Novel CD38xCD3 Bispecific IgM T Cell Engager, IGM-2644, Potently Kills Multiple Myeloma Cells Through Complement and T Cell Dependent Mechanisms

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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).

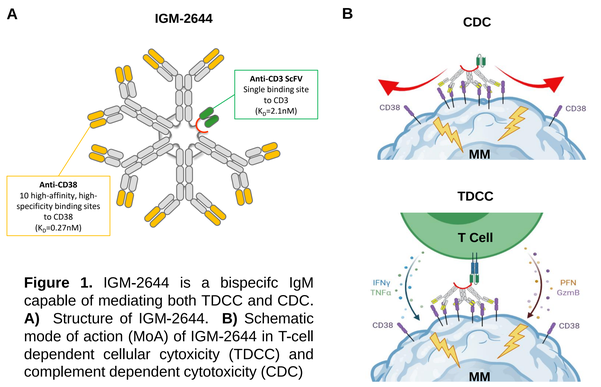
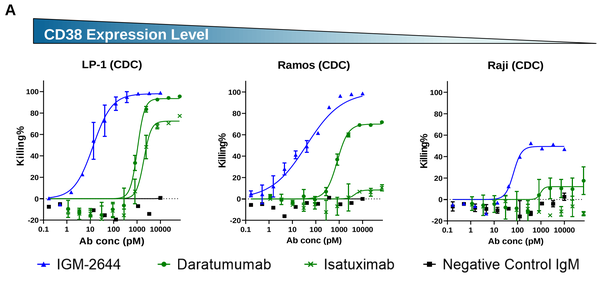


Figure 1. IGM-2644 is a bispecifc IgM capable of mediating both TDCC and CDC. **A)** Structure of IGM-2644. **B)** Schematic mode of action (MoA) of IGM-2644 in T-cell dependent cellular cytoxicity (TDCC) and complement dependent cytotoxicity (CDC)

IGM-2644 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 2. 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

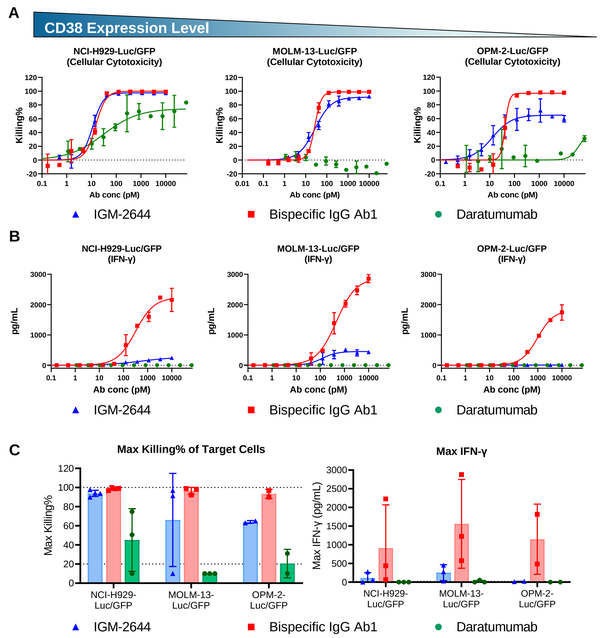


Figure 3. IGM-2644 was tested in a 72-hour cellular cytotoxicity assay using human PBMC as effector cells against luciferase/GFP tagged MM (NCI-H929 and OPM-2) and AML (MOLM-13) cell lines that are CDC resistant. IGM-2644 demonstrated TDCC activities similar to that of a CD38xCD3 bispecific IgG while 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. **C)** Summary of max killing% and max IFN-γ across multiple donors. 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 Suppresses CD38+ Tumor Growth in Xenograft Models

