Dose Response Profile of IGM-2323, a CD20xCD3 IgM Bispecific T Cell Engager, in Translational Models Supports Phase 2 Dose Selection in Non-Hodgkin's Lymphoma

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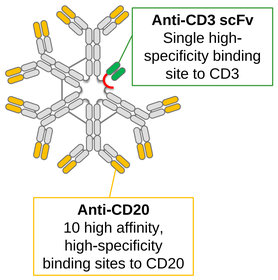
Background

- IGM-2323 is an engineered high-affinity, high-avidity anti-CD20 pentameric IgM antibody with an anti-CD3 scFv fused to the joining (J) chain. IGM-2323 offers a novel treatment strategy in NHL through multiple mechanisms: the recruitment of T cells to kill CD20-expressing tumor cells through T cell dependent cellular cytotoxicity (TDCC), complement-dependent cytotoxicity (CDC), and enhanced immune modulation via IFNγ-dominant cytokine stimulation.



- Preliminary results from the first-in-human study of IGM-2323 show a 60% ORR at a titration dose level of 100 mg, and an excellent safety and tolerability profile up to 1000 mg with low CRS, no ICANS and limited neutropenia. Interestingly, lower response rates of IGM-2323 were observed at the highest dose levels of 600 mg and 1000 mg.
- The aims of this study were to (1) characterize the concentration versus response relationship of IGM-2323 *in vitro* and compare with bispecific IgG TCEs, and (2) build a mechanistic binding model based on preclinical *in vitro* data to aid in prediction of an optimal dose of IGM-2323 in the clinic.
- To evaluate the dose response of IGM-2323, a concentration range that encompassed the peak and trough plasma levels up to the 1000 mg dose of IGM-2323 and equivalent concentrations of bispecific IgG TCEs were tested in preclinical *in vitro* assays.

Potential Mechanisms for Dose-Dependent Changes in T Cell Activation for Bispecific TCEs

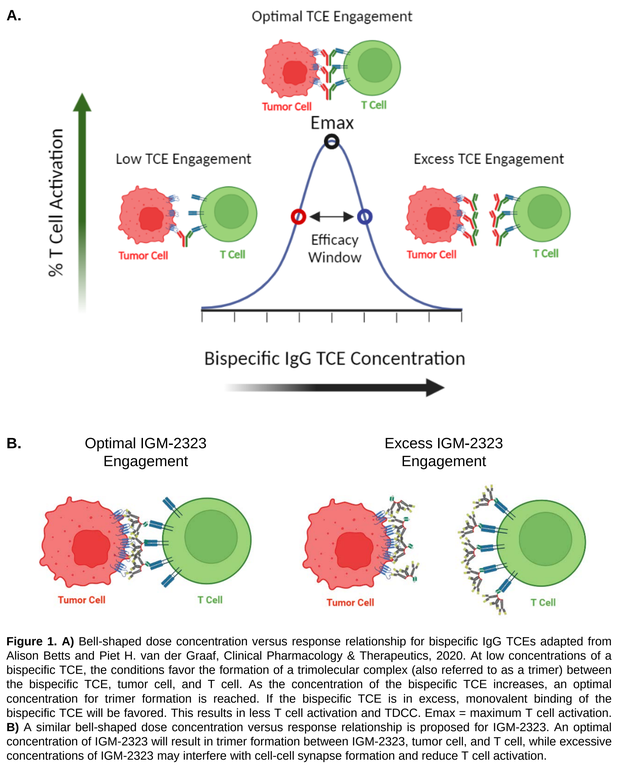


Figure 1. A) Bell-shaped dose concentration versus response relationship for bispecific IgG TCEs adapted from Alison Betts and Piet H. van der Graaf, Clinical Pharmacology & Therapeutics, 2020. At low concentrations of a bispecific TCE, the conditions favor the formation of a trimolecular complex (also referred to as a trimer) between the bispecific TCE, tumor cell, and T cell. As the concentration of the bispecific TCE increases, an optimal concentration for trimer formation is reached. If the bispecific TCE is in excess, monovalent binding of the bispecific TCE will be favored. This results in less T cell activation and TDCC. Emax = maximum T cell activation. **B)** A similar bell-shaped dose concentration versus response relationship is proposed for IGM-2323. An optimal concentration of IGM-2323 will result in trimer formation between IGM-2323, tumor cell, and T cell, while excessive concentrations of IGM-2323 may interfere with cell-cell synapse formation and reduce T cell activation.

