSIS

All the analyses were conducted in accordance with the statistical analysis plan. The primary analysis set (Fig. S1), defined with input from the Food and Drug Administration (FDA), was based on the first 105 patients who were consecutively enrolled across both the phase 1 and 2 portions of the trial and who met the following criteria: documented *RET* fusion-positive NSCLC as determined by local testing; measurable disease according to RECIST, version 1.1; and receipt of one or more lines of chemotherapy, including platinum-based chemotherapy, and one or more doses of selpercatinib. By agreement with the FDA, patients with nonmeasurable disease who were enrolled in the phase 1 dose-escalation part of the trial were also included in the primary analysis. Efficacy was also separately investigated in a supplemental analysis set composed of the first 39 consecutively enrolled untreated patients with *RET* fusion-positive NSCLC who otherwise met the above criteria.

Efficacy analyses were performed according to the intention-to-treat principle. The incidence of a true objective response of at least 50% in the primary analysis set was hypothesized, and we estimated that a sample of 105 patients would provide the trial with 98% power to establish a lower boundary of 30% for a two-sided 95% exact binomial confidence interval. Ruling out a lower limit of 30% for the objective response was considered to be clinically meaningful for patients who had tumor that had progressed while they were receiving previous platinum-based chemotherapy and who had limited remaining treatment options for advancing dis-

ease. No power calculations were carried out in relation to the previously untreated patients. Confidence intervals for responses were calculated with the use of the Clopper–Pearson method. The duration of response and progression-free survival were estimated with the Kaplan–Meier method. Safety was analyzed in both the patients with *RET* fusion–positive NSCLC who had received platinum-based chemotherapy and those who had been previously untreated (as defined above) as well as in the overall cohort of 531 patients in the trial who had received selpercatinib by June 17, 2019. The data cutoff date was December 16, 2019.

RESULTS

PATIENTS

From May 2017 through December 2018, a total of 105 patients with *RET* fusion–positive advanced NSCLC who had previously received

at least platinum-based chemotherapy were consecutively enrolled and received treatment across both the phase 1 dose-escalation portion of the trial (49 patients) and the phase 1 dose-expansion or phase 2 portion of the trial (56 patients). In addition, from December 2017 through June 2019, a total of 39 previously untreated patients with advanced *RET* fusion–positive NSCLC were enrolled. The demographic characteristics of the patients in both cohorts are summarized in Table 1.

The patients who had previously received platinum-based chemotherapy were heavily pretreated. They had received a median of 3 previous systemic therapy regimens (range, 1 to 15); 55% had received previous anti–programmed cell death protein 1 (PD-1) or anti–programmed cell death ligand 1 (PD-L1) therapies, and 48% had received previous multitargeted kinase inhibitors with anti-*RET* activity. A total of 36% of the patients had brain metastases at baseline as

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Previous Platinum Chemotherapy (N=105)	Previously Untreated (N=39)
Age — yr		
Median	61	61
Range	23–81	23–86
Sex — no. (%)		
Female	62 (59)	22 (56)
Male	43 (41)	17 (44)
Race — no. (%) [†]		
White	55 (52)	28 (72)
Asian	40 (38)	7 (18)
Black	5 (5)	3 (8)
Other	3 (3)	1 (3)
Missing data	2 (2)	0
Smoking status — no. (%)		
Never smoked	75 (71)	29 (74)
Former smoker	29 (28)	9 (23)
Current smoker	1 (1)	1 (3)
ECOG performance-status score — no. (%) [‡]		
0	31 (30)	18 (46)
1	72 (69)	21 (54)
2	2 (2)	0

