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Exposure-Response Analysis of Ziftomenib Combined with Venetoclax/ Azacitidine or Cytarabine/Daunorubicin in Newly Diagnosed and Relapsed/Refractory *NPM1*-m or *KMT2A*-r Acute Myeloid Leukemia

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INTRODUCTION

Ziftomenib is a potent, selective, oral menin inhibitor that is U.S. FDA approved as monotherapy for adults with relapsed/refractory *NPM1*-m AML at 600 mg QD. It has also shown clinical activity and tolerability in combination for adults with newly diagnosed (ND) and relapsed/refractory (R/R) *NPM1*-m or *KMT2A*-r AML. KOMET-007 (NCT05735184) is an ongoing, multi-cohort, open-label, Ph1a/b (dose-escalation and expansion) study of ziftomenib combined with standard chemotherapies, including venetoclax/azacitidine (ven/aza) or cytarabine/daunorubicin (7+3), in adults with *NPM1*-m or *KMT2A*-r AML.

AIM

The objectives were to –

1. Develop a population pharmacokinetic (popPK) model to describe ziftomenib PK in adults with ND or R/R AML and to evaluate covariates that could potentially affect the exposure of ziftomenib, including co-administration of ven/aza or 7+3.
2. Assess exposure-response (ER) relationships between ziftomenib PK and efficacy/safety endpoints for ND and R/R *NPM1*-m or *KMT2A*-r patients treated with ziftomenib in combination with ven/aza or 7+3.

METHOD

- A non-linear mixed effect model (NLME) in NONMEM VII (level 7.5) was developed using the pooled concentration-time data for ziftomenib from 14 healthy adult subjects and 436 adult AML patients (N=174 from KOMET-001 and N=262 from KOMET-007).
- The selection of covariates was done formally using a univariate forward addition (with significance level of p<0.01). All significant covariates were then included in a full model and then a backward elimination was conducted (with significance level of p<0.001) to obtain the final model.
- Logistic regression models were constructed to assess the statistical relationships between ziftomenib exposure levels, risk factors, and the probability of responses based on various combinations of the following efficacy endpoints from 260 patients in KOMET-007 – *complete remission (CR); partial hematologic response (CRh); morphological CR without measurable residual disease (CR_{MRD-}); complete remission with incomplete count recovery (CRi); complete remission with incomplete platelet recovery (CRp); morphologic leukemia free state (MLFS); partial remission (PR); stable disease (SD); clinical benefit (CB).*
- ER analyses were conducted for a total of 16 safety endpoints, which included all adverse events (AE) with toxicity grade ≥3, except for differentiation syndrome (DS), where probability was assessed across all toxicity grades.
- The best fitting ER model according to Akaike information criterion was selected.

RESULTS

Ziftomenib population PK

- The observed plasma concentration-time profiles of ziftomenib were adequately described by a 2-compartment, linear-elimination model with first-order absorption and lag time.
- The prediction corrected visual predictive check (VPC) plots indicated well fitting and predictiveness of the model for ziftomenib (**Figure 1**).
- A thorough covariate analysis using the popPK model demonstrated that co-administration of ven/aza or 7+3 and patient's mutational status (ie, *NPM1*-m or *KMT2A*-r) had no impact on ziftomenib PK.
- Food, proton pump inhibitors (PPI), strong CYP3A inhibitors, and health status were identified as covariates that contributed to the variability of ziftomenib PK in the studied population (**Figure 2**).

Exposure-response for ziftomenib/ven/aza combination

- There was no relationship between steady-state ziftomenib area under the curve (AUC) and probability of overall response rate (MLFS, CRp, CRi, CRh, CR, or CR_{MRD-}) when ziftomenib was dosed at 200 mg, 400 mg, and 600 mg once daily in combination with ven/aza in ND and R/R *NPM1*-m (p=0.935) or *KMT2A*-r (p=0.695) patients (**Figure 3**). Similarly, no correlation was observed for ziftomenib C_{max} and C_{trough}.
- There was no statistically significant (p=0.264) relationship between steady-state ziftomenib AUC and treatment-emergent (TE) differentiation syndrome when ziftomenib was dosed at 200 mg, 400 mg, and 600 mg once daily in combination with ven/aza in *NPM1*-m ND and R/R patients (**Figure 4**).
- ER analysis could not be conducted for TE differentiation syndrome in *KMT2A*-r patients as there were not enough events.
- No statistically significant ER relationship was observed for any grade ≥4 TEAE in *NPM1*-m or *KMT2A*-r patients.

Exposure-response for ziftomenib/7+3 combination

- ER analysis for ORR could not be performed for ziftomenib/7+3 in *NPM1*-m ND patients because ORR was >90% across the evaluated exposure range, resulting in an efficacy ceiling effect that precluded reliable estimation of an ER relationship in this subgroup.
- No ER relationship (p=0.924) was observed between ziftomenib AUC and ORR in *KMT2A*-r ND patients (**Figure 5**).
- There was no statistically significant relationship between steady-state ziftomenib AUC and TE differentiation syndrome in *NPM1*-m (p=0.991) or *KMT2A*-r (p=0.216) ND patients (**Figure 6**).
- No statistically significant ER relationship was observed for any grade ≥4 TEAE in *NPM1*-m or *KMT2A*-r ND patients.

