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MECHANISTIC MODELLING OF CRS IN T CELL ENGAGERS - AN APPLICATION FOR BLINATUMOMAB

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Background

- Blinatumomab is a CD19/CD3 bispecific T-cell engager (TCE) that redirects cytotoxic T cells against CD19⁺ B-cell malignancies, including B-ALL [1, 2].
- Treatment is associated with transient cytokine elevation within the first 24–48 hours — a clinically significant on-target toxicity whose underlying mechanisms remain poorly understood [1].
- Quantitative Systems Pharmacology (QSP) provides a mechanistic framework linking drug exposure to immune cell kinetics and cytokine dynamics, enabling model-informed dose optimisation [3].

Objective

- Implement a modular QSP T-cell engager platform in QSP Designer [4], integrating physiologically based pharmacokinetic (PBPK) modelling, bispecific TCE avidity [5], cytotoxicity, and cytokine distribution modules [3].
- Calibrate and validate against published blinatumomab pharmacokinetics (PK), T/B-cell kinetics, and cytokine data [1, 2, 6].
- Generate a virtual population to simulate variability in B-cell depletion and cytokine release syndrome (CRS) associated cytokine responses across MT103-104 dose levels [2, 7].
- Identify the optimal dose maximising B-cell complete response (CR) while minimising IL-6-associated CRS risk.

Methods

- **PK calibration:** Simulated blinatumomab concentrations were within 2-fold of observed steady-state values [2] **(Fig 1a-b)**.
- **T-/B-cell kinetics:** The model reproduced T-cell redistribution and sustained B-cell depletion [1] **(Fig 2c-d)**.
- **Cytokine validation:** Simulated cytokine peaks were within 2-fold of observed clinical data [6] **(Fig2e)**.
- **PD validation:** Simulated T-/B-cell timing and count endpoints were consistent with clinical observations [1] **(Fig3)**.

Fig. 1 Schematic diagram of model description and end-to-end modelling methodology.

