

Bridging Oncology and Autoimmune Disease: Using QSP to Select T-Cell Engager Doses by CRS Risk and Efficacy

Joshua F. Apgar^{1*}, Suruchi Bakshi^{1,2}, Doug Chung^{3†}, Birses Debir¹, David Flowers¹, Piet van der Graaf^{1,2}, Joshua Grant¹, Fei Hua^{4†}, Andrzej Kierzek¹, Kimiko McGirr¹, Robert Mines¹, Marc Presler¹, Michelle Przedborski^{5†}, Rachel Rose¹, Harshbir Sandhu¹, Saheli Sarkar¹, Kevin Snyder¹

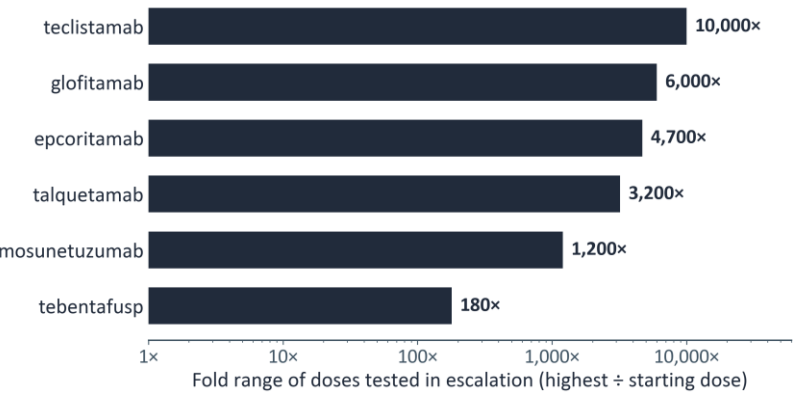
¹ Applied BioSimulation, MID3, Certara ² Leiden Academic Centre for Drug Research, Leiden University ³ Nurix Therapeutics ⁴ Eli Lilly and Company ⁵ GlaxoSmithKline
† Contribution made while at Certara * Corresponding author: joshua.apgar@certara.com Authors are listed alphabetically by surname.

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Autoimmune TCEs need a tighter CRS window. An oncology-validated QSP platform lets you start first-in-human closer to an efficacious dose.

1 The problem

Oncology TCEs found their dose the hard way



Approved oncology TCEs were escalated across 180- to 10,000-fold dose ranges¹.

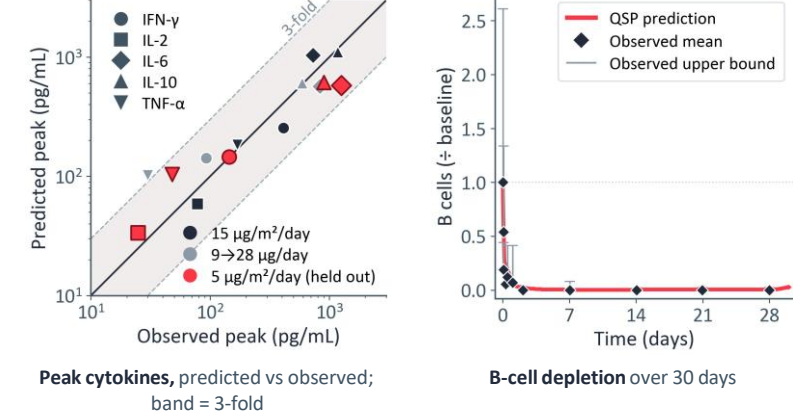
Why TCE FIH dosing is hard

- **Occupancy-based MABEL doesn't fit:** activity needs binding to both targets, so receptor occupancy says little about effect^{1,2}
- **Exposure-based MABEL ignores in vitro → in vivo differences,** so safe starts are often sub-therapeutic^{1,3}
- **Bell-shaped dose–response:** affinity, avidity, target expression, E:T and PK all shape it^{1,2}
- **CRS is dose-limiting:** intra-patient escalation helps but complicates design⁴

FDA's analysis of 17 CD3 bispecifics found RO-, HNSTD- and NOAEL-based starts unacceptable: they landed near or above the MTD⁴.
FDA's 2026 draft QSP guidance provides a clear path for QSP-based FIH study designs⁵.
Certara has already done this in ≥9 autoimmune programmes across 5 indications (mechanistic TCE models; results confidential).

