LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers


1Memorial Sloan Kettering Cancer Center, New York, NY; 2MD Anderson Cancer Center, Houston, TX; 3Dana-Farber Cancer Institute, Boston, MA; 4Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; 5Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; 6START Midwest, Grand Rapids, MI; 7Institut Gustave Roussy, Villejuif, France; 8Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 9University of Chicago, Chicago, IL; 10City of Hope Comprehensive Cancer Center, Duarte, CA; 11START Madrid CIOCC Hospital Universitario Sanchinarro, Madrid, Spain; 12The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong; 13Peter MacCallum Cancer Centre, East Melbourne, Australia; 14Loxo Oncology, Stamford, CT; 15The Ohio State University Comprehensive Cancer Center, Columbus, OH; 16Massachusetts General Hospital Cancer Center, Boston, MA
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%)

**Kinase Dimerization**

- Activation by ligand-independent dimerization
- Direct kinase activation

**Common mutation:** RET M918T

**KIF5B** (most common in lung cancer)

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

**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 C634W (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

Subbiah et al. Ann Oncol 2018 (accepted manuscript/available online); Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRCA = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily
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)

Key endpoints

- Determine MTD or recommended dose
- Safety/tolerability
- PK
- Overall response rate (RECIST v1.1)
- Duration of response

3 + 3 design

28-day cycles

- Intra-patient dose escalation allowed
- Additional enrollment permitted at doses deemed safe

LIBRETTO-001: phase I dose escalation design

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20 mg QD
n=6

20 mg BID
n=10

40 mg BID
n=16

60 mg BID
n=10

80 mg BID
n=18

120 mg BID
n=4

160 mg BID
n=12

240 mg BID
n=6

QD = once-daily; BID = twice-daily
PK = pharmacokinetics; MTD = maximum tolerated dose
April 2, 2018 data cut-off date
### LIBRETTO-001: patient demographics and molecular features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n (%)</td>
<td>40 (49%) / 42 (51%)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>61 (17–88)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (26%)</td>
</tr>
<tr>
<td>1</td>
<td>58 (71%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
</tr>
<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>Other</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Median prior systemic regimens (range)</td>
<td>3 (1–9)</td>
</tr>
<tr>
<td>≥1 prior multikinase inhibitor (MKI), n (%)(^1)</td>
<td>54 (66%)</td>
</tr>
<tr>
<td>0</td>
<td>28 (34%)</td>
</tr>
<tr>
<td>1</td>
<td>30 (37%)</td>
</tr>
<tr>
<td>≥2</td>
<td>24 (29%)</td>
</tr>
<tr>
<td>Prior chemotherapy regimen, n (%)</td>
<td>38 (46%)</td>
</tr>
<tr>
<td>Prior immunotherapy regimen, n (%)</td>
<td>20 (24%)</td>
</tr>
<tr>
<td>Brain metastases, n (%)</td>
<td>12 (15%)</td>
</tr>
</tbody>
</table>

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**RET fusion partner (n=49)**

- CCDC6 25%
- KIF5B 47%
- NCOA4 10%
- Unknown 6%
- KTN1 2%
- RUFY3 2%
- ERC1 2%
- CLIP1 2%

**RET mutation (n=29)**

- M918T 62%
- 898 del 3%
- C630R/Y 4%
- D378_G385>E 3%
- D631_L633 del 3%
- E632_L633 del 3%
- C630R/Y 4%
- C620F/R/S 4%
- V804M 7%
- M918T 62%

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**NSCLC** = non-small-cell lung cancer; **MTC** = medullary thyroid cancer

1. Cabozantinib, vandetanib, or other MKI; 2. Only found in RET fusion-positive cancers; 3. FISH+

April 2, 2018 data cut-off date
LOXO-292 pharmacokinetics

Patient plasma exposures exceeded IC_{90} targets

- Horizontal lines represent the plasma level at which the unbound LOXO-292 concentration corresponds to IC_{50} or IC_{90} of the indicated target based on cellular assays.

- Concentration of LOXO-292 in plasma (ng/mL)

- Estimated AUC_{0–24} of LOXO-292 in plasma (ng*h/mL)

- AUC_{0–12} with BID dosing was multiplied by 2 to estimate AUC_{0–24}.

- BID = twice-daily; QD = once-daily; AUC = area under the curve.

- April 2, 2018 data cut-off date.