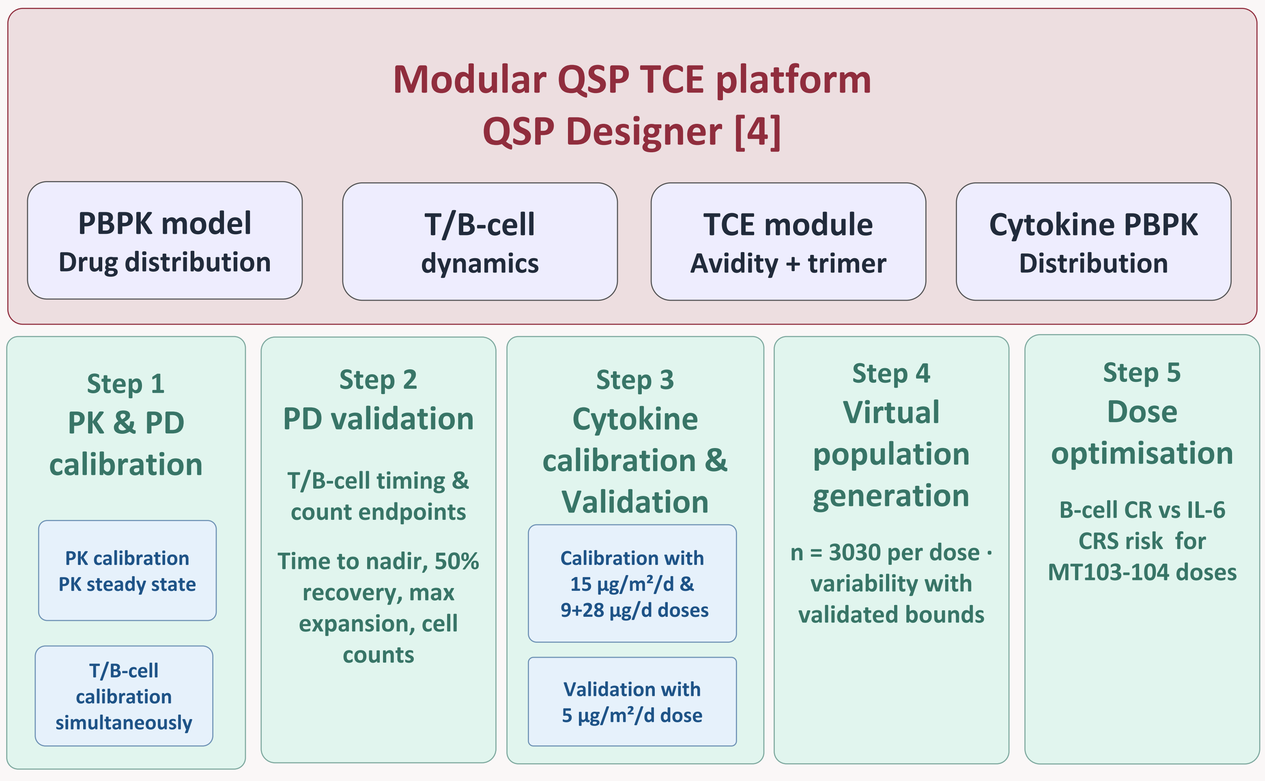


Figure 2. a. b. Simulated vs. observed blinatumomab PK profiles for continuous IV infusion regimens [2], **c.** Simulated vs. observed T-cell dynamics over 30 days [1], **d.