Registralional results of LIBRETTO-001: A phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET-altered thyroid cancers

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## DISCLOSURES

<table>
<thead>
<tr>
<th>Commercial interest</th>
<th>Relationship(s)</th>
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<tbody>
<tr>
<td>Bayer</td>
<td>Consultant</td>
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<tr>
<td>Cue Biopharma</td>
<td>Consultant</td>
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<tr>
<td>Eisai</td>
<td>Advisory Board, consultant</td>
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<td>Exelixis</td>
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<td>Loxo Oncology</td>
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<tr>
<td>Rakuten Medical</td>
<td>Advisory Board</td>
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</tbody>
</table>
**RET** is activated by two major mechanisms in thyroid cancer

**RET mutations**
- Medullary thyroid cancer
  - Sporadic (>60%)
  - Hereditary (>90%)
  - Activation by ligand-independent dimerization
  - Direct kinase activation
  - Covalent disulfide bonds in cysteine-rich region
  - Kinase domain mutation
  - Common mutation: **RET M918T**

**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%)

**Anti-RET multikinase inhibitors (MKIs): approved for MTC and differentiated thyroid cancers but highly toxic; treatment options after failure of 1st MKI are limited**

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

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-mutant medullary thyroid cancer**
- n=226

**RET fusion-positive thyroid cancer**
- n=27

**RET fusion-positive NSCLC**
- n=253

**Other**
- n=25

**Primary analysis set**
- n=55

**Prior cabozantinib and/or vandetanib**
- n=124

**Cabozantinib/vandetanib-naïve**
- n=88

**Non-measurable disease**
- n=14

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

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

**Treatment beyond progression permitted with continued benefit**

**3 populations to be discussed:**
1. MTC PAS
2. MTC, cabozantinib/vandetanib naïve
3. RET fusion-positive thyroid cancer

*Per agreement with FDA, patients with non-measurable disease enrolled during phase 1 dose escalation were eligible for the primary analysis set.*
Patient characteristics: RET-mutant MTC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PAS (n=55)</th>
<th>Cabo/Vande-Naïve (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n (%)</td>
<td>19 (35) / 36 (65)</td>
<td>30 (34) / 58 (66)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>57 (17–84)</td>
<td>58 (15–82)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (20)</td>
<td>43 (49)</td>
</tr>
<tr>
<td>1</td>
<td>41 (75)</td>
<td>42 (48)</td>
</tr>
<tr>
<td>2</td>
<td>3 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Median prior systemic regimens (range)</td>
<td>2 (1–8)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>Prior cabozantinib and/or vandetanib, n (%)</td>
<td>55 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Cabozantinib only</td>
<td>13 (24)</td>
<td>-</td>
</tr>
<tr>
<td>Vandetanib only</td>
<td>18 (33)</td>
<td>-</td>
</tr>
<tr>
<td>Cabozantinib and vandetanib</td>
<td>24 (44)</td>
<td>-</td>
</tr>
<tr>
<td>Prior multikinase inhibitor (MKI), n (%)</td>
<td>55 (100)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>1</td>
<td>26 (47)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>≥2</td>
<td>29 (53)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Prior non-MKI systemic therapy, n (%)</td>
<td>17 (31)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Brain metastases, n (%)‡</td>
<td>4 (7)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Measurable disease, n (%)</td>
<td>53 (96)</td>
<td>86 (98)</td>
</tr>
</tbody>
</table>

Activity of selpercatinib: \textit{RET}-mutant MTC PAS (n=55)

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.

4 patients not shown in waterfall plot: 2 discontinued prior to any post-baseline imaging assessments, and 2 did not have measurable disease at baseline. *Includes 2 unconfirmed PRs awaiting confirmatory response assessments. Cabo–cabozantinib; NE—not evaluable, n=2 patients who discontinued prior to any post-baseline imaging assessments. Vande–vandetanib.
Activity of selpercatinib: cabozantinib/vandetanib-naïve RET-mutant MTC (n=76)

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.

Data include patients with at least one evaluable post-baseline imaging assessment and those who discontinued therapy prior to any post-baseline imaging assessment. 4 patients not shown in waterfall plot: 2 patients discontinued prior to any post-baseline imaging assessments and 2 did not have measurable disease at baseline. *Includes 9 unconfirmed PRs awaiting confirmatory response assessments. NE—not evaluable, n=2 patients who discontinued prior to any post-baseline imaging assessments.

<table>
<thead>
<tr>
<th>Best Tumor Response (%)</th>
<th>n=76</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1%</td>
<td>59% (47%-70%)*</td>
</tr>
<tr>
<td>PR</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>
Durability of selpercatinib benefit: primary analysis set

- ORR, DOR, PFS similar regardless of prior therapy (e.g. cabozantinib only, vandetanib only, or cabozantinib and vandetanib) or RET mutation status (M918T vs other)
- Of 15 patients in the PAS that progressed, 13 continued treatment post-progression, for 1.0–19.9 months

Data cutoff: June 17, 2019. Shading in PAS Kaplan-Meier curves indicates the 95% confidence band.
Durability of selpercatinib benefit: cabozantinib/vandetanib-naïve

**Duration of response**
- Median DOR: not reached (95% CI: NE–NE)
- Number of events: 0/36
- Median follow-up: 5.5 months

**Progression-free survival**
- Median PFS: not reached (95% CI: NE–NE)
- Number of events: 1/76
- Median follow-up: 5.7 months

Data cutoff: June 17, 2019. No shading to show 95% confidence band due to a very low number of events.
Activity of selpercatinib: biochemical response in MTC PAS

