**Introduction**

- Even though epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have improved treatment outcomes for EGFR mutant, resistance inevitably emerges with disease progression and often with CNS metastasis.
- C797S mutation is one of the most common on-target resistance mutation after the use of 3rd generation TKIs such as Osimertinib.
- Importantly, the allelic context in which C797S is acquired has potential implications for treatment. When C797S positive cells are in cis with the T790M mutation, there are no available treatment.
- JIN-A02 is a new 4th generation investigational EGFR-TKI, which is highly selective and potent against C797S double and triple mutations.
- JIN-A02 has a strong inhibitory activity against both cis and trans allele of C797S with high brain penetration.
- We describe the preclinical data which indicates that JIN-A02 is a highly effective EGFR-TKI targeting C797S mutations and is potent to treat CNS metastases.

**Method**

- Cellular activities of JIN-A02 were evaluated on phosphorylation-EGFR expression with AlphaLISA assay in EGFR mutant cell lines and cell viability assay in Ba/F3 cell lines overexpressing human EGFR mutants and patient-derived cell (PDC) lines harboring EGFR mutations.
- Antitumor activities of JIN-A02 were evaluated in cell derived xenograft (CDX) and patients-derived xenografts (PDX).
- The in vivo anti-tumor activity of JIN-A02 was evaluated in an intracranial tumor models which were generated through implanting H1975-luc into brains of female BALB/c nude mice. MRI analysis was performed to monitor the tumor growth.

**JIN-A02, highly selective and potent inhibitor**

- In AlphaLISA assay, JIN-A02 showed high potency in EGFR mutants.
- JIN-A02 is highly selective away from EGFR WT and showed convincing results.
- JIN-A02 is a highly potent 4th generation EGFR-TKI targeting C797S mutations and is selective away from EGFR WT.
- JIN-A02 was observed with intracranial implanted NCI-H197S tumors.
- JIN-A02 showed a tendency to delay tumor growth in a dose-dependent manner compared to the control group (Vehicle) on Day 21.

**Conclusion**

- JIN-A02 is a highly potent 4th generation EGFR-TKI against double and triple C797S resistance mutations, including both cis and trans isomers.
- JIN-A02 is selective away from EGFR WT and showed BBB penetration with strong intracranial anti-tumor effects.
- JIN-A02 is scheduled to start the First-in-human clinical trial (NCT05394833) this year based on these convincing results.

**References**

2. Cho BC et al. IASLC 2022 WCLC poster and provided their final approval of all content.

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