ESMO ADVANCED COURSE ON NTRK GENE FUSION:
Acquired resistance to NTRK inhibitors

Ulrik Lassen, Professor, MD, PHD.
Lyon, 13-14 September 2019
DISCLOSURE OF INTEREST

Advisory boards and honorarium: Bayer and Pfizer
Grants: none
Stocks: none
Others: none
Active Clinical Trials of TRK Inhibitors in Patients With NTRK Fusion Tumors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Kinase Targets</th>
<th>Phase</th>
<th>NTRK Fusion Tumor Type</th>
<th>Start Date</th>
<th>Status</th>
<th>Estimated Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larotrectinib</td>
<td>TRKA, TRKB, TRKC</td>
<td>I</td>
<td>Advanced solid tumors</td>
<td>May 2014</td>
<td>Recruiting</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>Advanced solid tumors</td>
<td>October 2015</td>
<td>Recruiting</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I/II</td>
<td>Advanced solid or primary CNS tumors (pediatric)</td>
<td>December 2015</td>
<td>Recruiting</td>
<td>92</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>TRKA, TRKB, TRKC, ALK, ROS1</td>
<td>I</td>
<td>Locally advanced or metastatic solid tumors[a]</td>
<td>June 2014</td>
<td>Recruiting</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>Locally advanced or metastatic solid tumors[a]</td>
<td>October 2015</td>
<td>Recruiting</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I/Ib</td>
<td>Recurrent or refractory solid tumors and primary CNS tumors (pediatric)</td>
<td>December 2015</td>
<td>Recruiting</td>
<td>190</td>
</tr>
<tr>
<td>DS-6051b</td>
<td>TRKA, TRKB, TRKC, ROS1</td>
<td>I</td>
<td>Advanced solid tumors[b]</td>
<td>September 2014</td>
<td>Not recruiting</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>Advanced solid tumors (Japanese patients)</td>
<td>February 2016</td>
<td>Not recruiting</td>
<td>15</td>
</tr>
<tr>
<td>TSR-011</td>
<td>TRKA, TRKB, TRKC, ALK</td>
<td>I/Ia</td>
<td>Advanced solid tumors and lymphomas[c]</td>
<td>October 2012</td>
<td>Unknown</td>
<td>72</td>
</tr>
<tr>
<td>TPX-0005[d]</td>
<td>TRKA, TRKB, TRKC, ALK, ROS1</td>
<td>I/Ii</td>
<td>Locally advanced or metastatic solid tumor (including non-Hodgkin lymphoma)[a]</td>
<td>February 2017</td>
<td>Recruiting</td>
<td>450</td>
</tr>
<tr>
<td>LOXO-195[d]</td>
<td>TRKA, TRKB, TRKC</td>
<td>I/Ii</td>
<td>Advanced solid tumor progressing after prior TRK inhibitor treatment</td>
<td>July 2017</td>
<td>Recruiting</td>
<td>93</td>
</tr>
</tbody>
</table>

- a. ClinicalTrials.gov;
- b. inclusion of patients with ROS1 gene rearrangements permitted;
- c. inclusion of patients with ALK gene rearrangements permitted;
- d. second-generation TRK inhibitor with activity against TRK proteins with resistance mutations.
Integrated efficacy and safety analysis of entrectinib: 
*NTRK* fusion-positive solid tumours

**Integrated analysis**

**Efficacy population**
54 adult patients with *NTRK* fusion-positive, TRK inhibitor-naive solid tumours

**Safety population**
355 patients overall have received entrectinib (all tumour types and gene rearrangements)

**STARTRK-2**
Phase II, multicentre, global basket study 600mg QD, 28-day cycle
n=51 *NTRK*+ patients

**STARTRK-1**
Phase I dose escalation
n=2 *NTRK*+ patients

**ALKA-372-001**
Phase I dose escalation
n=1 *NTRK*+ patient

**Primary endpoints**
- ORR and DoR

**Secondary endpoints**
- PFS and OS
- Intracranial ORR
- Safety and tolerability

Data cut-off at 31 May 2018
Demetri G et al. Presented at ESMO 2018
Baseline characteristics: Adult patients with NTRK fusion-positive solid tumours

