IASLC
2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain
wclc2019.iaslc.com | #WCLC19
Conquering Thoracic Cancers Worldwide

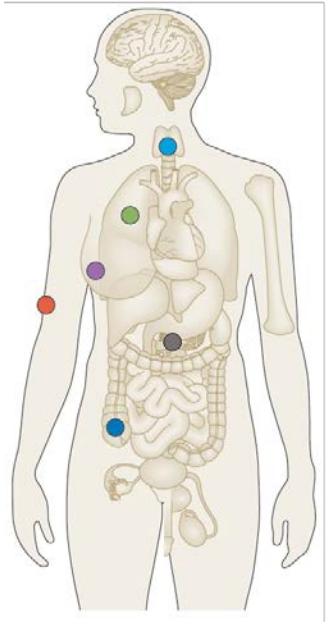
Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of Selpercatinib (LOXO-292) in Patients with *RET* Fusion-Positive Lung Cancers

A. Drilon[1], G. Oxnard[2], L. Wirth[3], B. Besse[4], O. Gautschi[5], S.W.D. Tan[6], H. Loong[7], T. Bauer[8], Y.J. Kim[9], A. Horiike[10], K. Park[11], M. Shah[12], C. McCoach[13], L. Bazhenova[14], T. Seto[15], M. Brose[16], N. Pennell[17], J. Weiss[18], I. Matos[19], N. Peled[20], B.C. Cho[21], Y. Ohe[22], K. Reckamp[23], V. Boni[24], M. Satouchi[25], G. Falchook[26], W. Akerley[27], H. Daga[28], T. Sakamoto[29], J. Patel[30], N. Lakhani[31], F. Barlesi[32], M. Burkard[33], V. Zhu[34], V. Moreno Garcia[35], J. Medioni[36], M. Matrana[37], C. Rolfo[38], D.H. Lee[39], H. Nechushtan[40], M. Johnson[41], V. Velcheti[42], M. Nishio[43], R. Toyozawa[44], K. Ohashi[45], L. Song[46], J. Han[47], A. Spira[48], M.Duca[49], K. Staal Rohrberg[50], S. Takeuchi[51], J. Sakakibara[52], S. Waqar[53], H. Kenmotsu[54], F. Wilson[55], B.Nair[56], E. Olek[56], J. Kherani[56], K. Ebata[56], E. Zhu[56], M. Nguyen[56], L. Yang[56], X. Huang[56], S. Cruickshank[56], S. Rothenberg[56], B. Solomon[57], K. Goto[58], V. Subbiah[59]

1.Memorial Sloan Kettering Cancer Center, New York, NY/United States of America. 2. Dana-Farber Cancer Institute, Boston, MA/United States of America. 3. Massachusetts General Hospital, Boston, MA/United States of America. 4. Institut Gustav Roussy, Villejuif/France. 5. Luzerner General Hospital, Luzern/Switzerland. 6. National Cancer Centre, Singapore/Singapore. 7. Prince of Wales Hospital, Shatin/Hong Kong PRC. 8. Sarah Cannon Research Institute, Nashville, TN/United States of America. 9. Seoul National University Bundang Hospital, Gyeonggido/ Democratic People's Republic of Korea. 10. The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo/Japan. 11. Samsung Medical Center, Seoul/Democratic People's Republic of Korea. 12. The Ohio State University, Columbus, OH/United States of America. 13. University of California, San Francisco, CA/United States of America. 14. University of California San Diego, Moores Cancer Center, La Jolla, CA/United States of America. 15. National Hospital Organization Kyushu Cancer Center, Fukuoka/Japan. 16. University of Pennsylvania, Philadelphia, PA/United States of America. 17. Cleveland Clinic, Cleveland, OH/United States of America. 18. University of North Carolina, Chapel Hill, NC/United States of America. 19. Vall d' Hebron Institute of Oncology, Barcelona/Spain. 20. Soroka Medical Center, Beer Sheva/Israel. 21. Severance Hospital, Yonsei University Health System, Seoul/ Democratic People's Republic of Korea. 22. National Cancer Center Hospital, Tokyo/Japan. 23. City of Hope Comprehensive Cancer Center, Duarte, CA/United States of America. 24. START Madrid-CIOCC, Madrid/Spain. 25. Hyogo Cancer Center, Akashi/Japan. 26.Sarah Cannon Research Institute, Denver, CO/United States of America. 27. Huntsman Cancer Institute, Salt Lake City, UT/United States of America. 28. Osaka City General Hospital, Osaka/Japan. 29. Tottori University Hospital, Yonago/Japan. 30. University of Chicago, Chicago, IL/United States of America. 31. South Texas Accelerated Research Therapeutics (START) Midwest, Grand Rapids, MI/United States of America. 33. University of Wisconsin - Carbone Cancer Center, Madison, WI/United States of America. 34 University of California - Irvine Medical Center, Irvine, CA/United States of America. 35. Fundacion Jimenez Diaz, START-Madrid-FJD, Madrid/Spain. 36. Hopital Europeen Georges Pompidou, Paris/France. 37. Ochsner Clinic Foundation, New Orleans, LA/United States of America. 38. University of Maryland Medical Center, Baltimore, MD/United States of America. 39. Asan Medical Center, Seoul/ Democratic People's Republic of Korea. 40. Hadassah Hebrew University Medical Center Ein Karem, Jerusalem/Israel. 41. Tennesse Oncology/Sarah Cannon Research Institute, Nashville, TN/United States of America. 42. NYU Langone Cancer Center, New York, NY/United States of America. 43. Cancer Institute Hospital of JFCR, Tokyo/Japan. 44. National Hospital Organization Kyushu Cancer Center, Fukuoka/Japan. 45. Okayama University Hospital, Okayama/Japan. 46. Kaiser Permanente - Santa Clara, CA/ United States of America. 47. National Cancer Center, Democratic People's Republic of Korea. 48. Virginia Cancer Specialists, VA/United States of America. 49. Istituto Nazionale Tumori - National Cancer Institute, Milan, Italy. 50. The Finsen Centre, Rigshospitalet, Denmark. 51. Kanazawa University Hospital, Kanazawa, Japan. 52. Hokkaido University Hospital, Hokkaido, Japan. 53. Washington University School of Medicine, Missouri/United States of America. 54. Shizuoka Cancer Center, Nagaizumi, Japan. 55. Yale University School of Medicine - Yale Cancer Center, CT/United States of America. 56. Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company, Stamford, CT/United States of America. 57. Peter MacCallum Cancer Center, Melbourne, ACT/Australia. 58. National Cancer Center Hospital East, Kashiwa/Japan. 59. MD Anderson Cancer Center, Houston, TX/United States of America

