BP-007

PII-081

A Systems Pharmacology Model to Characterize the Effect of Blinatumomab in Patients With Adult B-Precursor Acute Lymphoblastic Leukemia

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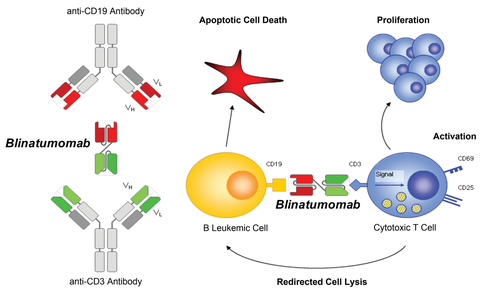
INTRODUCTION

B-Precursor Acute Lymphoblastic Leukemia (B-ALL)

- Rare malignant disease with an overall incidence of 1 to 1.5 per 100,000 persons[1]
- Comprises 20% of leukemia cases in adults[1]
- Caused by malignant transformation of a hematopoietic progenitor cell into a primitive, abnormally differentiated, long-lived, and highly proliferative cell[2]
- May lead to displacement of normal bone marrow (BM) tissue and hematopoietic cells, and infiltration of the liver, spleen, lymph nodes, and central nervous system[3]
- May cause anemia, thrombocytopenia, and neutropenia[3]
- Characterized by
  - Cell doubling time: 1–20 days
  - Blast count: ≤ 90% of white blood cells in the peripheral blood and 25%–90% of cells in the BM
  - Survival time if untreated: 3–6 months



Blinatumomab

- Blinatumomab is an investigational, bispecific T-cell engager (BiTE®) antibody designed to direct cytotoxic T cells to CD19-expressing B cells[4]
- CD19 is highly expressed throughout B-cell development and is present on the surface of blast cells in > 90% of B cell-lineage cancers[5,6]
- Blinatumomab-mediated engagement of B cells by T cells leads to the killing of B cells while, at the same time, causing the activation and proliferation of T cells[7]
- In a phase 2 study of patients with chemotherapy-refractory minimal residual disease (MRD+) B-ALL, 80% of patients who responded to blinatumomab treatment achieved MRD negativity[8]

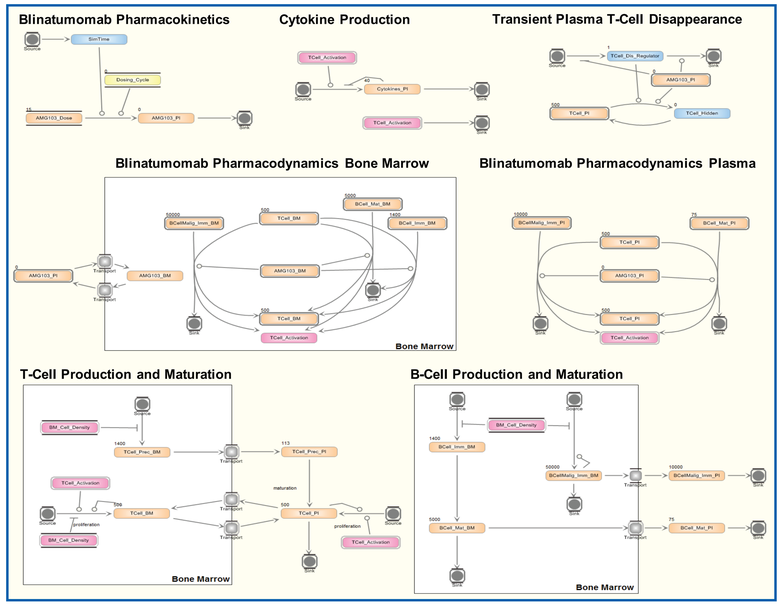
OBJECTIVES

- Develop a quantitative systems pharmacology (QSP) model (PhysioPD™ Model) that describes the pathophysiology of B-ALL and the effect of blinatumomab on adult patients with B-ALL
- Use the QSP model to address key biological and clinical questions such as:
  - What are the biological pathways that have the greatest impact on blinatumomab activity?
  - What are the key factors that contribute to blinatumomab efficacy in B-ALL treatment?
  - What are the factors that contribute to making individual patients responders or nonresponders?

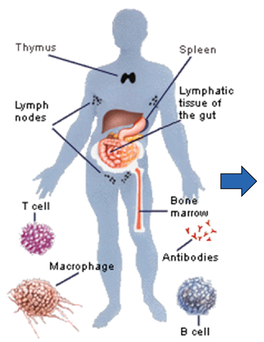
METHODS

- A QSP model (based on differential equations) was developed that integrates underlying physiology, disease pathophysiology, blinatumomab mechanism of action, and pharmacokinetics
- Virtual patients (responders / nonresponders / relapsers) were created, and data from a blinatumomab clinical trial[4] were used to calibrate model parameters
- Simulations were performed to predict cellular dynamics in patients with B-ALL
- Univariate sensitivity analyses used to identify key factors that affect patient response to blinatumomab
- The baseline condition used in the model was post-chemotherapy and pre-blinatumomab treatment

PhysioMap® Structure of B-ALL



Creating a Virtual Patient



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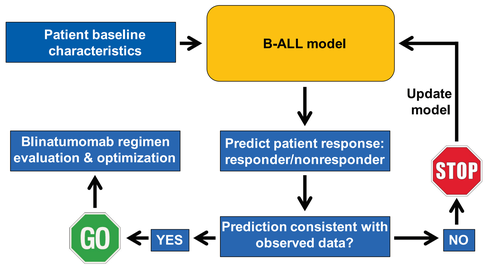