Table 1. (Continued.)		
Characteristic	Previous Platinum Chemotherapy (N=105)	Previously Untreated (N=39)
NSCLC histologic subtype — no. (%)		
Adenocarcinoma	90 (86)	34 (87)
Large-cell neuroendocrine carcinoma	2 (2)	0
Squamous-cell carcinoma	1 (1)	0
NSCLC-NOS	12 (11)	5 (13)
Median previous systemic regimens — no. (range)	3 (1–15)	0
Previous regimen		
Platinum-based chemotherapy — no. (%)	105 (100)	NA
Anti-PD-1 or anti-PD-L1 therapy — no. (%)	58 (55)	NA
Multitargeted kinase inhibitor — no. (%)§	50 (48)	NA
1 — no./total no. (%)	37/50 (74)	NA
≥2 — no./total no. (%)	13/50 (26)	NA
Brain metastases — no. (%)	38 (36)	7 (18)
Measurable disease — no. (%)	104 (99)	39 (100)
RET fusion — no. (%)		
<i>KIF5B-RET</i>	59 (56)	26 (67)
<i>CCDC6-RET</i>	24 (23)	8 (21)
<i>NCOA4-RET</i>	2 (2)	0
<i>RELCH-RET</i>	2 (2)	0
Other¶	6 (6)	1 (3)
Not determined	12 (11)	4 (10)

* Percentages may not total 100 because of rounding. Anti-PD-1 denotes anti-programmed cell death protein 1 (PD-1), anti-PD-L1 anti-programmed cell death ligand 1, NA not applicable, NOS not otherwise specified, and NSCLC non-small-cell lung cancer.

† Race was reported by the patients.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

§ Multitargeted kinase inhibitors administered included cabozantinib (in 16 patients), vandetanib (in 8), lenvatinib (in 7), and others (in 36). Patients may have received more than one multitargeted kinase inhibitor.

¶ Other fusions identified in single tumors included *CLIP1-RET*, *RBPM5-RET*, *DOCK1-RET*, *ARHGAP12-RET*, *CCDC88C-RET*, *TRIM24-RET*, *PRKARIA-RET*, and *ERC1-RET*.

|| RET fusion was indicated by molecular analysis, but the fusion partner was not identified.

assessed by the investigators. Baseline characteristics (other than previous therapy) were generally similar in the previously treated and previously untreated groups, although previously untreated patients tended to have better performance status and had a lower incidence of brain metastases at enrollment. A total of 88% of the patients who had previously received platinum-based chemotherapy received at least one dose of selpercatinib at the recommended phase 2 dose

of 160 mg twice daily. All the previously untreated patients received 160 mg twice daily.

In patients who had received platinum-based chemotherapy, RET fusions were prospectively identified by next-generation sequencing (in tumor in 85 patients and in blood or plasma in 9), FISH (in 9), or reverse-transcriptase PCR assay (in 2). In total, 62 unique locally obtained assays were used to enroll patients across all groups (Table S2).

Table 2. Efficacy.*

Response	Previous Platinum Chemotherapy		Previously Untreated	
	Independent Review (N=105)	Investigator Assessment (N=105)	Independent Review (N=39)	Investigator Assessment (N=39)
Objective response — % (95% CI)	64 (54–73)	70 (60–78)	85 (70–94)	90 (76–97)
Best response — no. (%)				
Complete response	2 (2)	2 (2)	0	1 (3)
Partial response	65 (62)	71 (68)	33 (85)	34 (87)†
Stable disease	30 (29)	25 (24)	4 (10)	2 (5)
Progressive disease	4 (4)	2 (2)	1 (3)	1 (3)
Could not be evaluated	4 (4)	5 (5)	1 (3)	1 (3)
Duration of response				
Patients with a response — no.	67	73	33	33‡
Patients with censored data — no./total no. (%)	44/67 (66)	45/73 (62)	26/33 (79)	26/33 (79)
Median duration of response — mo (95% CI)	17.5 (12.0–NE)	20.3 (15.6–24.0)	NE (12.0–NE)	NE (12.0–NE)
Median follow-up — mo	12.1	14.8	7.4	7.4
Progression-free survival				
Patients with censored data — no. (%)	61 (58)	58 (55)	30 (77)	30 (77)
Median progression-free survival — mo (95% CI)	16.5 (13.7–NE)	18.4 (16.4–24.8)	NE (13.8–NE)	NE (13.8–NE)
Median follow-up — mo	13.9	16.4	9.2	9.2
1-yr progression-free survival — % (95% CI)	66 (55–74)	68 (58–76)	75 (56–87)	75 (55–87)

* Percentages may not total 100 because of rounding. NE denotes could not be evaluated.

