Durability of Efficacy and Safety with Selpercatinib in Patients with RET Fusion+ Non-Small-Cell Lung Cancer: LIBRETTO-001

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Background

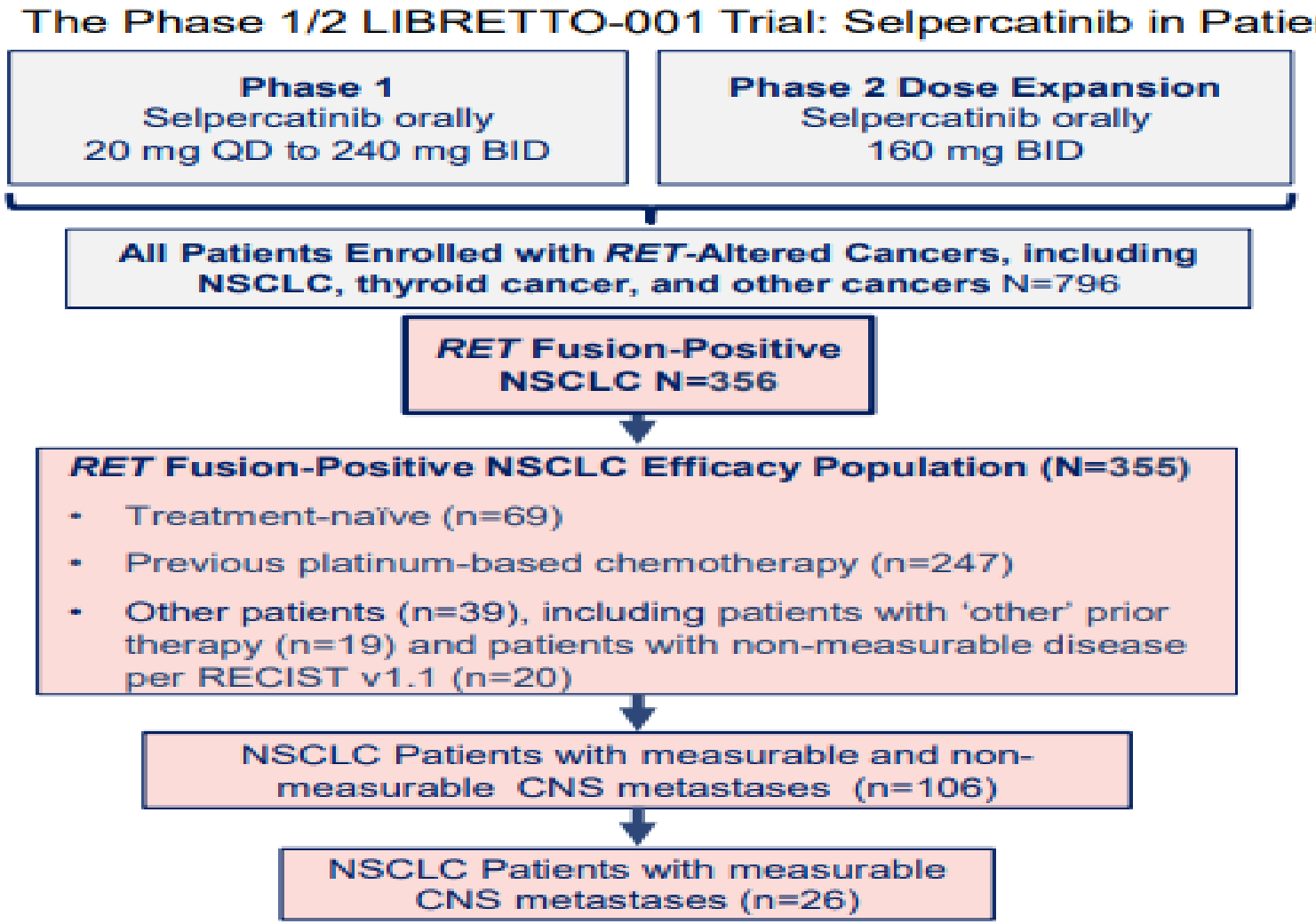
- Selpercatinib is a first-in-class, highly selective and potent RET-inhibitor1 with CNS activity.
- RET fusions are oncogenic drivers in ~2% of patients with NSCLC.
  - Based on compelling and durable responses in the Phase 1/2 Study LIBRETTO-001, selpercatinib gained regulatory approval for patients with metastatic RET fusion-positive NSCLC.
- In the initial registration data set (December 2019, 144 patients), 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

- To evaluate selpercatinib efficacy and safety data from LIBRETTO-001 in patients (n=316) with RET fusion-positive NSCLC.

