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# Durability of Efficacy with Selpercatinib in Patients (pts) with *RET* Fusion+ Non-Small-Cell Lung Cancer (NSCLC)

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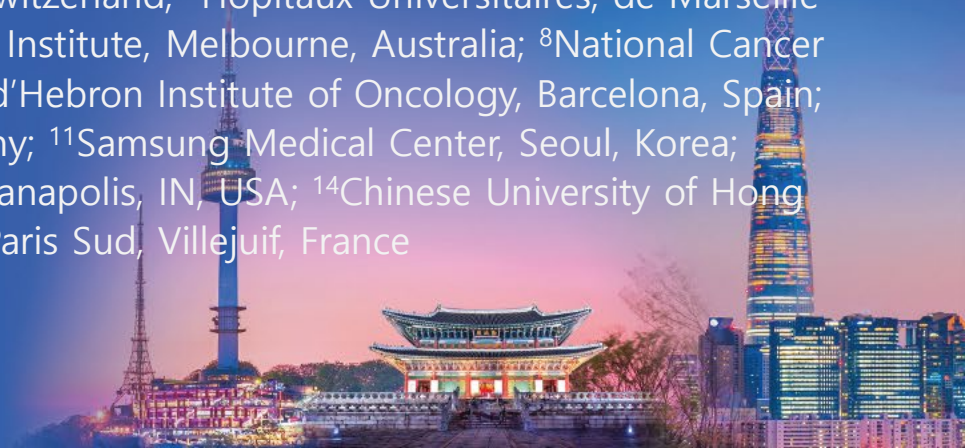

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# Background and Aim

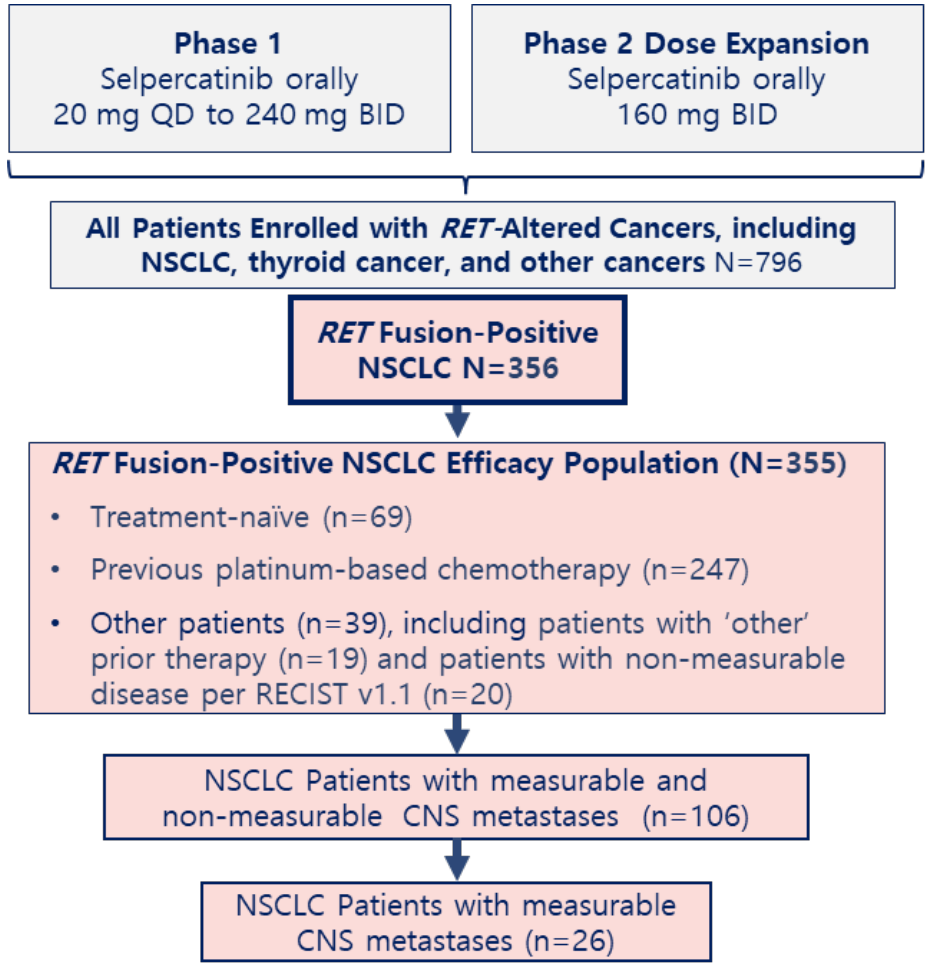
- Selpercatinib is a first-in-class, highly selective and potent RET-inhibitor[1] with CNS activity[2,3]
- *RET* fusions are oncogenic drivers in ~2% of patients with NSCLC[4]
- Based on compelling and durable responses in the Phase 1/2 Study LIBRETTO-001, selpercatinib gained regulatory approval for patients with metastatic *RET* fusion-positive NSCLC[5,6]
- In the initial registrational data set (December 2019, 144 patients)[5], the majority of patients were alive and progression-free at the time of initial approval. As a result, the median DOR and PFS could not be accurately estimated

