

ORIGINAL ARTICLE

Selpercatinib in Early-Stage *RET* Fusion–Positive Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Selpercatinib, a highly selective, potent, and central nervous system–penetrant rearranged during transfection (*RET*) inhibitor, is approved for *RET* fusion–positive advanced or metastatic non–small-cell lung cancer (NSCLC). The efficacy and safety of selpercatinib in early-stage NSCLC are unknown.

METHODS

We conducted a phase 3, double-blind trial involving patients with *RET* fusion–positive NSCLC who had received definitive therapy with curative intent (surgery or radiotherapy with adjuvant systemic anticancer therapy, if applicable). Patients were randomly assigned to receive adjuvant selpercatinib or placebo for up to 3 years. The primary end point was investigator-assessed event-free survival in patients with stage II or IIIA disease. Secondary end points were investigator-assessed event-free survival in patients with stage IB, II, or IIIA disease; event-free survival as assessed by blinded independent central review; overall survival; and safety.

RESULTS

A total of 151 patients were assigned to receive selpercatinib (75 patients) or placebo (76 patients). Median follow-up was 24 months and 27 months in the respective groups. Among 109 patients with stage II or IIIA disease, 2-year investigator-assessed event-free survival was 92% with selpercatinib and 61% with placebo (hazard ratio for disease recurrence, progression, or death, 0.17; 95% confidence interval [CI], 0.06 to 0.51; $P < 0.001$). Event-free survival as assessed by blinded independent central review was consistent with investigator-assessed event-free survival. Among the 151 patients with stage IB, II, or IIIA NSCLC, investigator-assessed event-free survival at 2 years was 94% with selpercatinib and 70% with placebo (hazard ratio for disease recurrence, progression, or death, 0.17; 95% CI, 0.06 to 0.49; $P < 0.001$). The most common adverse events during the treatment period were increased levels of alanine aminotransferase and aspartate aminotransferase (grade ≥ 3 in 17% and 19% of patients, respectively, in the selpercatinib group). Three deaths occurred, all in the placebo group, owing to disease progression.

CONCLUSIONS

Among patients with stage II or IIIA *RET* fusion–positive NSCLC, event-free survival was significantly longer with adjuvant selpercatinib than with placebo. (Funded by Lilly; LIBRETTO-432 ClinicalTrials.gov number, NCT04819100.)

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APPROXIMATELY 30 TO 40% OF PATIENTS with non–small-cell lung cancer (NSCLC) present with early-stage disease (stage IB, II, or IIIA).^{1,2} Standard-care options for resectable early-stage NSCLC include surgery and neoadjuvant or perioperative chemoimmunotherapy.³ Unfortunately, despite these interventions, up to two thirds of patients have disease recurrence and may eventually die from metastatic disease.^{4,5}

In patients with oncogene-driven NSCLC, immunotherapy has shown limited efficacy,⁶ whereas targeted therapies have shown more favorable outcomes in the context of adjuvant treatment. The ADAURA trial showed significantly greater improvement in disease-free survival with adjuvant osimertinib than with placebo among patients with epidermal growth factor receptor (EGFR)–mutant NSCLC,⁷ and the ALINA trial showed substantial disease-free survival benefits with adjuvant alectinib as compared with chemotherapy among patients with anaplastic lymphoma kinase (ALK)–positive NSCLC.⁸ These results led to the approval of both agents as adjuvant treatment in early-stage disease.^{9,10}

Rearranged during transfection (RET) fusions are actionable, oncogenic drivers identified in 1 to 2% of all patients with NSCLC.^{11,12} Selpercatinib, a highly selective, potent, and central nervous system–penetrant RET inhibitor, has been approved by the health authority in many countries for the treatment of patients with advanced RET-driven cancers.^{13–15} In advanced or metastatic RET fusion–positive NSCLC, selpercatinib results in a high percentage of patients with a response and durable disease control, as shown in the phase 1–2 LIBRETTO-001 trial¹⁶ and the phase 3, randomized LIBRETTO-431 trial.¹⁷ No adjuvant targeted therapy is approved for early-stage RET fusion–positive NSCLC.

The phase 3, multinational LIBRETTO-432 trial was designed to evaluate the efficacy and safety of adjuvant selpercatinib as compared with placebo in patients with early-stage NSCLC. The results of a preplanned analysis of this clinical trial are reported here.