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>NTRK+ patients (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>57.5 (21–83)</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>59.3</td>
</tr>
<tr>
<td>Male</td>
<td>40.7</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79.6</td>
</tr>
<tr>
<td>Asian</td>
<td>13.0</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42.6</td>
</tr>
<tr>
<td>1</td>
<td>46.3</td>
</tr>
<tr>
<td>2</td>
<td>11.1</td>
</tr>
<tr>
<td>Prior lines of systemic therapy, %</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37.0</td>
</tr>
<tr>
<td>1</td>
<td>20.4</td>
</tr>
<tr>
<td>≥2</td>
<td>42.6</td>
</tr>
<tr>
<td>CNS mets at baseline, %</td>
<td>22.2</td>
</tr>
</tbody>
</table>
Entrectinib activity in NTRK fusion-positive solid tumours: individual patient responses by tumour type

<table>
<thead>
<tr>
<th></th>
<th>NTRK+ patients (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>57.4% (43.2–70.8)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Non-CR/PD, missing or unevaluable</td>
<td>10 (18.5)</td>
</tr>
</tbody>
</table>

Results per Blinded Independent Central Review (BICR)

Cut-off date: 31 May 2018

Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot. CI: confidence interval; CRC: colorectal cancer; MASC: mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer.
Entrectinib activity in \textit{NTRK} fusion-positive solid tumours: Individual patient responses by type of \textit{NTRK} gene

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
 & \textbf{NTRK1 (n=22)} & \textbf{NTRK2 (n=1)} & \textbf{NTRK3 (n=31)} \\
\hline
\textbf{ORR (95\% CI)} & 59.1\% (36.3–79.3) & 0\% & 58.1\% (39.1–75.5) \\
\hline
\end{tabular}
\end{table}

\textbf{Results per Blinded Independent Central Review (BICR)}

- \textbf{NTRK1}
- \textbf{NTRK2}
- \textbf{NTRK3}

\textit{Cut-off date: 31 May 2018}

\textit{Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot}

\textit{CI: confidence interval; CRC: colorectal cancer; MASC: mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer}
Entrectinib activity in NTRK fusion-positive solid tumours: Duration of response, PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>DoR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients included in</td>
<td>31</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>analysis, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with event, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD, n</td>
<td>13</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Death, n</td>
<td>3</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Median time to event</td>
<td>10.4</td>
<td>11.2</td>
<td>20.9</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI for median</td>
<td>7.1–NE</td>
<td>8.0–14.9</td>
<td>14.9–NE</td>
</tr>
</tbody>
</table>

Median duration of survival follow-up (PFS, OS): 12.9 months
Median duration of response follow-up (DoR): 13.1 months

Demetri G et al. Presented at ESMO 2018
Larotrectinib
Secondary Efficacy Endpoints (Investigator Assessed)

At median follow-up of 17.2 months, median duration of response was not reached.
At median follow-up of 13.6 months, median progression-free survival was 25.8 months and median overall survival was not reached.


Hong DS, et al. ASCO 2019; abstract 3122
Larotrectinib: Duration of Treatment

Data cut-off: July 30, 2018. Circles denote category of first response, per investigator assessment.

Hong DS, et al. ASCO 2019; abstract 3122
NTRK RESISTANCE

- The TRK family includes TRKA, TRKB, and TRKC proteins encoded by the genes \textit{NTRK1}, \textit{NTRK2}, and \textit{NTRK3}, respectively
- Oncogenic TRK fusions that lead to constitutive activation of TRK signaling have been identified in many solid malignancies in both adults and children \(^1\)
- 1st generation TRK inhibitors including Larotrectinib and entrectinib have demonstrated clinical benefit in patients with solid malignancies harboring oncogenic \textit{NTRK} fusions \(^2,3,4,5\)
- Solvent front mutation, gatekeeper mutation, and glycine mutation of DFG at the beginning of the A-loop have been reported in clinical trials from larotrectinib-and entrectinib-refractory patients \(^2,3,4,5\)
- Both Loxo-195 and Repotrectinib was designed to systematically overcome resistant mutations