## Objective

- Here we present updated selpercatinib efficacy and safety data from LIBRETTO-001 in patients (n=316) with *RET* fusion-positive NSCLC

# Study Design

## The Phase 1/2 LIBRETTO-001 Trial: Selpercatinib in Patients with *RET*-altered Cancers




**Study Design**
- Ongoing, global, multicenter Phase 1/2 trial (NCT03157128)
- Patients enrolled based on locally identified *RET* alterations using NGS, FISH, or PCR
- Key inclusion criteria: Diagnosis of advanced or metastatic disease, ECOG PS 0 to 2, asymptomatic CNS metastases permitted.

**Primary Endpoint**
- ORR (RECIST v 1.1) by Independent Review

**Secondary Endpoints Included**
- Duration of Response (DOR)
- CNS ORR/DOR by IRC
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Safety

Safety population includes all patients who received at least one selpercatinib dose prior to June 2021 data cutoff
Efficacy population includes all patients enrolled 6 months prior to data cutoff date, to allow adequate follow-up. One patient with NSCLC who received prior treatment with another selective RET inhibitor was not included in the efficacy analysis but was included in the NSCLC safety population

# Clinicopathologic Features

| Characteristic | Treatment-naïve (N=69) | Previous platinum chemotherapy (N=247) |
|---|---|---|
| Age— median (range) in years | 63.0 (23-92) | 61.0 (23-81) |
| Female—n (%) | 43 (62.3) | 140 (56.7) |
| Race—n (%)[a] | | |
| White | 48 (69.6) | 108 (43.7) |
| Asian | 13 (18.8) | 118 (47.8) |
| Black | 4 (5.8) | 12 (4.9) |
| Smoking status—n (%) | | |
| Never smoker | 48 (69.6) | 165 (66.8) |
| Former smoker | 19 (27.5) | 78 (31.6) |
| Current smoker | 2 (2.9) | 4 (1.6) |
| ECOG performance-status score—n (%) | | |
| 0 | 25 (36.2) | 90 (36.4) |
| 1 | 40 (58.0) | 150 (60.7) |
| 2 | 4 (5.8) | 7 (2.8) |
| Median previous systemic lines—n (range) | 0 | 2 (1-15) |
| 1 | 0 | 73 (29.6) |
| 2 | 0 | 67 (27.1) |
| ≥3 | 0 | 107 (43.3) |
| Previous regimen—n (%)[b] | | |
| Platinum-based chemotherapy | NA | 247 (100) |
| Anti-PD-1 or anti-PD-L1 therapy | NA | 144 (58.3) |
| Multitargeted kinase inhibitor[c] | NA | 85 (34.4) |
| RET fusion—n (%)[d] | | |
| KIF5B-RET | 48 (69.6) | 153 (61.9) |
| CCDC6-RET | 10 (14.5) | 53 (21.5) |
| NCOA4-RET | 1 (1.4) | 5 (2.0) |