** Simulated vs. observed B-cell depletion over 30 days [2], **e.** Cytokine calibration and validation goodness-of-fit analysis[6].

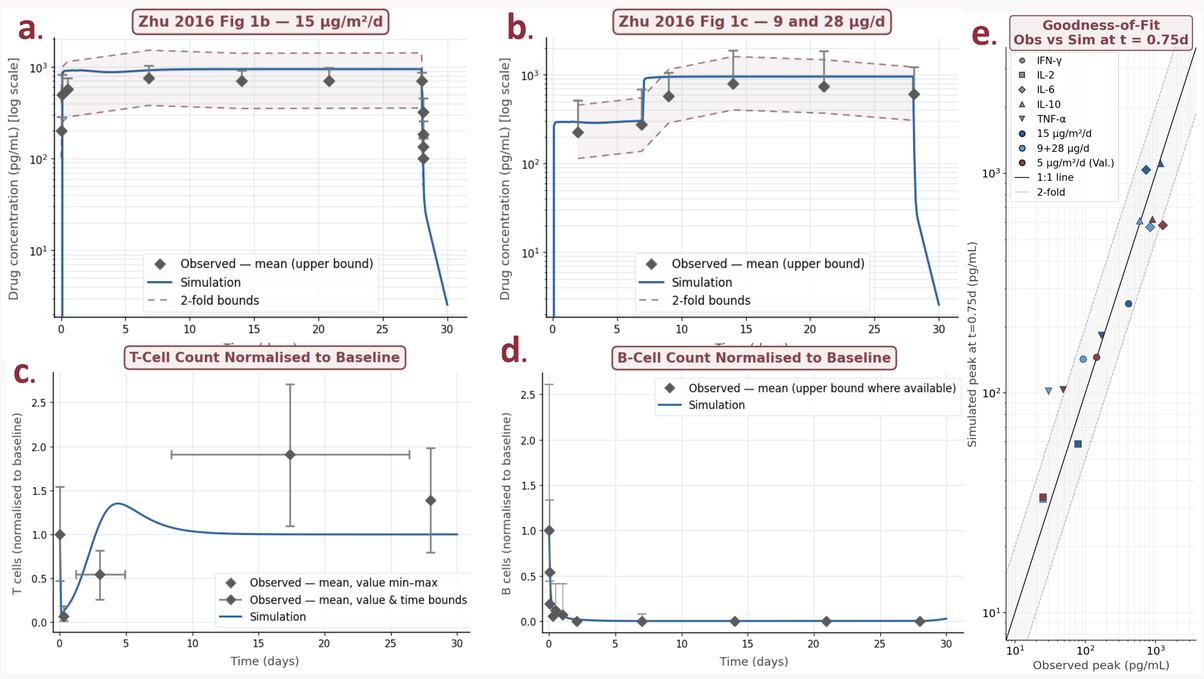
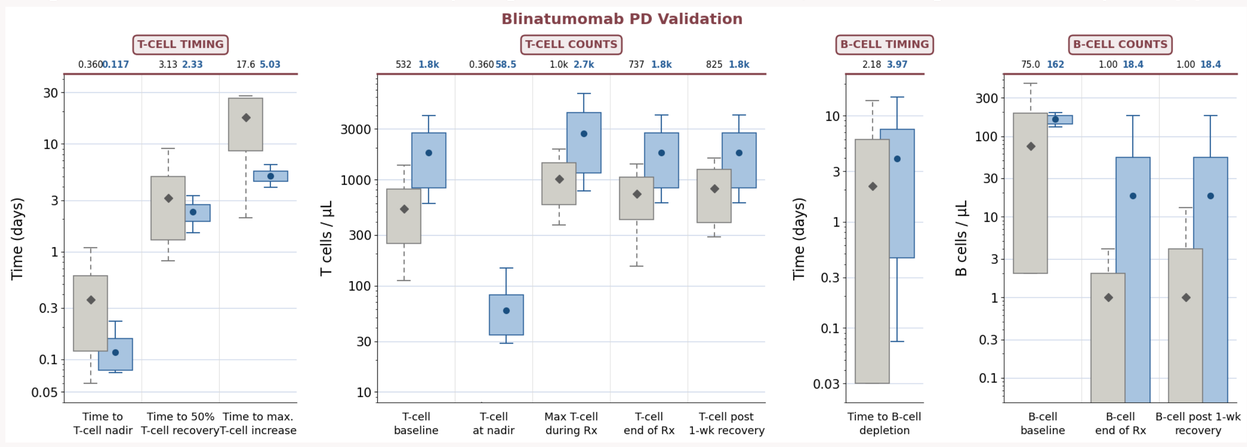


