Development of a Translational Pharmacokinetic-Biomarker-Efficacy Model in Mouse as a Tool for the Human Therapeutic Dose Estimation


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OBJECTIVE

- MEN1703 is a novel drug dual kinase inhibitor targeting PIM and FLT3 kinases which represents a promising new approach for Acute Myeloide Leukemia (AML) therapy and is currently in phase 1 development.
- A fundamental step of the preclinical development of oncology drugs is the in vivo evaluation of the antitumor effect, and Xenograft models are commonly used for this purpose. Moreover, the inclusion of biomarkers, which provide useful information regarding tumor engagement of efficacy, is a key step towards a more general mechanism-based strategy.
- The aim of this analysis is to establish a quantitative relationship between MEN1703 plasma/tumor concentration, pharmacological effect as measured by biomarkers and tumor growth inhibition in MOLM16 cell line xenograft which can be used to identify the target exposure in human associated with efficacy.
- To address this aim, a predictive pharmacokinetic/pharmacodynamic (PK/PD) model which integrates preclinical pharmacokinetic, biomarker and efficacy data has been developed.

METHODS

These PK/PD analysis was carried out in four steps:

1. **MEN1703 Pharmacokinetics (PK) model in mouse** was developed using data both at single and multiple doses from four different studies.

2. The **relationship between MEN1703 in plasma and tumor was established** to correlate biomarker data measured in tumor with drug concentration in the same matrix using data from two preclinical studies in mouse.

3. A model describing the time course of S6 (Ser235/236) phosphorylation inhibition (%) in tumor in MOLM-16 xenograft mouse was developed based on the same studies used in step 2.

4. **Tumor growth and tumor growth inhibition data** from four studies in xenograft mouse were modelled by means of the modified biomarker-driven TGI model developed by Simeoni et al. [1] and Sardu et al. [2].

RESULTS

1. **MEN1703 Pharmacokinetics (PK) model in mouse**

Disposition of MEN1703 in plasma was best described with a one compartment model with a linear elimination (Kel).

![Model-based PK profiles in plasma superimposed over actual PK data observed for different dosing regimens. Solid lines represent model-based MEN1703 PK individual predictions, dashed lines represent model-based MEN1703 PK population predictions and black dots represent observed data.](image)

2. **PK data in plasma and tumor in mouse**

The estimate of partition coefficient Kp between MEN1703 plasma concentrations (Cp) and MEN1703 tumor concentrations (Ct) is ~10.

3. **Biomarker model in mouse**

The time course of S6 phosphorylation (Ser235/236) inhibition in MOLM16 cell line was properly described using a direct response model (IC50=760 ng/mL and γ=3.5).

![Model-based pS6 percentage of inhibition in tumor superimposed over actual data for different dosing regimens.](image)

4. **Tumor growth and tumor growth inhibition model in mouse**

- The model captured well the behavior of the tumor growth and the effect of the anticancer treatment k2 for all the studies.
- **Efficacious concentration in mouse and target exposure in human**
  - The secondary parameter CTH derived from the model in mouse may be corrected for observed differences in plasma protein binding such that free exposure is being matched.
  - **Confirmation of target exposure using a different preclinical model**
  - The efficacious target exposure range established by this PK/PD analysis in MOLM16 xenograft data has been confirmed by a similar PK/PD assessment conducted on data from diffuse patient-derived xenograft (PDX) experiments.

CONCLUSIONS

- An integrated PK-biomarker-efficacy model for MEN1703 has been developed in mouse. The model provide a very good description of the observed data.
- The secondary parameter CTH in mouse has been used to identify the target exposure in human which is associated with efficacy. The exposure will be corrected for observed differences in plasma protein binding such that free exposure is being matched.
- The developed modelling framework applies to be a predictive tool for human therapeutic exposure estimation.
- Emerging clinical data from the ongoing study (e.g. PK and biomarker) will be used for further model validation and refinement.

REFERENCES