1.Goto et. al., J Clin Oncol 2020 2.Subbiah et. al., J Clin Oncol 2020 3.Subbiah et al., Clin Cancer Res 2021 4.Drilon et. al., Nat Rev Clin Oncol 2018 5.Drilon et. al., NEJM 2020 6.Markham A., Drugs 2020

Study design



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

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Clinico-pathologic 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)

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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)

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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.

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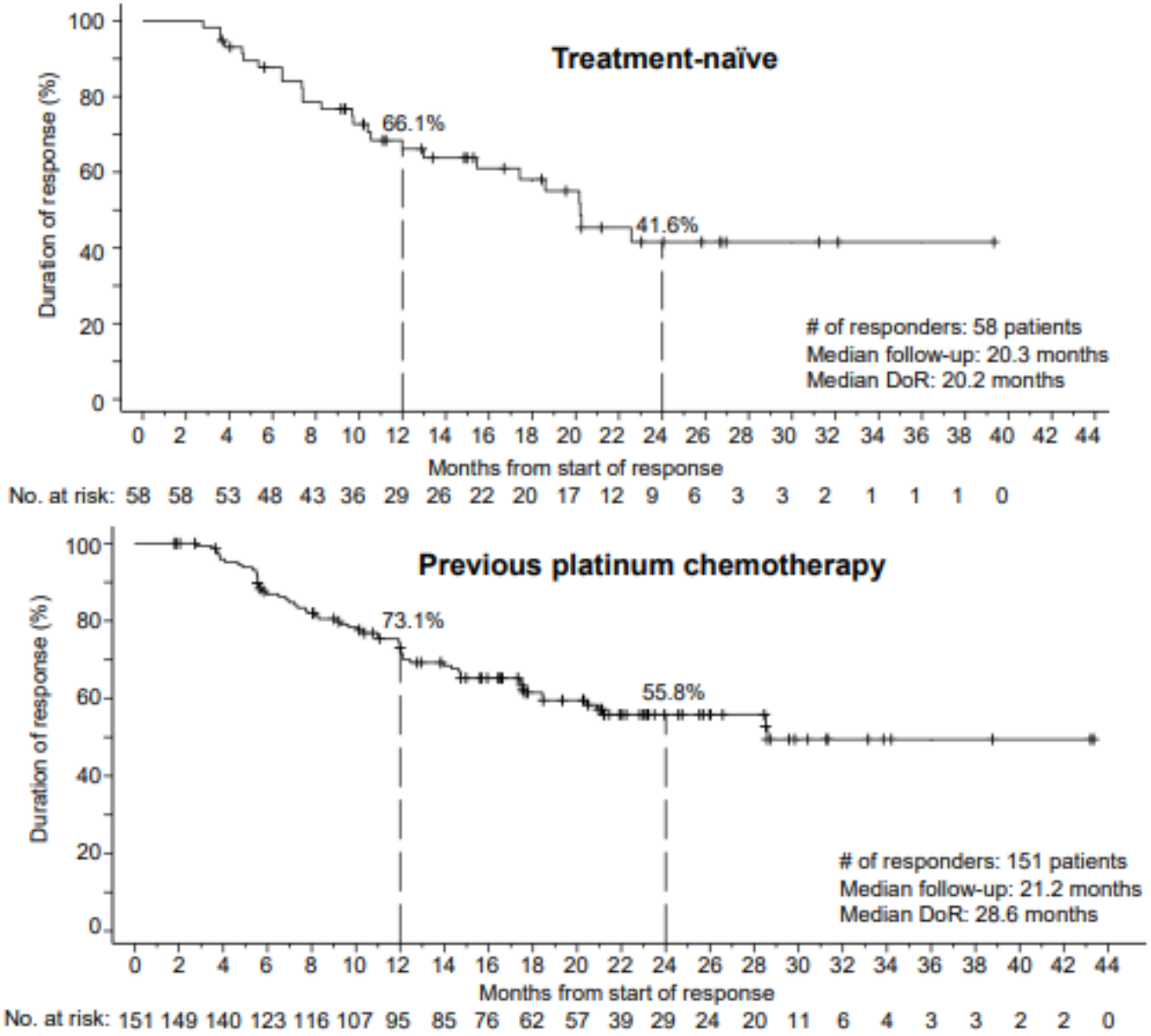
Duration of Response

- **Median DoR** was
  - **20.2 months in treatment-naïve** NSCLC at a median follow up of 20.3 months
  - **28.6 months in platinum-based chemotherapy** pretreated NSCLC at a median follow-up of 21.2 months.