## On-Target Resistance to First-Generation TRK Inhibitors

<table>
<thead>
<tr>
<th>TRK Inhibitor</th>
<th>Tumor type</th>
<th>Gene fusion</th>
<th>Resistance mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrectinib</td>
<td>Colorectal</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R, G667C</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Colorectal</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R, F589L</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Colorectal</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Pancreas</td>
<td>CTRC-NTRK1</td>
<td>TRKA A608D</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Colangio carcinoma</td>
<td>LMNA-NTRK1</td>
<td>TRKA F589L</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>NSCLC</td>
<td>TPR-NTRK1</td>
<td>TRKA G595R, G667C</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Soft tissue sarcoma</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Thyroid</td>
<td>IRF2BP2-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>MASC</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R, G623E</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>IFS</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>GIST</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R, G696A</td>
</tr>
</tbody>
</table>

Can We Sequence TRK Inhibitors to Address Resistance?

First-generation drug

Larotrectinib
Entrectinib

Next-generation drug
TRK Resistance Mutations Are Paralogous to Other Mutations that Mediate Resistance in ALK/ROS1

Second-Generation TRK Inhibitors Are in Testing

First generation TRK inhibitors

- Larotrectinib
  - MW 428.44

- Entrectinib
  - MW 560.65

Next generation TRK inhibitors

- Repotrectinib
  - MW 355.37

- LOXO-195
  - MW 380.43
Second-Generation TRK Inhibitors are in Development

First-generation drug
- Larotrectinib
- Entrectinib

Next-generation drug
- LOXO-195
- Repotrectinib

Phase I and Expanded Access Experience of LOXO-195 (BAY 2731954), a Selective Next-Generation TRK Inhibitor

David M. Hyman, Shivaani Kummar, Anna F. Farago, Birgit Georger, Morten Mau-Sorensen, Matthew Taylor, Elena Garralda, Ramamoorthy Nagasubramanian, Michael Nathenson, Lucy Song, Michael Capra, Mette Jorgensen, Alan Ho, Neerav Shukla, Steve Smith, Xin Huang, Brian Tuch, Nora Ku, Theodore W. Laetsch, Alexander Drilon, and David S. Hong

1. Memorial Sloan Kettering Cancer Center, New York, NY; 2. Stanford Cancer Center, Stanford University, Palo Alto, CA; 3. Massachusetts General Hospital, Boston, MA; 4. Gustave Roussy Cancer Center, Villejuif, France; 5. The Finsen Center Rigshospitalet, Copenhagen, Denmark; 6. Oregon Health & Science University; 7. Vall D’Hebron, Barcelona, Spain; 8. Nemours Children’s Hospital, Orlando, FL; 9. Dana-Farber Cancer Institute, Boston, MA; 10. Kaiser Permanente Medical Center, Santa Clara, CA; 11. Our Lady’s Children’s Hospital, Dublin, Ireland; 12. Great Ormond Street Hospital for Children NHS Trust, London, UK; 13. Loxo Oncology, South San Francisco, CA; 14. University of Texas Southwestern Medical Center/Children’s Health, Dallas, TX; 15. MD Anderson Cancer Center, Houston, TX, USA

Presented at AACR Annual Meeting 2019, March 29-April 3, Atlanta, GA.
On-target resistance to TRK inhibitors

Acquired TRK kinase domain mutations in 3 recurrent motifs result in on-target resistance to current generation of inhibitors

Hyman D, et al. AACR 2019
LOXO-195 (BAY 2731954)

- Potent second-generation inhibitor of all 3 TRK tyrosine kinases with IC$_{50}$ <5 nM
- Selective: >1000x more selective for TRK over 98% of 226 non-TRK kinases
- Activity against acquired solvent front, xDFG, gatekeeper, and TRK mutations demonstrated in enzyme- and cell-based assays and in vivo tumor models
- Excellent drug properties: orally dosed, high exposure
# Phase I and SPP design and eligibility