† Data include two patients with an unconfirmed partial response pending confirmation at the data cutoff date.

‡ Data include only confirmed responses.

EFFICACY

Among patients who had previously received platinum-based chemotherapy, the percentage with an objective response was 64% (95% confidence interval [CI], 54 to 73), as determined by the independent review committee (Table 2 and Fig. S2). Two patients (2%) had a complete response, 65 (62%) had a partial response, 30 (29%) had stable disease, 4 (4%) had progressive disease, and 4 (4%) could not be evaluated (NE). Responses were observed regardless of previous therapy with anti-PD-1 or anti-PD-L1 agents (Table S3) or multitargeted kinase inhibitors (Table S4). The median duration of response according to the independent review committee was 17.5 months (95% CI, 12.0 to NE), and 63% (42 of 67) of the responses were ongoing at a median follow-up of 12.1 months (Fig. S3). At 1 year, 66% (95% CI, 55 to 74) of all the patients were progression-free, and the median progres-

sion-free survival was 16.5 months (95% CI, 13.7 to NE). Overall, 5 patients (5%) were lost to follow-up or withdrew.

According to investigator assessment, the percentage of patients with a response was 70% (95% CI, 60 to 78) (Table 2 and Fig. 1). Responses were also observed regardless of the specific RET fusion partner (Fig. S4). The median time to response was 1.8 months, consistent with the first protocol-mandated assessment (Fig. S5). The median duration of response according to investigator assessment was 20.3 months (95% CI, 15.6 to 24.0) (Fig. 2A). Overall, 58% (42 of 73) of the responses were ongoing at a median follow-up of 14.8 months, and 71% (52 of 73) of the patients with a response continued to receive treatment (treatment was administered beyond RECIST progression in some patients because of ongoing clinical benefit). The longest response was ongoing at 26.0 months. The median dura-