DISCLOSURES

Commercial Interest	Relationship(s)
Advisory Boards/Honoraria	Loxo/Bayer/Lilly, Ignyta/Genentech/Roche, Takeda/Ariad/Millenium, TP Therapeutics, AstraZeneca, Pfizer, Blueprint, Helsinn, Beigene, BergenBio, Hengrui, Exelixis, Tyra, Verastem, MORE Health, Abbvie
Research Funding Paid to Institution	Pfizer, Exelixis, GlaxoSmithKlein, Teva, Taiho, PharmaMar
CME Honoraria	Medscape, OncLive, PeerVoice, Physicians Education Resources, Targeted Oncology, Research to Practice, Oncology
Other	Wolters Kluwer (royalties), Merck, Puma, Foundation Medicine (research)



***RET* fusions**

Non-small cell lung cancer (2%)

Thyroid cancers (10–20%)

Pancreatic cancer (<1%)

Salivary gland cancer (<1%)

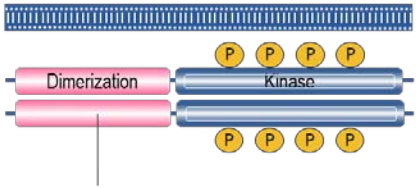
Spitz tumors (<1%)

Colorectal cancer (<1%)

Ovarian cancer (<1%)

Myeloproliferative disorders (<1%)

Many others (<1%)



KIF5B (most common in lung cancer)

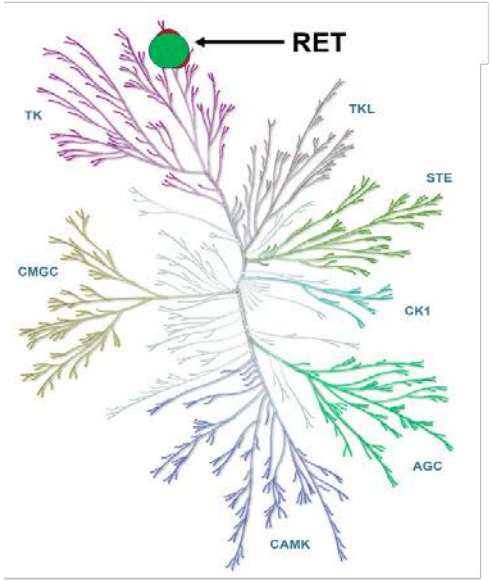
CCDC6* or *NCOA4 (most common in thyroid cancer)

- ***RET* Fusions are *bona fide* lung cancer drivers**
  - Mutually exclusive with other driver alterations[1,2]
  - Transforming and actionable *in vitro* and *in vivo*[3,4]
  - Up to half of patients with advanced disease have brain metastases[5]
- **To date, no RET inhibitor has received regulatory approval for the treatment of RET-dependent cancers**
  - Multikinase inhibitors
    - modest clinical benefit
    - significant toxicity (non-RET kinase inhibition[6])
  - Immunotherapy drugs (PD-1/PD-L1 inhibitors)
    - may be less efficacious in driver-positive NSCLCs patients, including *RET* fusions[7,8]

