NTRK fusions: A novel target with emerging therapeutic traction

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  - Pfizer, Lilly, Advantagene, Inovio, Celgene, Vertex, Ariad (Takeda), Merck, Stemcentrex (Takai), Genentech/Roche, AstraZeneca, Trizell, GSK, Guardant

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- **Data Safety Monitoring Committees:**
  - Lilly, Amgen, Peregrine, Incyte, Synta, SWOG
Neurotrophic Tropomyosin Kinase Receptor encompasses three different transmembrane proteins (*TrkA*, *TrkB* and *TrkC* encoded respectively by NTRK 1, 2 and 3).

Critical role in neuronal development and differentiation

- Regulates pain, proprioception, appetite and memory

Gene rearrangements/fusions lead to overexpression of chimeric protein, constitutive, ligand independent activation of downstream signaling.
NTRK FUSIONS

Cocco et al. Nature Review 2018
The TRK pathway was discovered several decades ago

- Identification of nerve growth factor (NGF), the first neurophin
- Purification of brain-derived neurotrophic factor (BDNF)
- Identification of neurophin-3 (NT-3)
- Identification of neurophin-4 (NT-4)
- Identification of TRKA, TRKB, and TRKC as high affinity neurophin receptors
- Severe neuropathies developed by NTRK knockout mice
- Identification of first NTRK3 fusion (ETV6-NTRK3) in infantile fibrosarcoma
- Loss of function NTRK1 mutations identified in patients with congenital insensitivity to pain with anhidrosis (CIPA)
- Data emerges implicating the involvement of TRK signaling in ovulation
- Crystal structure of NGF in complex with TRKA determined
- First activating TRKA alternative variant identified
- TRKB downregulation associated with hyperphagia and hyperdipsia in mice
- Crystal structures of the kinase domains of TRKA and TRKB determined
- Identification of NTRK2 fusions in pilocytic astrocytoma
- First-generation TRK inhibitors enter clinical trial testing
- Second-generation TRK inhibitors enter clinical trial testing
- Larotrectinib achieves histology- and age-agnostic responses in NTRK fusion-positive solid tumors
- Larotrectinib and entrectinib receive FDA breakthrough designation for the treatment of NTRK fusion-positive solid tumors
The TRK pathway was discovered several decades ago.
NTRK fusions are found in diverse cancers including lung cancers

Cancers enriched for TRK fusions
- Secretory breast carcinoma
- Mammary analogue secretory carcinoma
- Infantile fibrosarcoma

Frequency: 75% to >90%

Cancers harboring TRK fusions at lower frequencies
- Congenital mesoblastic nephroma
- Pontine glioma
- Spitzoid melanoma
- Thyroid Cancer
- GIST ("pan-negative")
- Lung cancer
- Astrocytoma/Glioblastoma
- Colorectal cancer
- Cholangiocarcinoma
- Pancreatic cancer
- Head and neck squamous cancer
- Breast cancer
- Melanoma

Frequency: 5% to 25%

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

Cocco, Scaltriti, and Drilon, In Review
Detection of TRK Fusions

- Several Modalities: DNA & RNA NGS, IHC, FISH
- Large NTRK introns can make DNA detection challenging
- NTRK 2 and 3 – large introns (17X longer), higher repetitive elements and high GC content
- LOXO Ventana Developing Pan-TRK IHC Companion Diagnostic
- NGS “universal” tests under FDA review including TRK fusion detection

Pan-TRK IHC detects expression, shared among TRK fusions

More info: www.TRKtesting.com
Larotrectinib development program for *NTRK* fusion-positive cancers

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

Data cut-off: April 14, 2017

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
Seventeen unique NTRK fusion-positive tumor types were treated

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

1/3 had received 3 or more lines of therapy
Seventeen unique *NTRK* fusion-positive tumor types were treated.

1/3 had received 3 or more lines of therapy.

Drilon et al, N Engl J Med 2017
**NTRK** fusion-positive cancers are sensitive to TRK TKI therapy in a tissue-agnostic manner

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*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 deterioration and no post-baseline tumor measurements were recorded.

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Drilon et al, New Engl J Med 2017

**larotrectinib**

OrR 75%, median PFS not reached

Active regardless of age or tumor type
Larotrectinib is active regardless of fusion partner

Drilon et al, New Engl J Med 2017

*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.

Active regardless of age or tumor type, or fusion partner
Larotrectinib is active regardless of patient 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.