METHODS

TRIAL DESIGN

We conducted a phase 3, multinational, double-blind, randomized, placebo-controlled trial. Patients were randomly assigned in a 1:1 ratio to

receive selpercatinib (160 mg twice daily for patients with a weight of ≥ 50 kg and 120 mg twice daily for patients with a weight of < 50 kg) or placebo in continuous 28-day cycles. Stratification factors included disease stage (stage IB, II, or IIIA) and type of previous definitive therapy (surgery or radiotherapy). Administration of selpercatinib or placebo continued until disease recurrence or progression, unacceptable toxic effects, or another protocol-defined reason for discontinuation of trial participation, up to a maximum duration of 3 years. Patients who were randomly assigned to receive placebo and who had disease recurrence or progression were eligible for optional crossover to selpercatinib.

The authors and the sponsor (Lilly) designed the trial, had access to the data, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). Assistance with manuscript preparation, including writing, was funded by the sponsor.

The trial was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, the general principles for planning and designing multicenter clinical trials, the principles of 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 site.

PATIENTS

Eligible patients were 18 years of age or older and had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (score range, 0 to 5, with higher scores reflecting greater disability), adequate organ function, and histologically confirmed stage IB, II, or IIIA RET fusion–positive NSCLC according to the 8th edition of the staging system for lung cancer.¹⁸ RET status was determined through local testing with a polymerase-chain-reaction assay, comprehensive genomic profiling, or another molecular test approved by the sponsor. Centralized testing was also offered to any patient for whom local testing was not available. Patients were required to have received definitive locoregional therapy with curative intent (surgery or radiotherapy) for stage IB, II, or IIIA NSCLC, including adjuvant systemic anticancer therapy, if applicable, before randomization.

Patients were excluded if they had evidence of additional oncogenic driver alterations or clinical or radiologic evidence of disease recurrence or progression after definitive therapy. Full eligibility criteria are provided in the trial protocol.

END POINTS AND ASSESSMENTS

The primary end point was investigator-assessed event-free survival according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and was assessed in the primary analysis population (all the patients with stage II or IIIA NSCLC who had undergone randomization). An event was defined as a new regional or metastatic lesion, progression of a locally treated lesion (confirmed by histopathological assessment), or death. Secondary end points included overall survival, investigator-assessed event-free survival in the intention-to-treat population (the overall population, which comprised all the patients with stage IB, II, or IIIA NSCLC who had undergone randomization), event-free survival as assessed by blinded independent central review in the primary analysis and overall populations, and safety end points according to the Common Terminology Criteria for Adverse Events, version 5.0, in the overall population. Event-free survival assessed by the investigator and that assessed by blinded independent central review was defined as the time from randomization until the occurrence of disease recurrence or progression (according to RECIST, version 1.1, or histopathological confirmation) or death.

Disease assessments were conducted at baseline, week 12, and week 24, followed by every 24 weeks until year 5 and then annually until disease recurrence, death, loss to follow-up, withdrawal of consent, or trial termination by the sponsor occurred. All disease assessments included magnetic resonance imaging (MRI) of the head or computed tomography of the head if MRI was not feasible.

Overall survival was defined as the time from randomization until death from any cause. Safety analyses were performed in all the patients who underwent randomization and received at least one dose of the trial regimen.

STATISTICAL ANALYSIS

All analyses were conducted in accordance with the statistical analysis plan, available with the protocol. For the primary end point of event-free

survival, we originally assumed a hazard ratio for disease recurrence, progression, or death of 0.5 in the primary analysis population. However, assumptions were formally reevaluated after the interim efficacy analysis of the LIBRETTO-431 trial¹⁷ showed positive results (hazard ratio for disease progression or death of 0.46 among patients with metastatic *RET* fusion-positive NSCLC receiving selpercatinib as compared with those receiving the control treatment) and after other trials showed a benefit of targeted therapies as adjuvant treatment for NSCLC, including the ADAURA trial⁷ (hazard ratio for disease recurrence or death, 0.17) and the ALINA trial⁸ (hazard ratio for disease recurrence or death, 0.24). Therefore, the trial was amended (before any trial unblinding) to reflect an effect size similar to that seen in the ADAURA and ALINA trials. The amended trial design required 150 to 170 patients to undergo randomization in order to observe at least 20 events of disease recurrence, progression, or death in the primary analysis population, which would provide approximately 88% power at a one-sided type I error of 0.025 under an updated assumption of a hazard ratio for disease recurrence, progression, or death of 0.24 for the primary end point.