Percentages may not total to 100 because of rounding. [a]Race was reported by the patients. 'Other' (n=11; e.g. American Indian, Alaska Native, and Pacific Islander) and missing (n=2) are not listed. [b]Other prior systemic therapies (n=97) included radioactive iodine, mTOR inhibitor, EGFR inhibitor, VEGF/VEGFR inhibitor, and selective RET inhibitor. [c]Multitargeted kinase inhibitors administered included cabozantinib, vandetanib, lenvatinib, and others. Patients may have received more than one multitargeted kinase inhibitor. [d]Additional *RET* fusion partners (n=10 [treatment-naïve], n=38 [previous platinum chemotherapy]) not shown.

# Efficacy

| Response | Treatment-naïve (N=69) | Previous platinum chemotherapy (N=247) |
|---|---|---|
| Objective response by IRC—% (95% CI) | 84.1 (73.3, 91.8) | 61.1 (54.7, 67.2) |
| Duration of response | | |
| Median —mo (95% CI) | 20.2 (13.0, NE) | 28.6 (20.4, NE) |
| Censoring rate (%) | 55.2 | 60.9 |
| 1-yr DoR—% (95% CI) | 66.1 (51.6, 77.3) | 73.1 (64.9, 79.7) |
| 2-yr DoR—% (95% CI) | 41.6 (25.6, 56.8) | 55.8 (46.4, 64.2) |
| Median duration of follow-up—mo | 20.3 | 21.2 |
| Progression-free survival | | |
| Median —mo (95% CI) | 22.0 (13.8, NE) | 24.9 (19.3, NE) |
| Censoring rate— n (%) | 37 (53.6) | 138 (55.9) |
| 1-yr PFS — % (95% CI) | 70.6 (57.8, 80.2) | 70.5 (64.1, 76.0) |
| 2-yr PFS — % (95% CI) | 41.6 (26.8, 55.8) | 51.4 (44.3, 58.1) |
| Median duration of follow-up—mo | 21.9 | 24.7 |
| Overall survival | | |
| Patients with censored data—n (%) | 49 (71.0) | 169 (68.4) |
| 1-yr OS —% (95% CI) | 92.7 (83.3, 96.9) | 87.9 (83.0, 91.4) |
| 2-yr OS —% (95% CI) | 69.3 (55.2, 79.7) | 68.9 (62.2, 74.7) |
| 3-yr OS —% (95% CI) | 57.1 (35.9, 73.6) | 58.5 (49.7, 66.3) |
| Median duration of follow-up —mo | 25.2 | 26.4 |

