ESMO ADVANCED COURSE ON NTRK GENE FUSION: 

Multi Kinases inhibitors with NTRK as a possible target

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Lyon, 13-14 September 2019
DISCLOSURE OF INTEREST

**Consulting, advisory role or lectures:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

**Honoraria:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

**Clinical trials research:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo

**Travel, Accommodations, Expenses:** AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer
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

Hyman ASCO 2017
Profiles of TRK inhibitor activity

<table>
<thead>
<tr>
<th></th>
<th>Altiretinib</th>
<th>Cabozantinib</th>
<th>Crizotinib</th>
<th>DS-6051ib</th>
<th>Foretinib</th>
<th>Lestaftinib</th>
<th>Merestinib</th>
<th>MGCD516</th>
<th>Nintedanib</th>
<th>PLX7486</th>
<th>Ponatinib</th>
<th>SR-011</th>
<th>Entrectinib</th>
<th>Larotrectinib</th>
<th>LOXO-195</th>
<th>ONO-5390556</th>
<th>TPK-0005</th>
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</tbody>
</table>

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

IC₅₀:
- <50 nM
- 50-200 nM
- >200 nM

E. Cocco et al, nature reviews 2018
# TRK Inhibitors in Development and Trials that Contributed Data to Regulatory Cohorts

<table>
<thead>
<tr>
<th>TKI Generation</th>
<th>Larotrectinib</th>
<th>Entrectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>✓</td>
<td>✓</td>
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<table>
<thead>
<tr>
<th>Drug Inhibits</th>
<th>Larotrectinib</th>
<th>Entrectinib</th>
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<tbody>
<tr>
<td>TRKA/B/C</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ROS1</td>
<td></td>
<td>✓</td>
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<tr>
<td>ALK</td>
<td></td>
<td>✓</td>
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</table>

<table>
<thead>
<tr>
<th>Contributory Trials</th>
<th>Larotrectinib</th>
<th>Entrectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult/Adolescent Trials</td>
<td>NAVIGATE Phase I Trial</td>
<td>STARTRK-2 STARTRK-1 ALKA-372001</td>
</tr>
<tr>
<td>Pediatric Trials</td>
<td>Phase I/II</td>
<td>STARTRK-NG</td>
</tr>
</tbody>
</table>

Demetri et al ESMO 2018, Drilon et al NEJM 2017
Larotrectinib a selective TRK inhibitor

**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

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

TRK fusions occur in a diverse range of cancers:\(^1\)
- Estimated incidence of TRK fusions in lung cancer: 0.2–3.3\(^\%\)^1,4
- Larotrectinib is a highly selective, CNS-active TRK inhibitor\(^2\)
- Approved by the FDA for the treatment of adult and paediatric patients with solid tumours that have an NTRK fusion\(^3\)
- ORR 81\%, median DoR was not reached\(^5\)

BACKGROUND: LAROTRECTINIB YIELDS HIGH RESPONSE RATE AND DOR ACROSS TUMOUR TYPES

ORR: 81%

Data cut off: 30 July 2018. ORR, overall response rate; TRK, Tropomyosin receptor kinase; DOR, Duration of Response
## Methods and Demographics: TRK Fusion Lung Cancer Subset

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

**Navigate: Adult/adolescent phase II ‘basket’ trial**
- Age ≥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

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

Data cut off: 30 July 2018. BID, twice-daily; ECOG, Eastern Cooperative Oncology Group; TRK, tropomyosin receptor kinase.
LAROTREX TINIB 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 (%)

- Treatment ongoing
- Start of complete response
- Start of partial response
- Treatment after progression

Median time to response = 1.8 months
Duration of response: 7.4* – 17.6* months*

Overall treatment duration (months)

* patient with brain metastases; # non-evaluable; *median duration of response not reached after a median follow up of 12.9 months
CI, confidence interval; ORR, objective response rate. Data cut off: 30 July 2018.
INTRA- AND EXTRACRANIAL RESPONSE TO LAROTRECTINIB

76/F with an \textit{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, JCO PO 2019 (In Press)
MULTI-KINASE-INHIBITOR

TRKA (NTRK1) fusion
TRKB (NTRK2) fusion
TRKC (NTRK3) fusion
ROS1 fusion

Ligand independent activation of receptors
Activation of signalling pathways
Cellular effects

MAPK pathway
PI3K-AKT pathway

Tumour cell proliferation
Cell survival

**Entrectinib** is a CNS-active, oral, potent and selective ROS1/TRK/ALK tyrosine kinase inhibitor designed to cross the blood–brain barrier and remain within the CNS.  