To ensure adequate follow-up, we planned to perform the primary analysis after the required number of events occurred at a minimum of 4 years after the first patient underwent randomization. If the between-group difference in event-free survival was statistically significant in the primary analysis population, then it was also evaluated in the overall population in a gated, hierarchical manner. All other end points were assessed without adjustment for multiplicity. All treatment-effect tests were conducted at a two-sided alpha level of 0.05, and confidence intervals were calculated at a two-sided 95% level, unless stated otherwise. Continuous variables were summarized descriptively as the number of patients, mean, median, standard deviation, or range. Categorical variables were summarized as frequency and percentages. All analyses and descriptive summaries were based on the observed data, and missing data were not imputed or carried forward unless otherwise specified.

The primary end point (investigator-assessed event-free survival) was compared between the trial groups with a stratified log-rank test, with stratification according to disease stage (stage II

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Primary Analysis Population (N = 109)		Overall Population (N = 151)	
	Selpercatinib (N = 54)	Placebo (N = 55)	Selpercatinib (N = 75)	Placebo (N = 76)
Sex — no. (%)				
Female	34 (63)	30 (55)	45 (60)	40 (53)
Male	20 (37)	25 (45)	30 (40)	36 (47)
Age — yr				
Median	59.5	61.0	59.0	59.0
Range	41.0–84.0	26.0–78.0	33.0–84.0	26.0–86.0
Age distribution — no. (%)				
<65 yr	39 (72)	34 (62)	54 (72)	48 (63)
≥65 yr	15 (28)	21 (38)	21 (28)	28 (37)
Smoking status — no. (%)				
Former or current smoker	17 (31)	17 (31)	22 (29)	23 (30)
Never smoked	37 (69)	38 (69)	53 (71)	53 (70)
Region — no. (%)				
East Asia	31 (57)	31 (56)	44 (59)	48 (63)
Europe	12 (22)	14 (25)	17 (23)	17 (22)
North America	6 (11)	7 (13)	8 (11)	8 (11)
Other	5 (9)	3 (5)	6 (8)	3 (4)
Race or ethnic group — no. (%)†				
Asian	33 (61)	32 (58)	47 (63)	49 (64)
White	21 (39)	21 (38)	27 (36)	24 (32)
Black	0	2 (4)	0	2 (3)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1)
ECOG performance-status score — no. (%)‡				
0	30 (56)	36 (65)	45 (60)	52 (68)
1	24 (44)	18 (33)	30 (40)	22 (29)
Initial disease stage — no. (%)				
Stage IB	0	0	21 (28)	21 (28)
Stage II	23 (43)	24 (44)	23 (31)	24 (32)
Stage IIIA	31 (57)	31 (56)	31 (41)	31 (41)
NSCLC histologic type — no. (%)				
Adenocarcinoma	51 (94)	51 (93)	72 (96)	71 (93)
Other§	3 (6)	4 (7)	3 (4)	5 (7)
RET fusion — no. (%)				
KIF5B–RET	33 (61)	34 (62)	50 (67)	51 (67)
CCDC6–RET	14 (26)	11 (20)	18 (24)	13 (17)
Other¶	7 (13)	10 (18)	7 (9)	12 (16)

Table 1. (Continued.)

Characteristic	Primary Analysis Population (N=109)		Overall Population (N=151)	
	Selpercatinib (N=54)	Placebo (N=55)	Selpercatinib (N=75)	Placebo (N=76)
PD-L1 expression — no. (%)				
Negative	11 (20)	16 (29)	18 (24)	22 (29)
Positive	25 (46)	28 (51)	29 (39)	33 (43)
Tumor proportion score of 1–49%	13 (24)	14 (25)	15 (20)	16 (21)
Tumor proportion score of ≥50%	12 (22)	9 (16)	14 (19)	11 (14)
Tumor proportion score unknown	0	5 (9)	0	6 (8)
Other	1 (2)	0	1 (1)	0
Not assessed	17 (31)	11 (20)	27 (36)	21 (28)
Previous anticancer therapy — no. (%)				
Surgery	54 (100)	54 (98)**	75 (100)	75 (99)**
Radiotherapy	2 (4)	6 (11)	2 (3)	7 (9)
Adjuvant systemic chemotherapy††	50 (93)	50 (91)	56 (75)	55 (72)
Immunotherapy‡‡	2 (4)	1 (2)	3 (4)	1 (1)
Platinum chemotherapy	48 (89)	49 (89)	54 (72)	54 (71)

* Percentages may not total 100 because of rounding. The primary analysis population includes all the patients with stage II or IIIA non-small-cell lung cancer (NSCLC) who underwent randomization, and the overall population includes all the patients with stage IB, II, or IIIA NSCLC who underwent randomization. PD-L1 denotes programmed death ligand 1.