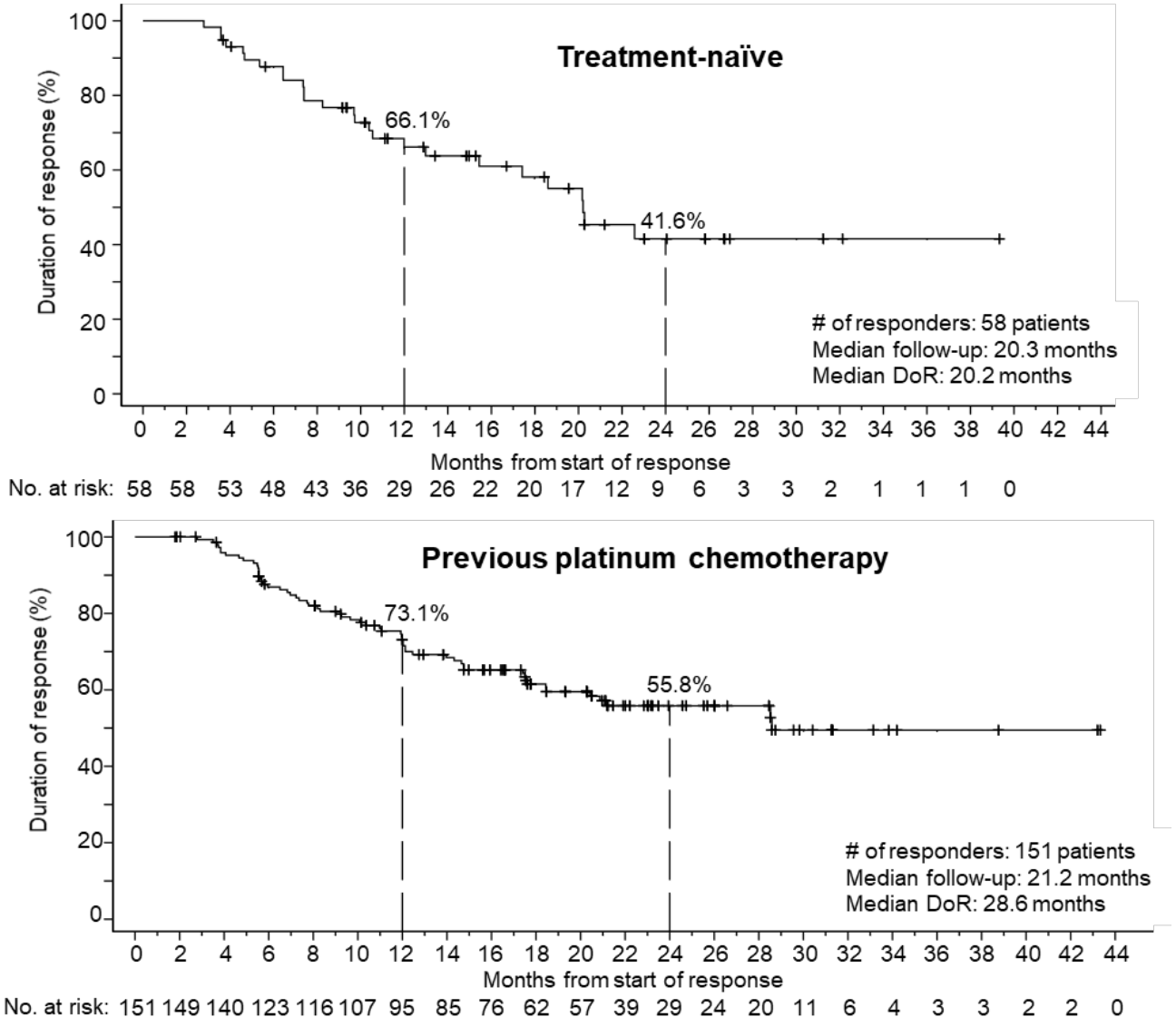
Note: ORR was consistent regardless of prior therapy or ethnicity (data not shown)

# CNS Efficacy

| CNS response | (N=26) |
|---|---|
| Objective response by IRC— % (95% CI) | 84.6 (65.1, 95.6) |
| Best response —n (%) | |
| Complete response | 7 (26.9) |
| Partial response | 15 (57.7) |
| Stable disease | 4 (15.4) |
| Progressive disease | 0 |
| Could not be evaluated | 0 |
| CNS duration of response | |
| Median —mo (95% CI) | 9.4 (7.4-15.3) |
| Censoring rate (%) | 27.3 |
| 1-yr DoR— % (95% CI) | 36.1 (16.4, 56.4) |
| 2-yr DoR— % (95% CI) | 20.6 (6.5, 40.2) |
| Median duration of follow-up—mo | 25.8 |

