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Intracranial activity of selpercatinib (LOXO-292) in *RET* fusion-positive non-small cell lung cancer (NSCLC) patients on the LIBRETTO-001 trial

Vivek Subbiah[1], Justin F Gainor[2], Geoffrey R. Oxnard[3], Daniel Shao-Weng Tan[4], Dwight Owen[5], Byoung Chul Cho[6], Herbert HF Loong[7], Caroline E McCoach[8], Jared Weiss[9], Yu Jung Kim[10], Lyudmila Bazhenova[11], Keunchil Park[12], Haruko Daga[13], Benjamin Besse[14], Oliver Gautschi[15], Sarah Ng[16], Xin Huang[16], Alexander E Drilon[17]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]National Cancer Centre Singapore, Singapore; [5]The Ohio State University, Columbus, OH, USA; [6]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [7] The Chinese University of Hong Kong, Hong Kong, PRC; [8]University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [9]University of North Carolina, Chapel Hill, NC, USA; [10]Seoul National University Bundang Hospital, Gyeonggido, Republic of Korea; [11]University of California, San Diego Moores Cancer Center, San Diego, CA, USA; [12]Samsung Medical Center, Sungkyunkwau University School of Medicine, Seoul, Republic of Korea; [13]Osaka City General Hospital, Osaka, Japan; [14] Institut Gustav Roussy, Villejuif, France; [15]University of Berne and Cantonal Hospital of Lucerne, Lucerne, Switzerland; [16]Loxo Oncology, a subsidiary of Eli Lilly and Co., Indianapolis, IN, USA; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA

OBJECTIVE AND BACKGROUND

Primary objective of this analysis:
To assess intracranial objective response rate (ORR) to selpercatinib by independent review committee (IRC) in patients with *RET* fusion-positive NSCLC with CNS metastases, with or without prior CNS radiotherapy.

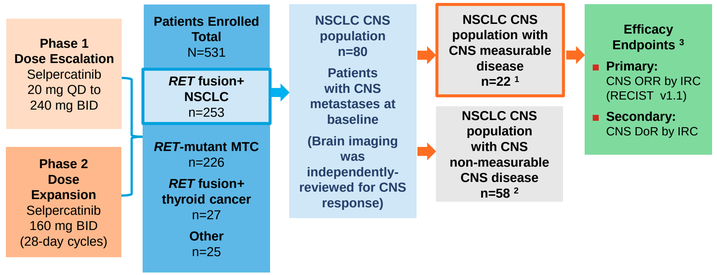
Secondary objective:
To assess intracranial duration of response (DoR) to selpercatinib by IRC in the same patient population.

Background

- *RET* codes for a transmembrane tyrosine kinase.[1]
- *RET* fusions have been identified in approximately 2 percent of patients with NSCLC.[2,3]
- Patients with *RET* fusion-positive NSCLC have a ~50% lifetime prevalence of developing CNS metastases.[4]
- Selpercatinib (LOXO-292) is a potent and selective *RET* inhibitor with CNS penetration.[5]
- LIBRETTO-001 is a registrational phase 1/2 trial (NCT03157128) assessing the activity of selpercatinib in patients with advanced *RET* fusion-positive solid tumors and *RET*-mutant medullary thyroid cancer.[6]
- Selpercatinib demonstrated robust and durable anti-tumor activity in *RET* fusion-positive NSCLC:

RET fusion-positive NSCLC population (as defined by prior therapy)	ORR (%) (95% CI)	Median DoR (mo) (95% CI)	Median follow-up (mo)	Median PFS (mo) (95% CI)	Median follow-up (mo)
Prior platinum doublet (n=105)					
Independent review	64 (54-73)	18 (12-NE)	12	17 (14-NE)	14
Investigator assessment	70 (60-78)	20 (16-24)	15	18 (16-25)	16
Treatment-naive (n=39)					
Independent review	85 (70-94)	NE (12-NE)	7	NE (14-NE)	9
Investigator assessment	90 (76-97)	NE (12-NE)	7	NE (14-NE)	9