**LOXO-EXT-17005 (Phase 1)**  
**NCT03215511**

- Eligible patients:
  - ≥1 month old
  - Advanced TRK fusion solid tumor: 1) **progressed** on prior TRK inhibitor, or 2) **intolerant** to prior TRK inhibitor
- Parallel 3+3 dose escalation for:
  - Children (<12 years old)
  - Adolescents & adults (≥12 years old)
- Dose cohorts: 50mg QD to 150mg BID

**Single patient protocols (SPPs)**  
**NCT03206931**

- Eligibility similar to Phase 1 but patient unable to enroll due to:
  - Medical comorbidity
  - Logistical barriers
- Starting dose:
  - Children: 20mg BID
  - Adolescents & adults: 50-150 mg BID
- Intra-patient dose escalation guided by PK and clinical assessment
## Combined patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (71)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (30)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>37 (1.25–72)</td>
</tr>
<tr>
<td>Pediatric (≤18), n (%)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Adult (&gt;18), n (%)</td>
<td>24 (77)</td>
</tr>
<tr>
<td><strong>Prior TKI, n (%)</strong></td>
<td>31 (100)</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>21 (69)</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>9 (28)</td>
</tr>
<tr>
<td>PLX7486</td>
<td>1 (3)</td>
</tr>
<tr>
<td><em><em>Median duration</em> of prior TRK TKI, months (range)</em>*</td>
<td>11 (2-30)</td>
</tr>
<tr>
<td><strong>TRK fusion, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>NTRK1</td>
<td>15 (48)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>15 (48)</td>
</tr>
<tr>
<td><strong>Enrollment, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>20 (65%)</td>
</tr>
<tr>
<td>CRP</td>
<td>11 (35%)</td>
</tr>
</tbody>
</table>

*Calculation excludes 3 patients who received >1 TKI

![Tumor types diagram](graph.png)

Hyman D, et al. AACR 2019
TRK Resistance Testing Methods

• Samples obtained following progression on prior TRK inhibitor and before LOXO-195 treatment were sequenced according to availability:
  • Plasma (centrally, via Guardant 360)
  • Tissue (locally, per institutional standards)
## Phase I Dose-Limiting Toxicities (DLTs) by Dose Level

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose / Schedule</th>
<th>Pts</th>
<th>DLTs</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed Dosing Schedule (Adults/Adolescents)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>150mg BID</td>
<td>2</td>
<td>2</td>
<td>Ataxia/Dizziness/Vomiting</td>
</tr>
<tr>
<td>2</td>
<td>100mg BID</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>100mg QD</td>
<td>2</td>
<td>2</td>
<td>Ataxia/Dizziness/Vomiting</td>
</tr>
<tr>
<td>4</td>
<td>50mg QD</td>
<td>7</td>
<td>1</td>
<td>Ataxia/Dizziness</td>
</tr>
</tbody>
</table>

|        | Titration Dosing Schedule* (Adults/Adolescents) |     |      |                           |
|        | 50mg QD → 50mg BID → 75mg BID                   |     |      |                           |
|        | 3        | 0    | -    |                           |

|        | Fixed Dosing Schedule (Pediatrics) |     |      |                           |
|        | 43mg/m² QD | 1    | 0    |                           |

- All DLTs:
  - ‘On-target’ (mediated by CNS TRK inhibition)
  - Reversible with dose interruption/reduction
- DLTs did not correlate closely with plasma PK (peak or AUC) or prior TRK inhibitor therapy
- SPP patients (n=11)
  - No DLTs observed
  - Dose range tested: 20 mg BID-300 mg QD
### LOXO-195 safety profile

#### Treatment-emergent AEs in ≥15% of patients in phase 1 study (n=20)

<table>
<thead>
<tr>
<th>Adverse Event Term, %</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>10</td>
<td>15</td>
<td>–</td>
<td>65</td>
</tr>
<tr>
<td>Ataxia</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>–</td>
<td>60</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30</td>
<td>–</td>
<td>10</td>
<td>–</td>
<td>40</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>30</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>–</td>
<td>30</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15</td>
<td>10</td>
<td>0</td>
<td>–</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Blood ALP increased</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>15</td>
</tr>
</tbody>
</table>