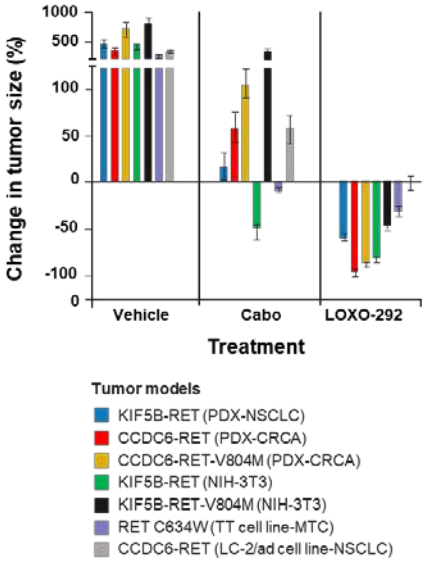
1. Drilon A, et al. Nat Rev Clin Oncol. 2018;15:151-167. 2. Wang R, et al. J Clin Oncol. 2012;30:4352-9. 3. Saito et al. Carcinogenesis. 2014 Nov;35(11):2452-6. 4. Takahashi et al. Cell. 1985 Sep;42(2):581-8. 5. Drilon, A. et al. J. Clin. Oncol. 35 (Suppl.), 9069 (2017). 6. Ferrara R, et al. J Thorac Oncol. 2018;13:27-45. 7. Sabari JK, et al. J Clin Oncol. 2018;36(15 suppl; abstr 9034). 8. Mazieres J, et al. J Clin Oncol. 2018;36(15 suppl; abstr 9010).

Selpercatinib* (LOXO-292) is a potent and selective RET Inhibitor

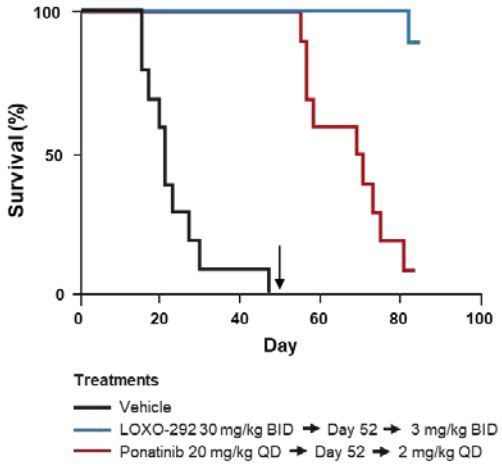
Kinome selectivity
Highly selective for RET



Xenograft models
Multiple fusions/mutations/histologies



Orthotopic brain model
CCDC6-RET orthotopic brain PDX



LIBRETTO-001: Selpercatinib in *RET*-altered cancers

Phase 1 dose escalation
Selpercatinib dosed at 20 mg QD–240 mg BID

Phase 2 dose expansion
Selpercatinib dosed at 160 mg BID

Total Enrolled n=531

- ***RET* fusion-positive NSCLC n=253**
- *RET*-mutant medullary thyroid cancer n=226
- *RET* fusion-positive thyroid cancer n=27
- Other n=25

Prior platinum chemotherapy n=184

- Prior non-platinum chemotherapy n=16
- Treatment-naïve n=39
- Non-measurable disease n=14

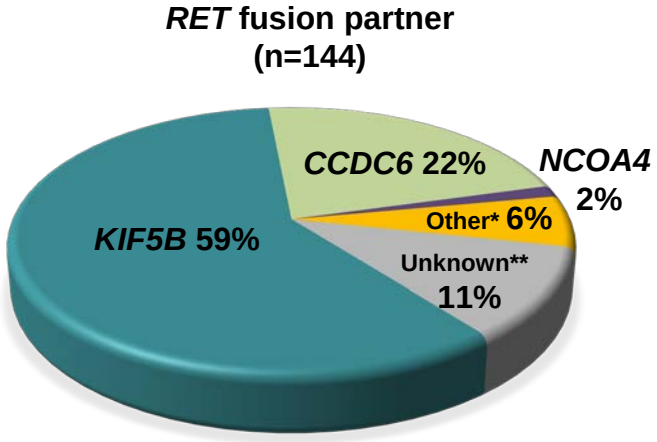
Primary Analysis Set n=105

First 105 patients with *RET* fusion-positive NSCLC who received prior platinum chemotherapy*

- ***RET*-alteration**
  - Determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Safety
- Treatment beyond progression permitted with continued benefit

