Abstract: P1797

Title: CLINICAL PHARMACOLOGY AND PHARMACOKINETIC PROFILE OF ZIFTOMENIB, A MENIN INHIBITOR, IN ADULTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

Abstract Type: e-Poster Presentation

Topic: Acute myeloid leukemia - Clinical

Background:

The menin and histone-lysine-*N*-methyltransferase 2A (KMT2A) protein complex is an essential epigenetic regulator of genes critical for leukemogenesis in multiple leukemia subtypes, including in *NPM*1-mutant (*NPM1*-m) and *KMT2A*-rearranged (*KMT2A*-r) acute myeloid leukemia (AML). Ziftomenib is a potent and selective inhibitor that targets the menin-mixed lineage leukemia (MLL) KMT2A interaction driving leukemogenesis. In ongoing clinical trials, ziftomenib has demonstrated meaningful clinical activity and tolerability as a monotherapy and in combination with standards of care

Aims:

To characterize the clinical pharmacology and pharmacokinetic (PK) properties of ziftomenib.

Methods:

Model-based analyses were performed using data from several clinical studies to gain a thorough understanding of the factors affecting the PK and dose of ziftomenib.

Results:

Noncompartmental analysis (NCA) of the phase 1 ziftomenib monotherapy dose escalation PK data demonstrated that ziftomenib AUC and Cmax increased dose proportionally up to 600 mg, which is the recommended phase 2 dose, beyond which saturation of exposure was observed. NCA demonstrated 5-fold accumulation of ziftomenib at steady state at the 600 mg dose. Physiologically based PK (PBPK) modeling based on the phase 1 dose escalation and expansion data projected that strong (e.g., itraconazole) and moderate (e.g., fluconazole) CYP3A4 inhibitors increased ziftomenib exposure by 1.7-fold and 1.4-fold, respectively, which is classified as weak interaction and not clinically relevant. PBPK modeling predicted that co-administration of ziftomenib with the sensitive CYP3A4 substrates, midazolam or venetoclax, increased exposure of those agents by only 5-6%, indicating no interaction. The simulated DDI data are summarized in the table below. Population PK modeling of the clinical data demonstrated that hepatic and renal impairment did not change ziftomenib clearance, as compared to patients with normal hepatic and renal function. Drug-induced prolongation of QTc interval was not observed at any dose across the clinical studies.

Summary/Conclusion:

Ziftomenib demonstrates a linear increase in exposure up to 600 mg, which is the therapeutic dose, thus simplifying the exposure-response profile and avoiding the need for dose adjustment due to non-linear changes in exposure with dose. High accumulation at steady state ensures adequate target engagement and maximizes potential response to treatment. Ziftomenib’s half-life supports a** once daily dosing regimen. Based on NCA and PBPK modeling using data from phase 1 monotherapy studies, ziftomenib does not require dose adjustment when co-administered with strong CYP3A4 inhibitors or in patients with hepatic and renal insufficiency. The projected lack of effect of ziftomenib on exposure of sensitive CYP3A4 substrates supports study of a ziftomenib-venetoclax combination without dose adjustment of either drug. In clinical studies to date, ziftomenib has not produced drug-induced QTc prolongation and dose reductions or drug holidays have not been warranted. The combination of a PK profile that supports once daily dosing, a low risk of clinically meaningful drug-drug interactions, and no evidence to date of drug-induced QTc prolongation make

ziftomenib an ideal candidate for combination with other agents for treatment of patients with *NPM1*-m or *KMT2A*-r AML.

Substrate	Inhibitor	AUC GMR (90%CI)	DDI Classification*
Ziftomenib	Itraconazole (Strong CYP3A4 inhibitor)	1.71 (1.64 – 1.78)	Weak DDI
Ziftomenib	Fluconazole (Moderate CYP3A4 inhibitor)	1.40 (1.36 – 1.43)	Weak DDI
Midazolam (Sensitive CYP3A4 substrate)	Ziftomenib	1.05 (1.04-1.06)	No DDI
Venetoclax (CYP3A4 substrate)	Ziftomenib	1.06 (1.05-1.06)	No DDI

*<1.25: No DDI; ≥1.25 – <2.00: Weak DDI (FDA clinical DDI guidance, 2020)

Keywords: AML, Pharmacokinetic, MLL, Drug interaction