- More potent ROS1 inhibitor than crizotinib in preclinical studies.
- Demonstrated clinical activity in multiple tumour histologies including primary brain tumours and secondary CNS metastases.

Entrectinib: a First-in-Class Trk Inhibitor

- Initially discovered by Nerviano Medical Sciences (NMS) as next-generation ALK inhibitor

- Later discovered to have potent TrkA/B/C and ROS1 activity

- Trk and ROS1 prone to fusion proteins, similar to ALK, that induce constitutive activation of cell signaling

- Entrectinib demonstrates inhibition of its RTK targets and downstream effectors in the PLCγ, MAPK and PI3K/AKT pathways

<table>
<thead>
<tr>
<th>Target</th>
<th>TrkA</th>
<th>TrkB</th>
<th>TrkC</th>
<th>ROS1</th>
<th>ALK</th>
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<tbody>
<tr>
<td>IC50* (nM)</td>
<td>1.7</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>1.6</td>
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</table>

* Biochemical kinase assay
Pooled analysis of three studies: entrectinib (NTRK, ALK, ROS1) in ROS1-fusion-positive NSCLC

Integrated analysis

Efficacy population
53 ROS1+, ROS1 inhibitor-naïve NSCLC patients

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

Primary endpoints
ORR and DOR*

Secondary endpoints
CBR*
PFS and OS
Intracranial ORR*†
Intracranial DOR*
Safety and tolerability

STARTRK-2
Phase II, multicenter, global basket study 600 mg QD, 28-day cycle
N=37 ROS1-positive patients

STARTRK-1
Phase I dose escalation;
N=7 ROS1-positive patients

ALKA-372-001
Phase I dose escalation;
N=9 ROS1-positive patients


Robert C. Doebele et al, IASLC
Objective response rate (BICR assessment) ROS1+

<table>
<thead>
<tr>
<th></th>
<th>Total N=53</th>
<th>CNS disease at baseline N=23</th>
<th>No CNS disease at baseline N=30</th>
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<tbody>
<tr>
<td><strong>ORR 95% CI (%)</strong></td>
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<td>41 (77.4)</td>
<td>17 (73.9)</td>
<td>24 (80.0)</td>
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<td>(63.7,87.7)</td>
<td>(51.5,89.7)</td>
<td>(61.4,92.2)</td>
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<tr>
<td>CR</td>
<td>3 (5.7)</td>
<td>0</td>
<td>3 (10.0)</td>
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<tr>
<td>PR</td>
<td>38 (71.7)</td>
<td>17 (73.9)</td>
<td>21 (70.0)</td>
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<td>SD</td>
<td>1 (1.9)</td>
<td>0</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (7.5)</td>
<td>4 (17.4)</td>
<td>0</td>
</tr>
<tr>
<td>Non-CR/PD</td>
<td>3 (5.7)</td>
<td>0</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Missing or unevaluable</td>
<td>4 (7.5)</td>
<td>2 (8.7)</td>
<td>2 (6.7)</td>
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<tr>
<td><strong>Clinical benefit rate</strong>*</td>
<td>41 (77.4)</td>
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</tr>
<tr>
<td>95% CI (%)</td>
<td>(63.7,87.7)</td>
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*Includes SD for at least 6 months. Data cut-off: May 31 2018 (median follow up: 15.5 months), ROS1-inhibitor-naïve patients with ROS1+ NSCLC (integrated analysis population); CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

**Change in tumour size: ROS1+ NSCLC population (n=53) (BICR assessment)**

Best % improvement from baseline in SLD

-100 -75 -50 -25 0 25 25

Individual Patients

- CNS=Yes (n=20)
- CNS=No (n=25)