2 Validated in oncology

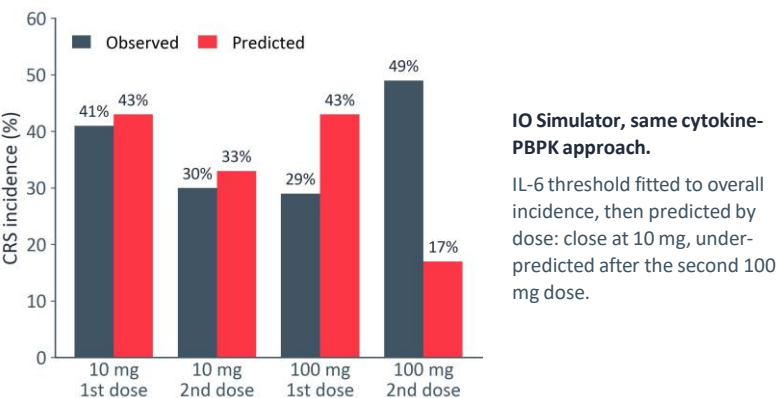
Blinatumomab: cytokines and B cells reproduced^{6*}



One model predicts both sides of the trade-off: 14 of 15 cytokine peaks within 3-fold, including all 5 at the held-out 5 μg/m²/day dose (red), and B-cell depletion over 30 days. One miss: TNFα over-predicted 3.4x at 9→28 μg/day.

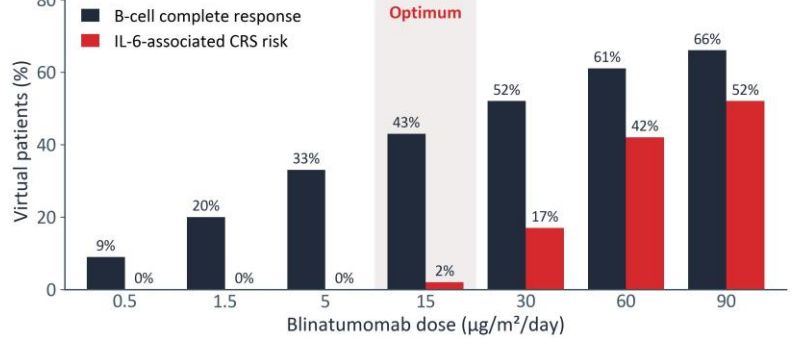
*Digitized from ref. 6. PK also within 2-fold (not shown). Data: Zhu 2016, Blincyto EPAR.

Tarlatamab: CRS incidence by dose⁷



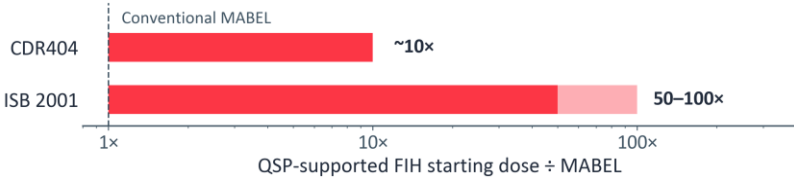
3 Model-informed dosing

Blinatumomab: efficacy vs CRS risk by dose⁶



Virtual population: 3,030 patients per dose⁶
Optimum 15 μg/m²/day: 43% CR with 2% CRS, consistent with the approved step-dose regimen

QSP starting doses closer to efficacy



- **CDR404 (CDR-Life):** QSP-derived start ~10x above exposure-based MABEL; accepted by FDA and European agencies⁸
- **ISB 2001 (IGI):** FIH 5 μg/kg vs MABEL 0.045–0.1 μg/kg; first stringent CR at 50 μg/kg⁹
- **Oncology bispecific:** model-informed start 1–2 dose levels above MABEL, ~6 months faster¹