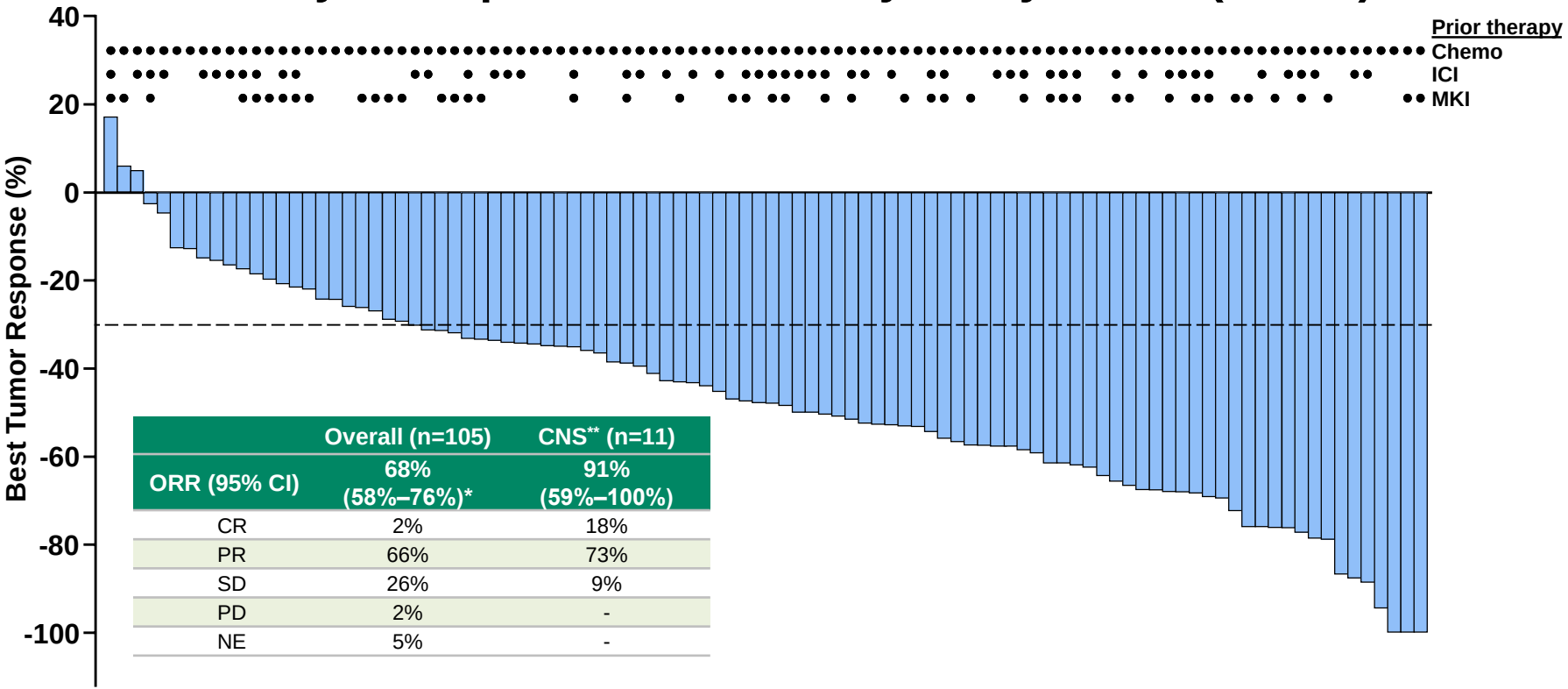
NCT03157128; Data cutoff: June 17th, 2019. *Per agreement with FDA, patients with non-measurable disease enrolled during phase 1 dose escalation were eligible for the primary analysis set.

Patient Characteristics	PAS (n=105)	Treatment-naïve (n=39)
Female / Male, n (%)	62 (59) / 43 (41)	22 (56) / 17 (44)
Median age (range), years	61 (23–81)	61 (23–86)
ECOG performance status, n (%)		
0	31 (30)	19 (49)
1	72 (69)	20 (51)
2	2 (2)	0
Median prior systemic regimens (range)	3 (1–15)	0
Prior platinum-based chemotherapy, n (%)	105 (100)	-
Prior PD-1/PD-L1 inhibitor, n (%)	58 (55)	-
Concurrent with platinum-based chemotherapy	9 (9)	-
Sequential to platinum-based chemotherapy	49 (47)	-
Prior multikinase inhibitor (MKI), n (%)	50 (48)	-
1	37 (35)	-
≥2	13 (12)	-
Brain metastases, n (%)‡	37 (35)	7 (18)
Measurable disease	104 (99)	39 (100)



Data cut-off: June 17th, 2019. Total % may be different than the sum of the individual components due to rounding. *Includes *KIAA1468* (2), *ARHGAP12*, *CCDC88C*, *CLIP1*, *DOCK1* + *RBPMS*, *ERC1*, *PRKAR1A and TRIM24* (all 1 each).
**FISH-positive or PCR-positive; ‡Includes patients with non-target CNS metastases.