#### Adverse events in SPP (n = 11)*

- Reported treatment-emergent adverse events:
  - Grade 1/2 dizziness (n=4)
  - Grade 1 diarrhea (n=3)
  - Grade 3 diarrhea (n=1)
  - Grade 1 ataxia (n=1)
  - Grade 1 skin sensitivity (n=1)
  - Grade 1 cough (n=1)
  - Grade 1/2 gait disturbance (n=1)
PK data support potential for inhibition of TRK resistance mutations

- Plasma levels of LOXO-195 after first dose of 50 mg led to unbound concentrations that exceed IC₅₀ for WT and mutant TRK
- Moderate to high intra- and inter-patient variability
Mechanism of TRK resistance on prior therapy (N=31)

Solvent front mutations appear to be the most frequent mechanism of resistance
# Objective response by resistance mechanism

**Investigator-assessed objective response rate per RECIST v1.1 (n=29)**

<table>
<thead>
<tr>
<th>Patient cohort</th>
<th>Patients, N</th>
<th>Complete/partial response, n</th>
<th>Stable disease, n</th>
<th>Progressive disease, n</th>
<th>Non-evaluable†, n</th>
<th>Objective response rate, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRK kinase mutation</td>
<td>20</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>45 (9/20)</td>
</tr>
<tr>
<td>Solvent front</td>
<td>14</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>50 (7/14)</td>
</tr>
<tr>
<td>Gatekeeper</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>25 (1/4)</td>
</tr>
<tr>
<td>xDFG</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>50 (1/2)</td>
</tr>
<tr>
<td>Identified bypass</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0 (0/3)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>6</td>
<td>1#</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>17 (1/6)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>29</strong></td>
<td><strong>10</strong></td>
<td><strong>9</strong></td>
<td><strong>5</strong></td>
<td><strong>5</strong></td>
<td><strong>34 (10/29)</strong></td>
</tr>
</tbody>
</table>

Data cutoff: December 3, 2018

Hyman D, et al. AACR 2019
Best tumor change by resistance mechanism

Resistance mechanism:
- SF
- GK
- xDEG
- Bypass
- None

Maximum change in tumor size (%)
Best tumor change in TRK kinase domain mutants

Kinase domain mutation:
- SF
- GK
- xDFG

Hyman D, et al. AACR 2019
Patient with **IRF2BP2-NTRK1, NTRK1 G595R** anaplastic thyroid cancer

58 year-old female
IRF2BP2-NTRK1 anaplastic thyroid cancer
Post-thyroidectomy and neck dissection

**LOXO-195 Phase I**
Best response: PR

9 months
Recurrence 5 months after completion of upfront chemoRT

8.5 months
Larotrectinib progression
Liver biopsy: **NTRK1 G595R** (solvent front)

Larotrectinib 100mg BID
Best response: PR

Baseline scan
1st Re-staging
Best response: PR (-48%)

Hyman D, et al. AACR 2019
Patient with *LMNA-NTRK1* G595R colorectal cancer

- **57 year-old female**
- **LMNA-NTRK1 colorectal cancer**
- **Post-surgery**

- **6 months**
  - Prior treatment: FOLFOX, FOLFIRI + bevacizumab
  - Larotrectinib 100mg BID
  - Best response: PR

- **22 months**
  - LOXO-195 SPP
  - Best response: PR

Baseline scan vs. 5 Months
- Best response: PR (-68%)

PR, partial response; SD, starting dose

Hyman D, et al. AACR 2019
Response to LOXO-195 in Patient with Colorectal Cancer

Case 1: CRC with $\text{LMNA-NTRK1}$ fusion

- $\text{NTRK1 G595R}$ resistance mutation after larotrectinib
- Treated with LOXO-195 at 50 mg twice daily
  - Dose increased to 100 mg twice daily at day 14
- Tolerability
  - Grade 2 dizziness and grade 1 diarrhea
  - LOXO-195 continued
  - Both AEs resolved
- Efficacy
  - 38% decrease in tumor burden after 4 weeks and 58% at time of report
  - Resolution of FDG-avidity
  - Decreasing abdominal pain and fullness

