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


## DISCLOSURES

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advisory Boards/Honoraria</td>
<td>Loxo/Bayer/Lilly, Ignyta/Genentech/Roche, Takeda/Ariad/Millenium, TP Therapeutics, AstraZeneca, Pfizer, Blueprint, Helsinn, Beigene, BergenBio, Hengrui, Exelixis, Tyra, Verastem, MORE Health, Abbvie</td>
</tr>
<tr>
<td>Research Funding Paid to Institution</td>
<td>Pfizer, Exelixis, GlaxoSmithKlein, Teva, Taiho, PharmaMar</td>
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<td>CME Honoraria</td>
<td>Medscape, OncLive, PeerVoice, Physicians Education Resources, Targeted Oncology, Research to Practice, Oncology</td>
</tr>
<tr>
<td>Other</td>
<td>Wolters Kluwer (royalties), Merck, Puma, Foundation Medicine (research)</td>
</tr>
</tbody>
</table>
• **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\(^7,8\)

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

Change in tumor size (%)

Survival (%)

Tumor models:
- KIF5B-RET (PDX-NsCLC)
- CCDC6-RET (PDX-CRCA)
- CCDC6-RET-V804M (PDX-CRCA)
- KIF5B-RET (NiH-3T3)
- KIF5B-RET-V804M (NiH-3T3)
- RET C834W (TT cell line-MTC)
- CCDC6-RET (LC-2/ad cell line-NsCLC)

Treatments:
- Vehicle
- LOXO-292 30 mg/kg BID Day 52 → 3 mg/kg BID
- Ponatinib 20 mg/kg QD Day 52 → 2 mg/kg QD

LIBRETTO-001: Selpercatinib in RET-altered cancers

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

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

**Prior platinum chemotherapy**
- n=184
- 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*

**Total Enrolled**
- n=531

**Prior non-platinum chemotherapy**
- n=16

**Other**
- n=25

**Primary endpoint**
- Objective response rate (RECIST 1.1)

**Secondary endpoints**
- Duration of response
- Progression-free survival
- Safety

**Treatment beyond progression permitted with continued benefit**

*PER agreement with FDA, patients with non-measurable disease enrolled during phase 1 dose escalation were eligible for the primary analysis set.

NCT03157128; Data cutoff: June 17th, 2019.
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>PAS (n=105)</th>
<th>Treatment-naive (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n (%)</td>
<td>62 (59) / 43 (41)</td>
<td>22 (56) / 17 (44)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>61 (23‒81)</td>
<td>61 (23‒86)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31 (30)</td>
<td>19 (49)</td>
</tr>
<tr>
<td>1</td>
<td>72 (69)</td>
<td>20 (51)</td>
</tr>
<tr>
<td>2</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Median prior systemic regimens (range)</td>
<td>3 (1‒15)</td>
<td>0</td>
</tr>
<tr>
<td>Prior platinum-based chemotherapy, n (%)</td>
<td>105 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Prior PD-1/PD-L1 inhibitor, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent with platinum-based chemotherapy</td>
<td>58 (55)</td>
<td>-</td>
</tr>
<tr>
<td>Sequential to platinum-based chemotherapy</td>
<td>9 (9)</td>
<td>-</td>
</tr>
<tr>
<td>Prior multikinase inhibitor (MKI), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50 (48)</td>
<td>-</td>
</tr>
<tr>
<td>≥2</td>
<td>37 (35)</td>
<td>-</td>
</tr>
<tr>
<td>Brain metastases, n (%)‡</td>
<td>37 (35)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>104 (99)</td>
<td>39 (100)</td>
</tr>
</tbody>
</table>

**FISH-positive or PCR-positive; ‡Includes patients with non-target CNS metastases.

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)**

<table>
<thead>
<tr>
<th>Best Tumor Response (%)</th>
<th>Prior therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemo</td>
</tr>
<tr>
<td></td>
<td>ICI</td>
</tr>
<tr>
<td></td>
<td>MKI</td>
</tr>
</tbody>
</table>

**Overall (n=105)** | CNS** (n=11)

<table>
<thead>
<tr>
<th>ORR (95% CI)</th>
<th>68% (58%‒76%)*</th>
<th>91% (59%‒100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2%</td>
<td>18%</td>
</tr>
<tr>
<td>PR</td>
<td>66%</td>
<td>73%</td>
</tr>
<tr>
<td>SD</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>PD</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>NE</td>
<td>5%</td>
<td>-</td>
</tr>
</tbody>
</table>

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 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)

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.

ORR (95% CI) 85% (69%–95%)*

- CR 3%
- PR 82%
- SD 9%
- PD 3%
- NE 3%

Best Tumor Response (%)

<table>
<thead>
<tr>
<th>Best Tumor Response (%)</th>
<th>n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>(69%–95%)*</td>
</tr>
<tr>
<td>CR</td>
<td>3%</td>
</tr>
<tr>
<td>PR</td>
<td>82%</td>
</tr>
<tr>
<td>SD</td>
<td>9%</td>
</tr>
<tr>
<td>PD</td>
<td>3%</td>
</tr>
<tr>
<td>NE</td>
<td>3%</td>
</tr>
</tbody>
</table>
Durability of Selpercatinib Efficacy: Primary Analysis Set

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.

- Median DOR: 20.3 months* (95% CI: 13.8–24.0)
- Median PFS: 18.4 months* (95% CI: 12.9–24.9)

Number of events:
- DOR: 16/69
- PFS: 33/105

Median follow-up:
- DOR: 8.0 months
- PFS: 9.6 months
Durability of Selpercatinib Efficacy: Treatment-Naïve

Duration of response

- Median DOR: Not reached (95% CI: 8.3–NE)
- Number of events: 2/22
- Median follow-up: 4.8 months

Progression-free survival

- Median PFS: Not reached (95% CI: 9.2–NE)
- Number of events: 4/34
- Median follow-up: 3.7 months

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**

<table>
<thead>
<tr>
<th></th>
<th>Treatment-emergent AEs (≥15% overall)</th>
<th>Treatment-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>19%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15%</td>
<td>4%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>14%</td>
<td>4%</td>
</tr>
</tbody>
</table>

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

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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

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
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