The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers


1Memorial Sloan Kettering Cancer Center, New York, NY; 2University of Texas Southwestern, Dallas, TX; 3Stanford University School of Medicine, Palo Alto, CA; 4Dana-Farber Cancer Institute/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; 5Massachusetts General Hospital, Boston, MA; 6St. Jude Children’s Research Hospital, Memphis, TN; 7Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; 8Fox Chase Cancer Center, Philadelphia, PA; 9Rigshospitalet, Copenhagen, Denmark; 10UH Cleveland Medical Center, Cleveland, OH; 11Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; 12START Madrid CIOCC, Hospital HM Universitario Sanchinarro, Madrid, Spain; 13Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 14Nemour's Children's Hospital, Orlando, FL; 15Lixo Oncology, Inc., San Francisco, CA; 16Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; 17The University of Texas MD Anderson Cancer Center, Houston, TX
Role of TRK in normal biology and cancer

Neurotrophin family of receptors

**TRKA (NTRK1)**  ➔  Pain, thermoregulation

**TRKB (NTRK2)**  ➔  Movement, memory, mood, appetite, body weight

**TRKC (NTRK3)**  ➔  Proprioception

**TRK fusions**

- Ligand binding domain (LBD) replaced by 5’ fusion partner
- Drives overexpression and ligand-independent activation

TRK uncommonly expressed in normal tissues or cancer

Fusion drives abnormally high expression and activation of TRK kinase domain
TRK fusions found in diverse cancer histologies

- Brain cancers (glioma, GBM, astrocytoma)
- Salivary (MASC)
- Thyroid cancer
- Lung cancer
- Secretory breast cancer
- Pancreatic Cholangiocarcinoma
- GIST
- Colon
- Melanoma
- Sarcoma (multiple)

- Gliomas
- Thyroid cancer
- Infantile fibrosarcoma
- Congenital nephroma
- Spitz nevi
- Sarcoma (multiple)

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

- Common cancer with low TRK fusion frequency
- Rare cancer with high TRK fusion frequency
Detecting TRK fusions

- Several modalities:
  - DNA & RNA NGS, FISH, IHC
- Large NTRK introns (compared to ALK, ROS1, RET) make DNA-based detection challenging
- Loxo/Ventana developing Pan-TRK IHC companion diagnostic (CDx)
- NGS “universal” CDx tests under FDA review include TRK fusion detection*

*FoundationOne, Oncomine Universal Dx

More info: www.TRKtesting.com

Pan-TRK IHC detects expression, shared among TRK fusions
Larotrectinib

- Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC
  - 5–11 nM IC$_{50}$ in cellular assays
- Highly selective
- Development timeline
  - March 2015: 1$^{st}$ TRK-fusion patient treated
  - July 2016: breakthrough therapy designation
  - February 2017: pivotal enrollment complete
Larotrectinib TRK fusion development program

**Adult phase I**
- Age ≥18 years
- Advanced solid tumors

**SCOUT: pediatric phase I/II**
- Age ≤21 years
- Advanced solid tumors

**NAVIGATE: adult/adolescent phase II ‘basket’ trial**
- Age ≥12 years
- Advanced solid tumors
- TRK fusion positive

N=55 TRK fusion patients

- **TRK fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (ORR)
  - RECIST v1.1 per investigator assessment
- **Secondary endpoints**
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cut-off: April 14, 2017
## Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (47)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>45.0 (0.3–76.0)</td>
</tr>
<tr>
<td><strong>Age group, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>6 (11)</td>
</tr>
<tr>
<td>2–6 years</td>
<td>5 (9)</td>
</tr>
<tr>
<td>6–15 years</td>
<td>1 (2)</td>
</tr>
<tr>
<td>15–39 years</td>
<td>12 (22)</td>
</tr>
<tr>
<td>≥40 years</td>
<td>31 (56)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 (49)</td>
</tr>
<tr>
<td>1</td>
<td>22 (40)</td>
</tr>
<tr>
<td>2</td>
<td>6 (11)</td>
</tr>
<tr>
<td><strong>No. of prior systemic chemotherapies, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>30 (55)</td>
</tr>
<tr>
<td>2</td>
<td>8 (15)</td>
</tr>
<tr>
<td>≥3</td>
<td>17 (31)</td>
</tr>
<tr>
<td><strong>CNS metastases, n (%)</strong></td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Diversity of cancers treated - 17 unique types

- Infantile fibrosarcoma (IFS) 13%
- Salivary gland 22%
- Thyroid 9%
- Melanoma 7%
- Lung 7%
- Colon 7%
- GIST 5%
- Spindle cell sarcoma 5%
- Cholangiocarcinoma 4%
- Myopericytoma 4%
- Sarcoma, NOS 4%
- Appendix 2%
- Breast 2%
- Pancreatic myofibromatosis 2%
- Inflammatory myofibroblastic kidney tumor 2%
- Infantile myofibromatosis 2%
- Peripheral nerve sheath tumor 4%

Presented at: ASCO Annual Meeting '17
#ASCO17
Hyman, LBA2501
Clinical activity of larotrectinib in patients with TRK fusion cancers

*Includes unconfirmed responses with confirmatory scans pending (4 PR, 1 CR). All remain in response and ongoing on study.