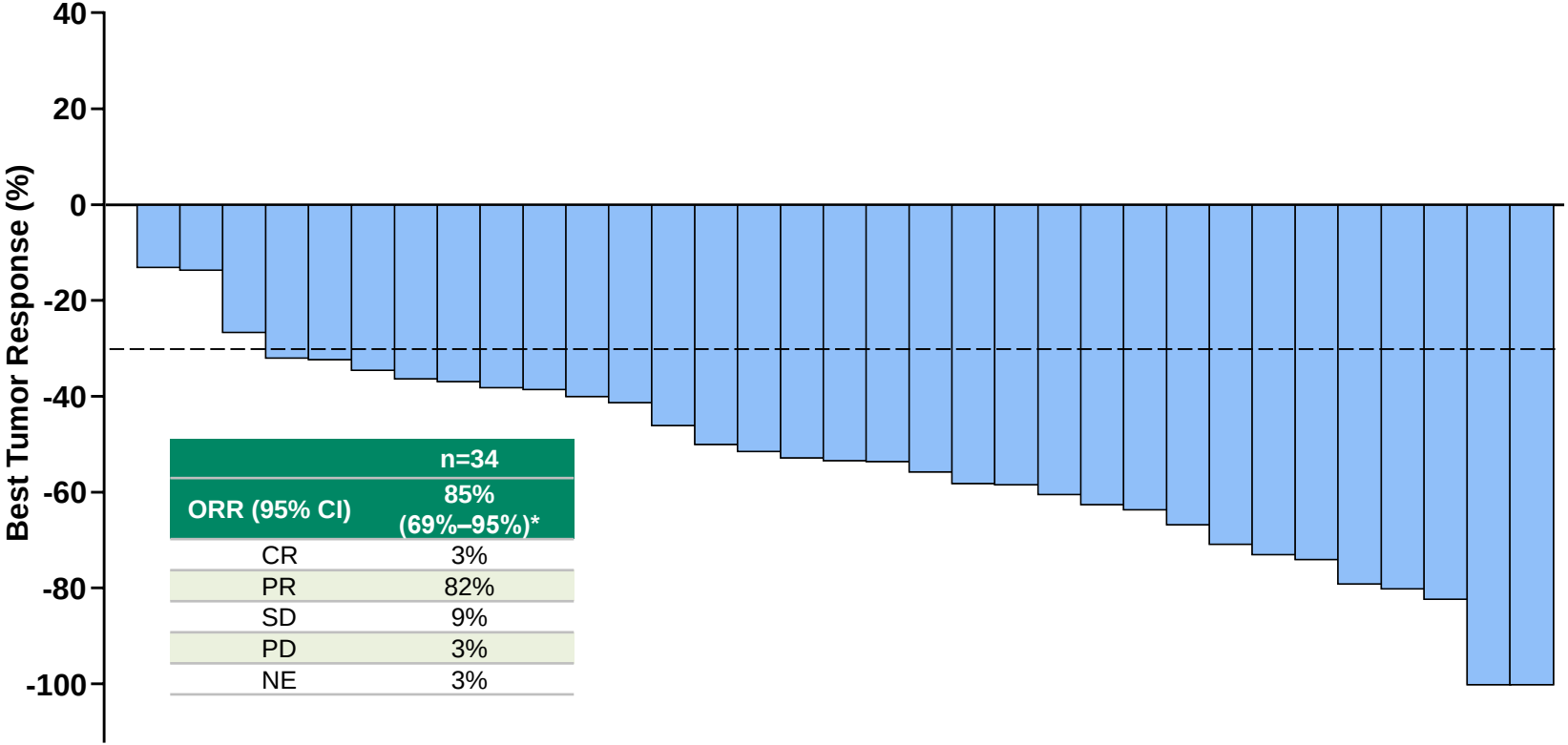
Efficacy of Selpercatinib: Primary Analysis Set (n=105)



	Overall (n=105)	CNS** (n=11)
ORR (95% CI)	68% (58%–76%)*	91% (59%–100%)
CR	2%	18%
PR	66%	73%
SD	26%	9%
PD	2%	-
NE	5%	-

Investigator response assessments as of June 17th, 2019. 5 patients not shown in waterfall plot: 3 discontinued prior to any post-baseline imaging assessments, 1 did not have measurable disease at baseline, and 1 deemed not evaluable on study by the Investigator. NE—Not evaluable, n=5 patients: 3 discontinued prior to any post-baseline imaging assessments, 1 deemed not evaluable on study by the Investigator, and 1 discontinued after a single post-baseline imaging assessment showing SD, less than 6 weeks after starting treatment. Total % may be different than the sum of the individual due to rounding. *N=105 dataset includes 2 unconfirmed PRs awaiting confirmatory response assessments. **Patients with CNS target lesions at baseline. Chemo—platinum-doublet chemotherapy; ICI—immune checkpoint inhibitors (anti-PD-1/PD-L1); MKI—multikinase inhibitors.