Subjects with missing SLD percent change were excluded from plot

Robert C. Doebele et al, IASLC
### PFS (BICR assessment) ROS1+

<table>
<thead>
<tr>
<th></th>
<th>Total N=53</th>
<th>CNS disease at baseline N=23</th>
<th>No CNS disease at baseline N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>25 (47.2)</td>
<td>11 (47.8)</td>
<td>14 (46.7)</td>
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<tr>
<td>Disease progression, n</td>
<td>20</td>
<td>8</td>
<td>12</td>
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<tr>
<td>Death, n</td>
<td>5</td>
<td>3</td>
<td>2</td>
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</table>

**Time to event (months)**
- **Median**
  - CNS disease at baseline: 19.0 (12.2, 36.6)
  - No CNS disease at baseline: 13.6 (4.5, NE)
  - Total: 26.3 (15.7, 36.6)

**Median PFS**
- **19.0 months**
  - (95% CI 12.2, 36.6)

**Median follow up:** 15.5 months

**12-month event-free probability:** 0.65

**Data cut-off date:** May 31 2018, ROS1-inhibitor-naïve patients with ROS1+ NSCLC (integrated analysis population)

**NE:** not evaluable

Robert C. Doebele et al, IASLC
Entrectinib, antitumor activity in ALK+ patients

<table>
<thead>
<tr>
<th>Fusion</th>
<th>Confirmed Responses (n)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK1/3</td>
<td>3/3</td>
<td>100%</td>
</tr>
<tr>
<td>ROS1</td>
<td>12/14</td>
<td>86%</td>
</tr>
</tbody>
</table>
Integrated efficacy of entrectinib: NTRK fusion tumors

N=54 pts

**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)

**Primary endpoints***
ORR and DoR

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

**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

Data cut-off at 31 May 2018
Demetri G et al. Presented at ESMO 2018
## Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>NTRK+ patients (n=54)</th>
<th>NTRK+ NSCLC patients (n=10)</th>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>Median (range)</td>
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<tr>
<td></td>
<td>57.5 (21–83)</td>
<td>62.5 (46–76)</td>
</tr>
<tr>
<td><strong>Sex, %</strong></td>
<td>Female</td>
<td>Male</td>
</tr>
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<td></td>
<td>59.3</td>
<td>40.7</td>
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<tr>
<td></td>
<td>50.0</td>
<td>50.0</td>
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<tr>
<td><strong>Race, %</strong></td>
<td>White</td>
<td>Asian</td>
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<td></td>
<td>79.6</td>
<td>13.0</td>
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<tr>
<td></td>
<td>70.0</td>
<td>30.0</td>
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<tr>
<td><strong>ECOG PS, %</strong></td>
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<td>1</td>
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<tr>
<td></td>
<td>42.6</td>
<td>46.3</td>
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<td>11.1</td>
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<tr>
<td></td>
<td></td>
<td>20.0</td>
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<tr>
<td><strong>Prior lines of systemic therapy, %</strong></td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>37.0</td>
<td>20.4</td>
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<tr>
<td></td>
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<td>42.6</td>
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<tr>
<td></td>
<td>30.0</td>
<td>30.0</td>
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<tr>
<td></td>
<td></td>
<td>40.0</td>
</tr>
<tr>
<td><strong>CNS mets at baseline, %</strong></td>
<td>22.2</td>
<td>60.0</td>
</tr>
</tbody>
</table>

**Legend:**
- Neuroendocrine 6%
- Gynaecological 4%
- Cholangiocarcinoma 2%
- Sarcoma 24%
- NSCLC 19%
- CRC 7%
- Thyroid 9%
- Breast 11%
- MASC 13%

Data cut-off date: 31 May 2018

CNS, central nervous system; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer

**EUROPEAN LUNG CANCER CONGRESS 2019**
Paz-Ares et al. Entrectinib in NTRK+ NSCLC
Entrectinib activity: individual pt responses by tumour type

ORR: 57.4%
Entrectinib activity in pts with NTRK fusion-positive NSCLC

**Results per Blinded Independent Central Review (BICR)**

Data cut-off date: 31 May 2018. Note: Patients without matched pre/post therapy scans were excluded from the plot.

