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

Background

- Bispecific T-cell engagers are emerging therapeutic modalities for treating hematological malignancies, especially tumors resistant to mAbs and CARTs.
- 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 IgM to provide high avidity binding to CD20, an sscFv fused to the N-terminus of J-chain to provide monovalent engagement of CD3 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 cytotoxicity (TDCC) killing of tumor cells without associated cytokine release, for potentially larger therapeutic index.
- Phase I clinical trial of IGM-2323 has been initiated in patients with Non-Hodgkin Lymphoma (NHL) in 2019 (ClinicalTrials.gov ID: NCT 04082936).

Superior Binding of Bispecific IgM vs IgG

Figure 3A. IGM-2323 vs IgG with identical CD20 binding variables domains to CD20 ECD construct in vitro. Highly and IgG shows more potent binding 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 0.11 nM vs 8.1 nM.

Bispecific IgM Shows Low Cytokine Release in Vitro

Figure 5. In vitro comparison of four cytokines elevated in “cytokine release syndrome” observed with bispecific IgG. IGM-2323 is a bispecific IgM with the same CD20 and CD3 binding units were incubated with human PBMCs for 48 hours with each cytokine 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 bispecific IgG indicating potential for greater therapeutic window using bispecific IgM T-cell engagers.

High Avidity Binding of Antibody with anti-CD20 IgM

Figure 2A. Schematic diagram of a bispecific IgM. For IGM-2323, the variable regions of IgM were engineered bound CD20 and the sscFv fused to J-chain binds CD3.

Figure 2B. Cryo-electron micrograph of bispecific IgM showing the asymmetric structure of the pentameric IgM with the J-chain fusion.

Summary

- We have developed a novel bispecific IgM platform that allows highly and engagement of tumor antigens with monovalent engagement of CD3 in 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 excessive in vitro cytokine release, commonly associated with CDC in clinical trials, nor with other bispecific mAbs or CART therapy.
- IGM-2323 has potent activity in vivo in NGS mice (data not shown) as well as in cynomolgus monkeys with durable depletion of B cells in cynomolgus monkeys and potential killing of rituximab resistant cells supports clinical development of IGM-2323 as a bispecific IgM to potentially treat Non-Hodgkin’s lymphoma patients.
- Phase I clinical trial is currently in progress. ClinicalTrials.gov ID: NCT 04082936.

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