Efficacy of Selpercatinib: Treatment-naïve Patients (n=34)

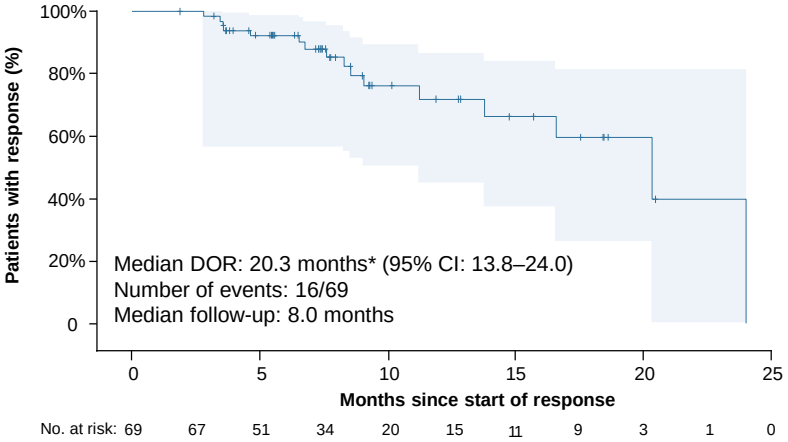


	n=34
ORR (95% CI)	85% (69%–95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

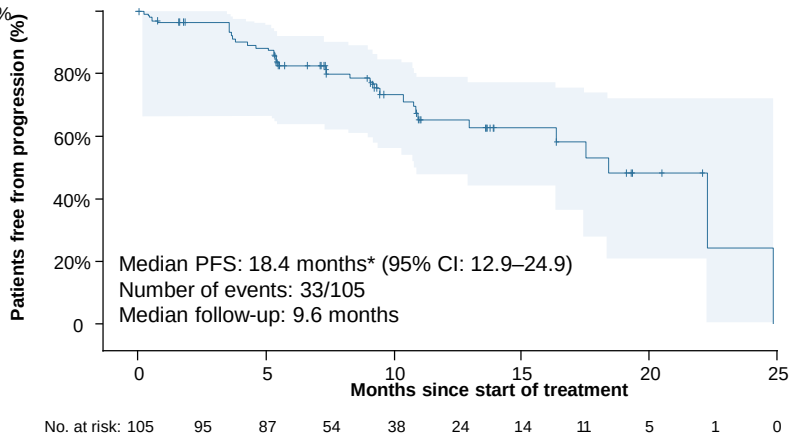
Investigator response assessments as of June 17th, 2019. Data include patients with at least one evaluable post-baseline imaging assessment and those who discontinued therapy prior to any post-baseline imaging assessment. 1 patient discontinued prior to any post-baseline imaging assessment and is not shown in the waterfall plot. NE—not evaluable, n=1 patient who discontinued prior to any post-baseline imaging assessment. Total % may be different than the sum of the individual due to rounding. *N=34 dataset includes 7 unconfirmed PRs awaiting confirmatory response assessments.

Durability of Selpercatinib Efficacy: Primary Analysis Set

Duration of response



Progression-free survival

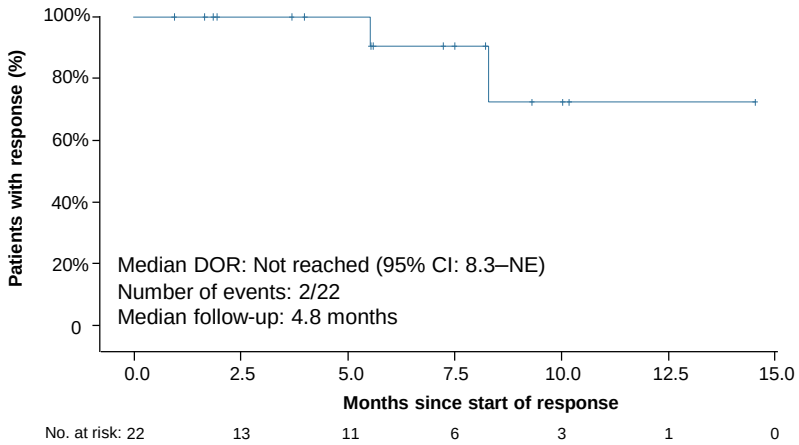


- Of 28 patients in the PAS that progressed, 23 continued treatment post-progression, for 0.2–16.4+ months
- ORR, DOR, PFS similar regardless of prior therapy (e.g. anti-PD-1/PD-L1, MKIs)

