IGM-2644, a Novel CD38xCD3 Bispecific IgM T Cell Engager Demonstrates Potent Efficacy on Myeloma Cells with an Improved Preclinical Safety Profile

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Introduction

- Multiple myeloma (MM) affects > 30,000 new patients every year in the USA. Despite improved treatment options, including anti-CD38 IgG antibodies, resistance eventually develops in most patients.
- Several bispecific (CD38xCD3) or trispecific (CD38xCD3xCD28) T cell engager antibody therapies are currently in development to further improve upon the efficacy of CD38 targeted therapies by leveraging T cell dependent cellular cytotoxicity (TDCC) of MM cells.
- A unique challenge for anti-CD38 T cell engagers is the balance of myeloma cytotoxicity without depleting CD38+ immune cells, including activated cytotoxic T cells (i.e., fratricide), along with avoiding cytokine release syndrome.
- IGM-2644 is a novel bispecific IgM with 10 binding sites for human CD38, and a single anti-CD3ε scFv fused to the joining chain. IGM-2644 is capable of mediating both T cell dependent cellular cytotoxicity (TDCC) and complement dependent cytotoxicity (CDC).

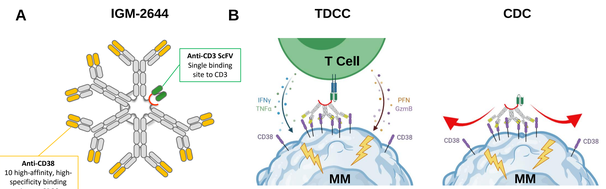


Figure 1. A) Structure of IGM-2644. **B)** Schematic mode of action (MoA) of IGM-2644 in T-cell dependent cellular cytoxicity (TDCC) and complement dependent cytotoxicity (CDC)

IGM-2644 Binds to CD38 and CD3ε with High Affinity

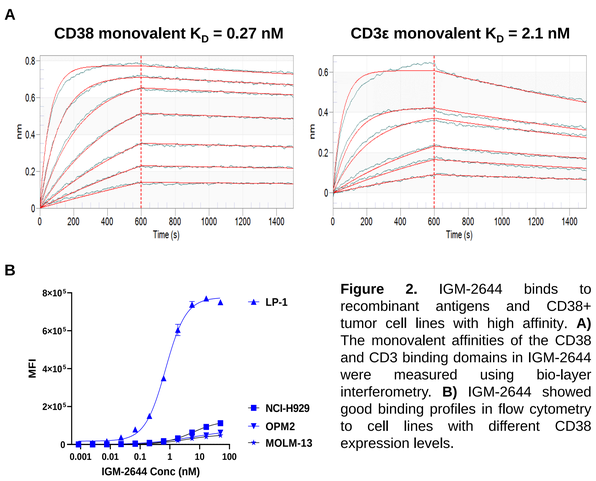
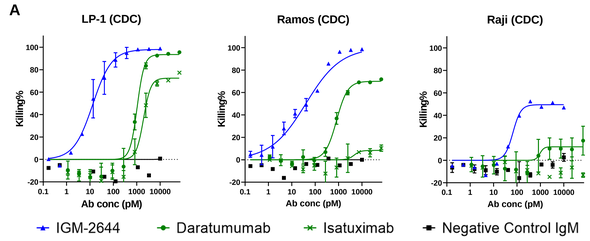


Figure 2. IGM-2644 binds to recombinant antigens and CD38+ tumor cell lines with high affinity. **A)** The monovalent affinities of the CD38 and CD3 binding domains in IGM-2644 were measured using bio-layer interferometry. **B)** IGM-2644 showed good binding profiles in flow cytometry to cell lines with different CD38 expression levels.

