**Characterization of the correlation between BTK degradation and tumor growth inhibition of the BTK target protein degraders using PK/PD modeling**

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**Introduction:** Chimeric degradation activation compound (CDAC) are heterobifunctional molecules causing target protein degradation by simultaneously binding to the target protein as well as an E3-ubiquitin ligase. As an emerging new therapeutic modality, it is critical to understand the contribution of compound-specific parameters (e.g. drug exposure and binding potency to the target protein) and the system-specific parameters (e.g. target protein turnover) of CDACs to its *in vivo* effect.

**Method:** To identify the key parameters for guiding compound optimization and to find the correlation between BTK degradation and the extent of tumor growth inhibition, a mechanistic PK/PD model was built (Phoenix WinNonlin 8.1) on a dataset generated from a BTK CDAC (Compound A). The PK/PD model was simplified mathematically compared to the target protein degradation full mechanistic models published previously[1-8]. Since the binding affinity of Compound A to BTK was much higher than the binding affinity of CDAC to E3 ligase, the model can be reduced with less parameters. This model can be linked to a tumor growth inhibition mathematical model to find the correlation between target degradation and efficacy.

**Result:** In mouse Rec-1 xenograft model, the BTK degradation and tumor growth inhibition was studied. The mice were dosed with Compound A orally at 0.3, 1, or 3 mg/kg, dose dependent PK and BTK degradation in tumor was observed. After a single dose administration of Compound A, ~50% BTK degradation was observed in tumor at 24 h post dosing and the tumor BTK rebound to baseline at 72 hours post dosing at 3 mg/kg. The tumor BTK degradation was deeper after repeated dosing. A PK/PD model was built based on the data in this PK/PD study. The calculated BTK turnover half-life in Rec-1 model is about 16 h. In the efficacy study, Compound A was dosed orally once a day to the mice at 0.3, 1, or 3 mg/kg. The 3 mg/kg group achieved ~90% tumor growth inhibition in Rec-1 xenograft model. The PK/PD model was then linked with a mathematical model describing tumor growth inhibition[9]. A threshold level of BTK degradation in tumor to achieve tumor stasis was identified to be 96% for Rec-1 tumor model. At 90% tumor growth inhibition, average of 70% BTK was predicted to be degraded in tumor at steady state. The model was subsequently used to characterize the PK/PD relationship of BGB-16673. The efficacy of BGB-16673 was predicted using the model and it agreed with the observed value.

**Conclusions:** The current model deepened our understanding of the PK/PD relationship of CDACs. The approach can be used to simulate the efficacy in a model with faster or lower BTK turnover, or a compound with different potency or PK exposure. It can also be used in compound selection and optimization to predict repeated dose PD and efficacy from a single dose PK/PD data.


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