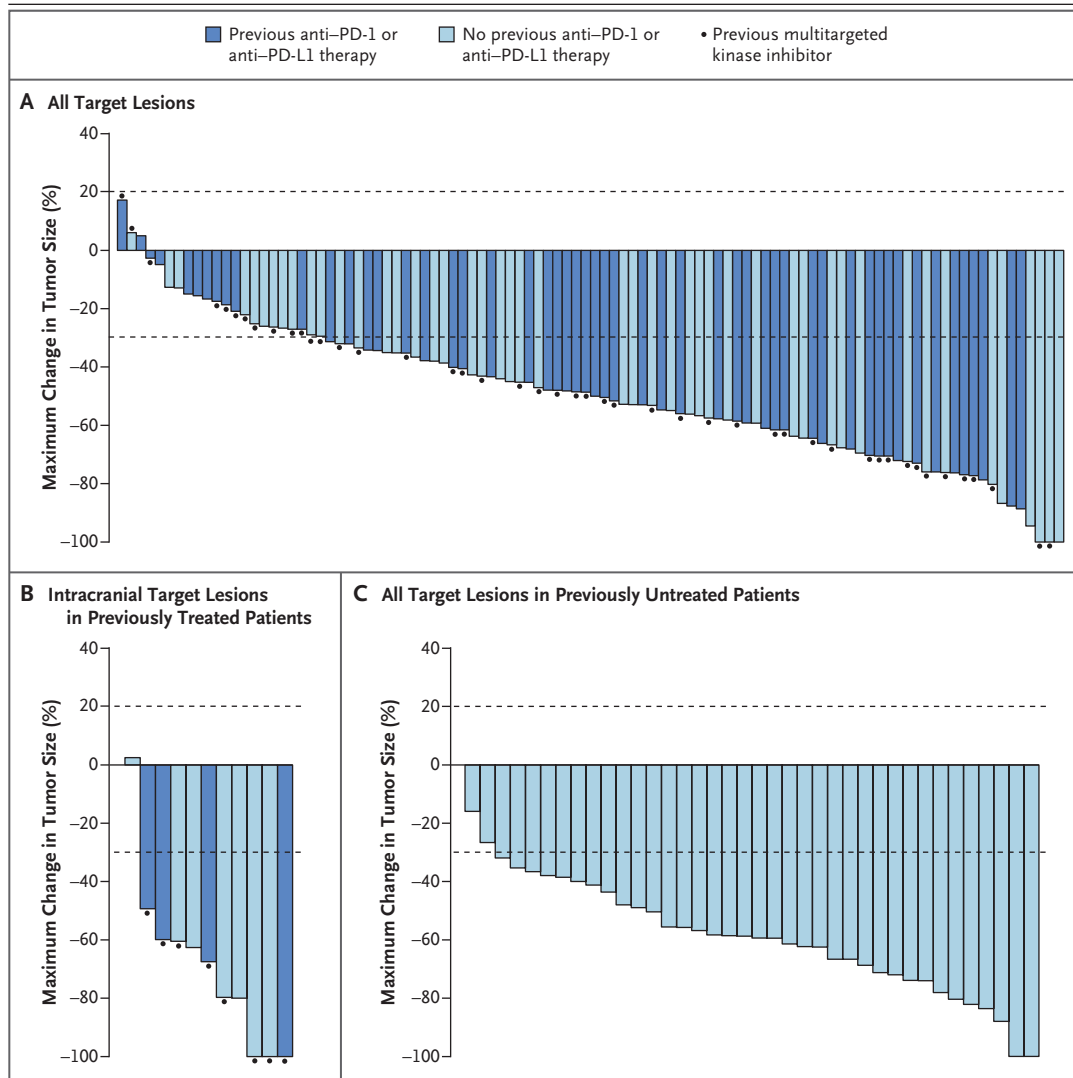


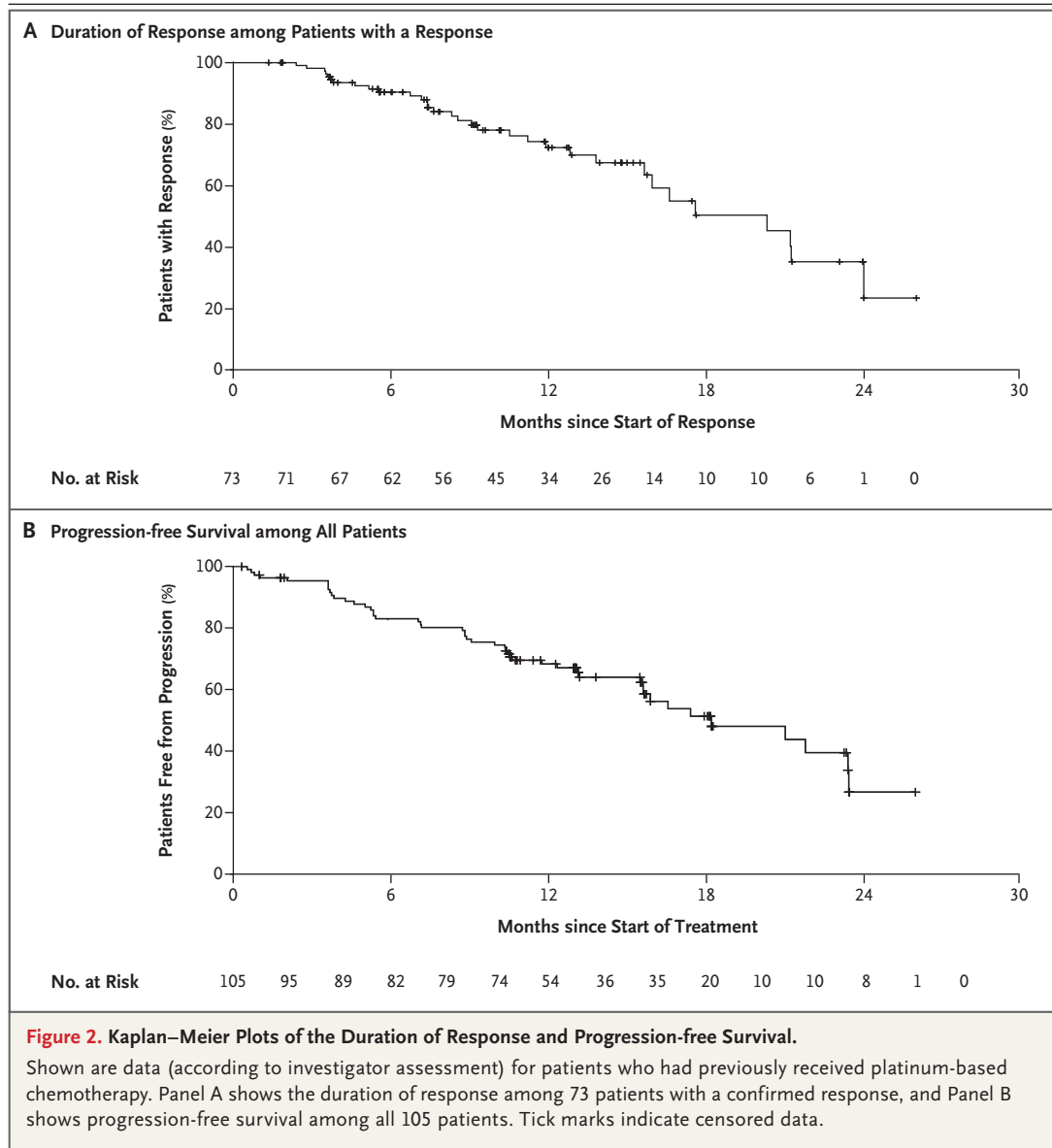
Figure 1. Efficacy.