Drilon et al, New Engl J Med 2017
### Table 3. Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Adverse Events, Regardless of Attribution</th>
<th>Treatment-Related Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Increased ALT or AST level</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Increased body weight</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>
Larotrectinib: ESMO Update

Patients with TRK fusion cancer: Supplementary dataset

- **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 cancer

- **Primary**
  - n=8

- **Supplementary**
  - n=2

- **Total**
  - 122 patients with TRK fusion cancer

- **TRK fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cutoff: 30 July 2018

BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors
### Larotrectinib: ESMO Update

#### Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary (n=55)</th>
<th>Supplementary (n=67)</th>
<th>Integrated (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (53)</td>
<td>31 (46)</td>
<td>60 (49)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (47)</td>
<td>36 (54)</td>
<td>62 (51)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>45.0 (0.3–76.0)</td>
<td>35.0 (0.1–80.0)</td>
<td>41.0 (0.1–80.0)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>6 (11)</td>
<td>12 (18)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>2–&lt;6 years</td>
<td>5 (9)</td>
<td>2 (3)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>6–&lt;15 years</td>
<td>1 (2)</td>
<td>13 (19)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>15–39 years</td>
<td>12 (22)</td>
<td>9 (13)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>≥40 years</td>
<td>31 (56)</td>
<td>31 (46)</td>
<td>62 (51)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (44)</td>
<td>33 (49)</td>
<td>57 (47)</td>
</tr>
<tr>
<td>1</td>
<td>27 (49)</td>
<td>26 (39)</td>
<td>53 (43)</td>
</tr>
<tr>
<td>2</td>
<td>4 (7)</td>
<td>8 (12)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>No. of prior systemic regimens, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>27 (49)</td>
<td>39 (58)</td>
<td>66 (54)</td>
</tr>
<tr>
<td>2</td>
<td>9 (16)</td>
<td>16 (24)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>≥3</td>
<td>19 (35)</td>
<td>12 (18)</td>
<td>31 (25)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status
Larotrectinib: ESMO Update

Sustained responses with larotrectinib (DOR)

**Primary dataset**
- Median follow-up 17.6 months
- Median DOR not reached

**Supplementary dataset**
- Median follow-up 7.4 months
- Median DOR not reached

**Kaplan-Meier landmark analysis**
- 17 Jul 2017
- 30 Jul 2018

- **6 months**
  - 83%
  - 88%

- **12 months**
  - 71%
  - 75%

*In patients with confirmed complete or partial responses
DOR, duration of response

Investigator response assessments, as of 30 July 2018

MUNICH 2018 ESMO Congress
**METHODS AND DEMOGRAPHICS:**

**TRK FUSION LUNG CANCER SUBSET**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>52 (25–76)</td>
</tr>
<tr>
<td>Female/Male, n</td>
<td>6/5</td>
</tr>
<tr>
<td>ECOG performance status, n</td>
<td>0 5 1 5 2 1</td>
</tr>
<tr>
<td>Fusions</td>
<td>(\text{EPS15-NTRK1} ) 2 (\text{TPM3-NTRK1} ) 2 (\text{SQSTM1-NTRK1} ) 2 (\text{IRF2BP2-NTRK1} ) 1 (\text{TPR-NTRK1} ) 2 (\text{ETV6-NTRK3} ) (\text{SQSTM1-NTRK3} )</td>
</tr>
<tr>
<td>Prior therapies</td>
<td>Surgery 7, Radiotherapy 6, Systemic therapy 10</td>
</tr>
<tr>
<td>Number of prior systemic therapies, n</td>
<td>0 1, 1–2 5, 3 or more 5</td>
</tr>
</tbody>
</table>

**Adult phase I**
- Age \(\geq 18\) years
- Advanced solid tumours

**NAVIGATE: adult/adolescent phase II ‘basket’ trial**
- Age \(\geq 12\) years
- Advanced solid tumours
- TRK fusion cancer

11 patients with TRK fusion lung cancer

- TRK fusion status
  - Determined by local CLIA (or similarly accredited) laboratories
- Primary endpoint
  - Best objective response rate (RECIST 1.1)
- Secondary endpoints
  - Duration of response
  - Progression-free survival
  - Overall survival
  - Safety
- Dosing
  - Larotrectinib, 100 mg BID continuously
  - 28-day cycle

Data cut off: 30 July 2018. BID, twice-daily; ECOG, Eastern Cooperative Oncology Group; TRK, tropomyosin receptor kinase.
Therapeutic Activity:
TRK fusion lung cancer subset