STUDY DESIGN



- An ongoing trial conducted in 16 countries and 89 sites (12 countries, 65 sites for the N=531 data set).
- All patients had *RET* alteration as determined by local CLIA-certified or similarly accredited laboratories. All patients also had ECOG performance status of 0-2

[1] This analysis includes data from the database cutoff of 16 Dec 2019, including the 11 patients with measurable CNS disease from the Primary Analysis Set (n=105) of *RET* fusion-positive NSCLC treated with prior platinum chemotherapy.
[2] Two of the 58 patients had no CNS disease by IRC.
[3] CNS response assessed by RECIST v1.1 at baseline, then every 8 weeks from Cycle 3-13, then every 12 weeks thereafter. Patients were treated until confirmed progressive disease or any other decision to discontinue.

Abbreviations: BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; DoR, duration of response; IRC, independent review committee; MTC, medullary thyroid cancer; NSCLC, non-small-cell lung cancer; ORR, objective response rate; QD, once daily.

RESULTS

Table 1. CNS Subgroup Baseline Characteristics

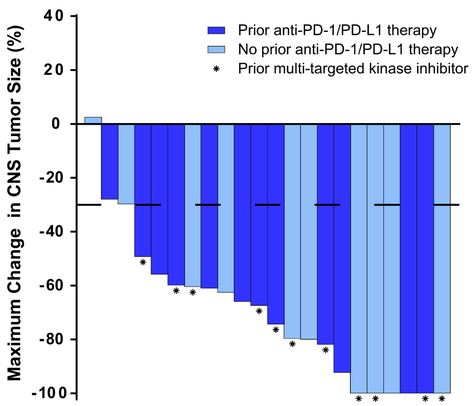
Characteristics	NSCLC patients with measurable CNS metastases (n=22)
Female, % (n)	81.8 (18)
Median age (range), years	64.0 (36, 80)
ECOG performance status, % (n)	
0	27.3 (6)
1	72.7 (16)
Race, % (n)	
White	63.6 (14)
Asian	27.3 (6)
Black, Other	9.1 (2)
Smoking history, % (n)	
Never	81.8 (18)
Former	18.2 (4)
RET fusion partner, % (n)	
KIF5B	72.7 (16)
CCDC6	13.6 (3)
CLIP1, ERC, unknown	13.6 (3)
Prior therapy type, % (n)	
Any systemic therapy	90.9 (20)
Platinum chemotherapy	72.7 (16)
Anti PD-1/PD-L1 antibody	54.5 (12)
Multi-kinase inhibitor	50.0 (11)
Brain radiotherapy	36.4 (8)
Completed >2 mo prior to selpercatinib treatment	27.3 (6)

Table 2. CNS Response Rate by IRC

	RET fusion-positive NSCLC patients with measurable CNS metastases (n=22) [1]		
Status	Total (n=22)	Without prior CNS RT (n=14)	With prior CNS RT [2] (n=8)
CNS Objective response rate, % (n)	81.8 (18)	85.7 (12)	75.0 (6)
95% CI	59.7 – 94.8	57.2 – 98.2	34.9 – 96.8
CNS best overall response, % (n)			
Complete response	22.7 (5)	28.6 (4)	12.5 (1)
Partial response	59.1 (13)	57.1 (8)	62.5 (5)
Stable disease	18.2 (4)	14.3 (2)	25.0 (2)
Progressive disease	0	0	0

Abbreviations: CNS RT, central nervous system metastases radiotherapy.
[1] Patients had CNS measurable lesions per RECIST v1.1.
[2] Of the 8 patients who received prior radiotherapy, 6 completed radiotherapy >2 months prior to treatment.

Fig 1. Waterfall Plot of CNS Response by IRC[1]



[1] Because CNS best overall response (Table 2) is based on RECIST requirements (e.g. need for a confirmatory scan), the Waterfall plot does not have an exact 1:1 correlation with Table 2 data.