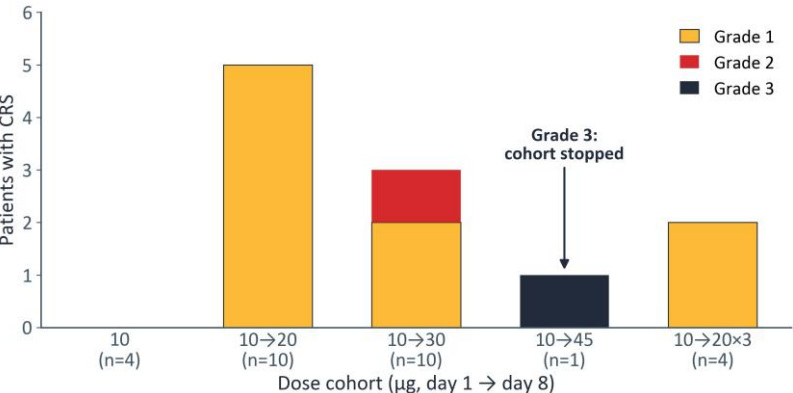
Step-up effects are predictable

- **Blinatumomab:** 9→28 μg/day step regimen: PK and cytokines reproduced⁶
- **Tarlatamab:** first-to-second dose CRS drop predicted at 10 mg (43→33% vs 41→30%)⁷
- **Teclistamab:** QSP-guided restart rules; 2/61 low-grade CRS on restart¹⁰
- **Tebentafusp:** cytokine peak suppression by step-up reproduced¹¹; priming effects captured¹²

APPLYING IT TO AUTOIMMUNE DISEASE

4 What is different

Autoimmune patients: a narrower CRS window



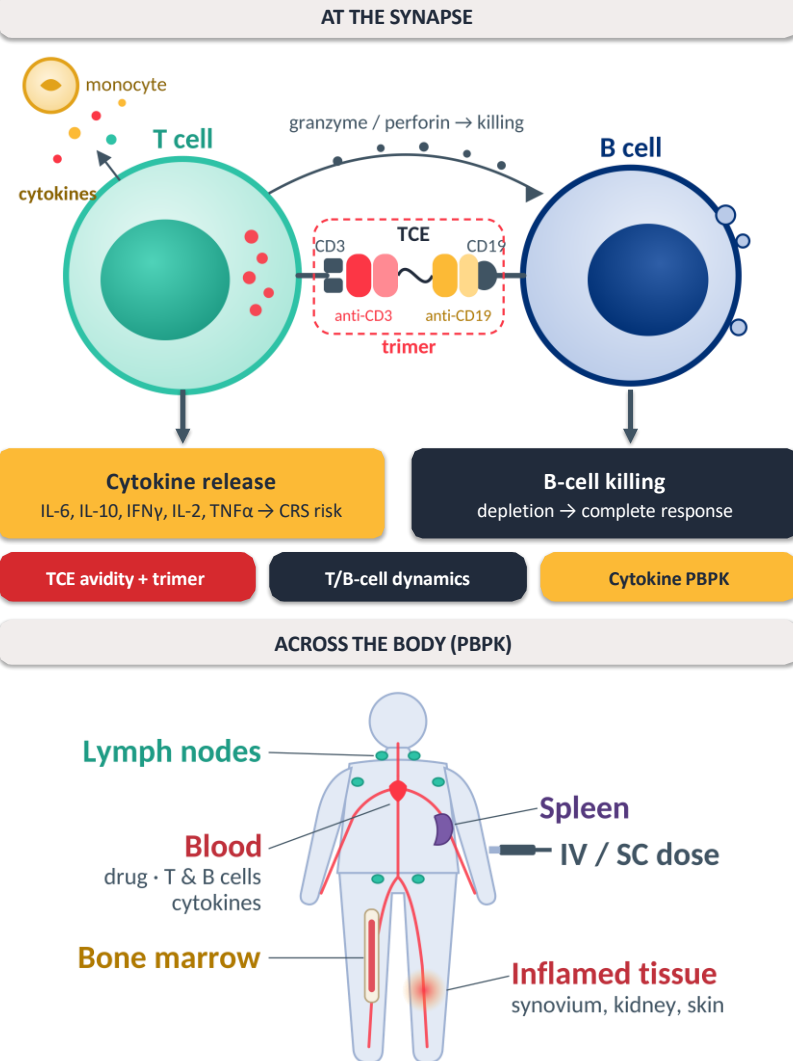
CLN-978 (CD19×CD3): 30 μg weekly in lymphoma¹³; in SLE/RA a 10→45 μg step caused grade 3 CRS¹⁴.