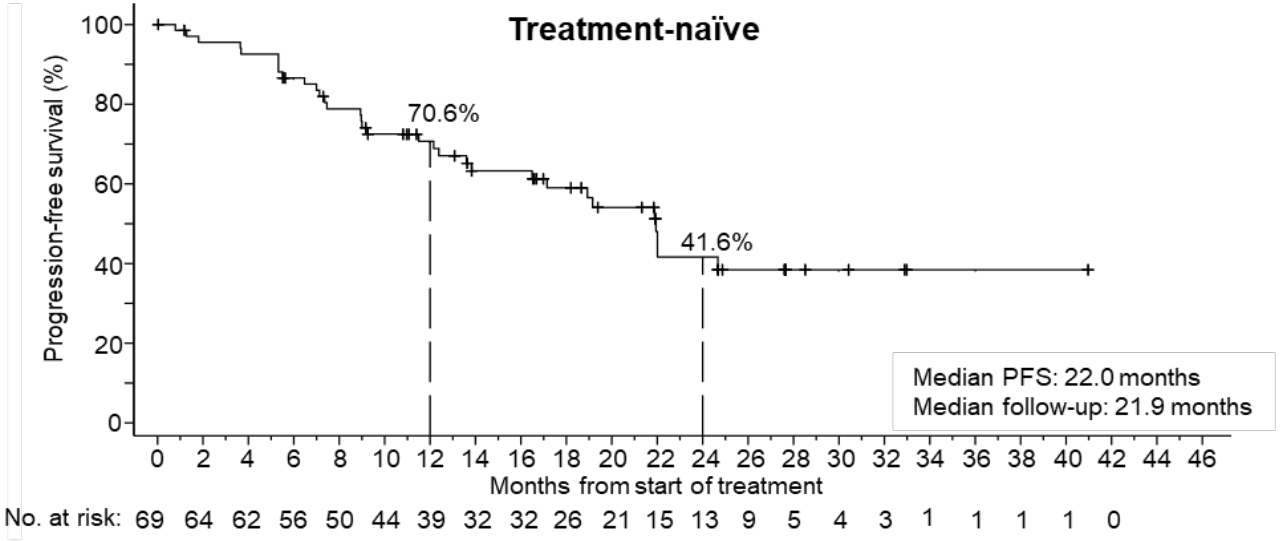
CNS efficacy is shown for the total number of patients with measurable CNS disease (n=26) at baseline among the 355 NSCLC patients of the efficacy population. Abbreviations: CI, confidence interval; CNS, central nervous system; IRC, independent review committee; N, number of patients; n, number of patients in group; mo, months; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

