Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with RET-Altered Thyroid Cancers: An Update from ASCO 2018


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Disclosures

- Ayala
- Bayer
- Eisai
- Loxo Oncology
- Merck
RET is activated by two major mechanisms in cancer

**RET fusions**
- Non-small cell lung cancer (2%)
  - Papillary and other 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%)

**RET mutations**
- Medullary thyroid cancer
  - Sporadic (>60%)
  - Hereditary (>90%)

**KIF5B** (most common in lung cancer)
**CCDC6 or NCOA4** (most common in thyroid cancer)

LOXO-292 is a potent and selective RET inhibitor

Subbiah et al. Ann Oncol 2018
Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily
LIBRETTO-001: phase I dose escalation and pharmacokinetics

- 82 patients enrolled across 8 dose levels

Eligibility
- Age ≥12 years, ECOG 0–2
- Patients with locally advanced or metastatic solid tumors refractory or intolerant to standard therapy
- Any number of prior therapies
- RET alteration not required initially (‘triggered’ by adequate PK)
- CNS metastases with stable symptoms allowed

Patient plasma exposures exceeded IC₉₀ targets

3 + 3 design
- 28-day cycles
- Intra-patient dose escalation allowed
- Additional enrollment permitted at doses deemed safe

QD = once-daily; BID = twice-daily; PK = pharmacokinetics

Patients enrolled as of April 2, 2018
**RET-altered thyroid cancers**

<table>
<thead>
<tr>
<th>Tumor type, n (%)</th>
<th>Total (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET fusion-positive NSCLC</td>
<td>38 (46%)</td>
</tr>
<tr>
<td>RET fusion-positive thyroid cancer</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>RET fusion-positive pancreatic cancer</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>RET-mutant MTC</td>
<td>29 (35%)</td>
</tr>
<tr>
<td>No known activating RET alteration</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

**RET-altered thyroid cancers**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n (%)</td>
<td>16 (42) / 22 (58)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>55.5 (17-88)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (37)</td>
</tr>
<tr>
<td>1</td>
<td>22 (58)</td>
</tr>
<tr>
<td>2</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
</tr>
<tr>
<td>RET-mutant MTC</td>
<td>29 (76)</td>
</tr>
<tr>
<td>RET fusion-positive thyroid cancer</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Median prior systemic regimens (range)</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>RET-mutant MTC</td>
<td></td>
</tr>
<tr>
<td>Prior cabozantinib or vandetanib</td>
<td>23 (79)</td>
</tr>
<tr>
<td>Prior cabozantinib and vandetanib</td>
<td>13 (45)</td>
</tr>
<tr>
<td>RET fusion-positive thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Prior radioactive iodine (RAI), n (%)</td>
<td></td>
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<tr>
<td>7 (78)</td>
<td></td>
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<tr>
<td>Prior sorafenib or levcitabin, n (%)</td>
<td></td>
</tr>
<tr>
<td>7 (78)</td>
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<tr>
<td>Brain metastases, n (%)</td>
<td>4 (44)</td>
</tr>
</tbody>
</table>

**RET mutations**

- A883F (3.4%)
- D898-E901 del (3.4%)
- D378-G385 del (3.4%)
- M918T (62.1%)
- Extracellular cysteine mutations^2 (10.4%)

**RET fusion partners**

- MTC = medullary thyroid cancer
1. Brain metastasis in RET fusion-positive thyroid cancer
2. Mutations include C618Y, C620R, C630R

Patients enrolled as of April 2, 2018
LOXO-292 safety profile

8 treatment-emergent AEs, regardless of attribution, in ≥10% of patients; most were Grade 1 and judged not related to LOXO-292

<table>
<thead>
<tr>
<th>Treatment-emergent AEs (≥10% overall)</th>
<th>Treatment-related AEs</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All doses and patients, n=82</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>21%</td>
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<tr>
<td>Constipation</td>
<td>17%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>12%</td>
</tr>
<tr>
<td>Cough</td>
<td>11%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
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- Four patients experienced treatment-related AEs ≥ grade 3 (all grade 3): diarrhea, increased ALT/AST, thrombocytopenia (DLT @ 240mg BID), tumor lysis syndrome (DLT @ 240mg BID); all were reversible with dose interruption
- 160mg BID selected as RP2D, with dose exploration ongoing at 200 mg BID to further characterize LOXO-292 safety and efficacy

