Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with RET Fusion+ Non-Small Cell Lung Cancer
An Update from ASCO 2018


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Disclosures

Honoraria/Consulting

• AstraZeneca
• DropWorks
• Inivata
• Loxo Oncology
• Sysmex
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%)

**Activation by ligand-independent dimerization**
- Covalent disulfide bonds in cysteine-rich region

**Direct kinase activation**
- Kinase domain mutation

**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

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

240 mg BID
n=6
160 mg BID
n=12
120 mg BID
n=4
80 mg BID
n=18
60 mg BID
n=10
40 mg BID
n=16
20 mg BID
n=10
20 mg QD
n=6

3 + 3 design

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

Patients enrolled as of April 2, 2018
### RET-altered 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>
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</table>

### RET-fusion positive NSCLC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / Male, n (%)</td>
<td>22 (58) / 16 (42)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>62.5 (36–80)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (16)</td>
</tr>
<tr>
<td>1</td>
<td>32 (84)</td>
</tr>
<tr>
<td>Median prior systemic regimens (range)</td>
<td>3 (1–9)</td>
</tr>
<tr>
<td>Prior multikinase inhibitor (MKI), n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (45)</td>
</tr>
<tr>
<td>≥1</td>
<td>21 (55)</td>
</tr>
<tr>
<td>Prior chemotherapy or immunotherapy, n (%)</td>
<td>33 (87)</td>
</tr>
<tr>
<td>Prior chemotherapy and immunotherapy, n (%)</td>
<td>15 (39)</td>
</tr>
<tr>
<td>Brain metastases, n (%)</td>
<td>8 (21)</td>
</tr>
</tbody>
</table>

**NSCLC** = non-small-cell lung cancer; **MTC** = medullary thyroid cancer;  
1 All 38 NSCLC pts have a RET fusion/rearrangement;  
2 FISH+;  
3 cabozantinib, vandetanib, or other MKI  
Patients enrolled as of April 2, 2018  

**RET fusion partner**

- **KIF5B** (60.6%)  
- **CCDC6** (26.3%)  
- **CLIP1** (2.6%)  
- **NCOA4** (2.6%)  
- Unknown (7.9%)
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>All doses and patients, n=82</th>
</tr>
</thead>
<tbody>
<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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<thead>
<tr>
<th>Treatment-related AEs</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>–</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>–</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
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</tr>
<tr>
<td>Headache</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>–</td>
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</tbody>
</table>

- 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
Efficacy of LOXO-292 in RET fusion-positive NSCLC (RECIST 1.1)

| ORR (95% CI) | 68% (n=26/38) (51–83%) |
| Confirmed ORR* (95% CI) | 68% (n=25/37) (50–82%) |
| CR | – |
| PR** | 26 |
| SD | 8 |
| PD | 2 |
| NE | 2 |

- All unconfirmed responses reported at ASCO have since been confirmed
- RECIST 1.1 responses were seen at all starting dose levels, prior to any intrapatient dose escalation, and in 18/26 (69%) responding patients at each patient’s starting dose
- Activity independent of prior therapy
- 4/4 confirmed intracranial responses (1 CR, 3 PR) in patients with measurable CNS lesions

ORR (95% CI): 68% (n=26/38) (51–83%)
Confirmed ORR* (95% CI): 68% (n=25/37) (50–82%)
CR: –
PR**: 26
SD: 8
PD: 2
NE: 2

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

Note: *Excludes one patient with unconfirmed PR pending confirmation at time of data cut-off; **25 confirmed PR, 1 unconfirmed PR pending confirmation NSCLC patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.
Duration of LOXO-292 treatment in RET fusion-positive NSCLC

- 24/38 (63%) escalated to/treated with 160 mg BID (RP2D)
- 25/26 (96%) responding patients remain on therapy
- 24/26 (92%) responses ongoing, 17 responses ≥6 months

Median follow up: 8.5 (0.3–14.1) months, 9.5 (4.4–14.1) months for responding patients

37 of 38 patients had plasma samples at screening.

27 samples had a detectable RET fusion.

22 samples with a detectable RET fusion had a subsequent C1D15 sample.

17/22 (77%) patients had >90% decrease in RET AF by C1D15.

20/22 (91%) patients had >90% decrease in RET AF by C5D1.

**CLIP1-RET** fusion-positive NSCLC response to LOXO-292

50 year old woman with **CLIP1-RET** fusion-positive non-small cell lung cancer with prior cabozantinib, cisplatin/pemetrexed/bevacizumab and RXDX-105

- New brain lesions after last prior treatment (no prior brain radiation)
- Initiated LOXO-292 at 120 mg BID, currently 160 mg BID (escalated at C5D1)
- RECIST PR observed at her first response assessment at C2D1, confirmed at C3D1 (maximum tumor reduction –63%)
- Intracranial CR observed at her first response assessment at C2D1, confirmed at C3D1
- Remains in response and on study in month 8

Courtesy of Dr. Alexander Drilon. Follow-up as of July 19, 2018.
**KIF5B-RET** fusion-positive NSCLC response to LOXO-292

43 year old woman with *KIF5B–RET* fusion-positive non-small cell lung cancer with prior cisplatin/pemetrexed, docetaxel, and vinorelbine

- Progressed in the lung, mediastinum and brain, no prior brain radiation
- Initiated LOXO-292 at 160 mg BID
- RECIST PR at C3D1, confirmed at C5D1 (maximum tumor reduction –56%)
- Intracranial confirmed PR observed at her first response assessment at C3D1, confirmed at C5D1
- Remains in response and on study in month 5

Conclusions

• LOXO-292 demonstrates robust anti-tumor activity in RET-fusion positive NSCLC, with evidence of durability

Since ASCO 2018:

• All unconfirmed responses have been confirmed
• 92% of responses are ongoing, majority of these ongoing for ≥6 months
• Anti-tumor activity in the CNS
• 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 cfDNA+ for RET alteration
Acknowledgements

• LOXO-292 patients, their families and caregivers
• LOXO-292 investigators and study staff
• Array Biopharma, Alturas Analytics