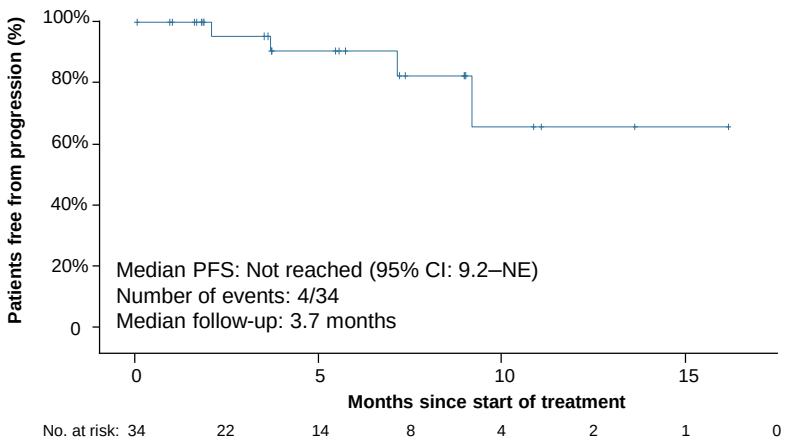
Data cut-off: June 17th, 2019. Shading in PAS Kaplan-Meier curves indicates the 95% confidence band. *Medians are not statistically stable due to a low number of events.

Durability of Selpercatinib Efficacy: Treatment-Naïve

Duration of response



Progression-free survival



Data cut-off: June 17th, 2019. No shading to show 95% confidence band due to a very low number of events.

Selpercatinib Safety Profile

	LIBRETTO-001 Safety Database, n=531							
	Treatment-emergent AEs (≥15% overall)					Treatment-related AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Dry mouth	29%	4%	–	–	32%	–	–	27%
Diarrhea	21%	8%	2%	–	31%	1%	–	16%
Hypertension	4%	11%	14%	<1%	29%	8%	<1%	18%
Increased AST	17%	5%	6%	1%	28%	4%	1%	22%
Increased ALT	13%	4%	7%	1%	26%	6%	1%	21%
Fatigue	15%	9%	1%	–	24%	<1%	–	14%
Constipation	19%	3%	<1%	–	22%	<1%	–	11%
Headache	15%	4%	1%	–	20%	<1%	–	7%
Nausea	15%	4%	<1%	–	19%	<1%	–	8%
Peripheral edema	16%	4%	<1%	–	19%	–	–	10%
Increased creatinine	14%	4%	–	<1%	18%	–	–	10%

9 patients (1.7%) discontinued due to treatment-related AEs

Data cut-off: June 17th, 2019. AE — adverse event; Total % for any given AE may be different than the sum of the individual grades, due to rounding.

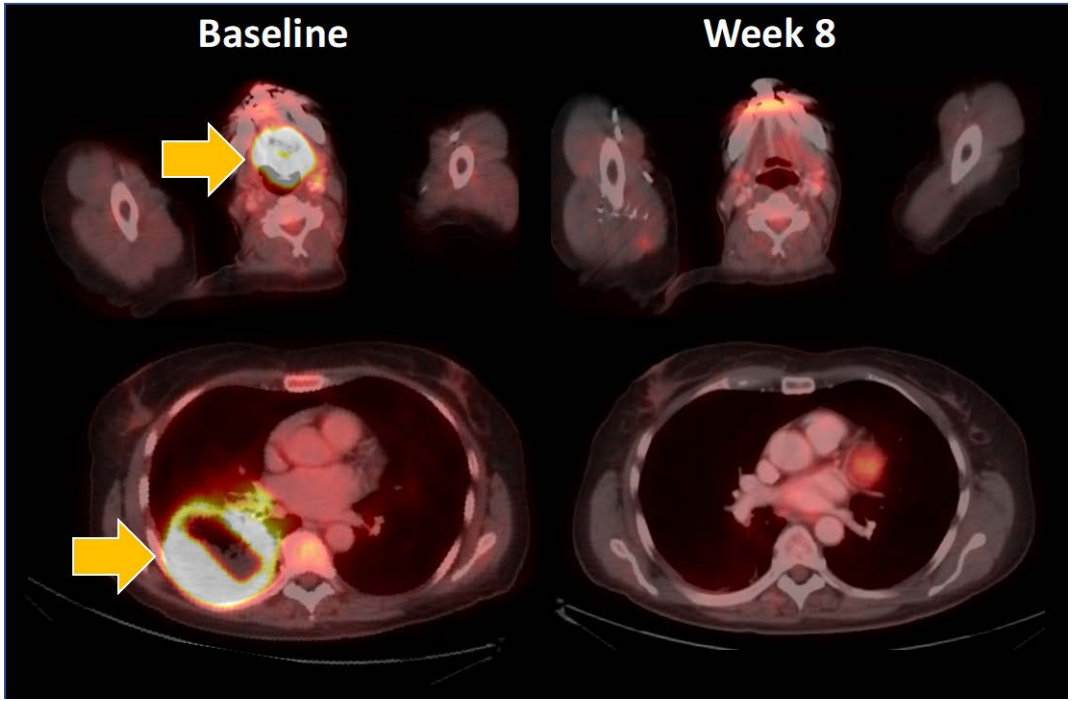
Selpercatinib Response in the Treatment-Naïve Setting

