Lymphoma cell-killing activity and cytokine release by CD20-directed bispecific IgM antibody-based T-cell engager (IGM-2323).

Authors:
Bruce Keyt, Ramesh Baliga, Keyu Li, Marigold Manlusoc, Paul Hinton, Dean Ng, Madeline Tran, Bing Shan, Hai Lu, Sachi Rahman, Avneesh Saini, Yuan Cao, Chitra Saraiya, Marvin Peterson, Wayne R Godfrey, Steve Carroll; IGM Bioscience, Mountain View, CA; IGM Biosciences, Mountain View, CA

Abstract Disclosures

Research Funding:
IGM Biosciences Inc

Background:
Bispecific antibodies which tether T-cells to cancer cells, and additionally activate T-cell mediated killing, have shown promise in treating B-cell malignancies. Dose intensity, however, is limited by cytokine release from the activated T-cells. Side effects include fever, hypotension, and hypoxia.

Methods:
A novel type of bispecific antibody (IGM-2323) was constructed using the pentameric IgM framework. Recombinant IgM heavy chains and kappa light chains with high affinity variable domains derived from an anti-CD20 IgG, were co-expressed with a J-chain fused to anti-CD3 single chain Fv domain. IGM-2323 has 10 binding domains for CD20, and one binding domain for CD3.

Results:
IGM-2323 binds to the CD20 antigen with > 1000-fold increased avidity relative to an IgG antibody format. IGM-2323 in human cell cultures shows highly potent T cell dependent cytotoxicity (EC_{50} 20 pM), even on cells with very low cell surface expression of CD20, rituximab-resistant lymphoma cell lines, and patient derived CLL cells. Significantly, IGM-2323 exhibits vastly reduced cytokine release, with equivalent T cell dependent killing of CD20-expressing cancer cells, as compared to corresponding IgG-based T cell bispecifics made with the same binding domains. IGM-2323 mediated killing can occur at low T-cell/cancer cell ratios, as low as (1:5). In addition, IGM-2323 mediates complement dependent cytotoxicity (CDC) of
CD20-expressing cells with > 100-fold higher potency than IgG. IgM-based bispecific (anti-CD20 x anti-CD3) completely depletes circulating B cells in cynomolgus monkeys at doses of > 300 µg per kg. Furthermore, durable depletion of B cells in spleen and lymphoid tissues was noted with multiple doses of > 1 mg/kg. Importantly, in these studies no observable adverse effects were seen, despite repeated doses at up to 25 mg/kg (the highest dose tested). Low levels of transiently increased circulating IL-6 and no increased levels of circulating TNF-α and IFN-γ were observed in these primate studies.

Conclusions:
These data indicate that IgM-based bispecifics can induce T cell engagement and very potent cytotoxicity that can be dissociated from cytokine release syndrome in the primate model. These preclinical data demonstrate the potential for broad application of this novel modular IgM-based bispecific antibody format. A Phase I dose-escalation study of IGM-2323 in patients with relapsed/refractory Non-Hodgkin's lymphoma has been initiated (NCT04082936) and is currently enrolling patients.