## Background

- ROS1 oncogenic fusions are observed in ~1% of NSCLC patients as well as in cholangiocarcinomas, glioblastomas, ovarian, gastric, and colorectal cancers.
- CNS metastasis occurs in 20–30% ROS1 TKI-naïve and in up to 50% pretreated ROS1-positive NSCLC patients.
- Resistance to first-generation ROS1 inhibitors often occurs with secondary mutations such as ROS1 G2032R solvent front mutation.
- Taletrectinib, a next-generation selective, resistant ROS1 tyrosine kinase inhibitor, is developed for:
  - exhibits resistance to first-generation ROS1 inhibitors
  - addresses CNS metastasis
  - improves efficacy and safety profile in ROS1-positive NSCLC patients
  - combines specific ROS1-related CNS adverse events by selectively inhibiting ROS1 over TKRs.

## Methods

The ongoing clinical study is a multicenter, open-label, single-arm, phase 2 study of taletrectinib in Chinese ROS1-positive NSCLC patients.

The study consists of two parts:

Part 1: A lead-in dose titration period in which taletrectinib was only administered with 600mg QD (N=3) and 600QD (N=3) dose.

Part 2: All patients are orally administered with 600mg QD regimen in both the ROS1 TKI naïve group and the ROS1 TKI pretreated group.

## Efficacy in Patients with Brain Metastases

### Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Male</th>
<th>CRizotinib-Positve (%)</th>
<th>Total</th>
<th>CRizotinib-Positve (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (81.4%)</td>
<td>20 (62.5%)</td>
<td>48 (44.1%)</td>
<td>44 (44.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (38.6%)</td>
<td>6 (17.5%)</td>
<td>18 (15.9%)</td>
<td>30 (15.9%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>55 (38-75)</td>
<td>39 (35-65)</td>
<td>54 (42-71)</td>
<td>55 (38-75)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>60 (45-75)</td>
<td>55 (45-75)</td>
<td>60 (45-75)</td>
<td>60 (45-75)</td>
</tr>
<tr>
<td>Histological Subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>64 (63%)</td>
<td>62 (61%)</td>
<td>126 (63%)</td>
<td>126 (63%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lymphoepitheliocarcinoma</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>6 (3%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Stages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>42 (41%)</td>
<td>35 (35%)</td>
<td>77 (39%)</td>
<td>77 (39%)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>40 (38%)</td>
<td>40 (35%)</td>
<td>80 (40%)</td>
<td>80 (40%)</td>
</tr>
<tr>
<td>Prior Anti-TCIT treatment</td>
<td>Yes</td>
<td>77 (76%)</td>
<td>120 (60%)</td>
<td>197 (97%)</td>
</tr>
<tr>
<td>Brain Metastasis (IRC assessed)</td>
<td>No</td>
<td>50 (49%)</td>
<td>30 (15%)</td>
<td>80 (39%)</td>
</tr>
<tr>
<td>Brain Metastasis (IRC assessed)</td>
<td>Yes</td>
<td>50 (49%)</td>
<td>132 (65%)</td>
<td>182 (87%)</td>
</tr>
</tbody>
</table>

### Efficacy in CRizotinib-Positive Patients

- **CRizotinib**
  - 92.5% (95% CI: 81%–100%)
  - SD: 2 (21%)
  - CR: 6 (6%)
  - BOR: 1 (1%)

- **Taletrectinib**
  - 95.4% (95% CI: 89%–100%)
  - SD: 0 (0%)
  - CR: 14 (12.8%)
  - BOR: 0 (0%)

### References


## Efficacy in CRizotinib-Naïve Patients

- **CRizotinib**
  - 92.5% (95% CI: 81%–100%)
  - SD: 2 (21%)
  - CR: 6 (6%)
  - BOR: 1 (1%)

- **Taletrectinib**
  - 95.4% (95% CI: 89%–100%)
  - SD: 0 (0%)
  - CR: 14 (12.8%)
  - BOR: 0 (0%)

### Summary

Taletrectinib is a potential best-in-class next-generation ROS1 inhibitor for treating both ROS1 TKI-naïve and pre-treated NSCLC patients.

- High ORRs observed in 5% and 5% of patients.
- Excellent potency against ROS1 activating mutations including G2032R solvent front mutation.
- Strong anti-proliferative activity in patients. Unphased preclinical data showed better brain penetration and intracranial activity than competitors, suggesting potentially longer-tail in efficacy for brain metastatic patients.
- Safe tolerability profile; AE results showed low-dose select inhibition of ROS1 over TRKB by taletrectinib may help significantly reduce TRKB-stabilizing (CRizotinib-Positive) NSCLC metastases.