Calcitonin and CEA biochemical response rate (BRR) defined as: normalization (CR); ≥ -50% reduction (PR); between -50% to +50% (SD); ≥ 50% increase (PD); of serum tumor markers for ≥ 4 weeks from baseline. Patients with normal serum tumor markers at baseline are excluded from BRR analysis. NE: patient discontinued treatment prior to determination of CR/PR/SD/PD or biochemical response could not be confirmed at a later time point. Adapted from: Wells, et al. J Clin Oncol. 2012; 30:134–41.
Patient characteristics: RET fusion-positive thyroid cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RET fusion-positive thyroid cancer (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n (%)</td>
<td>13 (48) / 14 (52)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>54 (20–88)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>8 (30) / 16 (59) / 3 (11)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td>21 (78) / 1 (4) / 3 (11) / 2 (7)</td>
</tr>
<tr>
<td>Median prior systemic regimens (range)</td>
<td>3 (1–7)</td>
</tr>
<tr>
<td>Prior radioactive iodine (RAI), n (%)</td>
<td>24 (89)</td>
</tr>
<tr>
<td>Prior systemic therapy other than RAI, n (%)</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Prior lenvatinib and/or sorafenib, n (%)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Brain metastases, n (%)**</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Measurable disease, n (%)</td>
<td>26 (96)</td>
</tr>
</tbody>
</table>

*Includes CCDC186, ERC1, KTN1 and RUFY3 (all 1 each). **Includes patients with non-target CNS metastases.

Data cutoff: June 17, 2019. Total % may be different than the sum of the individual components due to rounding.
Activity of selpercatinib: *RET* fusion-positive thyroid cancer (n=26)

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.

Data include patients with at least one evaluable post-baseline assessment and those who discontinued therapy prior to any post-baseline imaging assessment. 2 patients not shown in waterfall plot: 1 did not have measurable disease at baseline, and 1 deemed not evaluable on study by the investigator. *Includes 2 unconfirmed PRs awaiting confirmatory response assessments. NE—not evaluable, n=1 patient deemed not evaluable on study by the investigator; RAI—radioactive iodine.

- **ORR (95% CI)**
  - CR 0%
  - PR 62%
  - SD 35%
  - PD 0%
  - NE 4%

**Best Tumor Response (%):**
- Papillary
- Hürthle cell
- Poorly differentiated
- Anaplastic

Prior therapy:
- Lenvatinib
- Sorafenib
- Taxane chemo
Durability of selpercatinib benefit: *RET* fusion-positive thyroid cancer

• Of 5 patients that progressed, 5 continued treatment post-progression, for 0.4–8.5+ months

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

**Duration of response**

- Median DOR: not reached (95% CI: 9.5 months–NE)
- Number of events: 2/14
- Median follow-up: 9.3 months

**Progression-free survival**

- Median PFS: not reached (95% CI: 10.0 months–NE)
- Number of events: 5/26
- Median follow-up: 9.9 months
## Selpercatinib safety profile

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Treatment-emergent AE (% overall)</th>
<th>Treatment-related AE (%)</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 toxicity

Data cutoff: June 17, 2019. AE—adverse event. Total % for any given AE may be different than the sum of the individual grades, due to rounding.
Selpercatinib overcomes germline RET V804M gatekeeper mutation

- 56-year-old man with hereditary RET V804M-mutant MTC
- Massive metastatic infiltration of the liver
- 3 prior anti-RET MKIs: cabozantinib, vandetanib, lenvatinib
- Initiated selpercatinib at 80 mg BID with escalation to 160 mg BID
- Rapid reduction in serum CEA and calcitonin, resolution of diarrhea, abdominal distension, and abdominal pain
- Confirmed CR by RECIST 1.1 after 8 weeks of treatment
- Remains on treatment at 20 months

Selpercatinib activity in *CCDC6-RET* fusion-positive anaplastic thyroid cancer

- 73-year-old man with *CCDC6-RET* fusion-positive anaplastic thyroid cancer
- Metastatic disease to lungs and brain*
- Previous surgery, SRS, and docetaxel/doxorubicin
- Initiated selpercatinib at 160 mg BID
- Confirmed PR by RECIST 1.1 after 8 weeks of treatment
- Remains on treatment at 14 months

Data cutoff: June 17, 2019. *All CNS lesions considered non-target due to prior radiation. Red arrow indicates target lesions, D – diaphragm. Dias-Santagata et al, Thyroid, manuscript in review. Images courtesy of L. Wirth.*
Conclusions

• Selpercatinib demonstrated robust and durable anti-tumor activity in RET-mutant MTC and RET fusion-positive thyroid cancer
  – Prior cabozantinib and/or vandetanib MTC (n=55):
    – Heavily pre-treated population (53% with ≥2 MKIs)
    – ORR 56% (95% CI: 42–70)
    – Median DOR not reached (95% CI: 11.1–NE), median PFS not reached (95% CI: 11.3–NE)
    – Significant and stable reductions in calcitonin and CEA in most patients
  – Cabozantinib/vandetanib-naïve MTC (n=76): ORR 59% (95% CI 47–70), median DOR, PFS not reached
  – RET fusion-positive thyroid cancer (n=26): ORR 62% (95% CI 41–80), 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 with selpercatinib after treatment with approved MKIs comparable to outcomes with MKIs when they are used in first line, and less toxic

• New Drug Application (NDA) submission to US FDA planned by the end of 2019

• Randomized, global phase 3 trial: selpercatinib vs. cabozantinib or vandetanib (investigator’s choice) in kinase inhibitor-naïve RET-mutant MTC (in the coming months)
Acknowledgements

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LIBRETTO-001 investigators and study staff

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International Thyroid Oncology Group