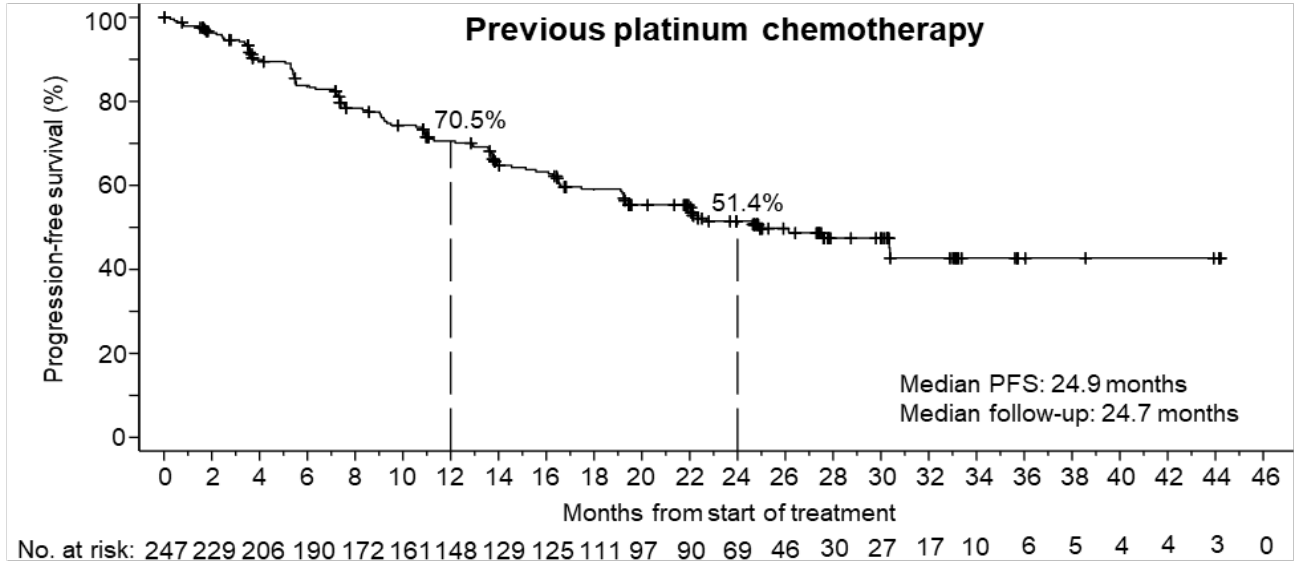
# Duration of Response




- Median DoR was 20.2 months in treatment-naïve NSCLC at a median follow-up of 20.3 months
- Median DoR was 28.6 months in platinum-based chemotherapy pretreated NSCLC at a median follow-up of 21.2 months
- Due to censoring rate, estimates are not yet mature