Figure 1. Prediction-corrected VPC for the final popPK model for ziftomenib

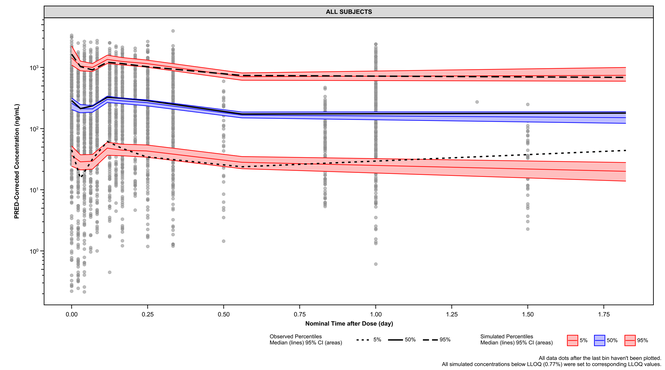


Figure 2. Effect of covariates on ziftomenib exposure

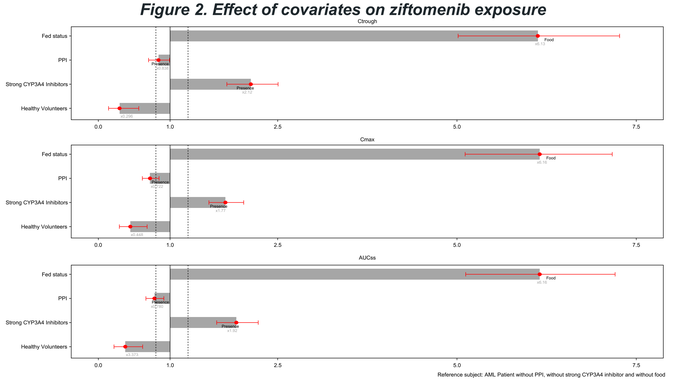


Figure 3. ORR profiles for ziftomenib and venetoclax/azacitidine combination in ND and R/R patients (Left panel:* NPM1*-m, Right panel:* KMT2A*-r)

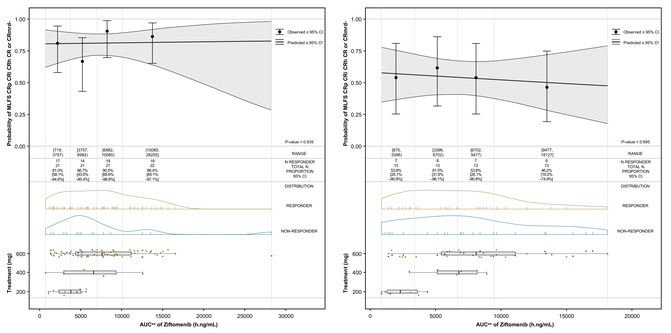


Figure 4. TE differentiation syndrome profiles for ziftomenib and venetoclax/azacitidine combination in* NPM1*-m ND and R/R patients

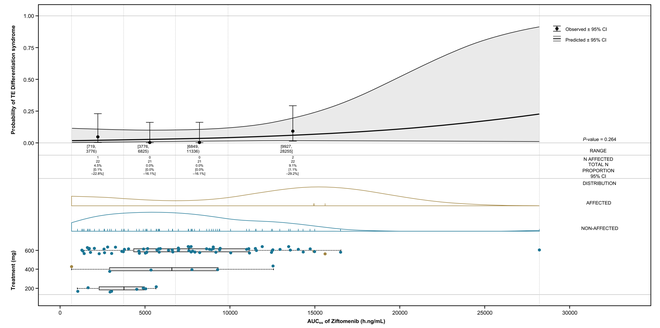


Figure 5. ORR profiles for ziftomenib and 7+3 combination in* KMT2A*-r ND patients

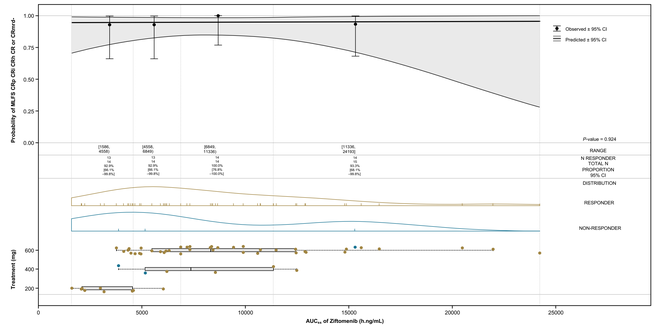
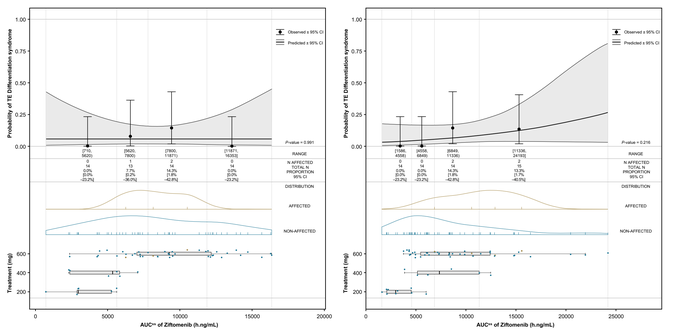


Figure 6. TE differentiation syndrome profiles for ziftomenib and 7+3 combination in ND patients (Left panel:* NPM1*-m, Right panel:* KMT2A*-r)



CONCLUSIONS

- ***There was no statistically significant relationship between ziftomenib exposure and efficacy/safety responses for doses ranging from 200–600 mg QD in combination with ven/aza or 7+3 in* NPM1*-m or* KMT2A*-r patients, demonstrating a wide therapeutic margin for ziftomenib.***
- ***The lack of drug-drug interaction supported coadministration of all agents, without any required dose adjustments.***
- ***These results, along with the totality of clinical safety/efficacy, PK, and pharmacodynamic data, support ziftomenib 600 mg QD as the optimal dose in combination with standard-of-care doses of ven/aza or 7+3 to provide the best benefit/risk outcomes in* NPM1*-m or* KMT2A*-r patients.***

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