Poster W-063

QSP Modeling to Support Development of Ziftomenib Combinations in Acute Myeloid Leukemia

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OBJECTIVE

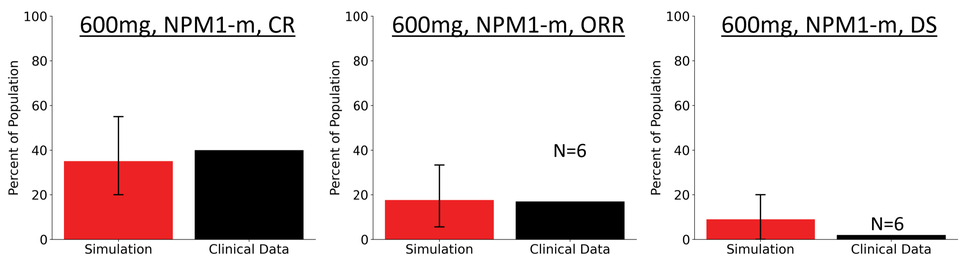
- Ziftomenib is a potent, selective, oral menin inhibitor that is U.S. FDA-approved as monotherapy at 600mg QD for adults with relapsed/refractory (R/R) *NPM1*-m AML and no other satisfactory treatments.
- It has shown clinical activity and tolerability in combination with venetoclax/azacitidine (ven/aza) and cytarabine/daunorubicin (7+3) standard-of-care (SOC) chemotherapies in adults with newly diagnosed (ND) or R/R, *NPM1*-m or *KMT2A*-r AML
- KOMET-007 (NCT05735184) is an ongoing, multi-cohort, open-label, Phase (Ph) 1a/b (dose-escalation and -expansion) study of ziftomenib combined with SOC therapies, including ven/aza and 7+3, in adults with *NPM1*-m or *KMT2A*-r AML
- A QSP model of AML progression was developed and used to characterize the efficacy and safety of these ziftomenib combinations, to support further development

METHODS

- The AML model was developed using Thales, a QSP software platform that automates and streamlines simulation and analysis for clinical trials [1]
- The model captures key AML-related processes in bone marrow and blood and relevant genomic aberrations
- A simulated population representing both ND and R/R patients was fit and validated with data from 24 clinical trials involving 14 unique therapies, including data from the KOMET-001 Ph1/2 ziftomenib monotherapy trial [2]
- The model captures efficacy measures, including ELN endpoints (complete remission with full/partial/incomplete hematologic recovery [CR / CRh / CRi], partial response, overall response rate [ORR], duration of response, measurable residual disease negativity), and safety measures, including differentiation syndrome (DS) rates
- Using the optimized virtual population, predictive simulations were conducted for ziftomenib 200/400/600mg QD with ven/aza in ND and R/R patients and with 7+3 in ND patients to evaluate the regimens in the KOMET-007 study

RESULTS

1a) Model Fitting Results for Ziftomenib Monotherapy; 600mg, *NPM1*-m



1b) Model Fitting Results for Ziftomenib Monotherapy; 600mg, *KMT2A*-r

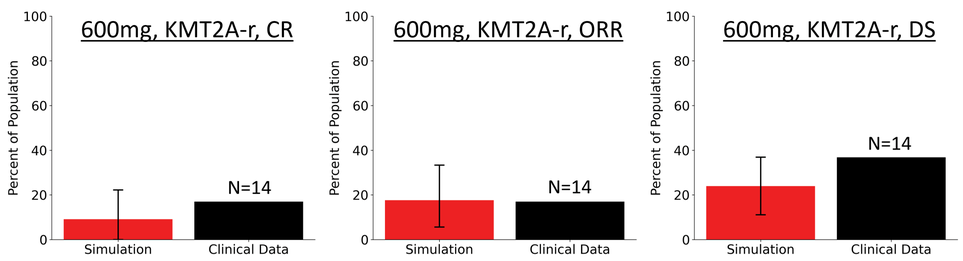
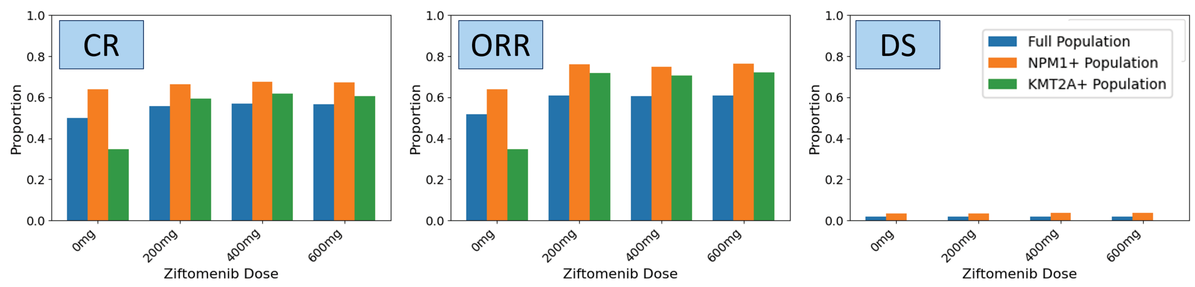


