TRUST: The Efficacy and Safety of Taletrectinib in TKI-Naive or Crizotinib-Pretreated ROS1-Positive Non-Small Cell Lung Cancer (NSCLC) Patients

**Background**

- ROS1 oncogenic fusions are observed in ~1% of NSCLC patients as well as in cholangiocarcinoma, glioblastoma, ovarian, gastric, and colorectal cancers.
- CNS metastasis occurs in 20-30% ROS1 TKI-naive and in up to 50% crizotinib-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, potent, ROS1 tyrosine kinase inhibitor, is developed to:
  - overcame resistance to first-generation ROS1 inhibitors.
  - addres CNS metastasis.
  - improve efficacy and safety profile in ROS1-positive NSCLC patients.
  - overcome crizotinib-related CNS adverse events by selectively inhibiting ROS1 over TKI.

**Methods**

The ongoing TRUST 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 orally administered with 600 mg (QD) and 600 mg (N=3) dose.
- **Part 2:** all patients are orally administered with 600mg QD dose regimen in both the ROS1 TKI-naive cohort (N=1) and the crizotinib-pretreated cohort (n=2) 2.0+).

**Key Efficacy Endpoints:**

- Primary endpoint: ORR of PFS1 assessed by an independent review committee (IRC).
- Secondary endpoints: ORR, DOR, PFS, IRF (IC)-CR, IC-DR, IC-PSF and PFS1 assessed by IRC and/or investigators.

**Key Inclusion Criteria:***

- Pathologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC.
- Age ≥ 18 years old.
- ECOG PS 0-1.
- ROS1 fusions in tumor tissue were determined by molecular assays.
- At least one measurable lesion per RECIST 1.1.

For more details see NCT04395677 at clinicaltrials.gov.

**Efficacy in Patients with Brain Metastases**

**Efficacy in Crizotinib-Pretreated Patients**

**Safety Profile (Pooled Data)**

**References**

5. ASCO 2020 poster (NCT04395677).
6. In a phase 1-2 pooled analysis, data from 19 patients in two phase 1b clinical trials (EN21 and EN23) were combined with TRUST (phase 2a, EN25) that was a first-in-
  human, phase 2b trial with advanced solid tumors in the US, 2020 was a phase 1-2 study that included a 2021 phase 3 trials were assessed by investigators as of Aug 19, 2021.
7. The 5 biomarkers used in TRUST-1 (NCT03490077, NCT03490166, NCT03704911, NCT02704535, and NCT01647584 at clinicaltrials.gov).

**Efficacy in ROS1 TKI-Naive Patients**

**CRITICALLY IMPORTANT:**

No evidence of taletrectinib-related CNS adverse reactions. All data were collected from all patients who were treated with taletrectinib. No patients had CNS adverse events.

**Acknowledgements**

- The authors would like to thank the patients and families for making these trials possible.
- The clinical trial teams and investigators for their work and contributions.
- Dr. Caihui Zhou and Dr. Xin Yang for their support.

**Abbreviations**

- NOS: not otherwise specified.
- BM: treatment related adverse event.
- BM: treatment related adverse event.
- AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cells.
- ORR: intracranial objective response rate.
- DCR: disease control rate.
- mPFS: median progression-free survival.
- mDOR: median duration of response.
- mCRRP: median clinical response rate progression.
- mTTP: median time to progression.
- cORR: complete response rate.
- dOR: duration of response.
- DCR (n/N) [95% CI]
- mPFS, month
- mDOR, month
- mCRRP, month
- cORR (n/N)
- cORR [95% CI]
- DCR [95% CI]
- mTTP, month
- cORR [95% CI]
- DCR [95% CI]
- mPFS, month
- mDOR, month
- mCRRP, month
- cORR (n/N)
- cORR [95% CI]
- DCR [95% CI]
- mTTP, month
- cORR [95% CI]
- DCR [95% CI]
- mPFS, month
- mDOR, month
- mCRRP, month
- cORR (n/N)
- cORR [95% CI]
- DCR [95% CI]
- mTTP, month

**Conclusion**

Taletrectinib is a potent lead-in-class next-generation ROS1 inhibitor for treating both ROS1 TKI-naive and pre-treated NSCLC patients.

**Summary**

Taletrectinib is a potent lead-in-class next-generation ROS1 inhibitor for treating both ROS1 TKI-naive and pre-treated NSCLC patients.

- **High ORRs observed in 9% and 3% patients.
- Excellent potency and selectivity of co-treated resistance mutations, including G2032R solvent front mutation.
- Strong intracellular activity in patient mutation. Unpublished preclinical data showed better brain penetration and intracranial efficacy compared to first-generation TKIs, suggesting potentially longer mPFS and OS for brain metastatic patients.
- **Tolerability safety profiles:** The survival of inhibition of ROS1 TKI by taletrectinib may be significantly lower with the lack of CNS adverse events.

A separate global phase 2 trial (TRUST-1, NCT04918977) is actively enrolling patients at clinical sites in North America, Europe and Asia. For details see ASCO 2022 Trials in Progress poster (Abstract #TPB8011).