IGM-2644 Mediates Improved CDC Compared to Anti-CD38 IgG Antibodies



B

Cell Line	Antibody	Max Killing (%)	EC_{50} (nM)
LP-1	IGM-2644	97 ± 2 (5)	0.061 ± 0.046 (5)
	Daratumumab	77 ± 12 (5)	1.6 ± 1.2 (5)
	Isatuximab	46 ± 17 (5)	2.5 ± 1.8 (5)
Ramos	IGM-2644	100 ± 0 (4)	0.14 ± 0.12 (4)
	Daratumumab	69 ± 6 (4)	0.95 ± 0.24 (4)
	Isatuximab	< 20 (4)	NA (4)
Raji	IGM-2644	76 ± 19 (4)	0.036 ± 0.024 (4)
	Daratumumab	32 ± 21 (4)	1.3 ± 0.8 (4)
	Isatuximab	< 20 (4)	NA (4)

Figure 3. IGM-2644 was tested in a 4-hour CDC assay using pooled normal human serum against MM (LP-1) and lymphoma (Ramos and Raji) cell lines. **A)** Representative CDC dose response curves comparing IGM-2644 with monospecific anti-CD38 IgG antibodies and a negative control IgM. **B)** Summary table of max killing percentages and EC50 values on these cell lines. Data presented as Mean ± SD (N). N represents the number of individual experiments.

IGM-2644 Achieves Similar TDCC Activity with Lower Cytokine Release than a Bispecific IgG Antibody

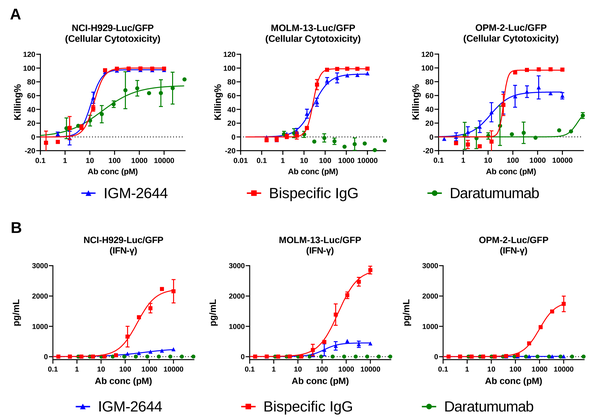


Figure 4. IGM-2644 was tested in a 72-hour cellular cytotoxicity assay using human PBMC as effector cells against luciferase/GFP tagged MM (NCI-H929 and OPM-2) and AML (MOLM-13) cell lines that are CDC resistant. IGM-2644 demonstrated TDCC activities similar to that of a CD38xCD3 bispecific IgG competitor while inducing lower cytokine release. **A)** Representative cellular cytotoxicity dose response curves comparing IGM-2644 with anti-CD38 monospecific and CD38xCD3 bispecific IgG antibodies. **B)** IFN-γ release dose response curves in the same PBMC co-culture assay. IGM-2644 also induced lower levels of IL-2, IL-6, IL-10 and TNF-α than the bispecific IgG (data not shown).

IGM-2644 Eliminates Myeloma Cells but Spares Normal Hematopoietic Progenitor Cells

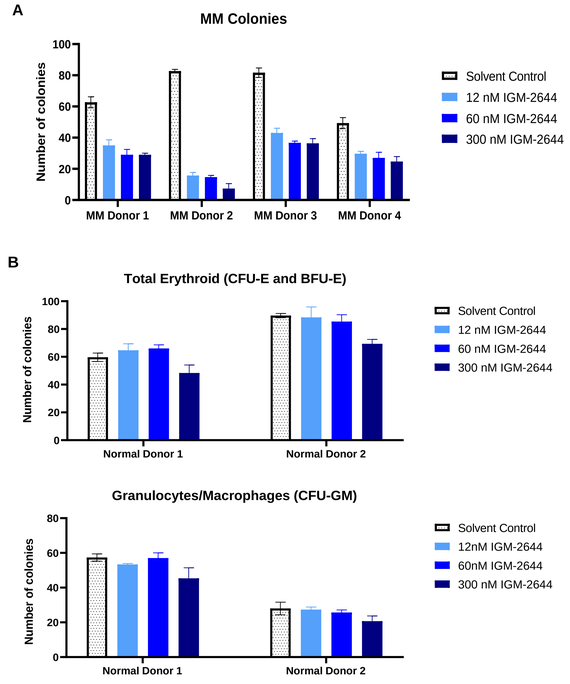


Figure 5. IGM-2644 was tested in a colony forming unit (CFU) assay using primary bone marrow samples. (5-day liquid culture in optimal conditioned media with various concentrations of IGM-2644, followed by CFU assay. Data presented as Mean ± SD). IGM-2644 was able to **A)** reduce MM colonies using primary MM patient bone marrow samples, and . **B)** show minimal effect on the colony formation of erythroid, granulocyte and macrophage using bone marrow samples from normal donors.