- **Best % change from baseline**:
  - NSCLC
  - CNS disease present at baseline

**ORR: 70.0%**

**Efficacy outcomes per BICR**

<table>
<thead>
<tr>
<th><strong>NTRK+ NSCLC patients (n=10)</strong></th>
</tr>
</thead>
</table>
| **ORR, b %**                   | 70.0%
| (95% CI: 34.75–93.33)          |
| **CR, n (%)**                  | 1 (10)
| **PR, n (%)**                  | 6 (60)
| **SD, n (%)**                  | 1 (10)
| **Median DoR, months**         | NE (95% CI 10.4–NE)
| **Median PFS, months**         | 14.9 (95% CI 4.7–NE)

**NTRK+ NSCLC patients with CNS disease at baseline (n=6)**

- **Intracranial response per BICR, n (%)**
  - CR: 2 (33.3)
  - PR: 2 (33.3)
  - SD: 1 (16.7)
  - Not evaluable: 1 (16.7)

---

*Investigator-assessed baseline CNS disease
  a. Best change at any single timepoint; b. Confirmed responses only
  CI, confidence interval; CR, complete response; DoR, duration of response; NE, not estimable; NSCLC, non-small cell lung cancer; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease
Entrectinib activity: individual pt responses by type of NTRK gene

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

Results per Blinded Independent Central Review (BICR)

Demetri G et al. Presented at ESMO 2018
Entrectinib activity in NTRK-fusion tumours

mDOR: 10.4m
First-generation TRK inhibitors are active in TRK fusion-positive cancers

Larotrectinib

**ORR 81%**
(95% CI 72-88%, n=109)
Median DoR not reached
Median PFS not reached

Entrectinib

**ORR 57%**
(95% CI 43-71%, n=54)
Median DoR 10 mos
Median PFS 11 mos

Lassen et al, ESMO 2018; Demetri et al, ESMO 2018
First-generation TRK inhibitors result in durable disease control in TRK fusion-positive cancers

Larotrectinib (n=122)
Median DoR not reached
Median PFS not reached

Entrectinib (n=54)
Median DoR 10 mos
Median PFS 11 mos

Lassen et al, ESMO 2018; Demetri et al, ESMO 2018
## Comparative activity of first-generation TRK inhibitors in TRK fusion-positive cancers

Lassen et al, ESMO 2018; Demetri et al, ESMO 2018; Drilon et al, NEJM 2017

<table>
<thead>
<tr>
<th>Population in the registrational data set</th>
<th>Larotrectinib</th>
<th>Entrectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=109 1 month-80 years &lt;5% brain metastases</td>
<td>80% (95% CI 72-88%)</td>
<td>57% (95% CI 43-71%)</td>
</tr>
<tr>
<td>n=54 21-80 years 22% brain metastases</td>
<td>Not reached</td>
<td>10 months</td>
</tr>
<tr>
<td>ORR</td>
<td>Not reached</td>
<td>11 months</td>
</tr>
<tr>
<td>Median DoR</td>
<td>United States Brazil (Europe – adopted “positive opinion”)</td>
<td>United States Japan</td>
</tr>
<tr>
<td>Median PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulatory Approval</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lassen et al, ESMO 2018; Demetri et al, ESMO 2018; Drilon et al, NEJM 2017
First-generation TRK inhibitors have activity in the CNS

<table>
<thead>
<tr>
<th>Patients with brain metastases</th>
<th>Larotrectinib</th>
<th>Entrectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (at all sites)</td>
<td>ORR 60% (n=5)</td>
<td>ORR 50% (n=12)</td>
</tr>
<tr>
<td>Intracranial ORR</td>
<td>ORR 66% (n=3)</td>
<td>ORR 55% (n=11)</td>
</tr>
<tr>
<td>Intracranial PFS</td>
<td>Not reported</td>
<td>14 months</td>
</tr>
</tbody>
</table>

TRK fusion-positive lung cancer with brain metastases treated with larotrectinib

- Confirmed PR (−34%)
- Near intracranial CR (−95%, volumetric)
- Remains on therapy at 6+ months

Drilon et al, ASCO 2019; Demetri et al, ESMO 2018; Rosen et al JCO-PO 2019
TRK fusion-positive pediatric gliomas respond to entrectinib and larotrectinib

- Prior treatment
  - Carboplatin and vincristine
  - Vinblastine

- ETV6-NTRK3 fusion identified
- Treated with larotrectinib
  - Partial response (~50%)*
  - Treatment ongoing at 1 yr (May 2019)