# Progression-free Survival

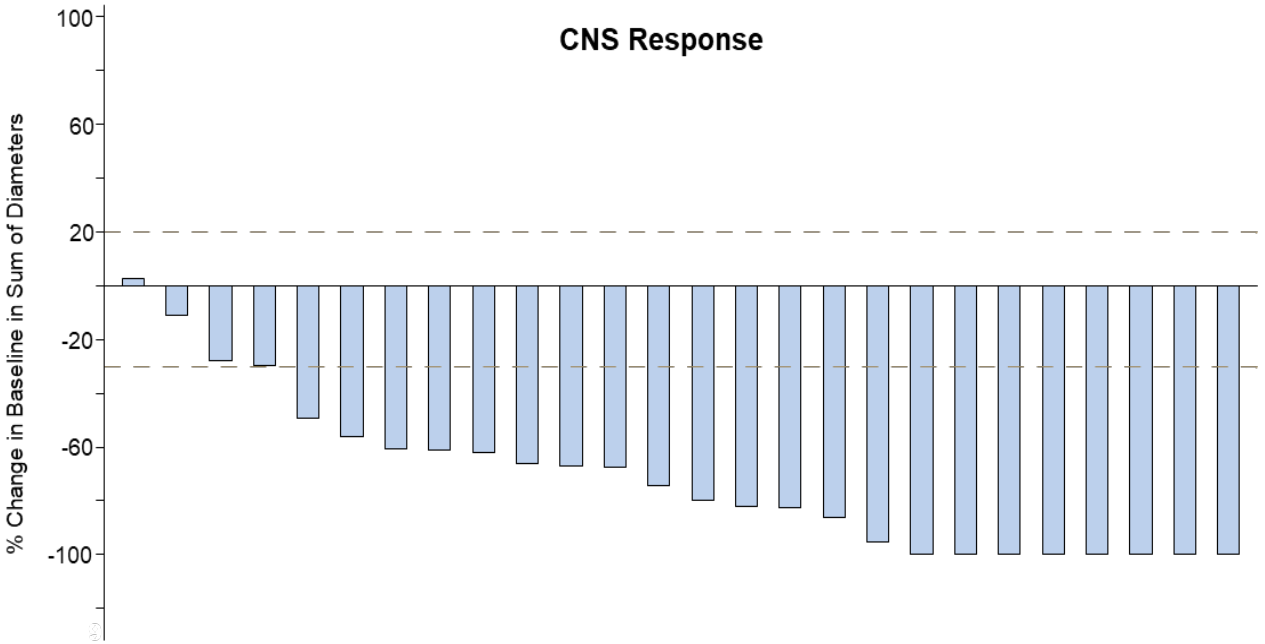


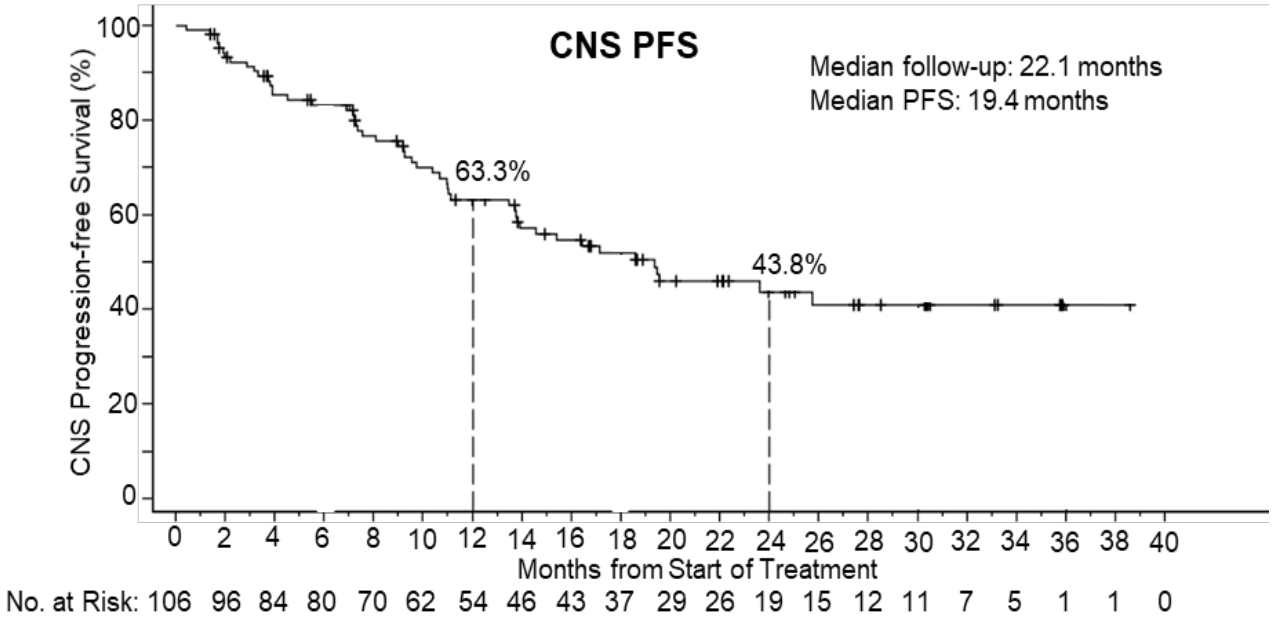




- Median PFS was 22.0 months in treatment-naïve and 24.9 months in patients previously treated with platinum-based chemotherapy
- Due to censoring rate, estimates are not yet mature

# CNS Response

- Of the 26 patients with measurable CNS disease, 22 had a confirmed best response of CR or PR




The waterfall plots of maximum change in intracranial tumor size for the 26 patients with measurable central nervous system (CNS) disease at baseline. Five of the 26 patients had no prior systemic therapy. Vertical bars represent the best percent change from baseline in the sum of diameters for all target lesions. Progressive disease (+20%) and partial response (-30%) are indicated with the dashed lines.

Intracranial PFS is shown for the 106 patients with measurable or non-measurable CNS disease at baseline among the 355 NSCLC patients of the efficacy population.