† Race and ethnic group were based on medical records. The denominator for selpercatinib in the overall population is 74 owing to missing data for one patient.

‡ In the placebo group, one patient had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 3 at cycle 1 day 1, and one patient had a missing ECOG performance-status score. ECOG performance-status scores range from 0 to 5, with higher scores reflecting greater disability.

§ “Other” includes mucinous adenocarcinoma of the lung and “not specified.”

¶ “Other” includes *COX10-RET*, *ERC1-RET*, *KIAA1468-RET*, *NCOA4-RET*, *PIBF1-RET*, *PICALM-RET*, *TRIM33-RET*, and “positive-RET fusion partner unspecified.”

|| Tumor proportion score is the percentage of tumor cells with PD-L1 expression.

** One patient in the placebo group did not undergo surgery but received radiotherapy alone, which was allowed according to the protocol. The other eight patients who underwent radiation received postoperative radiotherapy.

†† The median duration of adjuvant systemic therapy was 2.2 months in the selpercatinib group and 2.3 months in the placebo group.

‡‡ Immunotherapy was administered in combination with chemotherapy.

or stage IIIA) and previous definitive therapy (surgery or radiotherapy). Cox regression modeling was used to determine the corresponding stratified hazard ratio for disease recurrence, progression, or death, and the Kaplan–Meier method was used to estimate event-free survival curves according to trial group, median event-free survival times with interquartile range, and event-free survival at various time points with 95% confidence intervals for each trial group. Event-free survival as assessed by blinded independent

central review was also analyzed with these same methods. The proportional-hazards assumption was assessed by visual inspection of log cumulative hazard plots; no meaningful departure from proportionality was observed. Event-free survival was censored at the date of the last assessment for patients who had not had disease recurrence or progression or had not died. Event-free survival was also censored if a new anticancer therapy was initiated before disease recurrence or progression or if disease recurrence or progres-

sion or death was documented immediately after at least two consecutive missed disease assessments. Discontinuation of the trial regimen in the absence of disease recurrence or progression was not considered to be an event nor a reason for censoring. Sensitivity analyses were prespecified to examine the effect of the methods used to assess these intercurrent events.

RESULTS

PATIENTS AND TREATMENT

A total of 151 patients with stage IB, II, or IIIA *RET* fusion–positive NSCLC were enrolled from January 2022 through March 2025 at 65 sites in 22 countries (Fig. S1 and Table S1 in the Supplementary Appendix, available at NEJM.org). All the patients were randomly assigned to receive either selpercatinib (75 patients) or placebo (76 patients). At the date of data cutoff (January 12, 2026), a total of 57% of the patients in the selpercatinib group and 50% in the placebo group were still receiving the trial regimen. The median follow-up was 24 months in the selpercatinib group and 27 months in the placebo group. Patients continued the trial regimen for a mean ($\pm$ SD) duration of 21.3 ± 11.7 months in the selpercatinib group and 19.8 ± 10.6 months in the placebo group.

The primary analysis population included 109 patients with stage II or IIIA NSCLC who were randomly assigned to receive selpercatinib (54 patients) or placebo (55 patients) (Table 1). Most of the patients were women, Asian, and younger than 65 years of age and had never smoked. Almost all the patients (>90%) had a diagnosis of adenocarcinoma, had previously undergone surgery, and had received adjuvant systemic chemotherapy. Demographic and clinical characteristics at baseline were generally balanced between the two trial groups. Black patients were underrepresented (Table 1 and Table S2). The primary analysis population and overall populations had similar baseline characteristics.