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Cohort Dosing:
- 240 mg BID (Cohort 8, n=5)
- 160 mg BID (Cohort 7, n=12)
- 120 mg BID (Cohort 6, n=4)
- 80 mg BID (Cohort 5, n=17)
- 60 mg BID (Cohort 4, n=10)
- 40 mg BID (Cohort 3, n=16)
- 20 mg BID (Cohort 2, n=9)
- 20 mg QD (Cohort 1, n=5)
## LOXO-292 safety profile

**All doses and patients, n=82**

<table>
<thead>
<tr>
<th></th>
<th>Treatment-emergent AEs (≥10% overall)</th>
<th>Treatment-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Constipation</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>12%</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Most treatment-emergent AEs were Grade 1 in severity
- Two treatment-related AEs ≥grade 3: grade 3 tumor lysis syndrome (DLT), grade 3 increased ALT
- MTD not reached

AE = adverse event; DLT = dose limiting toxicity; ALT = alanine aminotransferase; MTD = maximum tolerated dose. Note: Total %s for any given AE may be different than the sum of the individual grades, due to rounding.

April 2, 2018 data cut-off date.
Clinical activity of LOXO-292 in RET-altered cancers

<table>
<thead>
<tr>
<th></th>
<th>RET fusion-positive cancers</th>
<th>RET-mutant MTC</th>
<th>No known activating RET alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>NSCLC</td>
<td>Other¹</td>
</tr>
<tr>
<td>Enrolled</td>
<td>49</td>
<td>38</td>
<td>11</td>
</tr>
<tr>
<td>Eligible for response evaluation²</td>
<td>39</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Overall Response Rate (95% CI)³</td>
<td>77% (61% – 89%)</td>
<td>77% (58% – 90%)</td>
<td>78% (40% – 97%)</td>
</tr>
<tr>
<td>Confirmed Overall Response Rate³,⁴</td>
<td>74%</td>
<td>74%</td>
<td>71%</td>
</tr>
<tr>
<td>CR</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>uCR⁵</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>25</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>uPR⁵</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>SD</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PD</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Not evaluable⁶</td>
<td>3</td>
<td>3</td>
<td>–</td>
</tr>
</tbody>
</table>

1. Patients eligible for response evaluation include thyroid cancer (n=7), pancreatic cancer (n=2). 2. Excludes patients recently enrolled that remain on treatment, but have not had a first post-baseline response assessment. 3. Response status per RECIST 1.1. Overall response rate = CR+uCR+PR+uPR. Overall response rate, Confirmed overall response rate: all RET fusion-positive (30/39, 25/34), RET fusion-positive NSCLC (23/30, 20/27), RET fusion-positive other (7/9, 5/7), RET-mutant MTC (10/22, 6/18). 4. Excludes patients with unconfirmed CR/PR pending confirmation at time of data cut-off. 5. Unconfirmed responses in patients that remain on treatment awaiting a confirmatory response assessment. 6. Patients that discontinued treatment prior to a first post-baseline response assessment.

NSCLC = non-small-cell lung cancer; MTC = medullary thyroid cancer; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

April 2, 2018 data cut-off date
RET fusion-positive cancers
Efficacy of LOXO-292 in RET fusion-positive cancers

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Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size

April 2, 2018 data cut-off date

Tumor type
- NSCLC
- Thyroid
- Pancreatic

Maximum change in tumor size (%)
Efficacy of LOXO-292 regardless of RET fusion partner

<table>
<thead>
<tr>
<th>RET fusion partner</th>
<th>NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIF5B</td>
<td>13/16 (81%)</td>
</tr>
<tr>
<td>Non-KIF5B</td>
<td>9/11 (82%)</td>
</tr>
</tbody>
</table>

*Denotes patient with 0% maximum change in tumor size
†Fusion partner unknown due to FISH+ detection; April 2, 2018 data cut-off date

Maximum change in tumor size (%)
Efficacy of LOXO-292 regardless of starting dose

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

Maximum change in tumor size (%)

Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size
April 2, 2018 data cut-off date
Efficacy of LOXO-292 regardless of prior therapy

Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size; †Includes alecetinib, cabozantinib, lenvatinib, pazopanib, ponatinib, RXDX-105, sitravatinib, sorafenib, and vandetanib; April 2, 2018 cut-off date
RET-mutant medullary thyroid cancer
Efficacy of LOXO-292 in *RET*-mutant medullary thyroid cancer

Note: Two patients not displayed (one due to treatment discontinuation prior to first post-baseline response assessment; one due to non-measurable disease at baseline (uCR)); †Includes cabozantinib, lenvatinib, pazopanib, RXDX-105, sorafenib, sunitinib, and vandetanib; *CR; April 2, 2018 data cut-off date

Maximum change in tumor size (%)

Prior multikinase inhibitor (MKI) †
- Yes
- No

Prior cabozantinib
Prior vandetanib
Prior other MKI

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Efficacy of LOXO-292 regardless of mutation and starting dose

Maximum change in tumor size (%)

Starting dose

-100
-80
-60
-40
-20
0
20
40

DR = twice-daily; QD = once-daily

Note: Two patients not displayed (one due to LOXO-292 discontinuation prior to first post-baseline response assessment; one due to non-measurable disease at baseline (uCR)); *CR April 2, 2018 data cut-off date
Substantial decline in MTC tumor markers