Shown are waterfall plots of the maximum change in tumor size in all target lesions, according to investigator assessment (Panel A), in intracranial target lesions in patients who had previously received platinum-based chemotherapy, according to independent review (Panel B), and in all target lesions in previously untreated patients, according to investigator assessment (Panel C). Data for five patients who had previously received platinum-based chemotherapy are not shown, since one had nontarget lesions only and four did not undergo measurement of the target lesion after the baseline measurement. Data for one patient in the untreated group are not shown because the patient discontinued treatment before any imaging after baseline was performed. The dashed lines at 20% and -30% indicate growth and shrinkage of target lesions, respectively. Anti-PD-1 denotes anti-programmed cell death protein 1 (PD-1), and anti-PD-L1 anti-programmed cell death ligand 1.

tion of response was similar in the overall group of patients who had previously received platinum-based chemotherapy and in the subgroup who had received previous anti-PD-1 or anti-PD-L1 treatment. At 1 year, 68% of all the patients were progression-free according to investigator assess-

ment, and the median progression-free survival was 18.4 months (95% CI, 16.4 to 24.8) (Table 2 and Fig. 2B).

Among 38 of 105 patients who had previously received platinum-based chemotherapy and who had investigator-assessed CNS metastasis at



baseline, 11 patients were deemed to have measurable lesions according to RECIST, version 1.1, by independent review. Among these 11 patients, the percentage with an objective intracranial response was 91% (10 of 11 patients; 95% CI, 59 to 100) according to independent review, including 3 complete responses (in 27%), 7 partial responses (in 64%), and 1 stable disease. The median CNS duration of response was 10.1 months (95% CI, 6.7 to NE).

A total of 39 previously untreated patients

were evaluated to determine efficacy. Among these patients, the percentage with a response was 85% (95% CI, 70 to 94) according to independent review and 90% (95% CI, 76 to 97) according to investigator assessment (Table 2 and Fig. S6). At 6 months, 90% of the responses were ongoing. Neither the median duration of response nor the median progression-free survival had been reached at a median follow-up of 7.4 and 9.2 months, respectively. None of the patients were lost to follow-up or withdrew.

