Abstract: S130

Title: THE NOVEL MENIN INHIBITOR ZE63-0302 HAS AN IMPRESSIVE SAFETY PROFILE AND UNIQUE CHEMISTRY THAT SUGGESTS IMPROVED EFFICACY AGAINST RESISTANCE MUTATIONS.

Abstract Type: Oral Presentation

Session Title: Acute myeloid leukemia - Clinical 1 - Menin inhibitor

Background:

MLL/KMT2A rearranged (KMT2Ar) and Mutant NPM1 AML which expresses a cytosolic restricted NPM1 protein (NPM1c) are driven by elevated expression of HOX genes that are dependent on the menin-KMT2A interaction, and this aberrant gene expression can be reversed by disrupting the binding of menin to KMT2A. However, therapies that have been developed to inhibit this interaction suffer from significant cardiac toxicities (QTc prolongation) or sensitivity to cytochrome P450 inhibition, which has limited their clinical development. Furthermore, early trials with menin inhibitors have reported the development of acquired somatic mutations in *MEN1* gene in about 40% of patients with prolonged monotherapy menin inhibitor treatment (> 2 months). These resistance mutations (most commonly M327 and G331) impede the interaction of the drug with the W346 residue which is a key determinant of inhibitor binding to menin, resulting in loss of therapeutic benefit.

Aims:

Our approach is to develop a novel potent and selective menin inhibitor that 1) limits these undesirable side effects and 2) reduces the likelihood of developing resistance mutations.

Methods:

Modeling of SNDX-5613 bound to mutated MEN1 suggest that the conformational change in the M327 or G331 mutants leads to steric hinderance of SNDX-5613 with the target residue W346. We therefore developed a series of compounds which form a specific interaction allowing the ligand to find favorable target interaction avoiding W346. A series of compounds were screened using cell free inhibition of the menin-KMT2A interaction and cellular proliferation assays in KMT2A-rearranged (MV4-11 and MOLM-13) and NPM1c mutant (OCI-AML3) cell lines. Purkinje fiber assays were performed as a surrogate for QTc prolongation and cardiotoxicity. *In vivo* single agent and combination studies were performed using the MOLM-13 cell line xenograft (CDX) model.

Results:

The lead compound, ZE63-0302, forms an energetically favorable conformation allowing the ligand to exhibit target interaction while avoiding W346. In cellular proliferation assays, ZE63-0302 exhibits similar IC50 compared to SNDX-5613, however notably, ZE63-0302 maintains potency in M327I mutant MV4-11 cells compared to SNDX-5613 which exhibits a significant shift in IC50 against the mutant cells. There was no change in the action potential duration (APD) in rabbit Purkinje fibers with ZE63-0302 up to 10 uM, whereas SNDX-5613 exhibit prolonged APD as low as 100 nM, consistent with QTc prolongation that has been noted in patients. *In vivo* efficacy studies in the MOLM-13 CDX model verify comparable survival with ZE63-0302 and SNDX-5613 with twice daily dosing. Finally, ZE63-0302 (with once daily dosing) exhibits impressive synergy when combined with either a FLT3 or BCL2 inhibitor *in vivo* ZE63-0302 shows no effect on QTc up to 100 mg/kg and was able to be safely administered up to 150 mg/kg twice daily in dogs with no evidence of cardiotoxicity. GLP studies in rat and primate have been completed without concerning toxicity. Pharmacology in primates appear to be ideal for clinical translation of this molecule into humans.

Summary/Conclusion:

ZE63-0302 is a novel menin inhibitor with comparable *in vitro* and *in vivo* activity compared to SNDX-5613, but

with a more favorable safety profile. The unique binding modality is expected to decrease the emergence of resistance mutations that have occurred with SYDX-5613 and other menin inhibitors. The promising single agent and combination studies with multiple validated targeted therapies in AML support clinical development of ZE63-0302 which are being initiated at this time

Keywords: AML, Therapy