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

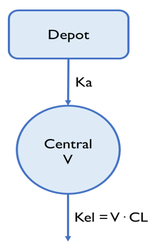
These PK/PD analysis was carried out in four steps:

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).



Parameter	Unit	Estimate (RSE%)	
		Values	IIV
K_a	1/hr	1.19 (45)	-
V	L	0.354 (15)	13.3% (54.6)
K_{el}	1/hr	0.1 (19)	24.6% (39)
Prop. err.	%	32.8 (22)	

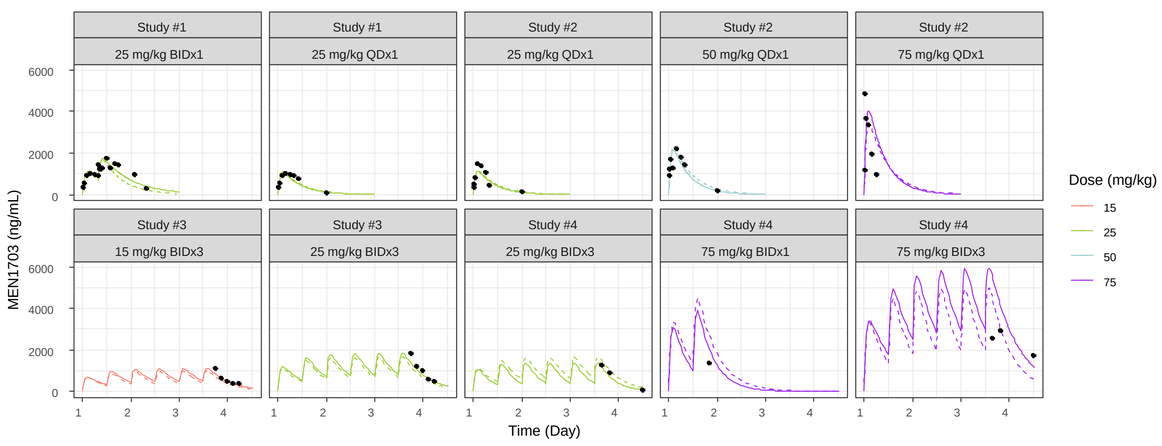


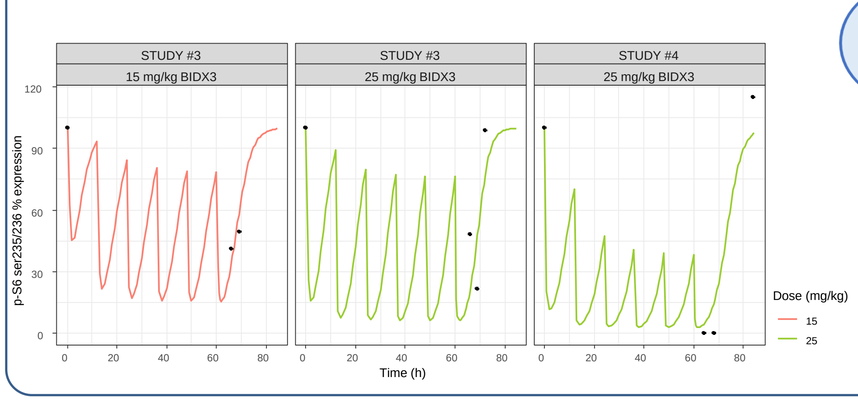
Fig 1. *Model-based PK profiles in plasma superimposed over actual PK data observed for different dosing regimens. Solid lines represent model-based MEN1703 PK individual predictions, dashed lines represent model-based MEN1703 PK population predictions and black dots represent observed data.*

2. PK data in plasma and tumor in mouse

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

3. Biomarker model in mouse

The time course of S6 phosphorilation (Ser235/236) inhibition in MOLM16 cell line was properly described using a direct response model (IC_{50}=7360 ng/mL and γ=3.5).



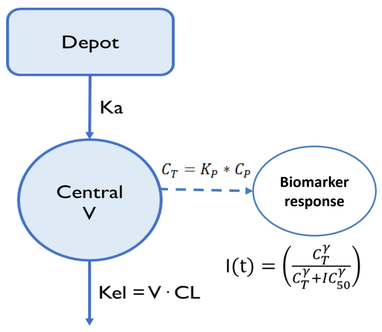
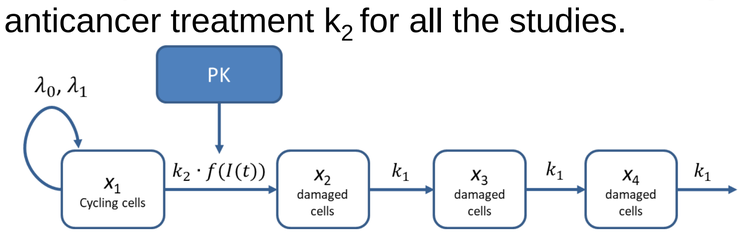


Fig 2. *Model-based pS6 percentage of inhibition in tumor superimposed over actual data for different dosing regimens.*

RESULTS

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 k_2 for all the studies.