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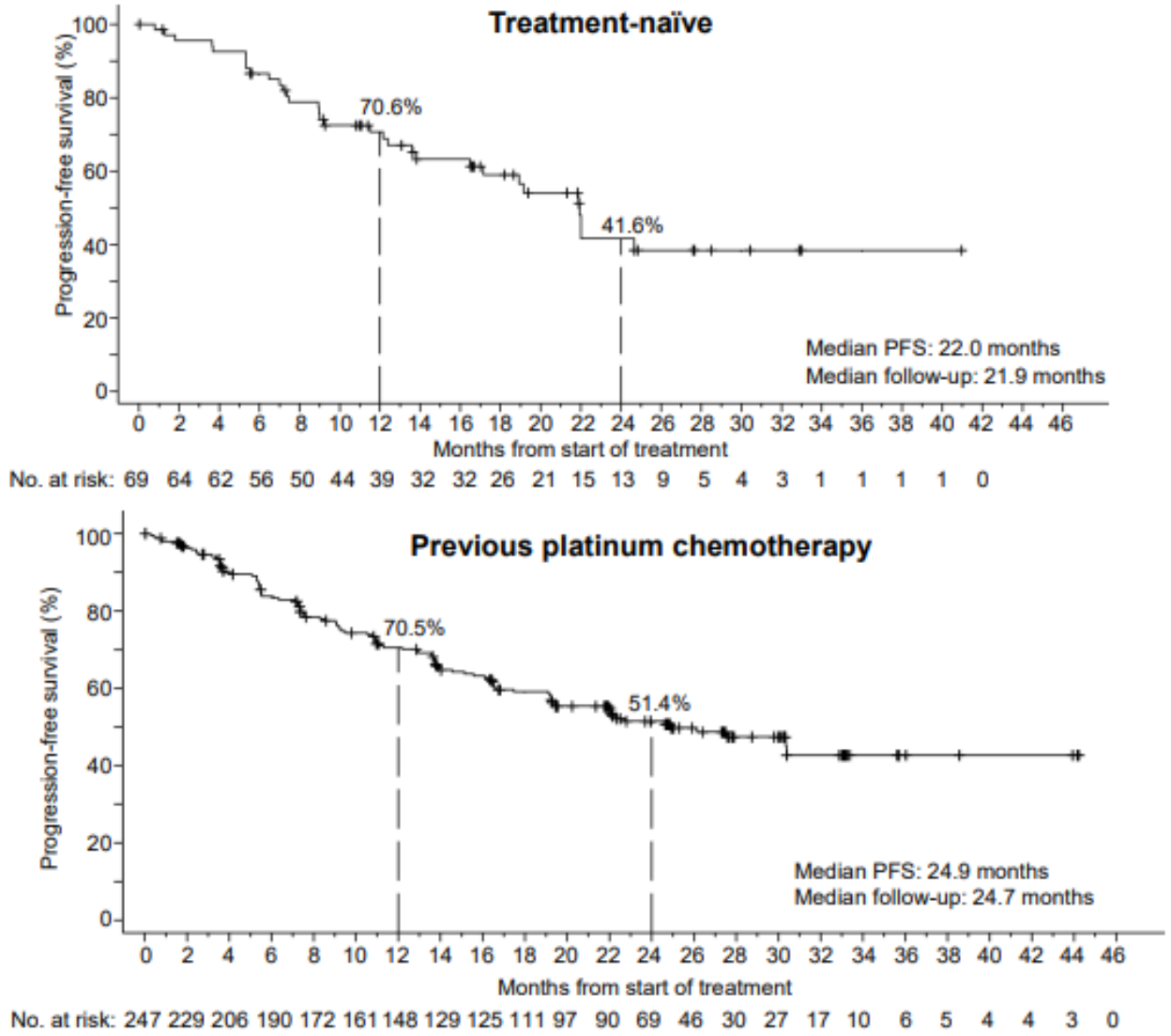
Progression-free Survival

- **Median PFS** was
  - **22.0 months in treatment-naïve** and
  - **24.9 months in patients previously treated with platinum-based chemotherapy.**



