Identification of STX-721, an EGFR exon 20 mutant inhibitor with superior selectivity and a potent best-in-class profile

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Introduction

EGFR mutations are well validated clinical targets in NSCLC. Osimertinib, a highly-selective EGFR mutation-targeting drug, shows therapeutic response rates of ~70% against cases with EGFR L858R mutations. However, ~30% of cases with EGFR T790M and deleterious adjacent EGFR mutations (EGFR T790M plus L858R, for example) do not respond to currently approved or investigational therapies between 28-52%. The suboptimal efficacy of existing EGFR inhibitors for patients with exon 20 mutation is likely due to poor mutant versus wild-type EGFR selectivity.

The apparent in vitro selectivity of EGFR inhibitors is highly dependent on the model systems used, limiting the predictive value of these systems for drug discovery. To address this issue, we optimized the selectivity of a high potency allosteric inhibitor of wild-type (WT) EGFR (Baf-B3 cells) as well as NSCLC cells with endogenous or knock-in exon 20 mutations. The high selectivity of Osimertinib in EGFR L858R/T790M mutant cells was used to benchmark EGFR mutant selectivity, given its exceptional response rate and wide therapeutic index. Compounds were tested in proliferation, cell signaling, and biochemical assays. Finally, we examined inhibitory efficacy, pharmacodynamics, pharmacoekinetics, and tolerability in novel patient-derived EGFR exon 20 mutant xenograft (PID) mouse models.

Herein, we describe a novel EGFR exon 20 inhibitor, STX-721, and characterize its in vitro/in vivo potency and selectivity vs EGFR WT. To this end, we report here, we screen across a wide panel of engineered and endogenous mutant EGFR exon 20 model systems.

Results

Using Osimertinib as benchmark in vitro cellular selectivity assays

- osimertinib selectivity vs EGFR vs EGFR mutant

STX-721 is highly selective for a common EGFR exon 20 insertion

- EGFR inhibitor selectivity in Ba/F3 EGFR family members

- STX-721 is a highly selective mutant EGFR binder

- Left panel: Kd(EGFR) values determined for the listed inhibitors using a CellTiter-Glo™ EGFR WT selectivity assay. Data are shown as mean ± SE with the concentration of each compound used (μM) in brackets. Osimertinib is shown as a reference.

- Right panel: STX-721 was profiled at 0.1 μM and 100 μM. Error bars represent mean ± SE.

- Selectivity is determined according to the Ba/F3 assay. Results are shown as mean ± SE with the concentration of each compound used (μM) in brackets.

- Ba/F3 cells with the noted EGFR and HER2 mutants were assessed via CellTiter-Glo™ WT selectivity assay. Data are shown as mean ± SE with the concentration of each compound used (μM) in brackets. Osimertinib is shown as a reference.

Conclusions

- STX-721 demonstrates potent and selective Ba/F3 and human cancer cell line proliferation assays.

- STX-721 potency and exon 20 selectivity is also observed in signaling (ΔEGFR) and biochemical assays.

- Exon 20 selectivity for STX-721 exceeds that of key clinical competitor benchmarks in these model systems, and approaches the selectivity of Osimertinib against a “classic” EGFR mutant.

- STX-721 displays strong in vivo antitumor activity across a variety of EGFR and HER2 exon 20 mutant CDX and PDX models, and in vivo selectivity in human lung cancer cell line xenografts.

- STX-721 has the potential to provide a best-in-class profile to improve outcomes in patients harboring cancers with EGFR/HER2 exon 20 mutations and is currently in IND enabling studies.

References / Acknowledgements

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