Robinson et al, ASCO 2019; Drilon et al, ASCO 2019
Selectivity and in vitro antiproliferative activity of repotrectinib (TPX-0005)

A. Drilon et al, Cancer Discovery 2018
TRIDENT-1: A Phase 1/2 Study of Repotrectinib

Study Design/Eligibility (Phase 1)
- Advanced solid tumors harboring ROS1/NTRK1-3/ALK fusions
- No limit on prior lines of therapy
- Asymptomatic CNS metastases allowed

Phase 1 Primary Objective
- Determine the MTD and RP2D

Phase 1 Secondary Objectives
- Safety and tolerability
- Preliminary objective response rate and clinical benefit rate

<table>
<thead>
<tr>
<th>Number of patients per dose cohort</th>
<th>40 mg QD</th>
<th>80 mg QD</th>
<th>160 mg QD</th>
<th>240 mg QD</th>
<th>160 mg BID</th>
<th>200 mg BID ( ^1 )</th>
<th>120 mg QD w/ Food</th>
<th>160 mg QD w/ Food</th>
<th>160 mg QD/BID w/ Food ( ^2 )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety population ( (ROS1+, NTRK1-3+, ALK+ solid tumors) )</td>
<td>13</td>
<td>12</td>
<td>23</td>
<td>10</td>
<td>12</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>83**</td>
</tr>
<tr>
<td>Efficacy population ( (ROS1+ NSCLC) )</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0*</td>
<td>33</td>
</tr>
</tbody>
</table>

\( ^1 \) 2 ALK patients enrolled
\( ^2 \) 160 mg QD for one week followed by 160 mg BID
\( ^* \) Not yet evaluable for efficacy by BICR
\( ** \) N=83 patients: 31 were ALK+, 9 were NTRK+, and 43 were ROS1+ (of which 33 ROS1+ NSCLC were evaluable for efficacy by BICR)

BICR: Blinded Independent Central Review

ASCO 2019 B.C. Cho, M.D., PhD

Data cut-off date of March 4, 2019
Repotrectinib (ROS1/TRK/ALK Inhibitor) in TKI-naïve ROS1+ NSCLC by BICR

**TKI-naïve (N=10)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, n/N (%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>(44 ─ 97)</td>
</tr>
<tr>
<td>Time to response (TTR), mo</td>
<td>1.6</td>
</tr>
<tr>
<td>Median</td>
<td>1.4 ─ 3.3</td>
</tr>
<tr>
<td>Intracranial ORR, n/N (%)</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>(measurable disease)</td>
<td></td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>(29 ─ 100)</td>
</tr>
<tr>
<td>CBR*, n/N (%)</td>
<td>10/10 (100%)</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>(69 ─ 100)</td>
</tr>
</tbody>
</table>

*aClinical benefit rate (CBR) = CR + PR + SD ≥ 2 cycles*

5 of 8 patients remain in cPR (3.7+ ─ 11.1+mo)

**Overall Response (N=10)**

- Confirmed ORR: 80%
- Intracranial ORR: 100%
- Median time to response: 1.6 months
- Range of time to response: 1.4 ─ 3.3 months

**Intracranial Response (N=3)**

- Intracranial ORR: 100%
- Median time to response: 1.6 months
- Range of time to response: 1.4 ─ 3.3 months

Presented by: Jessica J. Lin, Massachusetts General Hospital, USA
Preliminary Efficacy of Repotrectinib in TKI-pretreated ROS1+ NSCLC by BICR

TKI-pretreated (N=17)

<table>
<thead>
<tr>
<th>Confirmed ORR, n/N (%)</th>
<th>3/17 (18%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI (%)</td>
<td>(4 — 44)</td>
</tr>
</tbody>
</table>

**ORR at 160 mg QD**

2/6 (33%)

**Time to response (TTR), mo**

Median 1.6

Range 1.5 — 1.8

**Intracranial ORR, n/N (%)** (measurable disease)

1/4 (25%)

**CBR*, n/N (%)**

13/17 (76%)

95% CI (%) (56 — 97)

*CBR = CR + PR + SD ≥ 2 cycles

1 of 3 patients remains in cPR (11.1+ mo)

