IGM-2323: High Avidity IgM-based CD20 x CD3 Bispecific Antibody for Enhanced T-Cell Dependent Killing with Minimal Cytokine Release

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Background

- Bispecific T-cell engagers are emerging therapeutic modalities for treating hematological malignancies, especially tumors resistant to mAbs and CAR-Ts.
- Current bispecific antibodies are largely based on IgG-like scaffolds. Although some early success has been seen in the clinic, adverse events related to cytokine release remain a major concern with IgG-based bispecific antibodies.
- IGM-2323 is an IgM-based bispecific that uses an anti-CD20 x anti-CD3 IgM to provide high avidity binding to CD20, an sFc fused to the N-terminus of J-chain to provide monomeric engagement of CD20 on T-cells, and human serum albumin (HSA) fused to the C-terminus of J-chain to improve pharmacokinetics.
- Our preclinical data show highly effective complement dependent cytotoxicity (CDC) and T-cell dependent cellular toxicity (TDCC) killing of tumor cells without associated cytokine release, for potentially larger therapeutic index.

Superior Binding of Bispecific IgM vs IgG

Figure 2. Schematic diagram of 1 T-cell engagement by B 8 bound IGM-2323. We believe that the bispecific IgM format allows simultaneous engagement of multiple antigens on the target cell surface and engages a single CD3 on T-cells for each IgM resulting in a more "physiological" immune synapse compared to BTEC or bispecific IgG format.

Bispecific IgM Format

- Anti-CD20 sFc for monoclonal T-cell engagement
- HSA for half-life extension

Bispecific IgM Antibody

- Anti-CD20 IgM for high avidity cell killing

High Avidity Binding of Antigen by anti-CD20 IgM

Figure 3A. IGM-2323 vs IgG with identical CD20 binding variable domains to CD20 ECD coated on a plate at 10 µg/mL. Highly avid and IgM binds more than 100 times higher than IgG.

Figure 3B. Binding of IGM-2323 or corresponding bispecific IgG (with CD20 and CD3 binding units) to CD20 expressing Ramos cells. IgM antibody bind cell surface CD20 more than 100 times higher than the bispecific IgG with apparent Kd of 11 nM as vs 81 nM.

Bispecific IgM Shows Low Cytokine Release in Vitro

Figure 5. In vitro comparison of four cytokines released in "cytolytic release syndrome" observed with bispecific IgG. IGM-2323 or a bispecific IgG with the same CD20 and CD3 binding units were incubated with human PBMC and the supernatant assayed for cytokines using flow cytometry. Levels of cytokine release observed for IGM-2323 are orders of magnitude lower than that for the corresponding IgG indicating potential for better therapeutic window using bispecific IgM T-cell engagers.

IGM-2323 Kills Cell Lines with Low CD20 Expression and Cell Line Selected for Rituximab Resistance

Figure 6. Depiction of peripheral B cells upon treatment of Cynomolgus monkeys with a single dose of either IGM-2323 IgM, IGM-2323 IgG, IGM-2324 (monomeric IgG and CD3 x CD20 cross reactive sFc). The dose response curves indicate the bispecific IgM IGM-2323 with dual mechanism of B-cell killing (both CDC and TDCC), has an EC50 of 0.04 mg/kg vs IGM-2323 which only has two CDC based B-cell killing and shows a roughly 25x higher EC50 of 0.34 mg/kg for B-cell depletion at 24 hours post administration.

Summary

- We have developed a novel bispecific IgM platform that allows highly and engagement of tumor antigens with monomeric engagement of CD3+ T cells.
- Bispecific IGM-2323 exhibits 100+ greater binding to CD20 antigen on a tumor cell line compared to a corresponding bispecific IgG.
- Highly potent CDC and TDCC based killing of tumor cell lines is demonstrated in vitro together with potent killing of rituximab resistant cells.
- Importantly, TDCC activity of IGM-2323 does not result in excess in vitro cytokine release, commonly associated with CRS in clinical settings and other bispecific mAbs or CART therapy.
- IGM-2323 has potent activity in vivo in NSG mice (data not shown) as well as in cynomolgus monkeys with durable depletion from spleen and lymph nodes.
- Very low cytokine release, durable depletion of B cells in cynomolgus and potent killing of rituximab resistant cells supports clinical development of IGM-2323 as a bispecific IgM that potentially treat Non-Hodgkin’s lymphoma patients.
- Phase I clinical trial is currently in progress. ClinicalTrials.gov ID: NCT 04808936

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