Less T Cell Activation is Observed *In Vitro* with High Concentrations of IGM-2323

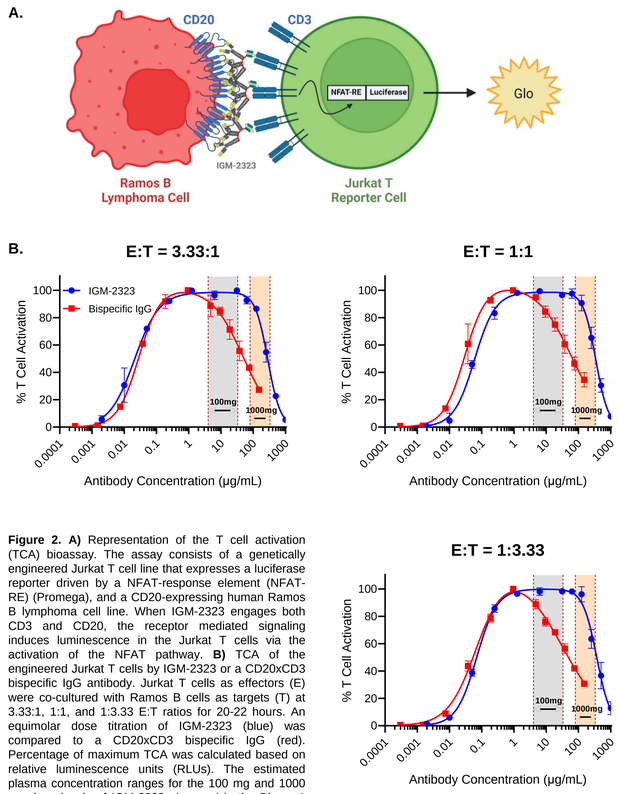


Figure 2. A) Representation of the T cell activation (TCA) bioassay. The assay consists of a genetically engineered Jurkat T cell line that expresses a luciferase reporter driven by a NFAT-response element (NFAT-RE) (Promega), and a CD20-expressing human Ramos B lymphoma cell line. When IGM-2323 engages both CD3 and CD20, the receptor mediated signaling induces luminescence in the Jurkat T cells via the activation of the NFAT pathway. **B)** TCA of the engineered Jurkat T cells by IGM-2323 or a CD20xCD3 bispecific IgG antibody. Jurkat T cells as effectors (E) were co-cultured with Ramos B cells as targets (T) at 3.33:1, 1:1, and 1:3.33 E:T ratios for 20-22 hours. An equimolar dose titration of IGM-2323 (blue) was compared to a CD20xCD3 bispecific IgG (red). Percentage of maximum TCA was calculated based on relative luminescence units (RLUs). The estimated plasma concentration ranges for the 100 mg and 1000 mg dose levels of IGM-2323 observed in the Phase 1 study are shown by the vertical bars.

Novel Mechanistic-Based Binding Model Describes the IGM-2323 *In Vitro* T Cell Activation