ADVERSE EVENTS

Table 3 shows adverse events that occurred during treatment, regardless of attribution, as well as adverse events that were judged by the investigators to be related to selpercatinib. The most common adverse events of grade 3 or 4 were hypertension (in 14% of the patients), an increased alanine aminotransferase level (in 13%), an increased aspartate aminotransferase level (in 10%), hyponatremia (in 6%), and lymphopenia (in 6%). Six grade 5 adverse events (in 4% of the patients) were observed; they included sepsis (in 2 patients) and cardiac arrest, multiple organ dysfunction syndrome, pneumonia, and respiratory failure (in 1 patient each). These events were deemed by the investigators to be unrelated to selpercatinib. The adverse-event profile of selpercatinib in the patients evaluated was broadly similar to the overall safety profile for all 531 patients who received selpercatinib (Table S5). Of all 531 patients who received selpercatinib, dose reduction was warranted in 160 (30%) because of treatment-related adverse events, and 12 patients (2%) discontinued selpercatinib because of treatment-related adverse events, the most common of which were an increase in the alanine aminotransferase level (in 2 patients) and drug hypersensitivity (in 2 patients).

DISCUSSION

It is estimated that *RET* fusions account for a global lung-cancer burden of more than 10,000 new cases each year. *RET* fusions were first identified in lung cancer in 2012.¹⁵ At that time, only multikinase inhibitors with some degree of pre-clinical anti-*RET* activity, such as cabozantinib and vandetanib, were available in the clinic. These drugs were repurposed and investigated in clinical trials for patients with *RET* fusion-positive lung cancer. Unfortunately, these agents were associated with both limited responses and limited response durability, probably because of poor pharmacokinetic features and substantial side effects resulting from non-*RET* kinase inhibition. For example, in a phase 2 trial of cabozantinib, the percentage of patients with an objective response was 28% and the median progression-free survival was only 6 months, and dose modifications were warranted in 73% of the patients.⁹

The initial clinical testing of selpercatinib in 2017 presented an opportunity to explore the efficacy and safety of a selective *RET* inhibitor in this genetically defined lung-cancer subgroup. Selpercatinib had rapid and durable antitumor activity in patients with *RET* fusion-positive lung cancer, and these outcomes surpassed those previously achieved with multikinase inhibitors.^{9-11,16} These findings established *RET* fusions as bona fide and clinically actionable drivers in lung cancer. Patients had meaningful benefit, even though 56% had been heavily pretreated with at least three previous systemic therapies and 55% had received previous immunotherapy. Nevertheless, 64% of the patients who received selpercatinib had an objective response, including durable responses. Among previously untreated patients, 85% had a response, and the responses appeared to be durable, although the period of follow-up for this subgroup of patients was less than 1 year.

The activity of selpercatinib in our trial was broadly similar to that of targeted therapy in patients with NSCLC that harbors other established oncogenic drivers (i.e., *EGFR* mutations,¹⁷ and *ALK*,¹⁸ *ROS1*,¹⁹ or *NTRK*^{20,21} fusions) for which tyrosine kinase inhibitors have been established as first-line therapy.²² Furthermore, the promising frequency of intracranial response to selpercatinib is important, given the high estimated lifetime risk of brain metastases among patients with *RET* fusion-positive lung cancer,⁸ although the incidence of brain metastases observed in our trial was lower than that in previous trials. Selpercatinib was also associated with mainly low-grade toxic effects; this finding is consistent with its *RET*-selective profile and lack of substantial off-target activity. Most treatment-related adverse events did not warrant dose interruption or modification. The most common grade 3 adverse events were reversible with dose modifications; this finding suggests that long-term treatment is feasible, particularly in light of the responses observed with selpercatinib at doses as low as 20 mg once daily. Only 2% of the patients discontinued selpercatinib because of a drug-related adverse event.