EFFICACY

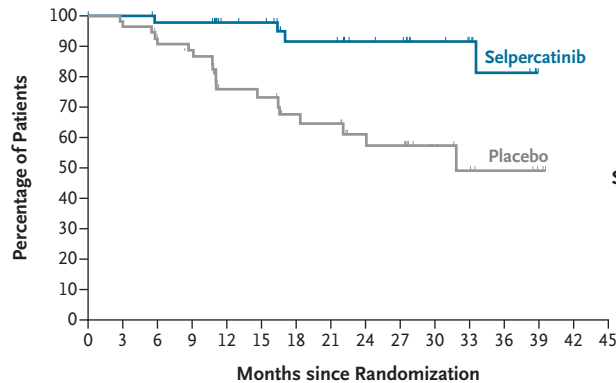
In the primary analysis population of patients with stage II or IIIA disease (109 patients), the 2-year event-free survival was 92% (95% confidence interval [CI], 75.4 to 97.2) in the selpercatinib group and 61% (95% CI, 44.2 to 74.3) in the placebo group (hazard ratio for disease recurrence, progression, or death, 0.17; 95% CI,

0.06 to 0.51; $P<0.001$) (Fig. 1A). Disease recurrence occurred in 4 patients (7%) in the selpercatinib group and in 19 (35%) in the placebo group. The majority of events occurred in patients with stage IIIA disease (in 2 patients in the selpercatinib group and in 16 in the placebo group) (Fig. 2). Recurrence in the brain occurred in 1 patient in the selpercatinib group and in 3 patients in the placebo group (Table S3). Most instances of disease recurrence occurred during the treatment period, with only two occurring after patients had discontinued the trial regimen (1 patient in each trial group). Blinded independent central review of event-free survival was consistent with these results, with a 2-year event-free survival of 96% (95% CI, 83 to 99) in the selpercatinib group and 71% (95% CI, 54 to 82) in the placebo group (hazard ratio for disease recurrence, progression, or death, 0.13; 95% CI, 0.03 to 0.55) (Fig. S2).

In the overall population of patients with stage IB, II, or IIIA disease (151 patients), the 2-year event-free survival was 94% in the selpercatinib group and 70% in the placebo group (hazard ratio for disease recurrence, progression, or death, 0.16; 95% CI, 0.06 to 0.48; $P<0.001$) (Fig. 1B). Blinded independent central review of event-free survival was consistent with these results, with a 2-year event-free survival of 97% (95% CI, 88 to 99) in the selpercatinib group and 78% (95% CI, 65 to 87) in the placebo group (hazard ratio for disease recurrence, progression, or death, 0.13; 95% CI, 0.03 to 0.55) (Fig. S3). Disease recurrence was observed in 4 patients (5%) in the selpercatinib group and in 20 patients (26%) in the placebo group.

Investigator-assessed event-free survival in prespecified subgroups in the primary analysis population is shown in Figure 2. Caution should be used when interpreting the findings in some of these subgroups because of the small number of patients enrolled and the few observed events. Subgroup analyses of event-free survival in the overall population were consistent with that in the primary analysis population (Fig. S4). Prespecified sensitivity analyses of event-free survival assessed by the investigator and that assessed by blinded independent central review in the primary analysis population are shown in Table S4.

At the date of the data cutoff, investigator-assessed best overall response among the 16 patients in the primary analysis population who

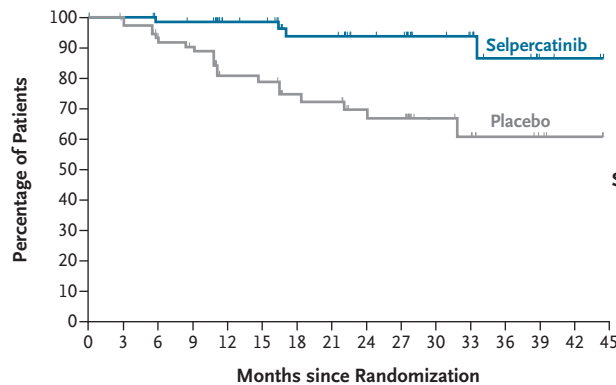
A Event-free Survival in the Primary Analysis Population

	No. of Patients	No. of Events	Median Event-free Survival (95% CI) mo
Selpercatinib	54	4	NE (33.5 to NE)
Placebo	55	19	31.8 (18.4 to NE)

Hazard ratio for disease recurrence, progression, or death, 0.17 (95% CI, 0.06–0.51)
P<0.001

No. at Risk

Selpercatinib	54	49	45	45	37	36	27	27	22	21	15	12	7	0	0
Placebo	55	54	47	44	28	27	22	21	16	15	8	6	4	2	0

B Event-free Survival in the Overall Population

	No. of Patients	No. of Events	Median Event-free Survival (95% CI) mo
Selpercatinib	75	4	NE
Placebo	76	20	NE (31.8 to NE)

Hazard ratio for disease recurrence, progression, or death, 0.16 (95% CI, 0.06–0.48)
P<0.001

No. at Risk

Selpercatinib	75	68	63	62	51	50	37	37	30	29	20	17	10	3	2	0
Placebo	76	73	64	61	40	39	31	30	25	24	12	10	6	4	2	0

Figure 1. Event-free Survival.