Model Development

- The QSP model integrates 69 parameters that were identified from internal data and 70 published articles
- The model describes
  - Disease biology in peripheral blood and BM
  - Production and maturation of normal and malignant B cells
  - Production and maturation of T cells
  - B-cell/T-cell engagement and killing
  - Blinatumomab pharmacokinetics
  - Transient blinatumomab-mediated cytokine elevation
- The model was qualified using Rosa's model qualification method[9] to ensure that it was "fit for purpose"

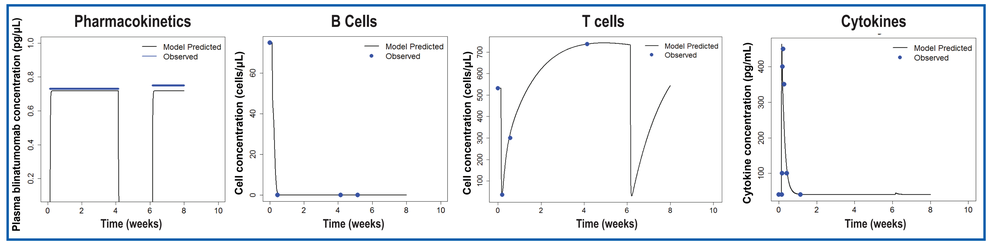
Clinical Data Used for Parameter Calibration

Study of blinatumomab in patients with MRD+ B-ALL[7,8] (NCT00560794)

- Open-label, multicenter, single-arm, phase 2 clinical trial
- Investigated the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of blinatumomab
- Eligible patients
  - Adults with B-lineage ALL in hematologic complete remission
  - Express the precursor B-phenotype
  - Molecularly refractory or following a molecular relapse
  - Quantifiable MRD load of ≥ 1 x 10^{-4}
- Patients received blinatumomab as a continuous IV infusion at a dose of 15 µg/m^2/d over a 4-week cycle followed by a treatment-free period of 2 weeks
- The primary endpoint was incidence of MRD negativity (ie, < 1 x 10^{-4}) within 7 blinatumomab treatment cycles
- Blinatumomab serum levels, lymphocyte subpopulations, and serum cytokines were measured in each treatment cycle

RESULTS

Model Calibration Based on MRD+ B-ALL Clinical Data[7]

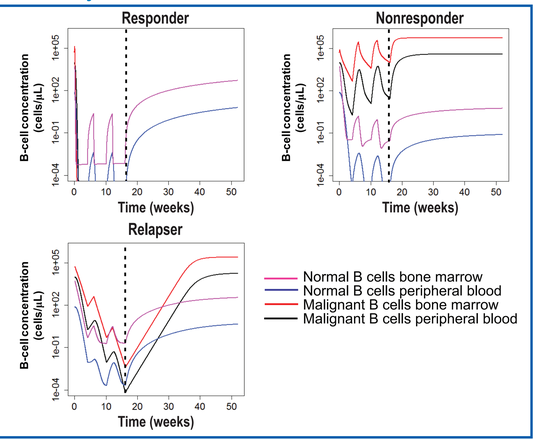


B-Cell Dynamics in Relapsed/Refractory B-ALL Adult Virtual Patients

Regimen: Blinatumomab 15 µg/m^2/day, 4 weeks on, 2 weeks off, 3 cycles

- Responder: B cells declined rapidly in the first cycle and malignant B cells remained suppressed long-term while healthy B cells recovered gradually
- Nonresponder: Malignant B cells were suppressed by treatment, but malignant cells were still detectable, and disease progressed after dosing ceased
- Relapser: Malignant B cells declined to undetectable levels over 2–3 treatment cycles, but disease progressed after dosing ceased

Note: The QSP model allows prediction of B-cell and T-cell dynamics at levels too low to detect in clinical practice (lower limit of detection = 1 cell/µL); dynamics at these low levels may distinguish responders from nonresponders



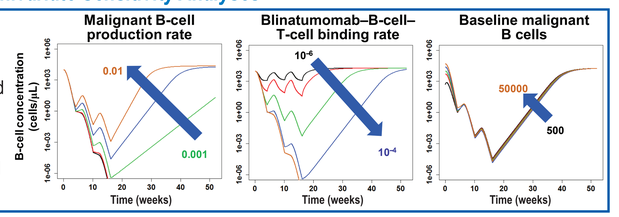
Univariate Sensitivity Analyses

B-ALL adult virtual patients were sensitive to

- Malignant B-cell production rate
- Binding efficiency of blinatumomab to B cells and T cells

B-ALL adult virtual patients were not sensitive to

- Baseline levels of malignant B cells in peripheral blood



ANSWERS TO KEY QUESTIONS

Question	Answer
✓ What are the biological pathways that have the greatest effect on blinatumomab activity?	Dynamics of B cells and T cells in BM and peripheral blood
✓ What are the key factors that contribute to blinatumomab efficacy in B-ALL treatment?	Cell mass in BM, cell cytotoxicity, blinatumomab binding affinity, drug distribution into BM and peripheral blood
✓ What are the factors that contribute to making individual patients responders or nonresponders?	Malignant cell production rate, effective T cells, drug affinity

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CONCLUSIONS

- The "fit for purpose" QSP model presented here improved our understanding of patient responses to blinatumomab treatment and the factors that influence these responses
- This model can be used to evaluate the effectiveness of various dosing regimens for adult patients with B-ALL
- The QSP framework developed for blinatumomab can be extended or modified to describe other BiTE® molecules or drugs with similar modes of action
- This model can be used to generate and test hypotheses, support discovery and clinical drug development, and improve predictions of efficacy and safety
- As new clinical response data are collected, they will be integrated into the model so as to further refine its ability to predict patient responses

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