STUDY	ARM	CELL LINE	N	DAY of 1st adm	PRIMARY PARAMETERS: λ_0 (d^{-1}) (RSE%)	λ_1 ($g^* d^{-1}$) (RSE%)	k_1 (d^{-1}) (RSE%)	k_2 ($\mu g^{-1} *mL/d$) (RSE%)	w0 (g) (RSE%)	ERR (%)	SECONDARY PARAMETERS: $C_{THTumor}$ (μg/mL)	$C_{THPlasma}$ (μg/mL)
STUDY 1	Control, 75 mg/kg PO BID 25 mg/kg PO BID	MOLM16	18	20	0.291 (4)	0.295 (15)	1 FIX	0.0162 (8)	0.4e-3 (20)	59.5 (8)	17.96	1.98
STUDY 2	Control 25 mg/kg PO BID	MOLM16	12	22	0.163 (3)	0.571 (11)	1 FIX	0.0160 (23)	1.8e-3 (12.6)	55.3 (11)	10.19	1.12
STUDY 3	Control 50 mg/kg PO QD 25 mg/kg PO BID 50 mg/kg PO EOD	MOLM16	24	24	0.258 (8)	0.128 (10)	1 FIX	0.0327 (10)	0.225e-3 (60)	38.6 (9)	7.89	0.87
STUDY 4	Control 100 mg/kg PO QD	MOLM16	12	37	0.307 (5)	0.293 (13)	1 FIX	0.0434 (27)	0.003e-3 (56)	39.7 (11)	7.07	0.78

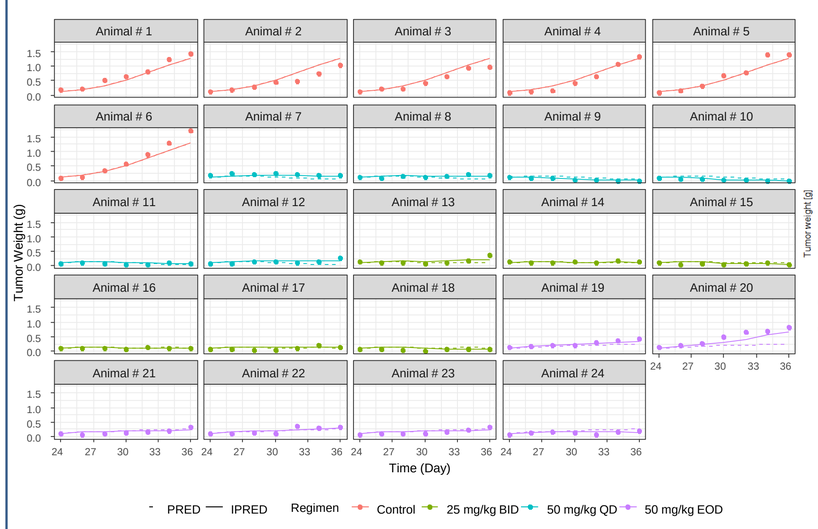


Fig 3*. Study 3 fitting and VPC results. Left Panel: Model-based tumor growth curves in control groups and treated groups superimposed over actual data for different dosing regimens. Solid lines correspond to the individual model predictions, dashed lines correspond to population model predictions and dots represent observed data. Right Panel: Visual predictive check.*

- **Efficacious concentration in mouse and target exposure in human**
  The secondary parameter C_{TH} derived from the model in mouse may be regarded as the reference concentration to be maintained for achieving a significant activity. The C_{TH} in mouse can be translated to the efficacious target exposure in human taking into account differences in protein binding and clinical dosing schedule.
- **Confirmation of target exposure using a different preclinical model**
  The efficacious target exposure range established by this PK/PD analysis in 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 provided a very good description of the observed data.
- The secondary parameter C_{TH} 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
[1] Simeoni M et al. Cancer research. 2004 Feb 1;64(3):1094-101.
[2] Sardu M.L. et al. 42:611–626, 2015

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