Shown are the Kaplan–Meier estimates of investigator-assessed event-free survival in the primary analysis population (all the patients with stage II or IIIA non–small-cell lung cancer [NSCLC] who underwent randomization) (Panel A) and in the overall population (all the patients with stage IB, II, or IIIA NSCLC who underwent randomization) (Panel B). Hazard ratios and 95% confidence intervals were calculated with a Cox proportional-hazards model, with stratification according to trial group (selpercatinib vs. placebo). Two-sided P values were calculated with a log-rank test, with stratification according to trial group. Tick marks indicate censored data. NE denotes could not be estimated.

had crossed over to selpercatinib included 2 patients with a complete response, 3 with a partial response, and 9 with stable disease; 2 patients were not evaluable or not assessed. Of these 16 patients, 12 were still taking selpercatinib at the data-cutoff date. In total, 5 patients (7%) in the selpercatinib group and 14 patients (18%) in the placebo group received therapy after discontinuing the trial regimen (Table S5).

Data on overall survival are not yet mature. At the data-cutoff date, three deaths had been re-

ported, all in the placebo group and attributed to disease progression. Overall, no patients died while receiving or within 30 days after discontinuation of selpercatinib or placebo.

SAFETY

A summary of the safety profile in the overall population is shown in Table 2. Grade 3 or higher adverse events occurred during the treatment period in 67% of the patients in the selpercatinib group and in 24% in the placebo group.