LAROTRECTINIB IS ACTIVE IN TRK FUSION NSCLC

ORR, 71% (95% CI, 29–96%)
CR, n=1/7
PR, n=4/7
SD, n=2/7
no primary progressive disease

Maximum change in tumour size (%)

Median time to response = 1.8 months
Duration of response: 7.4* – 17.6* months*
76/F with an EPS15-NTRK1+ NSCLC metastatic to lung/brain

- No prior systemic therapy, surgery or RT
- Refused platinum doublet therapy
- Treated with larotrectinib
- Confirmed PR (-34%)
- Near CR intracranially (-95%, volumetric)
- Remains on therapy at 6+ months

Rosen et al, In Submission
Entrectinib: Background

- **NTRK1/2/3 genes encode TRK A/B/C proteins**
- **NTRK1/2/3 gene fusions are oncogenic drivers**
- **NTRK fusions occur in ~0.3% of solid tumors**

Nucleus

Cytoplasm

Membrane

TRKA (NTRK1) fusion

TRKB (NTRK2) fusion

TRKC (NTRK3) fusion

ROS1 fusion

Fusion proteins may also be located in other cellular compartments and activate additional signalling pathways, potentially depending on the fusion partner.
Entrectinib: Background

Entrectinib is a CNS-active, oral, potent TRK/ROS1/ALK inhibitor designed to cross the blood-brain-barrier and remain within the CNS\(^1,2,3\).

- Demonstrated clinical activity in primary brain tumors and secondary CNS metastases\(^4\).

Fusion proteins may also be located in other cellular compartments and activate additional signalling pathways, potentially depending on the fusion partner.

Design of integrated analysis across phase I/II trials of entrectinib

Efficacy population*
Adult patients with NTRK fusion-positive, TRK inhibitor-naïve solid tumors N=54
CNS metastases, n=12; no CNS metastases, n=42

Safety populations
NTRK fusion-positive patients receiving entrectinib n=68
Patients receiving entrectinib (all tumor types and gene rearrangements) N=355†

Data cut-off: 31 May 2018

Phase I (ALKA-372-001)
Phase I dose-escalation study
NTRK fusion-positive patient n=1

Phase I (STARTRK-1)
Phase I dose-escalation study
NTRK fusion-positive patients n=2

Phase II (STARTRK-2)
Phase II, multicenter, global basket study
Entrectinib 600mg once daily, 28-day cycle
NTRK fusion-positive patients n=51

• Primary endpoints‡
  – ORR
  – DoR

• Secondary endpoints‡
  – PFS and OS
  – intracranial ORR and DoR§
  – safety and tolerability

*Patients with at least 6 months of follow-up
†All patients from STARTRK-1, STARTRK-2, ALKA-372-001 and STARTRK-NG (regardless of tumor type or gene rearrangement) who received ≥1 entrectinib dose
‡Per blinded independent central review (RECIST v1.1); §Patients with measurable and non-measurable CNS lesions at baseline
CNS: central nervous system; DoR: duration of response; ORR: objective response rate; OS: overall survival
NSCLC: non-small cell lung cancer; PFS: progression-free survival; RECIST: response evaluation criteria in solid tumors
Baseline characteristics: adult patients with NTRK fusion-positive solid tumors

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>NTRK+ patients (n=54)</th>
<th>NTRK+ NSCLC patients (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>57.5 (21–83)</td>
</tr>
<tr>
<td>Sex, %</td>
<td>Female</td>
<td>59.3</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>40.7</td>
</tr>
<tr>
<td>Race, %</td>
<td>White</td>
<td>79.6</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>13.0</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td>0</td>
<td>42.6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>46.3</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>11.1</td>
</tr>
<tr>
<td>Prior lines of systemic therapy, %</td>
<td>0</td>
<td>37.0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>20.4</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>42.6</td>
</tr>
<tr>
<td>CNS mets at baseline, %</td>
<td></td>
<td>22.2</td>
</tr>
</tbody>
</table>

Data cut-off date: 31 May 2018

CRC: colorectal cancer; ECOG PS: Eastern Cooperative Oncology Group performance status
MASC: mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer
Entrectinib activity in NTRK fusion-positive solid tumors: individual patient responses by tumor type

Efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>NTRK+ patients (n=54)</th>
<th>NTRK+ NSCLC patients (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong>, % (95% CI)</td>
<td>57.4 (43.2–70.8)</td>
<td>70.0 (34.75–93.33)</td>
</tr>
<tr>
<td><strong>CR</strong> n (%)</td>
<td>4 (7.4)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td><strong>Median DoR</strong>, * months (95% CI)</td>
<td>10.4 (7.1–NR)</td>
<td>NE (10.4–NE)</td>
</tr>
<tr>
<td><strong>Median PFS</strong>, * months (95% CI)</td>
<td>11.2 (8.0–14.9)</td>
<td>14.9 (4.7–NE)</td>
</tr>
<tr>
<td>**Median OS, months (95% CI)</td>
<td>20.9 (14.9–NR)</td>
<td>NE (5.9–NE)</td>
</tr>
</tbody>
</table>

CI: confidence interval; CR: complete response; CRC: colorectal cancer; DoR: duration of response; MASC: mammary analogue secretory carcinoma; NE: not estimable; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival

Data cut-off date: 31 May 2018 *By blinded independent central review
Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot
Entrectinib activity in \textit{NTRK} fusion-positive solid tumors: individual patient responses by specific \textit{NTRK} gene (1, 2 or 3)

<table>
<thead>
<tr>
<th>\textbf{}</th>
<th>\textbf{NTRK1 (n=22)}</th>
<th>\textbf{NTRK2 (n=1)}</th>
<th>\textbf{NTRK3 (n=31)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>59.1% (36.3–79.3)</td>
<td>0%</td>
<td>58.1% (39.1–75.5)</td>
</tr>
</tbody>
</table>

*NSCLC patients

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

Data cut-off date: 31 May 2018

ORR: overall response rate
Entrectinib activity in NTRK fusion-positive solid tumors: individual patient responses by CNS metastases status at baseline

<table>
<thead>
<tr>
<th></th>
<th>CNS mets at baseline (n=12)</th>
<th>No CNS mets at baseline (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>50.0% (21.1–78.9)</td>
<td>59.5% (43.3–74.4)</td>
</tr>
</tbody>
</table>

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

Data cut-off date: 31 May 2018

Patients with assessable CNS metastases at baseline as per BICR, does not include patients enrolled with a primary CNS tumor.

*NSCLC patients
## Intracranial ORR in NTRK fusion-positive patients with CNS metastases at baseline

### Intracranial response – CNS metastases at baseline by BICR

<table>
<thead>
<tr>
<th></th>
<th>NTRK+ patients (n=11*)</th>
<th>NTRK+ NSCLC patients (n=6†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial ORR, n (%)</td>
<td>6 (54.5) (23.4–83.3)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>CR</td>
<td>3 (27.3)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (27.3)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (9.1)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (27.3)</td>
<td>0</td>
</tr>
<tr>
<td>Non CR/PD, Missing or</td>
<td>NE (5.0–NE)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>unevaluable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial median DoR,</td>
<td>14.3 (5.1–NE)</td>
<td>NE</td>
</tr>
<tr>
<td>months (95% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients with assessable CNS metastases at baseline as per BICR, does not include patients enrolled with a primary CNS tumor
†Investigator-assessed baseline CNS disease; all assessments using RECIST v1.1

CR: complete response; NE: not estimable; PD: progressive disease, PR: partial response, SD: stable disease
Safety overview

- Most AEs were grade 1/2 and reversible
- Treatment-related AEs leading to:
  - dose reduction: 39.7%
  - dose interruption: 30.9%
  - discontinuation from treatment: 4.4%
- No grade 5 treatment-related events were reported
- Treatment-related AEs reported in the NTRK fusion-positive and the overall safety populations were comparable

<table>
<thead>
<tr>
<th>Treatment-related AEs reported in ≥10% of patients</th>
<th>NTRK fusion-positive safety population (n=68)**†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>Grade 1/2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>32 (47.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>19 (27.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (27.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (26.5)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>16 (23.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (23.6)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>12 (17.7)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8 (11.8)</td>
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<tr>
<td>Weight increased</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (7.4)</td>
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</tbody>
</table>

* NTRK fusion-positive safety population comprises all patients who have received at least 1 dose of entrectinib regardless of dose or follow-up
† There were five Grade 4 TRAEs in 3 patients (1 increased aspartate aminotransferase; 1 increased alanine aminotransferase; 1 increased blood uric acid 2 hyperuricaemia)

Data cut-off date: 31 May 2018
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.