Figure 1: Model simulation results compared to clinical data of CR, ORR, and DS in ziftomenib monotherapy in the optimized virtual population. Bars represent the outcomes as a percentage of the full population with red bars showing simulation results with associated 90% credible intervals (CIs) and black bars showing comparison clinical data from Wang 2024 [2]. Results here show a) a 600mg dose in R/R *NPM1*-m patients and b) a 600mg dose in R/R *KMT2A*-r patients. Data from 200mg in R/R *KMT2A*-r and R/R *NPM1*-m patients were also used in calibration but are not shown.

2a) Model Predictions for Ziftomenib with 7+3 in ND AML



2b) Model Predictions for Ziftomenib with Ven/Aza in R/R AML

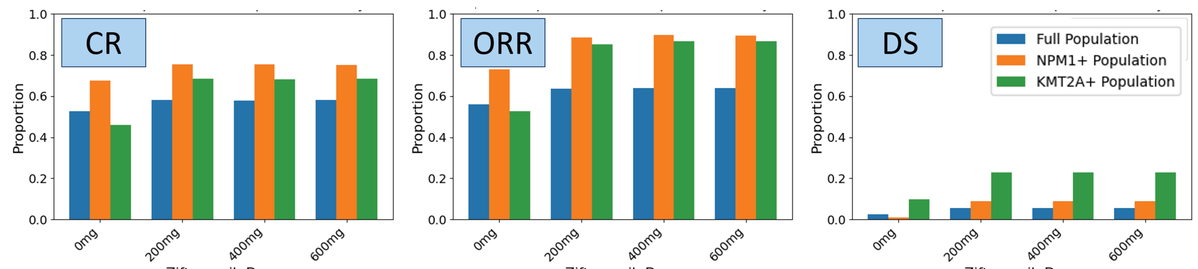


Figure 2: Model predictions for ziftomenib in combination with SOC therapies: 7+3 and ven/aza for CR, ORR, and DS in the full population, *NPM1*-m subpopulation, and *KMT2A*-r subpopulation compared across three doses and the SOC backbone alone. Bars represent the outcomes as a percentage of the full virtual population. Not shown here are similar predictions made for ziftomenib in combination with venetoclax in ND and R/R AML, ziftomenib in combination with 7+3 in R/R AML, and ziftomenib in combination with ven/aza in ND AML. Similar minimal dose response was observed across 200mg, 400mg, and 600mg in those predictions not included here.

3) Prospective Validation of Model Predictions to Clinical Data: Ziftomenib 600mg with Ven/Aza in ND *NPM1*-m AML

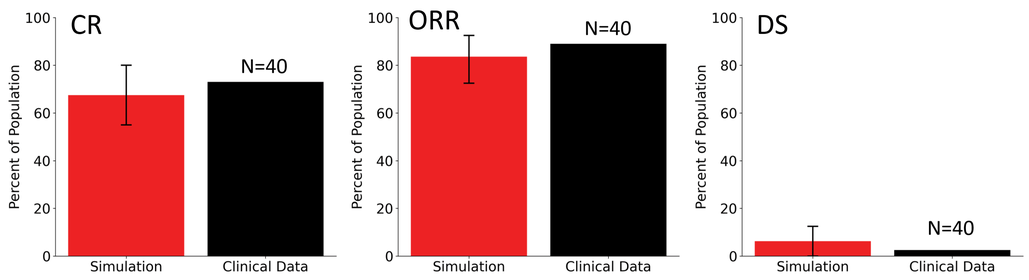


Figure 3: Prospective validation of model predictions to subsequently released clinical trial results for combination of 600mg ziftomenib with ven/aza in ND *NPM1*-m AML. Bars represent the outcomes as a percentage of the full population with red bars showing simulation results with associated 90% CIs and black bars showing comparison with clinical data [3]. Other model predictions showed similar accuracy [4].

