Safety and Preliminary Clinical Activity of Repotrectinib (TPX-0005), a ROS1/TRK/ALK Inhibitor, in Advanced ROS1 Fusion-Positive Non-Small Cell Lung Cancer

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Disclosures

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Introduction: Repotrectinib, a Next-Generation ROS1/TRK/ALK TKI

- **ROS1** rearrangement is an oncogenic driver in 1-2% of NSCLC

- Crizotinib is the only approved targeted therapy for patients with advanced **ROS1**+ NSCLC

- **G2032R** is the most common **ROS1** resistance mutation after crizotinib treatment\(^1\)

- **Repotrectinib** is a next-generation **ROS1/TRK**-C/ **ALK** inhibitor, designed to overcome TKI resistance mutations, especially solvent front **ROS1 G2032R**\(^2\)

\(^{1}\) Gainor JF et al., JCO Precis Oncol 2017
\(^{2}\) Drilon A et al., Cancer Discov 2018

### CD74-ROS1 Ba/F3 Cell Proliferation IC\(_{50}\) (nM)*

<table>
<thead>
<tr>
<th>ROS1</th>
<th>Crizotinib</th>
<th>Ceritinib</th>
<th>Cabozantinib</th>
<th>Entrectinib</th>
<th>Lorlatinib</th>
<th>Repotrectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>14.6</td>
<td>42.8</td>
<td>0.5</td>
<td>10.5</td>
<td>0.2</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>G2032R</td>
<td>266.2</td>
<td>1391</td>
<td>11.3</td>
<td>1813</td>
<td>160.7</td>
<td>3.3</td>
</tr>
<tr>
<td>D2033N</td>
<td>200.9</td>
<td>535.4</td>
<td>0.2</td>
<td>169.2</td>
<td>3.3</td>
<td>1.3</td>
</tr>
<tr>
<td>L2026M</td>
<td>606.4</td>
<td>ND</td>
<td>29.1</td>
<td>2026</td>
<td>930.6</td>
<td>10</td>
</tr>
<tr>
<td>S1986F</td>
<td>63.7</td>
<td>68</td>
<td>5.5</td>
<td>3.4</td>
<td>0.4</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>L1951R</td>
<td>157.6</td>
<td>785.5</td>
<td>91.8</td>
<td>35.4</td>
<td>2.8</td>
<td>&lt;0.2</td>
</tr>
</tbody>
</table>

\* Unpublished data
# TRIDENT-1: A Phase 1 Study of Repotrectinib

## Study Design / Eligibility
- Multicenter study in advanced/metastatic solid tumors harboring \textit{ROS1/NTRK1-3/ALK} fusions
- Measurable disease (RECIST v1.1)
- No limit on prior lines of therapy (including prior TKIs)
- Asymptomatic treated or untreated CNS metastases/leptomeningeal disease allowed

## Primary Objective
- Determine the maximum tolerated dose and recommended phase 2 dose

## Secondary Objectives
- Safety and tolerability
- Food effect
- Preliminary objective response rate and clinical benefit rate

## Number of patients per dose level

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Safety population</th>
<th>Efficacy population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\text{ROS1}^+, \text{NTRK1-3}^+, \text{ALK}^+) solid tumors</td>
<td>(\text{ROS1}^+) NSCLC</td>
</tr>
<tr>
<td>40 mg QD</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>80 mg QD</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>160 mg QD</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>240 mg QD</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>160 mg BID</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>200 mg BID</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Total: 72

Data cut-off date of July 13, 2018
*N=30 by Investigator assessment and N=27 by BICR (3 not evaluable by BICR analysis)
### TRIDENT-1: ROS1+ NSCLC Patient Demographics

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=30*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>52 (30, 75)</td>
</tr>
<tr>
<td>Sex, female n (%)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Race, Asian n (%)</td>
<td>17 (57)</td>
</tr>
<tr>
<td><strong>CNS metastases at baseline, n/N (%)</strong></td>
<td>16/30 (53)</td>
</tr>
<tr>
<td>TKI-naïve, n/N (%)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>TKI-pretreated, n/N (%)</td>
<td>11/20 (55)</td>
</tr>
<tr>
<td><strong>ROS1 fusion detection method, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>FISH</td>
<td>22 (73)</td>
</tr>
<tr>
<td>NGS</td>
<td>8 (27)</td>
</tr>
<tr>
<td><strong>Median lines of prior systemic therapy (range)</strong></td>
<td>2 (1, 8)</td>
</tr>
<tr>
<td>Prior ROS1 TKI, n (%)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Crizotinib only, n (%)</td>
<td>11 (37)</td>
</tr>
<tr>
<td><strong>Median # of prior TKIs (range)</strong></td>
<td>1 (0, 3)</td>
</tr>
<tr>
<td>No prior TKI(s), n (%)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>1 prior TKI, n (%)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>≥2 prior TKIs, n (%)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Prior chemotherapy, n (%)</td>
<td>27 (90)</td>
</tr>
</tbody>
</table>