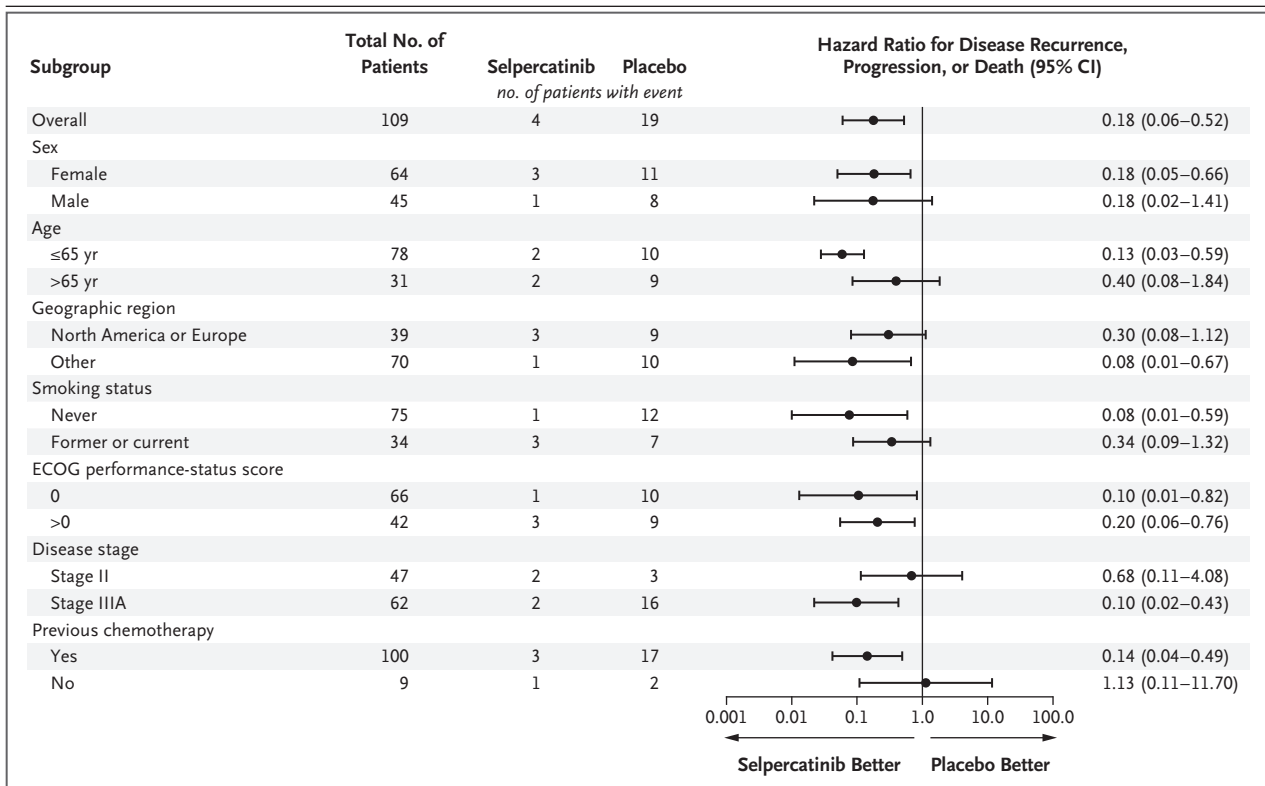


Figure 2. Forest Plot of Investigator-Assessed Event-free Survival in the Primary Analysis Population.

Shown are the number of patients with an event of disease recurrence, progression, or death, with stratification according to prespecified subgroups. Data on Eastern Cooperative Oncology Group (ECOG) performance-status score were missing for one patient in the placebo group. ECOG performance-status scores range from 0 to 5, with higher scores reflecting greater disability. Hazard ratios and 95% confidence intervals were estimated with an unstratified Cox model of selpercatinib as compared with placebo. Firth correction was applied when an event did not occur in either trial group or when the total number of events in a subgroup was 6 or lower.

The most common adverse events of grade 3 or higher, which had an incidence that was at least 10 percentage points higher with selpercatinib than placebo, were increases in levels of alanine aminotransferase and aspartate aminotransferase (incidence of 17% and 19%, respectively, in the selpercatinib group), both of which were manageable with dose adjustments. Serious adverse events were reported in 23% of the patients in the selpercatinib group and in 13% in the placebo group, with no fatal events during the treatment period (Table S6). The median relative dose intensity was 81% with selpercatinib and 99% with placebo (Table S7). Dose reductions due to adverse events occurred in 55% of the patients in the selpercatinib group and in 8% in the placebo group, and dose omissions because of adverse events occurred in 77% and 26%, respectively.

Adverse events leading to permanent discon-

tinuation of the trial regimen were reported in 17% of the patients in the selpercatinib group and in 1% in the placebo group (Table S8). In the selpercatinib group, the most common adverse events leading to treatment discontinuation were increased alanine aminotransferase level (in four patients), increased aspartate aminotransferase level (in two patients), and interstitial lung disease (in two patients, grade 1 in both). Most discontinuations in the selpercatinib group were attributable to low-grade adverse events (grade 1 in five patients and grade 2 in five patients), with fewer discontinuations because of grade 3 events (in two patients) or grade 4 events (in one patient). At the date of data cutoff, adverse events leading to discontinuation of selpercatinib had been resolved in nine patients (69%), including both cases of interstitial lung disease and all grade 3 and grade 4 events.

Table 2. Adverse Events during the Treatment Period.*

Event	Selpercatinib (N = 75)		Placebo (N = 76)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients (percent)</i>			
Any adverse event	75 (100)	50 (67)	74 (97)	18 (24)
ALT level increased	47 (63)	13 (17)	14 (18)	1 (1)
AST level increased	45 (60)	14 (19)	12 (16)	2 (3)
Diarrhea	29 (39)	3 (4)	13 (17)	0
Dry mouth	30 (40)	0	12 (16)	0
Cough	20 (27)	0	18 (24)	0
Blood bilirubin level increased	20 (27)	1 (1)	11 (14)	0
Hypertension	23 (31)	8 (11)	8 (11)	2 (3)
Constipation	17 (23)	0	10 (13)	0
Upper respiratory tract infection	12 (16)	1 (1)	13 (17)	0
Rash	14 (19)	1 (1)	10 (13)	0
Coronavirus disease 2019	12 (16)	0	11 (14)	0
Hyperuricemia	15 (20)	0	8 (11)	0
Nausea	12 (16)	0	11 (14)	0
Fatigue	11 (15)	0	11 (14)	0
Headache	14 (19)	0	7 (9)	0
Blood creatinine level increased	14 (19)	0	6 (8)	0
Dizziness	13 (17)	0	6 (8)	0
Peripheral edema	13 (17)	0	6 (8)	0
Neutrophil count decreased	8 (11)	0	10 (13)	3 (4)
Pyrexia	12 (16)	1 (1)	6 (8)	1 (1)
Abdominal pain	14 (19)	2 (3)	3 (4)	0
Dyspnea	10 (13)	0	6 (8)	0
White-cell count decreased	8 (11)	1 (1)	8 (11)	0