Selpercatinib had substantial antitumor activity in patients with *RET* fusion-positive lung cancers, including those who received selpercatinib as first-line therapy, those who had pre-

Table 3. Adverse Events in 144 Patients with RET Fusion–Positive NSCLC Who Received Selpercatinib.*

Adverse Event	Adverse Events, Regardless of Attribution (N = 144)				Treatment-Related Adverse Events (N = 144)			
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	<i>number of patients (percent)</i>							
Any adverse event	8 (6)	47 (33)	69 (48)	14 (10)	144 (100)	39 (27)	2 (1)	131 (91)
Diarrhea	46 (32)	18 (12)	5 (3)	0	69 (48)	2 (1)	0	36 (25)
Dry mouth	48 (33)	11 (8)	0	0	59 (41)	0	0	52 (36)
Hypertension	3 (2)	22 (15)	20 (14)	0	45 (31)	13 (9)	0	25 (17)
Increased aspartate aminotransferase level	18 (12)	11 (8)	12 (8)	2 (1)	43 (30)	7 (5)	1 (1)	32 (22)
Fatigue	26 (18)	16 (11)	0	0	42 (29)	0	0	19 (13)
Increased alanine aminotransferase level	14 (10)	6 (4)	15 (10)	3 (2)	38 (26)	11 (8)	2 (1)	29 (20)
Constipation	33 (23)	3 (2)	2 (1)	0	38 (26)	1 (1)	0	16 (11)
Nausea	32 (22)	5 (3)	1 (1)	0	38 (26)	0	0	14 (10)
Peripheral edema	29 (20)	6 (4)	0	0	35 (24)	0	0	19 (13)
Urinary tract infection	4 (3)	21 (15)	7 (5)	0	32 (22)	0	0	0
Headache	21 (15)	7 (5)	2 (1)	0	30 (21)	0	0	6 (4)
Rash	20 (14)	6 (4)	2 (1)	0	28 (19)	2 (1)	0	17 (12)
Abdominal pain	18 (12)	8 (6)	1 (1)	0	27 (19)	0	0	5 (3)
Cough	24 (17)	3 (2)	0	0	27 (19)	0	0	3 (2)
Increased blood creatinine level	21 (15)	3 (2)	0	0	24 (17)	0	0	13 (9)
Dyspnea	15 (10)	6 (4)	3 (2)	0	24 (17)	0	0	4 (3)
Vomiting	17 (12)	6 (4)	1 (1)	0	24 (17)	1 (1)	0	5 (3)
Prolonged QT on electrocardiography	9 (6)	7 (5)	7 (5)	0	23 (16)	3 (2)	0	14 (10)
Pyrexia	14 (10)	8 (6)	1 (1)	0	23 (16)	1 (1)	0	8 (6)
Dry skin	19 (13)	3 (2)	0	0	22 (15)	0	0	13 (9)
Thrombocytopenia	13 (9)	6 (4)	3 (2)	0	22 (15)	2 (1)	0	15 (10)

* The adverse events listed are those that occurred at any grade in at least 15% of the patients, regardless of attribution. The relatedness of the treatment to adverse events was determined by the investigators. The total percentage for any given adverse event may be different than the sum of the components for the individual grades because of rounding. In total, six patients had grade 5 adverse events, including sepsis (in two patients), and cardiac arrest, multiple organ dysfunction syndrome, pneumonia, and respiratory failure (in one each); all these events were deemed by the investigators to be unrelated to selpercatinib.

viously received at least platinum-based chemotherapy, and those with brain metastases. The follow-up of this patient cohort was shorter for patients who received selpercatinib as first-line therapy than for those who had previously received at least platinum-based chemotherapy, but responses continued in the majority of patients more than 1 year after the initiation of treatment. Antitumor activity was observed regardless of previous exposure to anti-PD-1 or anti-PD-L1 agents or multikinase inhibitors. The continued implementation of molecular screening strategies that include the ability to detect

RET fusions will be critical for identifying patients with NSCLC who may benefit from selpercatinib.

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APPENDIX

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