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Carcinoembryonic antigen (CEA)

Calcitonin

MTC = medullary thyroid cancer
April 2, 2018 data cut-off date
Duration of LOXO-292 therapy

44/49 (90%) of patients with RET fusion-positive cancers remain on therapy

27/29 (93%) of patients with RET-mutant medullary thyroid cancer remain on therapy

NSCLC = non-small cell lung cancer; MTC = medullary thyroid cancer
April 2, 2018 data cut-off date
Duration of LOXO-292 therapy in patients with brain metastases

NSCLC = non-small cell lung cancer

1. Initiated treatment at 120 mg BID; dose escalated at C5D1 to 160 mg BID; on study in month 4
2. Derived based on investigator assessments of brain metastases per RECIST 1.1

Brain metastases only observed in RET fusion-positive cancers; April 2, 2018 data cut-off date

3/3 intracranial responses in patients with intracranial target lesions

CLIP1-RET fusion-positive NSCLC previously received two multikinase inhibitors and chemotherapy

Presence of brain metastases
- Yes
- No
- First response
- Still on treatment

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PRESENTED AT: 2018 ASCO ANNUAL MEETING
PRESENTED BY: Dr. Alexander Drilon

Baseline
Week 4

19
52 year old man with KIF5B–RET fusion-positive non-small cell lung cancer who refused platinum doublet chemotherapy

- Initiated LOXO-292 at 80 mg BID, currently 160 mg BID (escalated at C4D1)
- Rapid improvement in shortness of breath and cough within a few days
- RECIST PR observed at his first response assessment at C2D1, confirmed at C3D1 (maximum tumor reduction –67%)
- Remains in response and on study in month 4
61 year old man with NCOA4–RET fusion-positive metastatic poorly differentiated thyroid cancer; developed progressive disease after lenvatinib

- Initiated LOXO-292 at 60 mg BID, currently 80 mg BID (escalated at C4D1)
- Shortness of breath, chest pain requiring opiates, fatigue & anorexia present at baseline significantly better by day 8, at which point he had stopped opiates and felt well enough to return to work
- RECIST PR observed at his first response assessment at C3D1, confirmed at C5D1 (maximum tumor reduction –72%)
- Remains in response and on study in month 7

BID = twice-daily; PR = partial response

Courtesy of Dr. Lori Wirth, Massachusetts General Hospital; April 2, 2018 data cut-off date

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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 6

Tumor marker decreases
• **LOXO-292 demonstrates robust anti-tumor activity across \textit{RET}-altered cancers**
  – 77% overall response rate in \textit{RET} fusion-positive cancers, with intracranial activity
  – 45% overall response rate in \textit{RET}-mutant medullary thyroid cancer
  – 71/78 (91%) of \textit{RET}-altered patients remain on therapy, including all responding patients

• **Activity independent of \textit{RET} fusion partner, \textit{RET} mutation, or prior therapy**
  – Heavily pretreated phase 1 population (66% of patients with prior multikinase inhibitor exposure)
  – Responses observed with \textit{RET} V804M gatekeeper (causes resistance to multikinase inhibitors)

• **Safety and tolerability profile consistent with highly selective drug design**
  – No evidence of off-target liabilities
  – Maximum tolerated dose not reached

• **LIBRETTO-001 expansion cohorts are open and enrolling, for patients with \textit{RET} fusion-positive solid tumors, medullary thyroid cancer, and other cancers with \textit{RET} activation**
Acknowledgements

**United States**
- City of Hope, CA
- UCSD, CA
- Sarah Cannon, CO
- University of Chicago, IL
- MGH and DFCI, MA
- START Midwest, MI
- Memorial Sloan Kettering, NY
- Cleveland Clinic, OH
- Ohio State, OH
- Sarah Cannon, TN
- MDACC, TX

**Europe**
- Gustave Roussy, France
- START Madrid CIO, Spain
- START Madrid FJD, Spain
- Hospital Universitario Vall d’Hebron, Spain
- Luzerner General Hospital, Switzerland

**Asia Pacific**
- Peter MacCallum Cancer Institute, Australia
- Royal North Shore Hospital, Australia
- Prince of Wales Hospital, Hong Kong
- National Cancer Centre, Singapore
- Samsung, South Korea

**With thanks to**
- LOXO-292 patients, families, and caregivers
- LOXO-292 Phase 1 investigators and research staff
- International Thyroid Oncology Group (ITOG)
- Alturas Analytics
- Array BioPharma
- Loxo Oncology

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Sunday June 3, 2018
8-11:30am CT poster session
Abstract 9048

“Detection and clearance of RET variants in plasma cell free DNA (cfDNA) from patients (pts) treated with LOXO-292.”