- Goodness-of-fit metrics suggest strong model performance with >72% of training data inside the model's 90% CIs, and >78% of hold-out validation data falling inside the 90% CIs
- Note that these results are for a single global population fit to all these data and other clinical data simultaneously; hence, the generated virtual population can predict responses to novel compounds
- The results capture several important dynamics in treatment of AML including differing responses to treatment in ND and R/R populations
- Simulations showed adding ziftomenib 600 mg QD to ven/aza or 7+3 increased ORRs compared to ven/aza or 7+3 in ND and R/R, *NPM1*-m and *KMT2A*-r AML patients
- The simulations predicted low rates of DS for ven/aza or 7+3 combinations with ziftomenib 200, 400, and 600mg QD doses vs. the respective SOC therapies

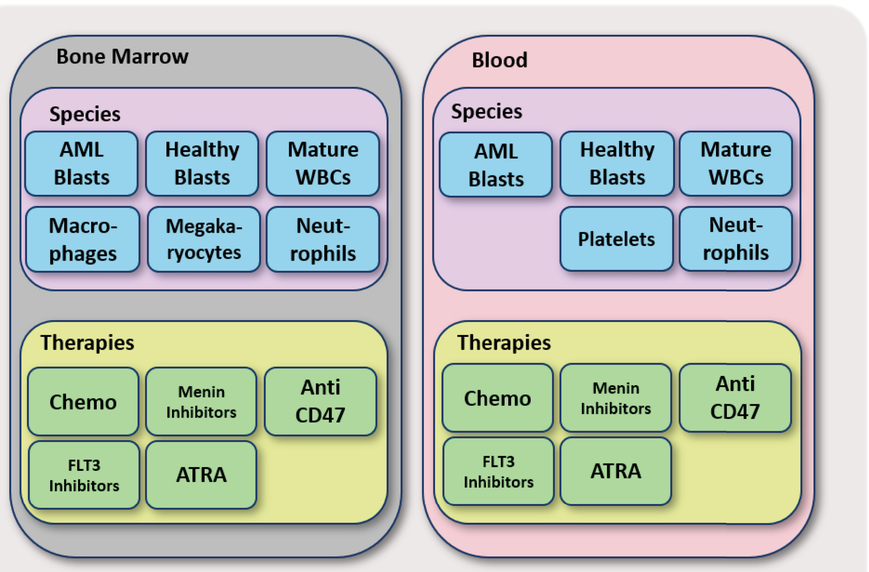


Figure 4: Diagram showing the compartments, species, and therapies included in the AML model. Species and therapies are modeled in the bone marrow and blood. Processes include proliferation, decay, differentiation, immune killing, and migration. The model includes representations of clinical endpoints CR/CRi/CRh, ORR, DS, measurable residual disease, duration of response, and relapse, and clinically relevant mutational subpopulations *NPM1*-m, *KMT2A*-r, and *FLT3* alterations.

CONCLUSIONS

- The QSP model simulations, combinations of ziftomenib with SOC therapies were predicted to exhibit efficacy above SOC alone, and a suitable DS safety profile, in ND and R/R, *NPM1*-m or *KMT2A*-r AML patient populations
- Taken together, these analyses predicted that ziftomenib 600mg QD would provide robust clinical responses, consistent with the recommended ziftomenib dose for combinations with ven/aza or 7+3
- These results highlight the utility of QSP models in late-stage clinical development by enabling optimization of dosing protocols and evaluation of dosing regimens within distinct patient populations

REFERENCES

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ACKNOWLEDGEMENT

The authors would like to thank the Kura Oncology Biometrics and Programming teams for providing the datasets used in the modeling. This study was sponsored by Kura Oncology, Inc., in partnership with Kyowa Kirin, Inc.

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Poster presented at: The American Conference on Pharmacometrics Annual Meeting; October 11-14, 2026; National Harbor / Oxon Hill, MD, USA