* Adverse events that occurred in at least 10% of patients are listed in order of decreasing frequency; grade was assessed according to the Common Terminology Criteria for Adverse Events. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

DISCUSSION

Among patients with early-stage *RET* fusion-positive NSCLC, event-free survival was significantly longer with selpercatinib than with placebo. The 2-year event-free survival was 92% in the selpercatinib group and 61% in the placebo group. The hazard ratio for disease recurrence, progression, or death was 0.17 (95% CI, 0.06 to 0.51) among patients with stage II or IIIA disease in the primary analysis population, which corresponded to an 83% lower risk with adjuvant sel-

percatinib than with placebo. Event-free survival assessments by the investigator and by blinded independent central review were concordant.

The LIBRETTO-432 trial results add to a growing body of data showing the value of targeted therapy in early-stage, oncogene-driven lung cancers.^{7,8,19} The effect size shown in the trial is in line with the data on adjuvant treatment reported for *EGFR*-mutant NSCLC (2-year disease-free survival of 90% with a hazard ratio of 0.17 for osimertinib vs. placebo in the ADAURA trial⁷) and for *ALK* fusion-positive NSCLC (2-year dis-

ease-free survival of 94% with a hazard ratio of 0.24 for alectinib vs. platinum-based chemotherapy in the ALINA trial⁸).

The safety profile of selpercatinib was generally consistent with that in the LIBRETTO-001 and LIBRETTO-431 trials.^{16,17} Grade 3 or higher adverse events were reported in 67% of the patients in the selpercatinib group and in 24% of those in the placebo group. The majority of adverse events, including elevated levels of alanine aminotransferase and aspartate aminotransferase, were manageable with established monitoring, supportive care, and dose-modification strategies. Adverse events leading to discontinuation of the trial regimen occurred in more patients in the selpercatinib group than in the placebo group (17% vs. 1%), and most discontinuations were attributed to either grade 1 or grade 2 adverse events; the majority of these adverse events resolved. The percentage of patients who discontinued selpercatinib because of adverse events was similar to that reported previously for osimertinib as an adjuvant treatment.⁷ Although the percentage of patients who discontinued selpercatinib because of adverse events was lower (10%) in a previous trial involving patients with advanced or metastatic disease than in our trial,¹⁷ the acceptability of adverse events associated with continuation of therapy in these patients may be lower in the context of adjuvant treatment, even in patients with low-grade adverse events.

Our trial has some limitations. First, the sample size reflects the relative rarity of *RET* fusions, which occur in 1 to 2% of patients with NSCLC,^{11,12} as compared with *ALK* fusions (4 to 5% of patients with NSCLC)⁸ and *EGFR* mutations (20 to 40% of patients²⁰); thousands of patients were screened to enroll 151 patients. The rarity of *RET* fusions poses considerable challenges to conducting adequately powered studies involving patients with NSCLC. Second, enrollment was challenging because of the coronavirus disease 2019 pandemic in the first years of the trial. Third, this trial primarily enrolled Asian and White patients; Black patients and those of other racial or ethnic minority groups (e.g., Native Hawaiian and Hispanic) are not as well represented. Fourth, the median duration of follow-up was 24 months in the selpercatinib group and 27 months in the placebo

group, and more than half the patients were receiving selpercatinib or placebo at the data-cutoff date. Longer follow-up would enable a more mature assessment of secondary end points, including overall survival; provide additional insights across subgroups, such as among patients with stage IB disease; and further strengthen the robustness of the overall dataset.

Among patients with stage II or IIIA *RET* fusion–positive NSCLC, event-free survival was significantly longer with adjuvant selpercatinib than with placebo. Selpercatinib was associated with liver-enzyme abnormalities of grade 3 or higher in less than 20% of the patients, and these adverse events were managed with dose reduction or interruption. These findings have the potential to change clinical practice in this subpopulation of patients with NSCLC and reinforce the value of comprehensive biomarker testing for actionable oncogenic drivers at the time of diagnosis across all stages of the disease to inform therapeutic decision making.

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