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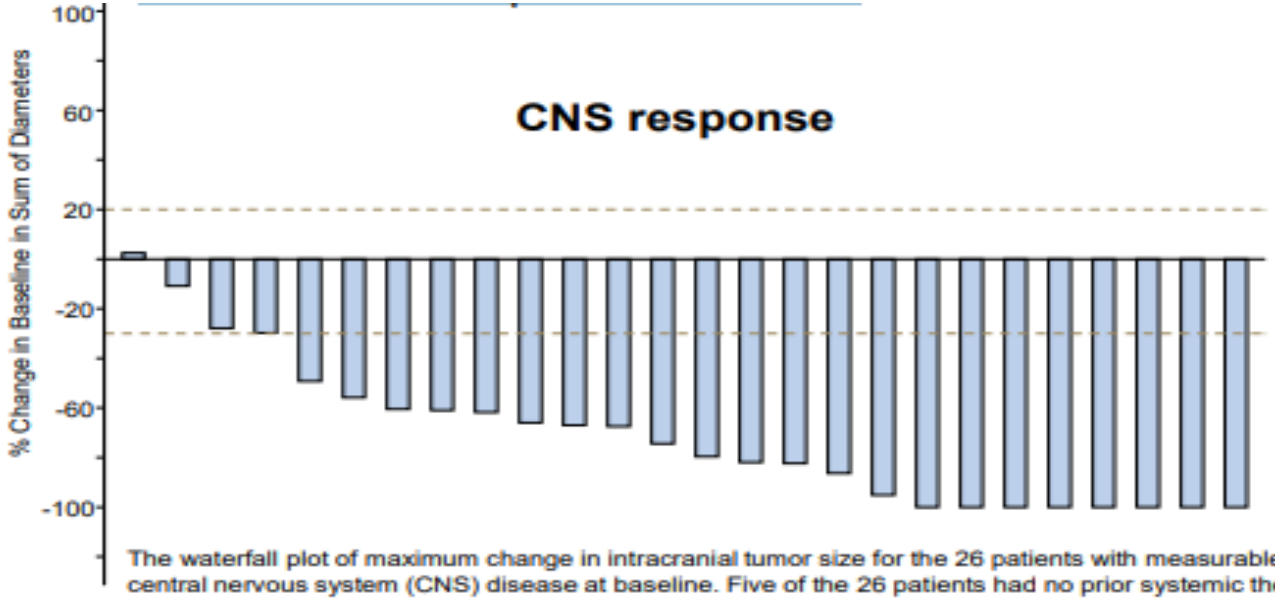
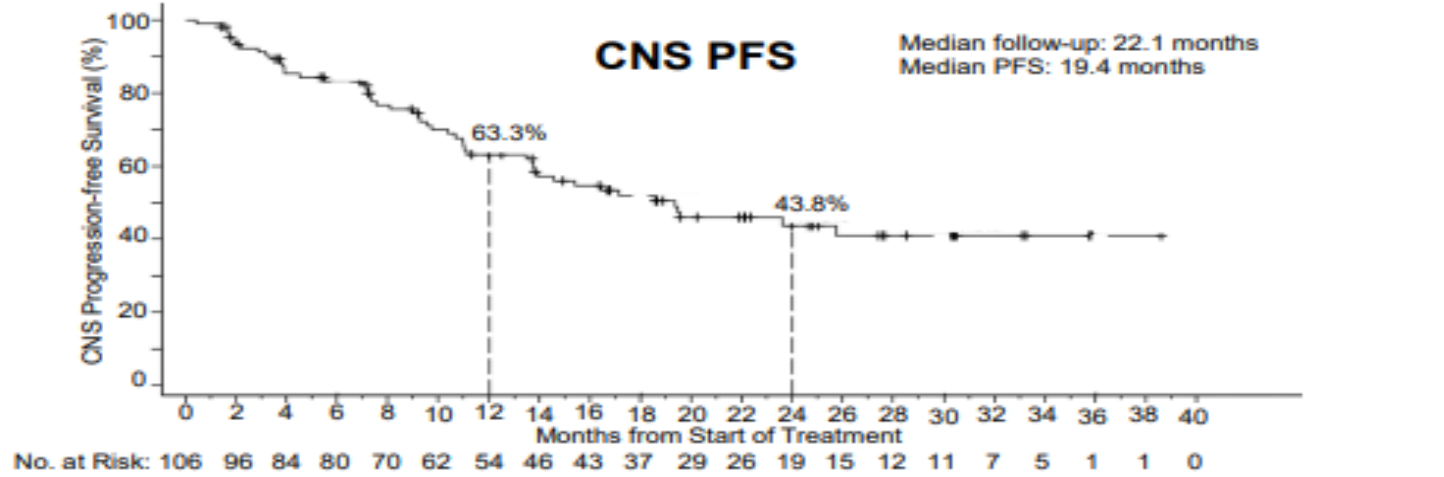
CNS Response

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



The waterfall plot 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.

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Adverse Events

- **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),
  - MODS, sudden death, somnolence, dyspnea, hypoxia, corona virus infection, acute respiratory failure, and cardio-respiratory arrest (in 1 each).
- No grade 5 TRAEs were observed.
- Of the 34 (9.6%) patients who discontinued due to AE,
  - 11 (3.1%) were deemed related to study treatment per the investigator

	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

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The table includes adverse events which occurred in ≥20% of patients

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 with 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

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THANK YOU