Response to LOXO-195 in Patient With Sarcoma

Case 2: Infantile fibrosarcoma with ETV6-NTRK3 fusion

- NTRK3 G623R resistance mutation after larotrectinib
- Treated with liquid LOXO-195 at 20 mg twice daily
  - Dose increased to 60 mg twice daily then to 100 mg twice daily
- Tolerability
  - Grade 2 dizziness
  - LOXO-195 continued
- Efficacy
  - 30% tumor regression after 28 days
  - Response ongoing at 66 days
  - New mediastinal mass and pleura effusion eventually led to patient expiration

LOXO-195 (BAY 2731954) Conclusions

• Well tolerated at doses of ≤100 mg BID; optimal dose and schedule still being explored

• Preliminary efficacy in TRK fusion-positive patients with acquired TRK kinase domain resistance mutations:
  – Additional data needed to define activity in each specific kinase mutation

• Patients with TRK-independent resistance may be less likely to benefit
  – Consistent with biologic expectations

• May provide a continuum of care for patients with TRK fusion cancer who progress on first-generation TRK inhibitors
Repotrectinib, a next generation TRK inhibitor, overcomes TRK resistance mutations including solvent front, gatekeeper and compound mutations

Alexander Drilon,1 Dayong Zhai,2 Wei Deng,2 Xin Zhang,2 Dong Lee,2 Evan Rogers,2 Jeffrey Whitten,2 John Huang,2 Armin Graber,2 Juliet Liu,2 Shanna Stopatschinskaja,2 J. Jean Cui,2 Dong-Wan Kim,3 Byoung Chul Cho,4 Robert C. Doebele,5 Sai-Hong Ignatius Ou,6 Jeeyun Lee,7 Alice T. Shaw8

1Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA; 2Turning Point Therapeutics, Inc., San Diego, CA, USA; 3Seoul National University Hospital, Seoul, Republic of Korea; 4Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; 5University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; 6Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA; 7Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 8Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Presented at AACR Annual Meeting 2019, March 29-April 3, Atlanta, GA.
Repotrectinib demonstrated marked antitumor effects in xenograft tumor models carrying wildtype or mutated TRK fusions

- Repotrectinib was more effective than entrectinib when dosed at the same dose level of 15 mg/kg BID with statistically significant change of tumor volume ($p = 0.01$) in the model carrying the wildtype LMNA-TRKA fusion.

- Repotrectinib was more effective than LOXO-195 when dosed at the same dose level of 30 mg/kg BID with statistically significant change of tumor volume ($p = 0.03$) in the model carrying the LMNA-TRKA G595R solvent front mutation.

- Repotrectinib was more effective than LOXO-195 when dosed at the same dose level of 30 mg/kg BID with statistically significant change of tumor volume ($p = 0.003$) in the model carrying the LMNA-TRKA F589L/G595R compound mutation.

Drilon A, et al. AACR 2019
CASE

• 48 year old Caucasian female
• Diagnosed with metastatic cholangiocarcinoma in 2012 followed by chemotherapy
• Detected LMNA-NTRK1 fusion in 2016 and then treated with larotrectinib for 14 months with best response as PR
• Detected resistance mutations G595R and F589L (trans) by liquid biopsy when enrolled into TRIDENT-1 trial
• Started repotrectinib at 40 mg QD (well tolerated and dose was escalated to 160 mg QD at Cycle 4 per protocol)
• Achieved tumor regression of -33% after 4 months treatment with repotrectinib by Investigator assessment
• Achieved tumor regression of -50% after 6 months treatment with new lesion detected

Drilon A, et al. AACR 2019
Response to Repotrectinib in a Patient With MASC

Case 3: MASC with ETV6-NTRK3 fusion

- NTRK3 G623E resistance mutation after entrectinib
- Treated with repotrectinib on phase I trial
- Tolerability
  - Grade 1 peripheral sensory neuropathy
- Efficacy
  - 82% disease regression by RECIST v1.1
  - Confirmed PR
  - Ongoing response at 13+ months

Repotrectinib was designed to bind completely inside the ATP pocket of the target kinase with greater precision and affinity and is able to target both wild type and mutant kinases.

