Applications of Translational Pre-clinical PK/PD/E Modeling and Simulation in the Development of MLN7243, an Investigational First-in-Class Ubiquitin-Activating Enzyme (UAE) Inhibitor

E. Kadakia, J. Shi, J. Huck, T. Traore, J. Ciavarri, B. Stringer, Y. Yang, R. Griffin, S. Faucette, N. Bence, Y. Ishii, C. Xia, J-T. Wu, A. Chakravarty, M. L. Hyer
Takeda Pharmaceutical Co., Ltd.

Purpose

MLN7243 is an investigational small molecule inhibitor of the ubiquitin-activating enzyme (UAE) currently being evaluated in a Phase-I solid tumor clinical trial. Pre-clinical studies in xenograft models have demonstrated MLN7243 induces a dose-dependent reduction of monoubiquitin and polyubiquitin proteins, resulting in robust anti-tumor activity across a range of solid and hematological tumors. This poster presents the application of pre-clinical PK/PD/E modeling in guiding key translational decisions during Phase-1 design. Using modeling and simulation (and two representative xenograft tumor models) the following two questions were investigated:

1) What is the optimal sampling window to collect tumor biopsies to monitor PD activity in the clinic?
2) What is the optimal schedule to maximize the efficacy of the drug i.e. is there a dosing schedule effect?

Methods

1.In-vivo experiments: MLN7243 plasma concentrations following IV dosing at 12.5 mg/kg, 18.75 mg/kg and 25 mg/kg were collected in WSU (DLBCL) and PHTX-132Lu (primary NSCLC) tumor bearing mice. Tumor tissues were stained and quantified for polyubiquitin status using the FK2 antibody which recognizes poly and monoubiquitinated proteins. An efficacy study was performed in PHTX-24C (primary colon) tumor bearing mice utilizing two dosing schedules to be evaluated in the clinic, i.e. BIW and QW. The study was designed to keep the Cmax and exposures uncorrelated such that true PK correlate of efficacy could be identified.
2.PK/PD/E modeling: Plasma concentrations following IV dosing were modeled using a compartmental modeling approach. The temporal disconnect observed between plasma PK & tumor PD was modeled using an indirect-response PK/PD model. Efficacy was calculated using a growth-rate metric called %GRI. Efficacy from different schedules was compared using linear regression.
3.PK/PD simulations for translation: Using the projected human PK parameters and the PD parameters estimated from the xenograft plasma PK/ tumor PD relationship, a clinical day 11 PD time profile was simulated following BIW dosing of MLN7243 at escalating doses.

Results

The optimal PD sampling window in the clinic predicted to capture the maximal PD effect in humans was predicted to be between 12-36 hours. Sensitivity analyses, using a 4-fold range of the PK/PD parameters, did not predict significant changes in the optimal sampling window. The results of PK/E analyses suggest efficacy correlated best with AUC alone and there was no Cmax component for the schedule effect. (A statistically strong (p-value < 0.0001) and significant correlation ($R2 = 0.91$) was observed between dosing density and efficacy.)

Conclusion

In a Phase-1 setting, tumor biopsy is often collected at a single time-point post-treatment and is used to infer the absence or presence of target engagement. The modeling approach described above enabled us to systematically factor-in differences between mouse and human PK, maximizing the likelihood of capturing a clinical PD signal. Furthermore, the pre-clinical PK/E modeling approach demonstrated MLN7243 plasma AUC was the driver of efficacy without any significant dependence on Cmax. In summary, this pre-clinical data suggests no scheduling effects for efficacy.