Table 3. CNS Duration of Response by IRC

	RET fusion-positive NSCLC patients with measurable CNS metastases (n=22) [1]		
Status	Total (n=22)	Without prior CNS RT (n=14)	With prior CNS RT [2] (n=8)
CNS best response of CR/PR, n	18	12	6
CNS duration of response (months)			
Median	9.4	9.4	NE
95% CI	7.4 – NE	6.7 – 10.1	5.1 – NE
CNS duration of follow-up (months)			
Median	9.5	15.7	9.5
25th, 75th percentile	9.2, 15.7	8.3, 15.7	9.2, 21.2
Response status, % (n)			
Censored	44.4 (8)	41.7 (5)	50.0 (3)

Abbreviations: CNS RT, central nervous system metastases radiotherapy; CR, complete response; PR, partial response.
[1] Patients had CNS measurable lesions per RECIST v1.1.
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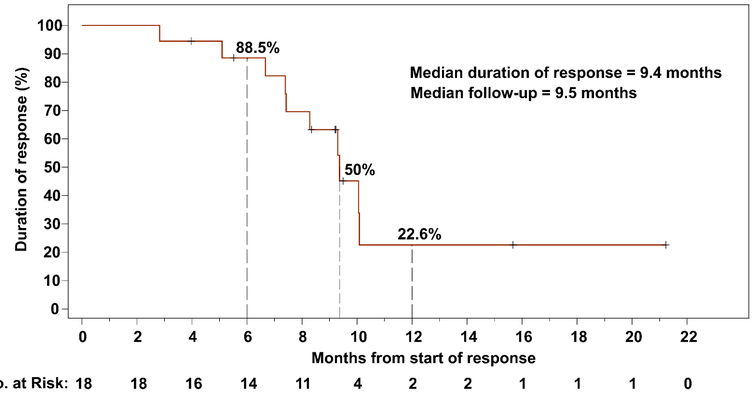
Fig 2. Kaplan-Meier Plot of CNS Duration of Response



CONCLUSIONS

- Selpercatinib had marked and durable intracranial anti-tumor activity in *RET* fusion-positive NSCLC patients with CNS metastases.
- Tumor responses were durable and independently-confirmed.
  - ORR 81.8% (95% CI = 59.7 – 94.8)
  - Median DoR 9.4 months (95% CI = 7.4 – NE)
- A randomized, global, phase 3 study of selpercatinib versus platinum-pemetrexed +/- pembrolizumab in treatment-naïve *RET* fusion-positive NSCLC is ongoing, including patients with asymptomatic brain metastases (NCT04194944).

References:

1. Mulligan LM. Nature Reviews Cancer 2014;14:173-86.
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Acknowledgments: The authors thank the patients, their families and caregivers, and the LIBRETTO-001 investigators and study staff.

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vsubbiah@mdanderson.org Twitter: @VivekSubbiah

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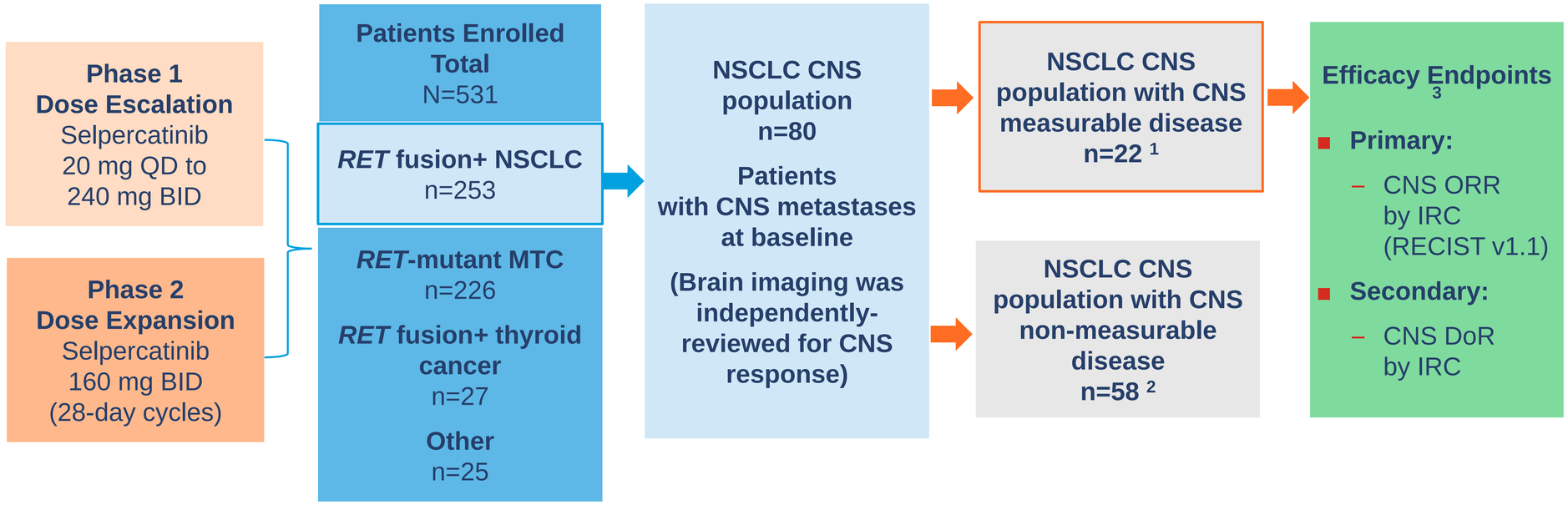