Repotrectinib potently inhibited WT and mutant TRKs *in vitro* and *in vivo*, including the solvent front mutations which render common resistance to TRK inhibitors larotrectinib and entrectinib.

Repotrectinib is a potent TRK inhibitor against both wildtype and mutated TRKs, especially solvent front, gatekeeper, and compound mutations in comparison with other TRK inhibitors.

Repotrectinib demonstrated antitumor effectiveness in refractory patients treated with 1st generation TRK inhibitors.

A Phase 1/2 clinical trial (TRIDENT-1) of repotrectinib is on-going for patients with advanced solid tumors harboring a ROS1, NTRK, or ALK fusion gene (NCT03093116).

Drilon A, et al. AACR 2019
Second-Generation TRK Inhibitors are developed parallel to First-line drugs

First-generation drug
- Larotrectinib
- Entrectinib

Next-generation drug
- LOXO-195
- Repotrectinib

### Timeline of Key Advances in TRK Biology and Targeting

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950s</td>
<td>Identification of NTRK as an oncogene: TPM3-NTRK1 found in a human colorectal carcinoma</td>
</tr>
<tr>
<td>1985</td>
<td>Identification of NTRK1 fusions in papillary thyroid carcinoma</td>
</tr>
<tr>
<td>1989-91</td>
<td>Identification of NTRK3 fusion (ETV6-NTRK3) in infantile fibrosarcoma</td>
</tr>
<tr>
<td>1993-94</td>
<td>Data emerges implicating the involvement of TRK signaling in ovulation</td>
</tr>
<tr>
<td>2000</td>
<td>Identification of NTRK2 fusions in pilocytic astrocytoma</td>
</tr>
<tr>
<td>2010</td>
<td>Loss of function NTRK1 mutations identified in patients with congenital insensitivity to pain with anhidrosis (CIPA)</td>
</tr>
<tr>
<td>2015</td>
<td>First activating TRK alternative variant identified</td>
</tr>
<tr>
<td>2018</td>
<td>Crystal structures of the kinase domains of TRKA and TRKB determined</td>
</tr>
<tr>
<td>2019</td>
<td>Larotrectinib and entrectinib FDA approved, and EMA also Approved larotrectinib</td>
</tr>
</tbody>
</table>

**Cocco E, et al. Nat Rev Clin Oncol. 2018.**
Resistance to TRK inhibition mediated by convergent MAPK pathway activation

Dynamics of select mutations detected in the cfDNA of the patient with CTRC–NTRK1-positive pancreatic adenocarcinoma during treatment with a series of targeted therapies.

Bottom panel, representative scans from the patients at baseline and on treatment with the combination of dabrafenib + trametinib.
Dynamics of select mutations detected in the cfDNA of the patient with *PLEKHA6–NTRK1*-positive cholangiocarcinoma during treatment with a series of targeted therapies.

Bottom panel, representative scans from the patients at baseline and on treatment with and LOXO-195 + crizotinib

CONCLUSION

- Both Loxo-195 and repotrectinib were designed to bind inside the ATP pocket of the target kinase with greater precision and affinity and is able to target both wild type and mutant kinases
- Loxo-195 and repotrectinib are potent TRK inhibitor against both wildtype and mutated TRKs, especially solvent front, gatekeeper, and compound mutations in comparison with other TRK inhibitors
- Loxo-195 and repotrectinib have demonstrated antitumor effectiveness in refractory patients treated with 1st generation TRK inhibitors
- Phase 1/2 clinical trials of Loxo-195 and repotrectinib are on-going for patients with advanced solid tumors and resistance to first generation TRK inhibitors
- Resistance to TRK inhibition mediated by convergent MAPK pathway activation may emerge
THANK YOU FOR YOUR ATTENTION

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