Overall Response (N=17)

- **ORR: 18%**

- **IC-ORR: 25%**

Intracranial Response (N=4)

- **ORR: 18%**

- **IC-ORR: 25%**

Presented by: Jessica J. Lin, Massachusetts General Hospital, USA
Duration of Repotrectinib Treatment in N=27 ROS1+ NSCLC by BICR

15 of 27 patients (56%) remain on treatment 13 Jul 2018
Preliminary Clinical Activity of Repotrectinib Against ROS1 G2032R

- 16 of 17 TKI-pretreated subjects had baseline plasma cfDNA tested by NGS (Guardant360)
- ROS1 G2032R detected in 4 subjects (25%) who had been crizotinib-pretreated
- All 4 subjects experienced tumor regressions on Repotrectinib
- 1 cPR at 160 mg QD (DOR 7.4 mos and remains on treatment at 11+ mos)

Presented by: Jessica J. Lin, Massachusetts General Hospital, USA
Case Example of the Clinical Activity of **Repotrectinib** Against **ROS1 G2032R**

Tumor regression on Repotrectinib in a patient with ROS1+ NSCLC, resistant to crizotinib and chemotherapy and found to have **ROS1 G2032R** on liquid biopsy.

Presented by: Jessica J. Lin, Massachusetts General Hospital, USA
CD74–ROS1-rearranged NSCLC with ROS1-G2032R-mediated resistance to crizotinib

A.Drilon et al, cancer discovery 2018
Pivotal Phase 2 Portion of TRIDENT-1: Plan to Initiate in 2H 2019

**ROS1+ Advanced NSCLC Pivotal Cohorts** (up to n=190)
- EXP-1: ROS1 TKI-naive
  - Advanced NSCLC (n=50)
- EXP-2: 1 Prior ROS1 TKI ROS1+ advanced NSCLC (n=100)
- EXP-3: 2 Prior ROS1 TKI ROS1+ advanced NSCLC (n=40)

**Exploratory Cohort** (up to n=26)
- EXP-4: ROS1 or ALK TKI-naive ROS1+ or ALK+ advanced solid tumors (non-NSCLC) (n=12-26)

**NTRK+ Advanced Solid Tumors Pivotal Cohorts** (up to n=90)
- EXP-5: TRK TKI-naive NTRK+ advanced solid tumors (n=50)
- EXP-6: TRK TKI-pretreated NTRK+ advanced solid tumors (n=40)

**Phase 2 Primary Objective**
- cORR by BICR in each expansion cohort

**Phase 2 Secondary Objectives**
- DOR, PFS, and OS
- IC-ORR and CNS-PFS

**Data cut-off date of March 4, 2019**
new-generation selective ROS1/NTRK inhibitor
DS-6051b

In vitro kinase assay

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC$_{50}$ (nM)</th>
<th>ATP: Km</th>
<th>ATP: 1 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROS1</td>
<td>0.207</td>
<td>0.898</td>
<td></td>
</tr>
<tr>
<td>NTRK1</td>
<td>0.622</td>
<td>3.01</td>
<td></td>
</tr>
<tr>
<td>NTRK2</td>
<td>2.28</td>
<td>9.52</td>
<td></td>
</tr>
<tr>
<td>NTRK3</td>
<td>0.980</td>
<td>9.28</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity of TPM3-NTRK1-induced Ba/F3 cells

Ryohei Katayama et al, nature 2019
Safety and pharmacokinetics of DS-6051b in Japanese patients with non-small cell lung cancer harboring ROS1 fusions: A phase I study