65-year-old woman with *KIF5B-RET* fusion-positive NSCLC

- Metastatic disease to the base of tongue, lungs, and bone

Initiated selpercatinib at 160 mg BID as first systemic therapy

- Brisk, durable, and confirmed PR by RECIST 1.1
- Remains on treatment at 10 months



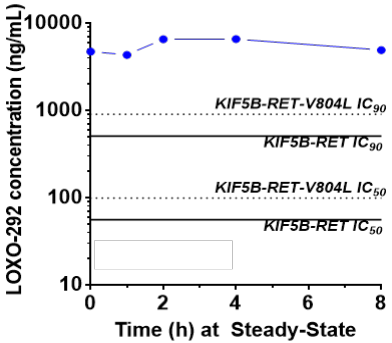
Data cut-off: June 17th, 2019. Images courtesy of A. Drilon.

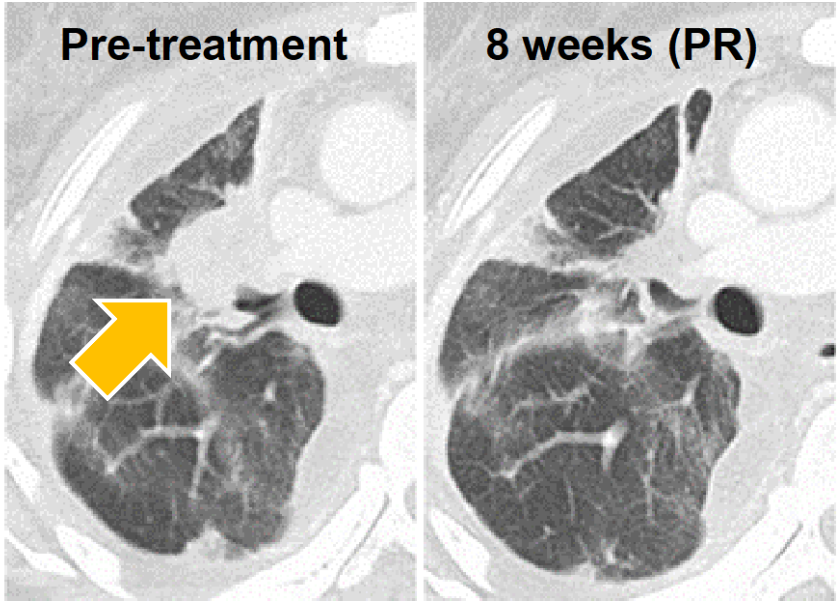
Selpercatinib Overcomes Acquired Gatekeeper Resistance

42-year-old woman with *KIF5B-RET* fusion-positive NSCLC

- 15 prior systemic therapy regimens
  - chemotherapy, immunotherapy, and investigational kinase inhibitors
- Acquired **RET V804L gatekeeper mutation** post-vandetanib therapy

Initiated selpercatinib at 160 mg BID





Decreased shortness of breath
Confirmed PR by RECIST 1.1
Remains on treatment at 11 months

Data cut-off: June 17th, 2019; Wirth et al, JCO Precision Oncology, In Press. Images courtesy of K. Goto.

Conclusions

- **Selpercatinib demonstrated robust and durable anti-tumor activity in *RET* fusion-positive NSCLC**
  - Prior platinum doublet (n=105):
    - ORR 68% (95% CI: 58–76), CNS ORR 91% (95% CI: 59–100)
    - Median DOR 20.3 months (95% CI: 13.8–24.0), median PFS 18.4 months (95% CI: 12.9–24.9)
    - Heavily pre-treated population (median of 3 prior systemic therapies)
  - Treatment-naïve (n=34): ORR 85% (95% CI 69–95), median DOR, PFS not reached
- **Favorable safety profile**
  - Safety database (n= 531):
    - Most AEs low grade and unrelated to selpercatinib
    - Only 1.7% discontinued therapy for treatment-related AEs
- Outcomes consistent with other potent, selective, and CNS-active targeted therapies for genomically-driven lung cancers (e.g. *EGFR*/*ALK*)
- **New Drug Application (NDA) submission planned by the end of 2019**
- **Randomized, global phase 3 trial:** selpercatinib vs. platinum-pemetrexed ± pembrolizumab in treatment-naïve *RET* fusion-positive NSCLC (in the coming months)

Acknowledgements

LIBRETTO-001 patients, their families and caregivers

LIBRETTO-001 investigators and study staff

Array Biopharma, Alturas Analytics