

## **A quantitative systems pharmacology (QSP) model to assess the action of blinatumomab in NHL patients (pts).**

Theresa Yuraszeck,<sup>1</sup> Derek Bartlett,<sup>2</sup> Indrajeet Singh,<sup>1</sup> Mike Reed,<sup>2</sup> Matthias Klinger<sup>3</sup>, Sharan Pagano,<sup>2</sup> Min Zhu<sup>1</sup>

<sup>1</sup>Clinical Pharmacology, Modeling, and Simulation; Amgen, Inc.; Thousand Oaks, CA, USA; <sup>2</sup>Rosa & Co, San Carlos, CA, USA; <sup>3</sup>Amgen Research (Munich) GmbH, Munich, Germany

**Background:** Blinatumomab is a bispecific T cell engager (BiTE<sup>®</sup>) antibody construct with dual specificity for CD3+ T cells and CD19+ B cells. We developed a QSP model to explore the blinatumomab target dose and factors influencing response in pts with diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL).

**Methods:** The QSP model (PhysioPD<sup>TM</sup>) integrates blinatumomab pharmacokinetics and mechanism of action (MOA) with NHL pathophysiology, including dynamics of T and B cells in circulation, lymph node and bone marrow. Virtual DLBCL and FL pts, sensitive or resistant to blinatumomab treatment, were constructed using data from clinical study MT103-104 (ClinicalTrials.gov NCT00274742). Parametric sensitivity analysis was performed; target treatment dose was explored through simulation.

**Results:** The model well described the observed clinical data and identified key drivers of response to blinatumomab: tumor doubling time, effector-to-target ratio, blinatumomab density on target B cells, drug partitioning between plasma and lymph node, and efficiency of redirected T cell lysis. It showed that ~2% of bound surface CD19 is needed to achieve a CD19 bound blinatumomab density of ~1/μm<sup>2</sup> and to initiate T cell activation; redirected T-cell lysis can occur at drug concentrations ≥20 pM at effective sites. *In silico* simulations predicted that shorter infusion durations and lower doses may be effective in sensitive pts, whereas continuous IV (cIV) infusion at either 60 μg/m<sup>2</sup>/day for ≥ 5 wks or > 70 μg/m<sup>2</sup>/day for 4 wks could be target treatments in resistant pts. Similar efficacy was predicted for daily IV bolus of 75 μg/m<sup>2</sup>/day for 3 wks if the regimen can be tolerated. The model suggested that T cell infiltration of the tumor, tumor growth rate, and the “fitness” of tumor-infiltrating lymphocytes could be biomarkers for predicting response.

**Conclusions:** The QSP model provided novel insights into the MOA of blinatumomab and drug regimen optimization in NHL pts. It showed that antitumor efficacy was a result of the interplay among blinatumomab and its surface presentation, rate of redirected T cell lysis, malignant cell growth rate and effector-to-target cell ratio. This provided direction for enhancing efficacy.