AE = adverse event; DLT = dose limiting toxicity; ALT = alanine aminotransferase; AST = aspartate aminotransferase; RP2D = recommended phase 2 dose
Note: Total %s for any given AE may be different than the sum of the individual grades, due to rounding. Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.
Efficacy of LOXO-292 in RET-mutant MTC and RET fusion-positive thyroid cancer (RECIST 1.1)

<table>
<thead>
<tr>
<th>RET-mutant MTC</th>
<th>RET fusion-positive thyroid cancer</th>
<th>ORR (95% CI)</th>
<th>Confirmed ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>59% (17/29)</td>
<td>56% (15/27)</td>
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<td>(39–77%)</td>
<td>(35–75%)</td>
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<tr>
<td></td>
<td></td>
<td>78% (7/9)</td>
<td>78% (7/9)</td>
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<tr>
<td></td>
<td></td>
<td>(40–97%)</td>
<td>(40–97%)</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>2</td>
<td>–</td>
<td></td>
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</tbody>
</table>

- All unconfirmed responses at ASCO have since been confirmed
- 17/24 (71%) responding patients responded at patient’s starting dose
- Activity independent of prior therapy
- 1/1 intracranial response (1 PR, pending confirmation) in RET fusion-positive thyroid patient with measurable CNS lesions

![Graph showing best tumor response (%)](image)

- Starting dose:
  - 20 mg QD
  - 80 mg BID
  - 20 mg BID
  - 120 mg BID
  - 40 mg BID
  - 160 mg BID
  - 60 mg BID
  - 240 mg BID

- RET-mutant MTC
- RET fusion-positive thyroid cancer

★ pending confirmation, ★ complete response. Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018. a. Includes 2 patients with non-measurable disease (confirmed CR and SD); b. Includes 1 patient with non-measurable disease (SD); c. Excludes two patients with unconfirmed PRs pending confirmation at time of data cut-off; d. RET-mutant MTC includes 13 confirmed PR, 2 unconfirmed PRs pending confirmation;
Note: The three patients with non-measurable disease are not shown on the waterfall plots.
Duration of LOXO-292 treatment in \textit{RET}-mutant MTC and \textit{RET} fusion-positive thyroid cancer

1. One patient withdrew consent from study treatment while in response.

Substantial decline in MTC tumor markers

Carcinoembryonic antigen (CEA)

Calcitonin

Hereditary *RET* V804M-mutant MTC response to LOXO-292

57 year old man with hereditary MEN2A, advanced MTC, and a germline RET V804M gatekeeper mutation

Progressive disease after cabozantinib, vandetanib, and lenvatinib

- Initiated LOXO-292 at 80 mg BID, escalated to 120 mg BID at C4D1, currently 160 mg BID (escalated at C6D1)

- RECIST CR observed at his first response assessment at C3D1, confirmed at C4D1

- Remains in response and on study in month 9

Follow-up as of July 19, 2018.
CCDC6-RET fusion-positive anaplastic thyroid cancer response to LOXO-292

73 year old man with CCDC6–RET fusion-positive anaplastic thyroid cancer with prior thyroidectomy and bilateral neck dissection, radioactive iodine, SRS, and docetaxel/doxorubicin\(^1\)

Metastasis to lung and brain

- Initiated LOXO-292 at 160 mg BID
- RECIST PR observed at his first response assessment at C3D1, confirmed at C4D1 (maximum tumor reduction –44.8%)
- Remains in response and on study in month 4

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1. Patient was enrolled after April 2, 2018 and not represented in 82 patient interim efficacy and safety analysis data set.
Follow-up as of July 24, 2018.
Conclusions

- LOXO-292 demonstrates robust anti-tumor activity in both \textit{RET}-mutant MTC and \textit{RET} fusion-positive thyroid cancer, with evidence of durability

\textbf{Since ASCO 2018:}

- All unconfirmed responses have been confirmed
- 94\% of MTC responses and 100\% of fusion thyroid cancer responses are ongoing
- Safety and tolerability consistent with highly selective drug design
- LOXO-292 was granted Breakthrough Therapy Designation in September 2018
- LIBRETTO-001 Phase 2 cohorts are currently enrolling:

1. RET Fusion+ Solid Tumors ≥1 Prior SOC
2. RET Fusion+ Solid Tumors Treatment Naive
3. RET-Mutant MTC ≥1 Prior SOC
4. RET-Mutant MTC Treatment Naive
5. RET-Altered Solid Tumors w/o measurable disease
   Other RET-altered tumors
   Other RET alteration cfDNA+ for RET alteration
Acknowledgements

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