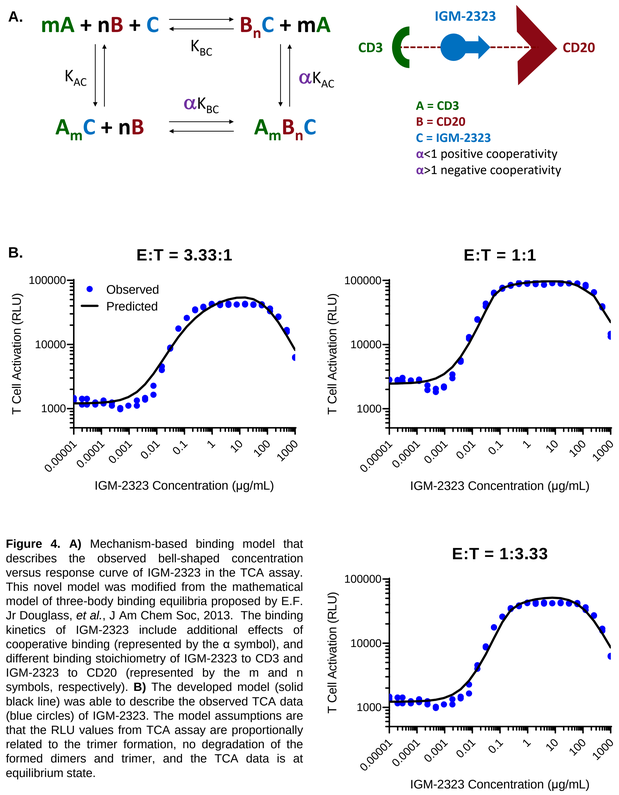


Figure 4. A) Mechanism-based binding model that describes the observed bell-shaped concentration versus response curve of IGM-2323 in the TCA assay. This novel model was modified from the mathematical model of three-body binding equilibria proposed by E.F. Jr Douglass, *et al.*, J Am Chem Soc, 2013. The binding kinetics of IGM-2323 include additional effects of cooperative binding (represented by the α symbol), and different binding stoichiometry of IGM-2323 to CD3 and IGM-2323 to CD20 (represented by the m and n symbols, respectively). **B)** The developed model (solid black line) was able to describe the observed TCA data (blue circles) of IGM-2323. The model assumptions are that the RLU values from TCA assay are proportionally related to the trimer formation, no degradation of the formed dimers and trimer, and the TCA data is at equilibrium state.

Less T Cell Activation Observed in Clinical Patient Samples with a High Dose of IGM-2323

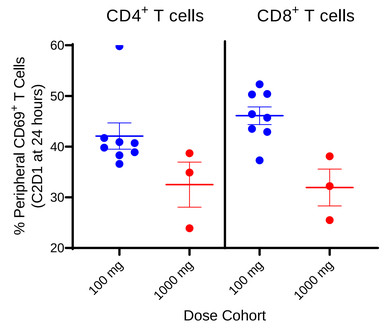


Figure 6. Frequency of activated peripheral blood T cells in NHL patients treated with either 100 mg or 1000 mg of IGM-2323. The percentage of $CD4^+CD69^+$ and $CD8^+CD69^+$ T cells was measured by flow cytometry in Cycle 2 at 24 hours post dose in the Phase 1 study with IGM-2323.

Less T Cell Activation with IGM-2323 at Additional E:T Ratios Observed in Clinical Patient Samples

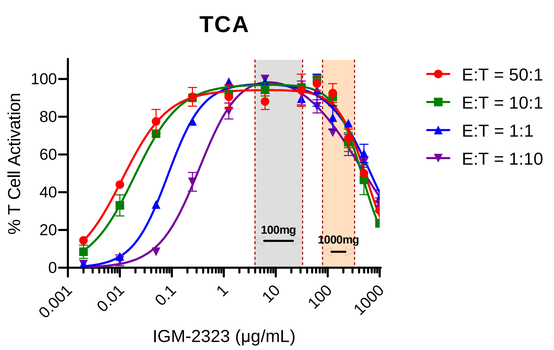


Figure 3. TCA of the engineered Jurkat T cells by IGM-2323. Jurkat T cells as effectors (E) were co-cultured with Ramos B cells as targets (T) at 50:1, 10:1, 1:1, and 1:10 E:T ratios, and a 2-fold dose titration of IGM-2323 starting at 1000 μg/mL for 20-22 hours. The E:T ratios examined in the TCA bioassay were representative of E:T ratios observed in NHL patients' tumors by IHC from the Phase 1 study with IGM-2323. Percentage of maximum TCA was calculated based on RLUs. The estimated plasma concentration ranges for the 100 mg and 1000 mg dose levels of IGM-2323 observed in the Phase 1 study are shown by the vertical bars.