*Assessed by Investigator*
Repotrectinib Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Most common (&gt;10%) treatment-related AEs</th>
<th>All Grades (%)</th>
<th>Grade 3# (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>60 (83.0)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>36 (50.0)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>33 (45.8)</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>21 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (12.5)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>

#Additional grade 3 treatment-related AEs: weight increased, dyspnea/hypoxia, pleural effusion, hypophosphatemia (1 each)

No grade 4 treatment-related AEs observed

- **Dose-limiting toxicities** (n=4)
  - Grade 2 or 3 dizziness
    - 160 mg BID (n=2)
    - 240 mg QD (n=1)
  - Grade 3 dyspnea/hypoxia
    - 160 mg BID (n=1)

- **Two deaths during study treatment**
  - 1 due to disease progression
  - 1 due to sudden death possibly related to study drug

- **RP2D determination is ongoing**

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

TKI-naïve (N=10)

- Confirmed ORR, n/N (%) 8/10 (80%)
  95% CI (%) (44 ─ 97)
- Time to response (TTR), mo
  Median 1.6
  Range 1.4 ─ 3.3
- Intracranial ORR, n/N (%) 3/3 (100%)
  (measurable disease)
  95% CI (%) (29 ─ 100)
- CBR*, n/N (%) 10/10 (100%)
  95% CI (%) (69 ─ 100)

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

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

Overall Response (N=10)

Intracranial Response (N=3)

- Stable Disease

- Patients with intracranial and extracranial cPR

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 (%)**
  - 1/4 (25%)
  - (measurable disease)

- **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)

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**Overall Response (N=17)**

- **Max change in tumor size (% from baseline**

**Intracranial Response (N=4)**

- **Max change in tumor size (% from baseline**

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**Presented by:** Jessica J. Lin, Massachusetts General Hospital, USA

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**Legend:**
- # Stable Disease
- • Progressive Disease
- ! Patient with intracranial and extracranial cPR
- b Response occurred after dose reduction to 160 mg QD
Duration of Repotrectinib Treatment in N=27 ROS1+ NSCLC by BICR

Presented by: Jessica J. Lin, Massachusetts General Hospital, USA

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

Baseline

After 7 weeks of Repotrectinib

Presented by: Jessica J. Lin, Massachusetts General Hospital, USA
Conclusions

- Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor designed to systemically overcome TKI resistance mutations, especially solvent front mutations

- Repotrectinib demonstrated preliminary clinical activity in ROS1+ NSCLC across all doses, with confirmed ORR 80% in TKI-naïve patients, 18% in all TKI-pretreated patients with 33% in patients treated at 160 mg QD
  - Tumor regressions observed in 4 crizotinib-pretreated patients with a ROS1 G2032R solvent front resistance mutation, with 1 confirmed PR having a duration of response of 7.4 months at 160 mg QD

- Intracranial antitumor activity was observed in TKI-naïve and TKI-pretreated subjects

- Repotrectinib was well tolerated with primarily Grade 1-2 treatment-related AEs
  - Dose-limiting dizziness is an on-target adverse event associated with TRK inhibition
  - Recommended phase 2 dose determination is ongoing

- The preliminary TRIDENT-1 phase 1 data warrant further clinical testing of Repotrectinib in ROS1+ NSCLC and other solid tumors harboring ROS1 fusions
We thank the patients, their families and caregivers and participating clinical sites

United States:
• University of California Irvine
  Ignatius Ou, MD - Principal Investigator
  Viola Zhu, MD - Sub-Investigator

• Memorial Sloan Kettering Cancer Center
  Alexander Drilon, MD - Principal Investigator

• University of Colorado
  Robert Doebele, MD - Principal Investigator
  Ross Camidge, MD - Sub-Investigator

• Massachusetts General Hospital
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• Samsung Medical Center
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