Fig. 3. Blinatumomab PD validation comparing simulated and observed T-/B-cell timing and count endpoints [1].



Results

Virtual Population

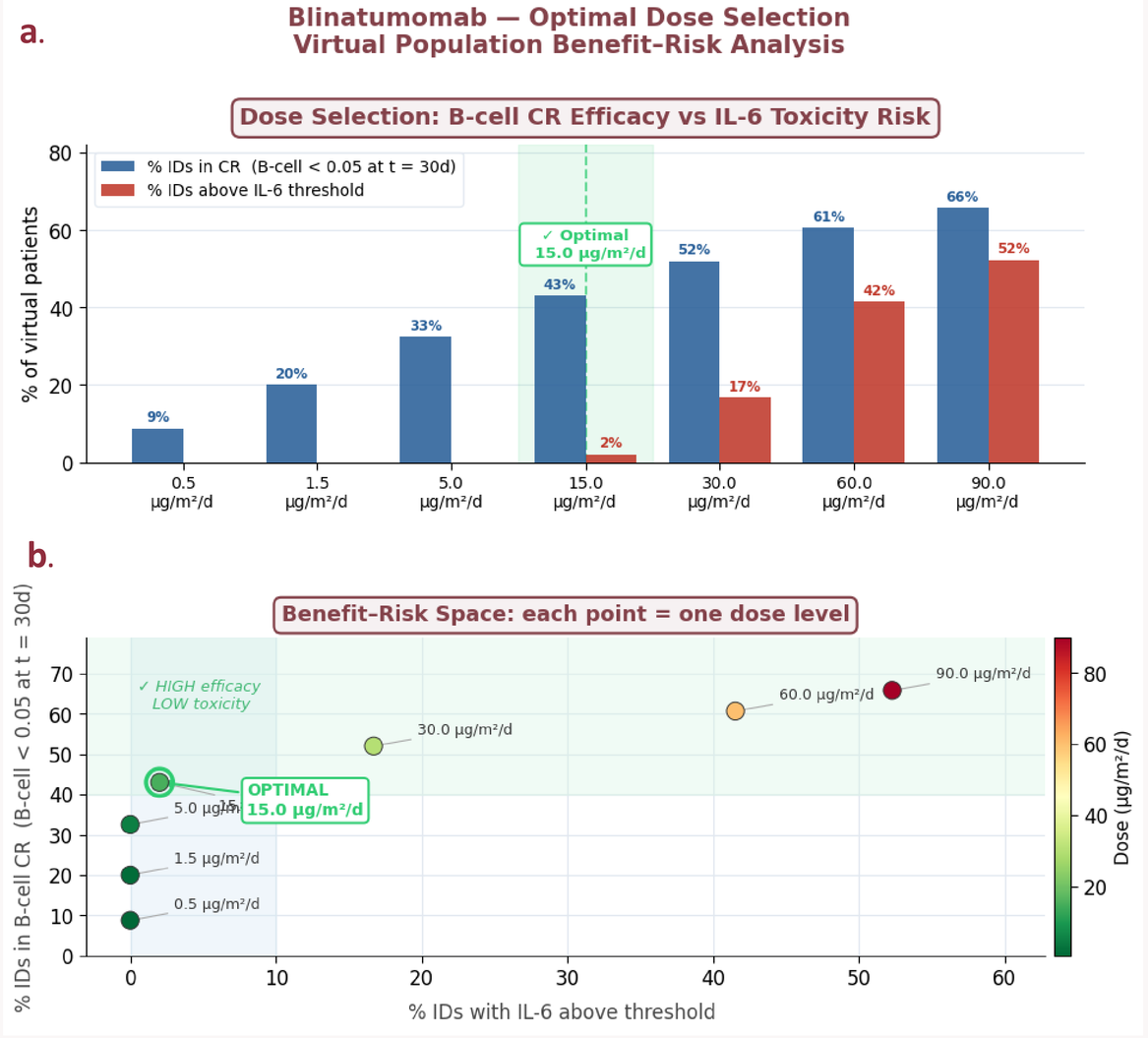
- **Virtual population:** A 3030-patient virtual population was generated [8] **(Fig. 3)**, and utilized for probabilistic CR and CRS risk prediction across dose levels [6].
- **Dose response:** B-cell CR increased with dose, reaching 66% at 90 µg/m²/day **(Fig. 4.a)**.

Dose Optimisation

- **CRS risk:** IL-6-associated CRS risk remained low at 15 µg/m²/day but increased substantially at higher doses **(Fig. 4.a)**.
- **Benefit–risk optimisation:** 15 µg/m²/day provided the optimal balance between efficacy and CRS risk **(Fig. 4.b)**.

Fig. 4a. Virtual population benefit–risk analysis identified 15 µg/m²/day as the optimal dose, **b.** balancing high B-cell CR with low IL-6-associated CRS risk [2, 6].

⚠️ **Note:** The conference abstract states 30 µg/m²/day as the optimal dose; full simulation analysis corrects this to 15 µg/m²/day based on the benefit–risk inflection point identified in the virtual population.



Conclusions

- A modular QSP TCE platform model was successfully applied to blinatumomab, linking systemic PK to T-/B-cell dynamics and cytokine-mediated CRS risk.
- Key PD endpoints were reproduced including T-cell redistribution, B-cell depletion, and cytokine dynamics within clinically acceptable limits.
- Virtual population simulations identified **15 µg/m²/day as the optimal target dose**, balancing B-cell CR (43%) with low IL-6-associated CRS risk (2%), consistent with the approved step-dosing regimen [7].
- The modular platform supports rapid adaptation to novel TCE modalities, enabling model-informed dose selection and early benefit–risk optimisation [3, 4, 5].

References

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