GK, gatekeeper; SF, solvent front.
### NTRK Resistance

<table>
<thead>
<tr>
<th></th>
<th>Altiratinib</th>
<th>Cabozantinib</th>
<th>Crizotinib</th>
<th>DS-6051b</th>
<th>Foretinib</th>
<th>Lesaritinib</th>
<th>Merestinib</th>
<th>MGCD516</th>
<th>Nintedanib</th>
<th>PLX7436</th>
<th>Ponatinib</th>
<th>TSR011</th>
<th>Enretinib</th>
<th>Larotrectinib</th>
<th>LOXO-105</th>
<th>ONO-5395556</th>
<th>TRX-0202</th>
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<td>F589L</td>
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<td>G667C</td>
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<td>G623R</td>
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<td>G696A</td>
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<td>*</td>
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</tr>
</tbody>
</table>

**IC₅₀**
- <50 nM
- 50–200 nM
- >200 nM

* Cell-based assays
  - In vitro kinase assays
  - In cell molecular assays

* Associated with clinical resistance
# NTRK Resistance

|             | Altiratinib | Cabozantinib | Crizotinib | DS-6051b | Foretinib | Lestaurtinib | Merestinib | MCCI516 | Nintedanib | PLX7476 | Ponatinib | Ronalinib | LARTECINIB | LOXO-105 | ONO-5390556 | TPX-0005 |
|-------------|-------------|--------------|------------|----------|-----------|-------------|------------|----------|------------|---------|-----------|-----------|------------|-----------|-----------|-----------|---------|
| WT          | #           | *            | #          | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| F589L       | #           | *            |            | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| G595R       | #           | #            | #          | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| G667C       | #           | *            | #          | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| G667S       | #           | *            |            | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| A608D       | #           | #            |            | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| TRKB        |             |              |            |          |           |              |            |          |            |         |           |           |            |           |           |           |         |
| WT          | #           | #            | #          | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| G623R       | #           | #            |            | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |
| G696A       | #           | *            | #          | #        | #         | #           | #          | #        | #          | #       | #         | *         | #          | #         | #         | #        | #        |

**Cell-based assays**

- # In vitro kinase assays
- α In cell molecular assays
- * Associated with clinical resistance

**IC₅₀**

- <50 nM
- 50–200 nM
- >200 nM
LOXO-195 (BAY 2731954)

- Potent second-generation inhibitor of all 3 TRK tyrosine kinases with IC₅₀ <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

Combined patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (71)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Median age (range), years</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>Prior TKI*, n (%)</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>Median duration^ of prior TRK TKI, months (range)</td>
<td>11 (2-30)</td>
</tr>
<tr>
<td>TRK fusion, n (%)</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>Enrollment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>20 (65%)</td>
</tr>
<tr>
<td>SPP</td>
<td>11 (35%)</td>
</tr>
</tbody>
</table>

Tumor types (n=15)

- Thyroid 3%
- Melanoma 3%
- Neuroendocrine carcinoma 3%
- Glioblastoma 3%
- Kidney 3%
- Colorectal 3%
- Cervical 3%
- Biliary tract 6%
- NSCLC 6%
- IFS 6%
- Breast** 10%
- MASC 10%
- Pancreas 10%
- Sarcoma 16%

^Calculation excludes 3 patients who received >1 TKI
**Two were secretory breast carcinoma
^30 patients resistant to and 1 patient intolerant to prior TRK inhibitor therapy
# LOXO-195

## 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>Completed</td>
<td>Fixed Dosing Schedule (Adults/Adolescents)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>100mg BID</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>150mg BID</td>
<td>2</td>
<td>2</td>
<td>Ataxia/Dizziness/Vomiting</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>8</td>
<td>1</td>
<td>Ataxia/Dizziness</td>
</tr>
<tr>
<td>Ongoing</td>
<td>Titration Dosing Schedule* (Adults/Adolescents)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5a</td>
<td>50mg QD → 50mg BID → → 75mg BID</td>
<td>2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5b</td>
<td>50mg QD → 100mg QD → → 150mg QD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fixed Dosing Schedule (Pediatrics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43mg/m² QD</td>
<td></td>
<td>1</td>
<td>0</td>
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</tr>
</tbody>
</table>

- 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

* - Dose titrate every 14 days based on tolerance, DLT monitoring window = 42 days
LOXO-195

Mechanism of TRK resistance on prior therapy (N=31)