What changes from oncology

	Oncology	Autoimmune
Target cells	Malignant B cells high tumour burden	Autoreactive B cells reservoirs in lymph node, spleen, synovium
E:T ratio	Low many target cells per T cell	High few B cells per T cell; binding calibrated across E:T ¹⁵
Calibration	Cell lines plus oncology patient data	Patient PBMCs from SLE and RA donors
Acceptable CRS	Grade 1–2 tolerated in life-threatening disease	Close to none chronic, non-malignant disease
Efficacy goal	Tumour response complete remission	Deep B-cell depletion durable, including tissue reservoirs

5 The model, recalibrated

One synapse drives both depletion and CRS



6 Putting it to work

A validated path from candidate to label

QSP has informed TCE decisions at every stage. • Certara work

- 1 **Design:** pick affinity and format
 - **Solitomab:** predicted toxic dose matched the observed MTD¹⁶
- 2 **Translate:** in vitro and animal data → patients
 - **ISB 2001:** bridged via mouse and clinical benchmarks⁹
 - **Cytokine assays:** in vitro release carried to the clinic¹²
 - **Binding model:** 2D matches the clinical blinatumomab dose¹⁵
- 3 **First-in-human:** start nearer efficacy, under a CRS ceiling
 - **ISB 2001:** ~50–100x MABEL⁹
 - **CDR404:** ~10x MABEL⁸
 - **P-cadherin LP-DART:** trimer-based MABEL¹⁷
- 4 **Step-up:** design schedule, priming and route
 - **Mosunetuzumab:** phase 1 switched to QSP-designed step-up¹⁸
 - **Priming and route:** effective priming and lower CRS with SC¹²
 - **Blinatumomab:** 9→28 μg/day step-up reproduced⁶
- 5 **RP2D:** read it off your CRS tolerance
 - **Blinatumomab:** ~0% CRS → 5 μg/m²/day, 33% CR; ≤2% → 15, 43%⁶
 - **Tarlatamab:** held-out dose predicted⁷
 - **Epcoritamab:** trimer model supported 48 mg¹⁷
- 6 **Regimen & label:** durability, interval, restart
 - **Autoimmune:** tissue depletion, B-cell recovery, retreatment •
 - **Teclistamab:** QW→Q2W¹⁹ and restart rules¹⁰ in label updates
 - **Elranatamab:** Q2W in responders¹⁷
 - **Tarlatamab:** atezolizumab combination predicted⁷

Regulators have accepted QSP-based doses: FDA and European agencies (CDR404⁸); FDA and Australian HREC (ISB 2001⁹); FDA label updates (teclistamab^{10,19}). FDA's 2026 draft guidance sets out how to submit them⁵.

Certara has run this workflow in ≥9 autoimmune programmes (results confidential).

- Mechanistic TCE platform reproduces oncology PK, PD, cytokines and CRS incidence.
- Autoimmune dosing should follow the efficacy–CRS trade-off at a stricter tolerance.
- Certara QSP has completed 95+ inflammation and immunology projects.

Partner with us

to bring CRS benefit–risk into your autoimmune TCE programme:
FIH and step-up design, patient-PBMC calibration, tissue depletion.

Contact: joshua.apgar@certara.com

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