Clinical Pharmacology and Pharmacokinetic Profile of Ziftomenib, A Menin Inhibitor, In Adults With Relapsed/Refractory Acute Myeloid Leukemia

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INTRODUCTION

- 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 *NPM1*-mutant (*NPM1*-m) and *KMT2A*-rearranged (*KMT2A*-r) acute myeloid leukemia (AML).[1,2]
- Ziftomenib is a potent, selective inhibitor that targets the menin-mixed lineage leukemia (MLL) KMT2A interaction and disrupts mutant NPM1 from chromatin sites, resulting in loss of oncogenic function, driving leukemogenesis.[3,4]
- In ongoing clinical trials, ziftomenib has demonstrated meaningful clinical activity and tolerability as a monotherapy (NCT04067336) and in combination with standards of care (NCT05735184).

OBJECTIVE

- To characterize the clinical pharmacology and pharmacokinetic (PK) properties of ziftomenib using non-compartmental analysis (NCA), population PK (popPK) and physiologically based PK (PBPK) modeling.

METHODS

- Intensive PK samples were collected in part 1a (dose escalation) and part 1b (dose validation) of KOMET-001 study (NCT04067336).
- These data were used to conduct NCA and popPK analysis to investigate the PK profile of ziftomenib such as dose proportionality of exposure, accumulation after multiple doses and effect of intrinsic/extrinsic covariates.
- Exposures in patients on azole antifungals (moderate or strong CYP3A4 inhibitors) and without were compared to get a preliminary estimate of the extent of change in ziftomenib exposure in presence of CYP3A4 inhibitors.
- A PBPK model was built and verified in simCYP® using available non-clinical physicochemical, ADME and biopharmaceutics properties, as well as clinical PK data.
- The PBPK model was then applied to investigate drug-drug interaction (DDI) potential of ziftomenib both as a victim and perpetrator for CYP3A4 mediated DDI when co-administered with CYP3A4 index inhibitors and substrates, respectively.

RESULTS

Ziftomenib PK Profile

- Dose proportional increase in exposure up to 600 mg, which is the recommended phase 2 dose (RP2D), beyond which saturation of exposure was observed (Figure 1).
- Demonstrated 5-fold accumulation at steady state at the 600 mg dose, ensuring adequate target engagement.
- Dose normalized AUC and C_{max} of ziftomenib co-administered with azoles which are strong (posaconazole and voriconazole), or moderate (fluconazole, isavuconazole and isavuconazonium) CYP3A4 inhibitors, demonstrated minimal increase in exposure, as compared to without azoles (Figure 2).
- Although there was a slight trend towards increase in ziftomenib exposure (average AUC = 3000 ng/mL*hr) when co-administered with a strong CYP3A4 inhibitor, this increase was not considered to be clinically meaningful as it was much lower than an AUC of 10,000 ng/mL*hr, up to which non-significant increases in adverse events have been observed based on exposure-response analysis of AUC versus AEs for patients on moderate/strong CYP3A4 inhibitors.
- Additionally, significant overlap in exposures were observed, as indicated by the 95% CI, for patients with and without CYP3A4 inhibitors further implying that the increase in ziftomenib exposure was in-significant.
- PopPK modeling of the clinical data demonstrated that mild or moderate hepatic impairment did not change ziftomenib clearance, as compared to patients with normal hepatic function (Figure 3).
- PopPK modeling of the clinical data demonstrated that mild or moderate renal impairment did not change ziftomenib clearance, as compared to patients with normal renal function (Figure 3). The lack of impact of renal function on ziftomenib exposure was supported by trace recovery of ziftomenib in urine in the human ADME study.

FIGURE 1. Dose proportional increase in ziftomenib AUC up to 600 mg

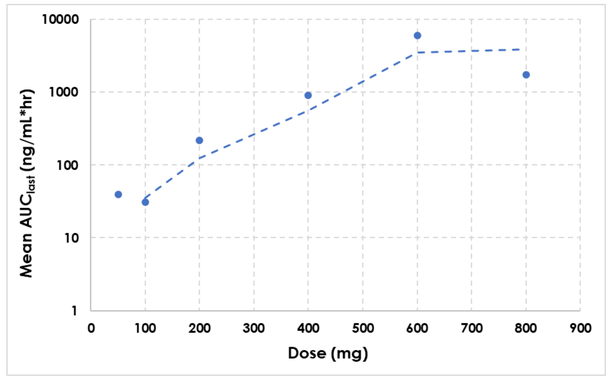


FIGURE 2. Lack of clinically meaningful interaction on co-administration of ziftomenib with CYP3A4 inhibitors

