The application of PK/PD modelling in the clinical development of BT5528 - a novel toxin delivery platform

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Session 1a: Modeling and Simulation in Support of New Modalities in Oncology Drug Development
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*Bicycles* are a new therapeutic modality – bicyclic peptides

- Short linear peptide
- Scaffold
- Chemical modification with scaffold

**Bicycles**

Diverse **Bicycles**

- Powerful/versatile platform
  - Immense combinatorial potential
  - Combines advantages of both small molecules and antibodies
- Multi-formats
  - Monomeric Bicycles
  - Bicycle Toxin Conjugates (BTCs)
  - Tumor-targeted immune cell agonists (**Bicycle TICAs**)
- Robust patent protection with 121 patent families*

*As of June 30, 2022*
Bicycle Toxin Conjugates (BTCs) – preclinical data indicate high potency with high specificity

- MW of 1.5-2kDa
- 50-100x smaller than antibodies
- High selectivity
- Allows more potent toxin to be delivered directly to tumor
BT5528 is a first-in-class BTC-targeting EphA2

• BT5528 is a novel BTC that binds to tumor cells expressing cell surface EphA2
  • High expression across wide range of solid tumors
  • Toxin is released and retained in tumor cells resulting in tumor cell death and bystander killing

• BT5528 is small and hydrophilic, allowing:
  • Rapid penetration into solid tumors
  • Short systemic exposure, renally excreted
BT5528 development status

• BT5528 is being investigated in patients with advanced solid tumors historically known for expression of EphA2

• The goals of this modeling activity are to:
  • Develop an integrated model of plasma and tumor concentrations of BT5528 and MMAE in mice and in humans
  • Link tumor concentrations of MMAE to tumor regression in mice and in humans
  • Provide a framework to support RP2D decision-making for BT5528 and for other bicyclic peptides
## Summary of data

<table>
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<tr>
<th>Study</th>
<th>Species</th>
<th>Doses</th>
<th>N</th>
<th>BT5528 PK samples</th>
<th>MMAE PK samples</th>
<th>Tumor size data</th>
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<tbody>
<tr>
<td>Study 01</td>
<td>Mouse</td>
<td>0, 0.167, 0.5, 1.5 mg/kg</td>
<td>24</td>
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<td>BT5528-100</td>
<td>Human</td>
<td>2.2, 4.4, 6.5, 8.5, 10 mg/m²</td>
<td>64</td>
<td>1609 plasma</td>
<td>1605 plasma 5 tumor</td>
<td>155</td>
</tr>
</tbody>
</table>
Modeling schematic

Mouse PBPK Model

Human PopPK + Scaled Human PBPK Model

Mouse Tumor Model

Scaled Human Tumor Model

PopPK: population PK
PBPK: physiologically based PK

Mouse Tumor Size Fits
Mouse PBPK-based model

**Plasma**
- BT5528
- CLconj
- CLm
- Kel
- Kpt
- Ktp

**Tumor**
- BT5528
- Tubulin
- CLt
- Kdeg
- Kon
- Koff

**Central**
- MMAE
- CLm
- Kin
- Kout
- Kpt
- Ktp

**Peripheral**
- MMAE

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CL: clearance  
Kdeg: degradation rate constant  
Kel: rate of elimination  
Kin: rate constant from plasma to tumor  
Koff: dissociation rate constant  
Kon: association rate constant  
Kout: rate constant from tumor to plasma  
Kpt: rate of plasma to tissue  
Ktp: rate of tissue to plasma
Mouse PBPK model described plasma and tumor PK data well.
Mouse tumor model

- Substantial tumor suppression was seen from 0.5 mg/kg, however rebound was observed after treatment discontinuation
- Complete suppression was observed at 1.5 mg/kg dose

\[ K_g \times \log(T_{\text{max}}/T) \]

\[ K_k \times f(C_{\text{MMAE}}) \times \text{Resistance}(t) \]

\[ K_d \]

\[ K_d \]

\[ C_{\text{MMAE}}: \text{MMAE concentration} \]
\[ K_d: \text{degradation rate constant} \]
\[ K_g: \text{growth rate} \]
\[ K_k: \text{killing rate} \]

Mouse tumor model describes the tumor volume data well.
Human PopPK Model

BT5528 Peripheral → BT5528 Central

TMDD CL

Lag

MMAE Central

CLm: MMAE clearance
Lag: lag time

MMAE Peripheral
The clinical PopPK model accurately describes the systemic concentrations of BT5528 and MMAE in cancer patients.

Model prediction (dashed line) versus observed mean (±SD)
Human PopPK-PBPK Model

**Assumptions**

- Similar tubulin binding parameters (KD, Kon, Koff) across species.
- Tumor flux parameters \( Q_{5528} \) and \( Q_{MMAE} \) were scaled to humans using standard allometry (0.75 coefficient).

Note: CLt and Kin scaled allometrically by weight (coefficient of 0.75)
The linked PopPK-PBPK model also describes the clinical tumor concentrations of MMAE well.

- Observed concentrations from different dose cohorts; median dose of 4.4 (2.2 to 8.5) mg/m².
- Model prediction from 4.4 mg/m².
Concentrations of MMAE in tumor are predicted to exceed concentrations of MMAE in plasma

Predicted clinical plasma concentrations of BT5528 and MMAE and tumor concentrations of MMAE following a single dose BT5528 at 6.5 mg/m²
Key findings of the PopPK-PBPK modeling

• BT5528 has a short terminal plasma half-life
• MMAE has rapid penetration into the tumor and is retained in the tumor through binding to tubulin
• Plasma concentrations of MMAE are a good surrogate for tumor concentrations of MMAE
  • validation based on extensive preclinical mouse data
  • emerging clinical data supports clinical translation
Conclusions

• This preclinical and clinical PBPK-PopPK-tumor size modeling paradigm has enabled a prediction of tumor payload profiles for new BTCs

• This paradigm also supports dose selection and dose optimization that fully leverages both preclinical and clinical data, which is aligned with Project Optimus
Acknowledgement

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