**Introduction**

- CD38 is highly expressed on malignant plasma cells and is an attractive target of new therapies for multiple myeloma (MM).
- Several anti-CD38 antibodies such as daratumumab are in clinical development; however, one limitation of these monospecific antibodies is their inability to stimulate cytotoxic T cell killing of myeloma cells.
- To exploit the potent mechanism of T cell immunotherapy yet preserve the favorable drug and dosing properties of therapeutic antibodies, we designed XmAb13243 & XmAb13551 as Fc-containing bispecific antibodies that recruit T cells to CD38+ myeloma cells.
- XmAb13243 and XmAb13551 are highly effective at killing CD38+ cells, are readily manufactured, and have prolonged serum half-life.

**A** CD38 x CD3 bispecific antibodies are readily produced & purified

- Portable T cell-recruiting design
- Efficient bispecific production

**B** Bispecific antibodies bind to human & monkey CD38 & CD3

- Human
- Cynomolgus monkey

**C** Bispecific antibodies kill myeloma cells

- RTCC by purified human T cells
- More potent than daratumumab
- T cells are serial killers even when outnumbered by target cells

**D** Bispecifics have long half-life & suppress human Igs in mice

- Fc domain prolongs half-life
- Greater IgG2 depletion vs daratumumab

**E** Bispecifics deplete monkey CD38+ cells in blood & especially bone marrow

- Blood
- Bone marrow

**F** CD38+ cell depletion correlates with T cell redistribution & activation

- Redistribution from blood
- CD69 induction

**Summary**

The anti-CD38 × anti-CD3 bispecific antibodies XmAb13243 & XmAb13551:
- Incorporate a human Fc domain for long serum half-life
- Effectively recruit T cells to kill CD38+ multiple myeloma cells in vitro
- Deplete human CD38+ cells and suppress human IgG, IgM, IgE, & anti-tetanus production in human PBMC-engrafted SCID mice
- Safety & effectively deplete CD38+ cells in blood & particularly in bone marrow of monkeys at doses from 0.5 to 20 μg/kg, with bone marrow depletion persisting to study end (Day 36, 2 weeks after last dose)
- Possess greatly increased efficacy & potency against myeloma cell lines & humanized mice compared to daratumumab, a monospecific anti-CD38 antibody
- Are efficiently manufactured using standard antibody production methods

These results support clinical testing of these bispecific antibodies in patients with multiple myeloma and other CD38+ malignancies.