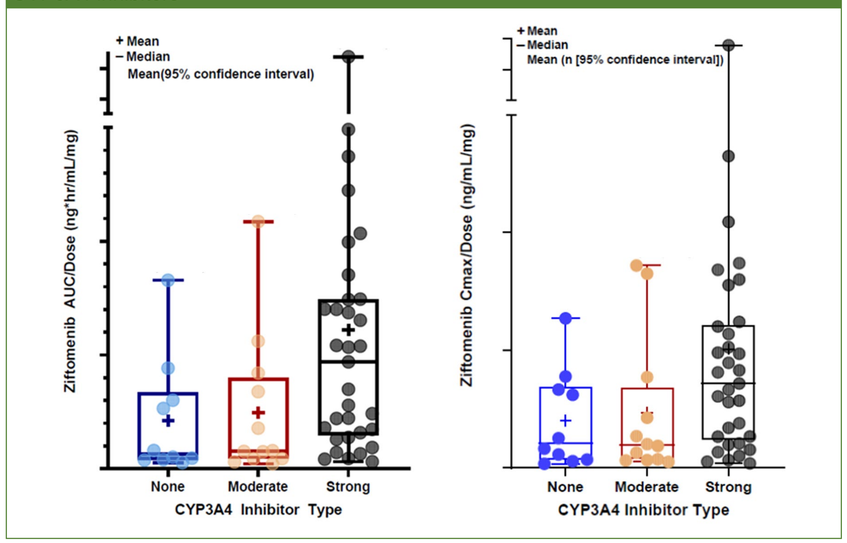
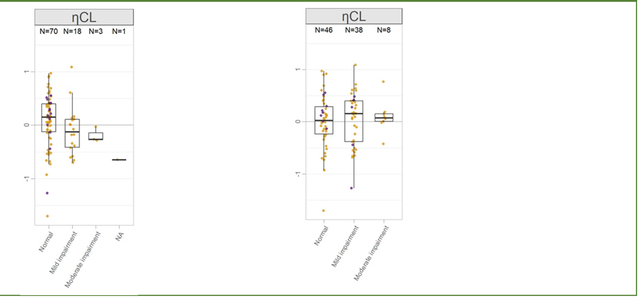


FIGURE 3. Lack of effect of hepatic impairment (left panel) and renal impairment (right panel) on ziftomenib clearance



Ziftomenib DDI Profile

- Preliminary PBPK modeling based on the projected KOMET-001 dose escalation and expansion data (Table 1) -
  - Weak interaction of ziftomenib with strong (e.g. itraconazole) and moderate (e.g., fluconazole, erythromycin) CYP3A4 inhibitors.
  - Weak interaction of ziftomenib with CYP2D6 inhibitor (e.g. bupropion) and CYP1A2 inhibitor (e.g. fluvoxamine).
  - Moderate interaction with strong CYP3A (e.g. rifampin) and moderate CYP3A4 (e.g. efavirenz) inducer
  - Co-administration of ziftomenib with the sensitive CYP3A4 substrates, midazolam or venetoclax, increased exposure of those agents by only 5-6%, indicating no interaction

TABLE 1. Preliminary simulated CYP mediated DDI profile of ziftomenib

Perpetrator	Mechanism	AUC GMR (90%CI)	DDI Classification*
CYP Inhibitors			
Itraconazole	Strong CYP3A4 inhibitor	1.71 (1.64 – 1.78)	Weak DDI
Fluconazole	Moderate CYP3A4 inhibitor	1.40 (1.36 – 1.43)	Weak DDI
Erythromycin	Moderate CYP3A4 inhibitor	1.45 (1.40 – 1.49)	Weak DDI
Bupropion	CYP2D6 inhibitor	1.45 (1.39 – 1.52)	Weak DDI
Fluvoxamine	CYP1A2 inhibitor	1.51 (1.44 – 1.57)	Weak DDI
CYP Inducers			
Rifampin	Strong CYP3A inducer	0.28 (0.26 – 0.29)	Moderate DDI
Efavirenz	Moderate CYP3A4 inducer	0.46 (0.44 – 0.48)	Moderate DDI
Dexamethasone	Weak CYP3A4 inducer	0.71 (0.69 – 0.73)	Weak DDI
CYP3A4 Substrate			
Ziftomenib	Midazolam	1.05 (1.04 – 1.06)	No DDI
Ziftomenib	Venetoclax	1.06 (1.05 – 1.06)	No DDI

*FDA CYP450 clinical DDI guidance 2020[5]

CONCLUSIONS

- **Ziftomenib demonstrates a linear increase in exposure up to 600 mg, RP2D, thus simplifying the exposure-response profile and avoiding the need for dose adjustment due to non-linear changes in exposure with dose.**
- **Ziftomenib does not demonstrate clinically meaningful DDI with strong CYP3A4 inhibitors, hence does not require dose adjustment when co-administered with those agents.**
- **Ziftomenib does not impact PK of CYP3A4 substrates (e.g. venetoclax) and can thus be combined without dose adjustment of either drug.**
- **Ziftomenib, an oral selective menin inhibitor, has a PK profile that supports once daily monotherapy dosing at 600 mg. This coupled with a low risk of clinically meaningful DDIs, and no evidence 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.**

Disclosures

AM, ML, SD: employment with Kura Oncology; equity interest in Kura Oncology; patents, royalties, or other intellectual property with Kura Oncology.

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Author contributions

All authors have contributed to study conception/design, or data collection/analysis/interpretation; development of this poster, or critical review of the content; and gave their approval for the final poster.

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