Reduced T Cell- and Complement-Mediated Killing *In Vitro* with High Concentrations of IGM-2323

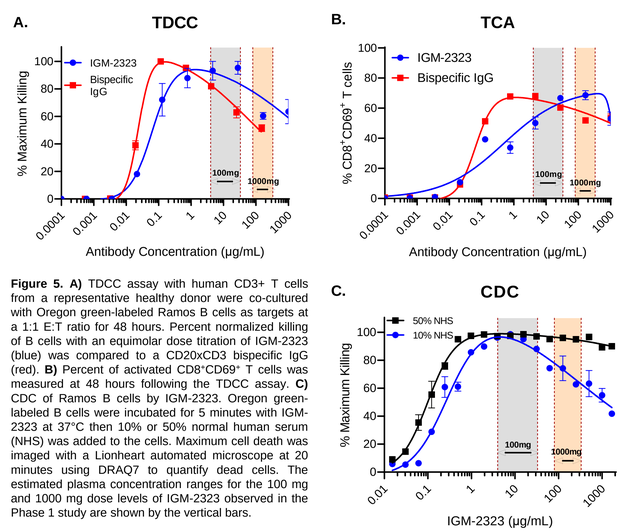


Figure 5. A) TDCC assay with human CD3+ T cells from a representative healthy donor were co-cultured with Oregon green-labeled Ramos B cells as targets at a 1:1 E:T ratio for 48 hours. Percent normalized killing of B cells with an equimolar dose titration of IGM-2323 (blue) was compared to a CD20xCD3 bispecific IgG (red). **B)** Percent of activated $CD8^+CD69^+$ T cells was measured at 48 hours following the TDCC assay. **C)** CDC of Ramos B cells by IGM-2323. Oregon green-labeled B cells were incubated for 5 minutes with IGM-2323 at 37°C then 10% or 50% normal human serum (NHS) was added to the cells. Maximum cell death was imaged with a Lionheart automated microscope at 20 minutes using DRAQ7 to quantify dead cells. The estimated plasma concentration ranges for the 100 mg and 1000 mg dose levels of IGM-2323 observed in the Phase 1 study are shown by the vertical bars.

Randomized Phase 2 Dose-Selection Study of IGM-2323

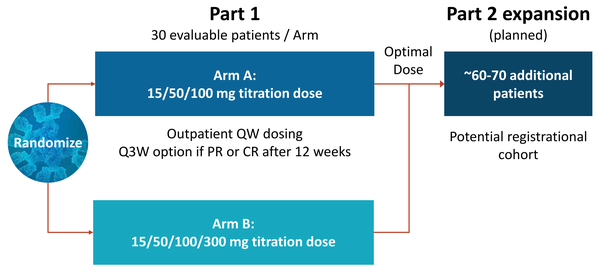


Figure 7. Study design of the randomized Phase 2 dose-selection of IGM-2323. Part 1 includes two arms (A & B) with 30 evaluable NHL patients randomized per arm. Arm A includes titration dosing of 15 mg, 50 mg and 100 mg of IGM-2323, while Arm B includes titration dosing of 15 mg, 50 mg, 100 mg, and 300 mg of IGM-2323 once weekly (QW) with the option for every 3 weeks (Q3W) if a partial or complete response is obtained after 12 weeks on treatment. There will be two dose-selection studies: one in diffuse large B-cell lymphoma (DLBCL) and the other in follicular lymphoma (FL). An optimal dose of either 100 mg or 300 mg will be selected. Part 2 is the expansion phase, which will include 60 to 70 additional patients. Data from these patients will potentially contribute to the registrational cohort.

Summary

- IGM-2323, as well as an IgG-based CD20xCD3 bispecific, show a bell-shaped dose versus response relationship preclinically, with high concentrations associated with reduced T cell activity.
- IGM-2323 exhibited peak T cell activation over a broad range of antibody concentrations which eventually declined at the highest concentrations tested.
- These data were well-described by the mechanistic-based binding model.
- Interestingly, the concentration range of IGM-2323 resulting in peak activity corresponded to the peak and trough plasma levels in patients following 100 mg dose. The high concentrations associated with reduced activity are similar to plasma levels following 1000 mg dose.
- A trend for higher frequency of activated $CD69^+$ peripheral T cells was detected in patients treated with 100 mg of IGM-2323 at 24 hours post dose compared to 1000 mg dose.
- The *in vitro* data support the decision to move forward with our randomized Phase 2 design testing 100 mg and 300 mg dose levels.

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