# Adverse Events in NSCLC Safety Population

| | Any Causality | | Related to Treatment | |
|---|---|---|---|---|
| N=356, n (%) | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Patients with ≥1 AE | 356 (100.0) | 263 (73.9) | 341 (95.8) | 143 (40.2) |
| *Edema* | 178 (50.0) | 2 (0.6) | 124 (34.8) | 2 (0.6) |
| *Diarrhea* | 184 (51.7) | 15 (4.2) | 114 (32.0) | 8 (2.2) |
| *Fatigue* | 153 (43.0) | 8 (2.2) | 78 (21.9) | 3 (0.8) |
| *Dry Mouth* | 163 (45.8) | 0 | 151 (42.4) | 0 |
| *Hypertension (AESI)* | 141 (39.6) | 68 (19.1) | 95 (26.7) | 49 (13.8) |
| *AST increased* | 149 (41.9) | 37 (10.4) | 122 (34.3) | 24 (6.7) |
| *ALT increased* | 147 (41.3) | 53 (14.9) | 120 (33.7) | 41 (11.5) |
| *Abdominal pain* | 101 (28.4) | 5 (1.4) | 28 (7.9) | 1 (0.3) |
| *Constipation* | 96 (27.0) | 5 (1.4) | 34 (9.6) | 2 (0.6) |
| *Rash* | 130 (36.5) | 4 (1.1) | 83 (23.3) | 4 (1.1) |
| Nausea | 112 (31.5) | 4 (1.1) | 40 (11.2) | 2 (0.6) |
| *Blood creatinine increased* | 92 (25.8) | 10 (2.8) | 50 (14.0) | 1 (0.3) |
| *Headache* | 94 (26.4) | 3 (0.8) | 23 (6.5) | 0 |
| *Cough* | 87 (24.4) | 0 | 9 (2.5) | 0 |
| *Dyspnea* | 84 (23.6) | 16 (4.5) | 10 (2.8) | 0 |
| *Vomiting* | 78 (21.9) | 4 (1.1) | 19 (5.3) | 2 (0.6) |
| *ECG QT prolongation (AESI)* | 74 (20.8) | 21 (5.9) | 57 (16.0) | 14 (3.9) |
| *Thrombocytopenia* | 74 (20.8) | 20 (5.9) | 52 (14.6) | 13 (3.7) |
| *Decreased appetite* | 73 (20.5) | 1 (0.3) | 34 (9.6) | 0 |
| *Pyrexia* | 79 (22.2) | 1 (0.3) | 21 (5.9) | 1 (0.3) |
| Urinary tract infection | 70 (19.7) | 8 (2.2) | 2 (0.6) | 0 |

- Safety profile consistent as previously observed
- Of the 34 (9.6%) patients who discontinued due to AE, 11 (3.1%) were deemed related to study treatment per the investigator

The total percentage for any given adverse event may be different than the sum of the components for the individual grades because of rounding. The table includes adverse events which occurred in ≥20% of patients.
Composite terms which are comprised of preferred terms are shown in italics. [a]In total, 24 (6.7%) patients had grade 5 TEAEs, including respiratory failure, (in 6 each), cardiac arrest (in 4 each), pneumonia, sepsis, cerebral hemorrhage (in 2 each), multiple organ dysfunction syndrome, sudden death, somnolence, dyspnea, hypoxia, corona virus infection, acute respiratory failure, and cardio-respiratory arrest (in 1 each). [b]No grade 5 TRAEs were observed.

# Conclusions

- With longer follow-up and additional patients, selpercatinib continued to demonstrate robust and durable efficacy in patients with *RET* fusion-positive NSCLC
- Selpercatinib demonstrated CNS activity
  - 85% intracranial ORR
  - Median duration of intracranial response 9.4 months
  - Intracranial PFS 19.4 months at a median follow-up of 22.1 months
- Selpercatinib's safety profile was consistent with previous reports with no new safety signals identified
- LIBRETTO-001 trial (NCT03157128) is still enrolling patients with *RET* altered solid tumors
- A global, randomized, Phase 3 trial (LIBRETTO-431; NCT04194944) will compare PFS of selpercatinib versus standard frontline chemotherapy-based treatment in treatment-naïve *RET* fusion-positive advanced or metastatic NSCLC[7]

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