Solvent front mutations appear to be the most frequent mechanism of resistance

*Includes 2 patients who did not have any plasma or tissue sequencing prior to LOXO-195 treatment
GK, gatekeeper; SF, solvent front. Bypass defined as a new activating MAPK pathway alteration (KRAS, BRAF, MET, etc)
LOXO-195

Objective response by resistance mechanism

<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>
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<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>
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<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>
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<tr>
<td>Gatekeeper</td>
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<td>1</td>
<td>0</td>
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<td>25 (1/4)</td>
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<td>xDFG</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>50 (1/2)</td>
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<td>0</td>
<td>3</td>
<td>0</td>
<td>0 (0/3)</td>
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<tr>
<td>Other/unknown</td>
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<td>1#</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>17 (1/6)</td>
</tr>
<tr>
<td>Total</td>
<td>29*</td>
<td>10</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>34 (10/29)</td>
</tr>
</tbody>
</table>

Data cutoff: December 3, 2018

*2 patients still on study drug and awaiting first response assessment not included.
†5 patients non-evaluable: 1 discontinued drug for unrelated new cancer diagnosis <28 days after start of study drug; 4 withdrew within 22 days of study drug start.
*Patient intolerant but not resistant to prior TRK inhibitor.
Repotrectinitib (TPX-005)

Clinical resistant mutations in TRKA

First generation TRK inhibitors
- Larotrectinib
  - MW 428.44
- Entrectinib
  - MW 560.65

Next generation TRK inhibitors
- Repotrectinitib
  - MW 355.37
- LOXO-195
  - MW 380.43
Repotrectinib potently inhibited WT and mutant TRK

Repotrectinib is the most potent TRK Inhibitor in Ba/F3 cell proliferation assays

<table>
<thead>
<tr>
<th>TRK Inhibitor</th>
<th>LMNA-TRKA</th>
<th>ETV6-TRKB</th>
<th>ETV6-TRKC</th>
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<tbody>
<tr>
<td></td>
<td>WT</td>
<td>G595R</td>
<td>G667C</td>
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<tr>
<td>Repotrectinib</td>
<td>&lt;0.1</td>
<td>0.2</td>
<td>9.2</td>
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<td>LOXO-195</td>
<td>4.6</td>
<td>15.1</td>
<td>94.9</td>
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<td>Larotrectinib</td>
<td>18.9</td>
<td>2817</td>
<td>1863</td>
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<tr>
<td>Entrectinib</td>
<td>0.4</td>
<td>711</td>
<td>186.7</td>
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</tbody>
</table>

* Other than repotrectinib, data based on evaluation of comparable proxy chemical reagents purchased from commercial sources. WT: wildtype
Repotrectinib

Drilon et al. Cancer Discovery 2018
Repotrectinib: Summary

- Demonstrated, in xenograft tumor models, significant tumor regression in tumors carrying WT or mutated TRK fusions (as well as ROS1)
- Over 10-fold more potent than LOXO-195 against WT TRK fusions and solvent front mutations (SFM)
- More than 100-fold more potent against the gatekeeper mutations TRKA F589L and TRKC F617I.
- Only TRKi active against the compound mutation TRKA G595R/F589L in cis in preclinical Ba/F3 cells.
- TRIDENT-1, a phase I clinical trial, is currently enrolling NTRK fusion-positive patients with advanced solid tumors.
  - SFMs TRKA G595R, TRKC G623R and TRKC G623E and the gatekeeper mutation TRKA F589L were detected in plasma cfDNA samples at baseline from three TRKi-resistant patients.
  - Active against ETV6-TRKC G623E in an entrectinib-resistant patient with a salivary gland tumor (-82%, confirmed partial response).
  - Tumor regression (-33%) was achieved in a larotrectinib-resistant cholangiocarcinoma patient with LMNA-TRKA G595R and F589L mutations in trans.

Drilon et al, AACR; Cancer Res 2019;79(13 Suppl):Abstract nr 442.
• TRK fusions are rare, yet targetable alterations in NSCLC and multiple other malignancies
• Larotrectinib and Entrectinib are the first two TRK inhibitors to be approved – both exhibit exquisite activity in patients harboring these fusions
• Multiple other TKR inhibitors are in development
• TRK resistance mechanisms have been identified
• LOXO-195 and repotrectinib are active against these resistance mechanisms
I think we need to place more patients on clinical trials, don’t you agree?

(Corey Langer preaching to the choir at the weekly Friday thoracic tumor board)
Thank You

Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA