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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Background and Purpose

- Chimeric degradation activation compounds (CDACs) 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
- A simplified mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model was used to establish the correlation between PK and PD
- The PK/PD model was further linked to a tumor growth inhibition (TGI) mathematical model to establish the correlation between PD and efficacy

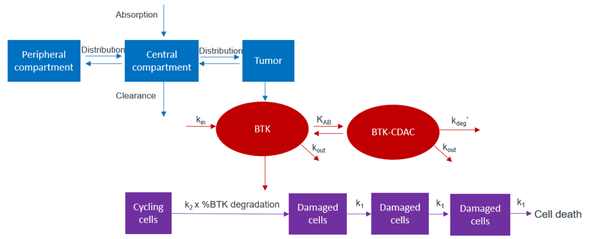
Method

Source of raw data:

- The drug exposure of Compound A or BGB-16673 in plasma and tumor, and BTK levels in tumor were characterized in Rec-1 xenograft model after a single oral dose or repeated oral doses of Compound A or BGB-16673
- The drug exposure of Compound A or BGB-16673 in plasma, and TGI were characterized in Rec-1 xenograft model after repeated oral doses of Compound A or BGB-16673

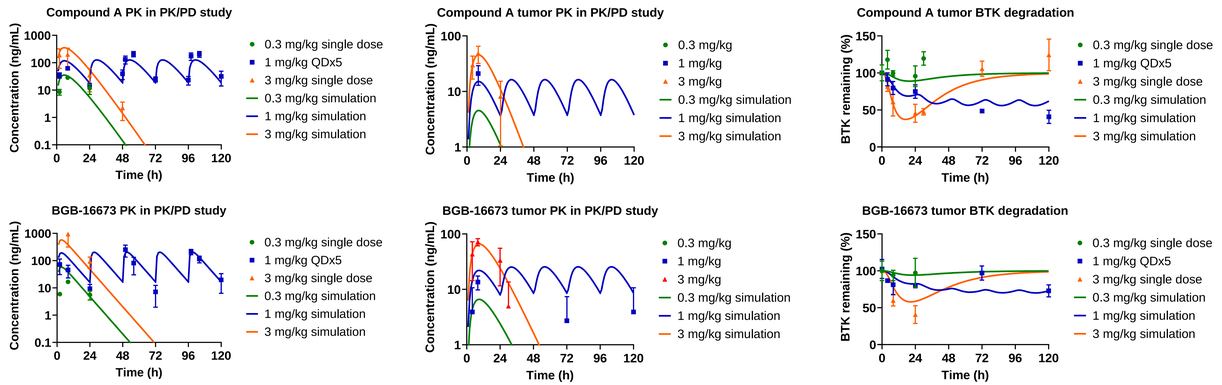
Modeling strategy:

- The PK/PD model was simplified mathematically compared to the full mechanistic models published previously[1-8], since the binding affinity of Compound A and BGB-16673 to BTK was much higher than the binding affinity of these CDACs to E3 ligase. The manuscript with the derivation of the simplified model is under review. This model was linked to a TGI mathematical model[9] to find the correlation between target degradation and efficacy
- The model was fitted using the dataset generated from Compound A using Phoenix NLME 1.3 (Certara, L.P., 210 North Tucker Boulevard Suite 350, St. Louis, MO 63101 USA). K_{AB} and k_{out} were identified as the sensitive parameters in the PK/PD model
  - K_{AB} represents the in vivo potency of the CDAC and is compound specific
  - k_{out} is the turnover rate of BTK protein which is not compound specific. Since BTK degradation is normalized to the baseline level in the data analysis, $k_{in} = k_{out} \times 100\%$
  - When the binding affinity between CDAC and the target protein is much higher than the binding affinity between CDAC and E3 ligase, k_{deg}' is determined by the degradation rate of the target protein by CDAC (k_{deg}), total concentration of E3 ligase (C_{total}), and the binding affinity between the target protein-CDAC binary complex and the E3 ligase (K_{BC}), where $k_{deg}' = k_{deg} * [C_{total}]/K_{BC}$
  - The definition of the PK and efficacy model parameters can be found in the references[9]



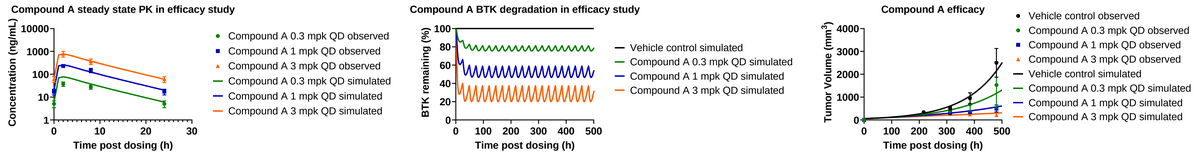
The schematic of the simplified model framework

Results: BTK CDACs showed dose-dependent PK exposure and tumor BTK degradation in Rec-1 xenograft model

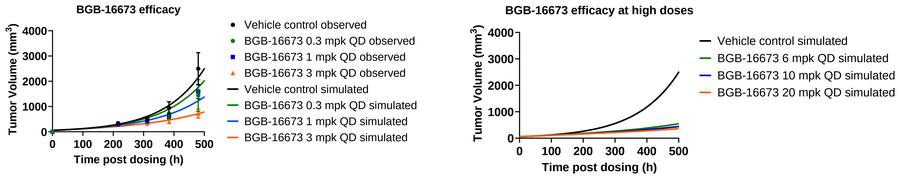


In mouse Rec-1 xenograft model, the mice were dosed with Compound A or BGB-16673 orally at 0.3, 1, or 3 mg/kg, dose-dependent PK and BTK degradation in tumor was observed. After a single dose administration of Compound A, ~50% BTK degradation was observed in tumor at 24 h post dosing and the tumor BTK rebound to baseline at 72 hours post dosing at 3 mg/kg. The tumor BTK degradation was deeper after repeated dosing. The PK/PD model calculated BTK turnover half-life in Rec-1 model was about 16 h.

Results: The efficacy of BGB-16673 can be well predicted with its PK/PD data using PK/PD modeling approach



In the efficacy study, Compound A or BGB-16673 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, with ~70% tumor BTK degradation predicted using PK/PD model. A threshold level of BTK degradation in tumor to achieve tumor stasis was calculated from the PK/PD model which was identified to be 96% for Rec-1 tumor model.



The efficacy of BGB-16673 was predicted based on the correlation between PK and BTK degradation of BGB-16673 characterized using the PK/PD model, and the relationship between BTK degradation and efficacy built with the data from Compound A. The predicted efficacy of BGB-16673 agreed with the observed data.

Conclusions

- BTK CDACs, including BGB-16673, achieved efficient tumor BTK degradation in vivo in Rec-1 xenograft mouse model
- BTK CDACs inhibited tumor growth in Rec-1 xenograft mouse model. The PK/PD model predicted that average of 70% BTK inhibition at steady state could result in about 90% TGI
- The simplified mechanistic PK/PD model can be used to build the PK, BTK degradation and efficacy correlation. The efficacy of BGB-16673 can be well predicted using its PK/PD data with PK/PD modeling approach
- The current model deepened our understanding of the PK/PD relationship of CDACs:
  - BTK turnover rate (k_{out}) and turnover half-life ($0.693/k_{out}$) can be calculated from the PK/PD model
  - A threshold level of BTK degradation in tumor to achieve tumor stasis can be calculated from this model
  - After the PD/efficacy correlation was built, the model can be used in compound selection and optimization to predict repeated dose PD and efficacy from a single dose PK/PD data
  - The model can be used to simulate different scenarios, e.g. different BTK turnover, potency or PK exposure, to understand the ideal compound profile

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