<table>
<thead>
<tr>
<th>Objective response rate (95% CI)</th>
<th>Enrolled patients with confirmatory response data available (n=50)</th>
<th>All enrolled patients (n=55)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate</strong></td>
<td>76% (62–87%)</td>
<td>78% (65–88%)</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>64%</td>
<td>65%*</td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
<td>12%</td>
<td>13%*</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>12%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Includes unconfirmed responses with confirmatory scans pending (4 PR, 1 CR). All remain in response and ongoing on study.
Efficacy of larotrectinib in TRK fusion cancers

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

<table>
<thead>
<tr>
<th>Objective response rate (95% CI)</th>
<th>76% (62–87%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>64%</td>
</tr>
<tr>
<td>Complete response</td>
<td>12%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12%</td>
</tr>
</tbody>
</table>

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of age

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of tumor type

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; *Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of NTRK gene

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of fusion partner

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
93% of responding patients and 75% of all patients remain on treatment or underwent surgery with curative intent.

No progressions in central nervous system observed.
Median duration of response not reached

In patients with confirmed complete or partial response (n=38)

N=38  3/38  2/17  0/7  0/3  0/0

Months from start of response

N=38

0.00  0.25  0.50  0.75  1.00

Probability

Median follow-up 5.8 months
Median progression-free survival not reached

In primary analysis population (n=55)

Median follow-up 7.7 months
**SQSTM1-NTRK1 lung cancer patient**

Baseline

Cycle 4

45F NSCLC & paraneoplastic hypertrophic ostearthropathy

Prior therapy: platinum/pemetrexed

Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms
ETV6-NTRK3 infantile fibrosarcoma patient

2F infantile fibrosarcoma

2 cycles of vincristine/actinomycin-D/cyclophosphamide → progression → leg amputation was only alternative option

4 cycles larotrectinib → referred for surgery

Pathologic complete response with clear margins

No functional deficit post-surgery
ETV6-NTRK3 secretory breast cancer patient

Baseline  
Day 6  
Day 20

14F, prior therapy: 4 lines of chemotherapy and repeated resections  
Treated with larotrectinib under expanded access

Courtesy of N. Shukla, Memorial Sloan Kettering
## Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Treatment-emergent AEs (%)*</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>15</td>
<td>18</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Increased AST</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

7 (13%) patients required dose reductions – all maintained tumor regression (1 CR, 5 PR, 1 SD) on reduced dose. No discontinuations for adverse events.

Entire safety database (n=125)

*TEAEs shown as reported by ≥15% of patients
LOXO-195 to Address TRK Acquired Resistance

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Fusion</th>
<th>Resistance mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Colorectal</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>NSCLC</td>
<td>TPR-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>IFS</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R</td>
</tr>
<tr>
<td>Cholangio</td>
<td>LMNA-NTRK1</td>
<td>TRKA F589L* + GNAS Q227H</td>
</tr>
</tbody>
</table>

TRK solvent front mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.
Larotrectinib conclusions

• Consistent and durable antitumor activity in TRK fusion cancers
  – ORR: 76% (12% CRs)
  – 6-month landmark DOR: 91%
  – Minimal side effects for patients

• Notable elements of larotrectinib program
  – Potentially the first new targeted therapy developed in a tissue type-agnostic manner
  – First new targeted therapy developed simultaneously in adults and pediatrics
  – Rapid path from first patient to last patient enrolled (24 months)
  – New Drug Application (NDA) to be submitted in late 2017 or early 2018
  – Real-time elucidation of convergent acquired resistance mechanism and treatment with LOXO-195

• For patients with TRK fusion cancer, larotrectinib may offer a potential new standard of care
  – Routine pan-cancer screening will be important to identify these patients, as well as those with other tumor-agnostic biomarkers (MSI-H)
Acknowledgements

• Patients and their families, many of whom traveled long distances to participate in these studies

• National Institutes of Health P30 CA008748

• Marie-Josée and Henry R. Kravis Center for Molecular Oncology