Yutaka Fujiwara et al, Oncotarget 2018

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Dose (mg QD)</th>
<th>Fusion gene</th>
<th>Prior regimen</th>
<th>Crizotinib treatment line and its BR</th>
<th>Treatment duration: BR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>02</td>
<td>400</td>
<td>ROS1</td>
<td>2</td>
<td>-</td>
<td>2M 4M 6M 8M 10M 12M 14M 16M 18M</td>
</tr>
<tr>
<td>03</td>
<td>400→600</td>
<td>ROS1</td>
<td>3</td>
<td>3rd/PR</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>800</td>
<td>ROS1</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>04</td>
<td>600→400</td>
<td>ROS1</td>
<td>2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>400</td>
<td>ROS1</td>
<td>8</td>
<td>9thPR</td>
<td></td>
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<tr>
<td>09</td>
<td>400</td>
<td>ROS1</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>600</td>
<td>ROS1</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>600</td>
<td>ROS1</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>600→400</td>
<td>ROS1</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>600</td>
<td>ROS1</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>600</td>
<td>ROS1</td>
<td>2</td>
<td>2nd/ND</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>600→400</td>
<td>ROS1</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>400</td>
<td>ROS1</td>
<td>11</td>
<td>5th/PD</td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>400</td>
<td>ROS1</td>
<td>2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>800</td>
<td>ROS1</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Progressive disease
Clinical progression
D/CAE
Over 3 weeks of study drug interruption

CT
MRI (brain metastases)
On-target resistance can occur after first-generation TRK inhibitor use

<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>Colorectal¹</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R, G667C</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Colorectal²</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R, F589L</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Colorectal²</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Pancreas²</td>
<td>CTRC-NTRK1</td>
<td>TRKA A608D</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Colangiocarcinoma²</td>
<td>LMNA-NTRK1</td>
<td>TRKA F589L</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>NSCLC²</td>
<td>TPR-NTRK1</td>
<td>TRKA G595R, G667C</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Soft tissue sarcoma²</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Thyroid²</td>
<td>IRF2BP2-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>MASC³</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>IFS²</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>GIST²</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R, G696A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>L1122 V1180 L1196 G1202 G1203 G1269</td>
</tr>
<tr>
<td>ROS1</td>
<td>L1951 L2026 G2032 D2033 L2155</td>
</tr>
<tr>
<td>RET</td>
<td>V804</td>
</tr>
<tr>
<td>NTRK1</td>
<td>V573 F589 G595 G667</td>
</tr>
<tr>
<td>NTRK2</td>
<td>V601 G623 G693 Q596 R630</td>
</tr>
<tr>
<td>NTRK3</td>
<td>G623</td>
</tr>
</tbody>
</table>

Second-generation TRK inhibitors can address on-target resistance

Drilon et al, Cancer Discov 2017; Drilon et al, Cancer Discov 2018
LOXO-195 (BAY 2731954) Best tumor change and treatment duration by resistance mechanism

David.M.Hyman et al, AACR 2019
Potential treatment algorithm for treating TRK fusion-positive cancers in infants, children, adolescents and adults

**On-Target Resistance**

<table>
<thead>
<tr>
<th></th>
<th>TRKA</th>
<th>TRKB</th>
<th>TRKC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent Front</td>
<td>G595R</td>
<td>G639R</td>
<td>G623R</td>
</tr>
<tr>
<td>Gatekeeper</td>
<td>FS89L</td>
<td>F633L</td>
<td>F617L</td>
</tr>
<tr>
<td>xDFG</td>
<td>G667C</td>
<td>G709C</td>
<td>G696A</td>
</tr>
<tr>
<td>Other</td>
<td>A608D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Repotrectinib**
LOXO-195 (BAY2731954)

**2nd generation TRK Inhibitor**

**Resistance**
For oligo/solitary site progression, consider local therapy and continued TKI use.

**Off-Target Resistance**

- Potential Mechanisms Identified
  - KRAS mutation
  - MET amplification
  - BRAF mutation
  - IGF1R activation

**1st generation TRK Inhibitor**
Entrectinib
Larotrectinib

**Standard of Care**
or clinical trial when available

Summary

• *NTRK* fusions are found across a wide variety of cancers

• *NTRK* fusions are clinically actionable
  – Iarotrectinib and entrectinib are approved for *NTRK* fusion-positive cancers of any histology
  – Both drugs have activity in the CNS: in solid tumors with brain metastases or primary brain tumors

• First-generation TRK inhibitors are well-tolerated overall

• Next-generation TRK inhibitors are currently in development
New data to come…

Patients with TRK Fusion–Positive

Larotrectinib (Loxo-101)
Entrectinib (ALK/ROS1/NTRK)
Repotrectinib (ALK/ROS1/NTRK)

Merestinib
LOXO-195
DS-6051b (ROS1/NTRK)
Foretinib
THANK YOU!

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