IGM-2644 Suppresses CD38+ Tumor Growth in Xenograft Models

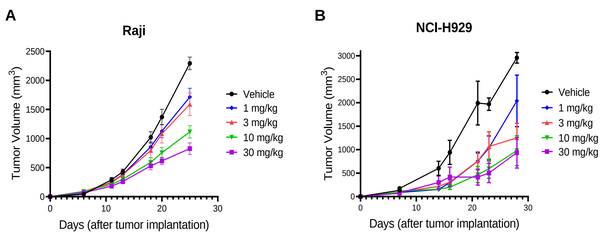


Figure 6. IGM-2644 was able to show in vivo efficacy and suppress CD38+ **A)** NCI-H929 (myeloma) and **B)** Raji (lymphoma) xenograft tumor growth in PBMC humanized MHC double-knockout (DKO) NSG mice. (3 doses every week. Data presented as Mean ± SEM. N=9 per group.)

IGM-2644 Shows Reduced Depletion of Immune Cells Compared to a Bispecific IgG Antibody

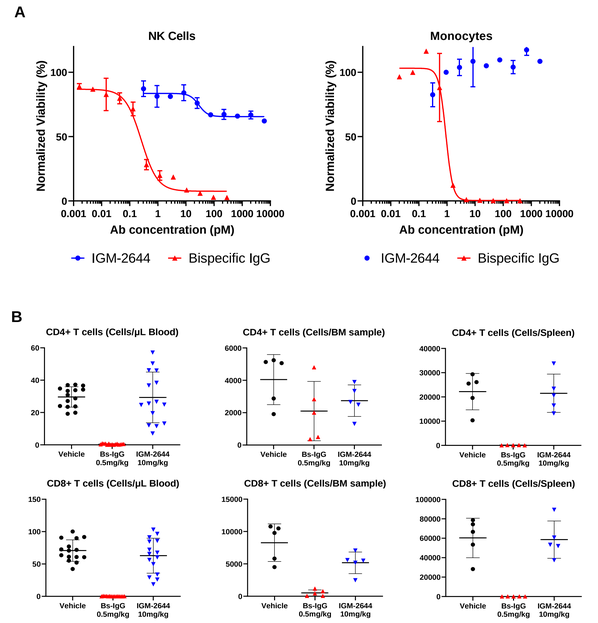


Figure 6. IGM-2644 demonstrated reduced immune cell depletion effects compared to a CD38xCD3 bispecific IgG competitor in various assays in vitro and in vivo **A)** In a 48-hour PBMC in vitro culture assay, the CD38xCD3 bispecific IgG showed complete killing of monocytes and NK cells in the PBMC sample, while IGM-2644 showed minimal effect on these immune cell subsets. **B)** The in vivo T cell fratricide effect was evaluated in MHC DKO NSG mice injected with ex vivo expanded human T cells. IGM-2644 demonstrated reduced T cell fratricide in blood, bone marrow (BM) and spleen samples compared to the bispecific IgG. (Q3D x 2; 5 days post first dose. Data presented as Mean ± SD)

Summary

- IGM-2644 is a novel CD38xCD3 bispecific IgM T cell engager that:
  - ✓ Has improved CDC activity compared to marketed anti-CD38 monospecific IgG antibodies.
  - ✓ Achieves potent TDCC activity on daratumumab resistant cell lines with minimal cytokine release.
  - ✓ Shows efficacy on myeloma patient samples in CFU assays.
  - ✓ Inhibits CD38+ tumor growth in humanized xenograft models
  - ✓ Preserves immune cell viability with minimal fratricide effect in vitro and in vivo
- Taken together, our data demonstrates IGM-2644 is a potent molecule with both CDC and TDCC activities and an improved preclinical safety profile compared to other CD38xCD3 bispecific T cell engagers. It has the potential to be active in daratumumab resistant tumors. A Phase I clinical study evaluating the activity and safety of IGM-2644 is planned.

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