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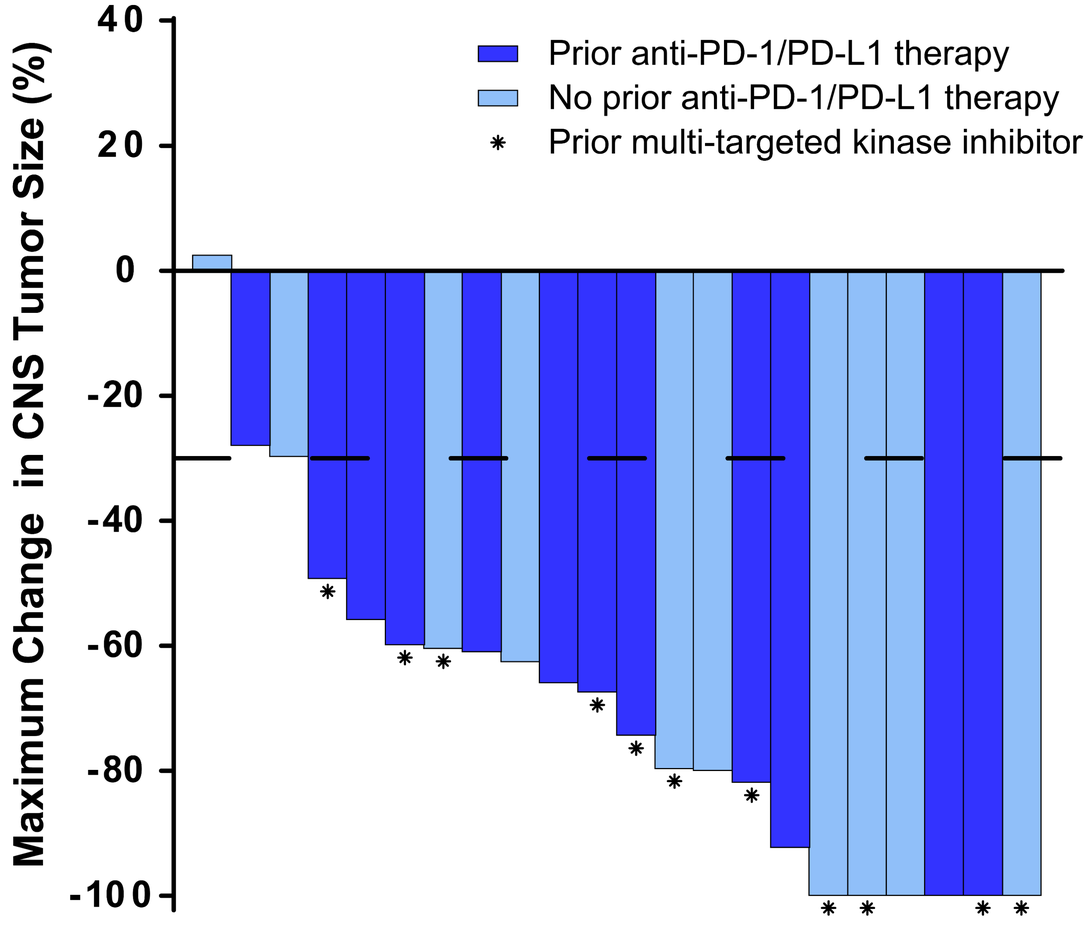

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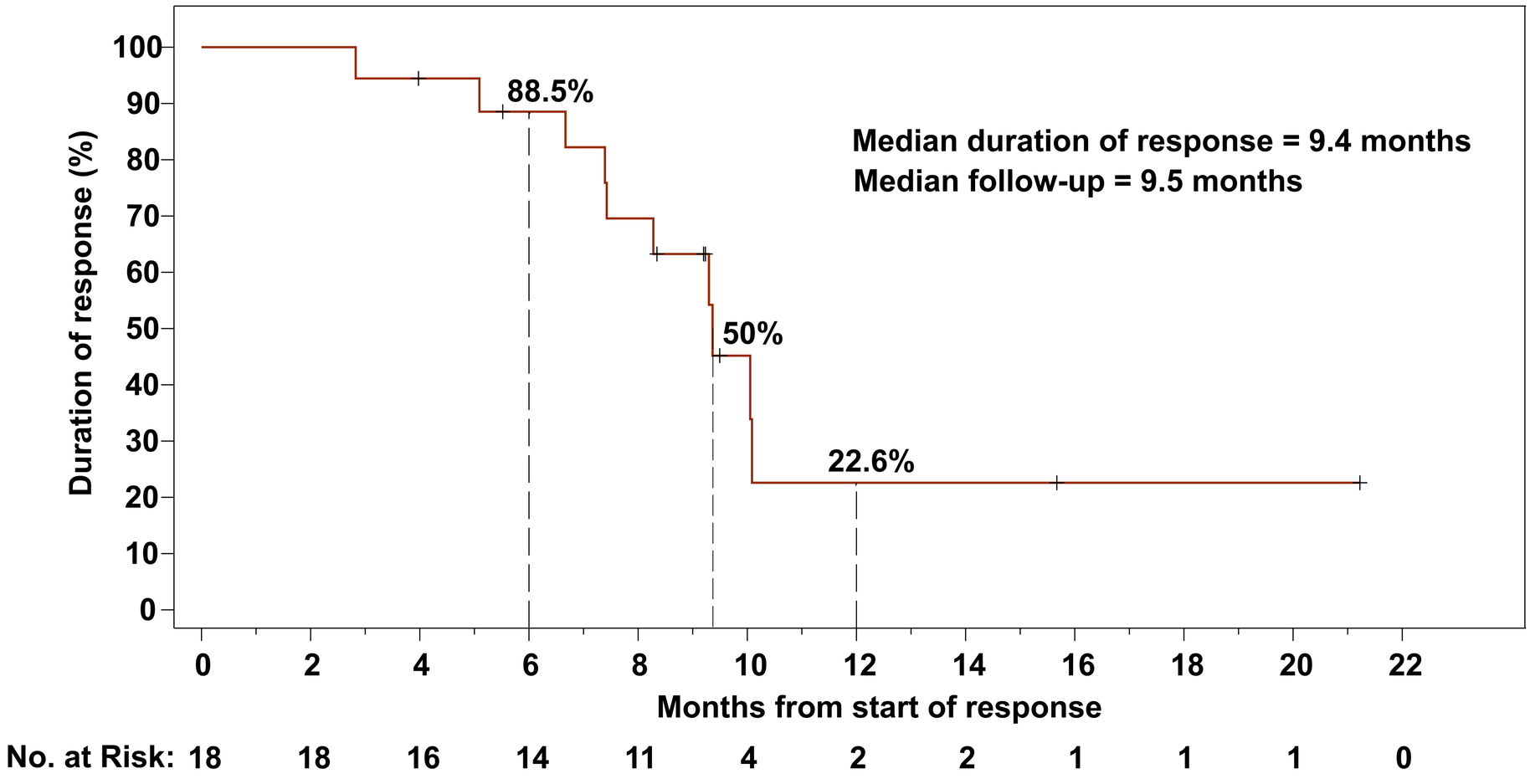

Conclusions

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