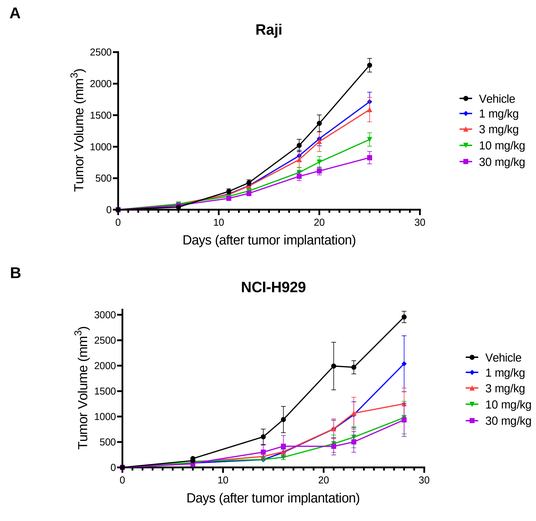


Figure 4. IGM-2644 was able to show in vivo activity in mouse models and suppress CD38+ **A)** NCI-H929 (myeloma) and **B)** Raji (lymphoma) xenograft tumor growth in PBMC humanized MHC double-knockout (DKO) NSG mice. (3 doses every week. Data presented as Mean ± SEM. N=9 per group.)

IGM-2644 Shows Minimal Binding to Human RBCs and Platelets

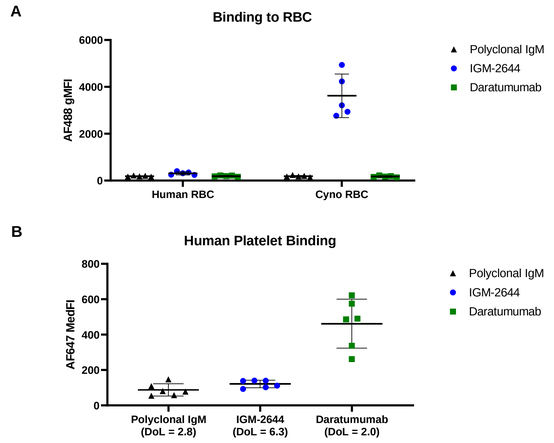


Figure 5. IGM-2644 shows minimal binding to human RBCs and platelets in flow cytometry. **A)** Binding to human and cynomolgus monkey RBCs were evaluated in flow assay using AF488 conjugated anti-human kappa secondary antibody. IGM-2644 and daratumumab showed similar low binding levels to human RBCs from 5 different donors. IGM-2644 showed strong binding to cyno RBCs which express much higher CD38 than human RBCs. Daratumumab does not cross react to cyno CD38 and didn't show binding to cyno RBCs as expected. **B)** Binding to human platelets were evaluated using AF647 directly conjugated antibodies. IGM-2644 showed lower binding to human platelets than daratumumab. Polyclonal IgM from human serum was used as negative control. (DoL: degree of labeling)

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

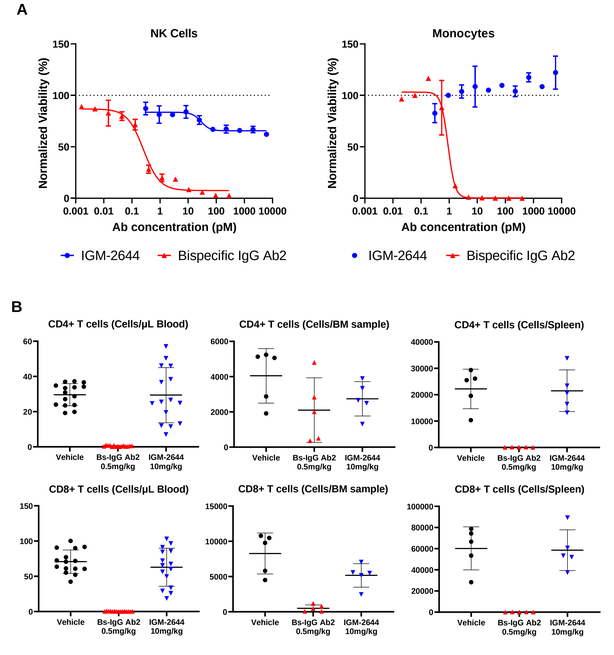


Figure 6. IGM-2644 demonstrated reduced immune cell depletion effects compared to another CD38xCD3 bispecific IgG in various assays in vitro and in vivo **A)** In a 48-hour PBMC in vitro culture assay, the CD38xCD3 bispecific IgG showed complete killing of monocytes and NK cells in the PBMC sample, while 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)

IGM-2644 Demonstrates Ex Vivo MM Depletion with No T Cell Fratricide & Low Cytokine Release

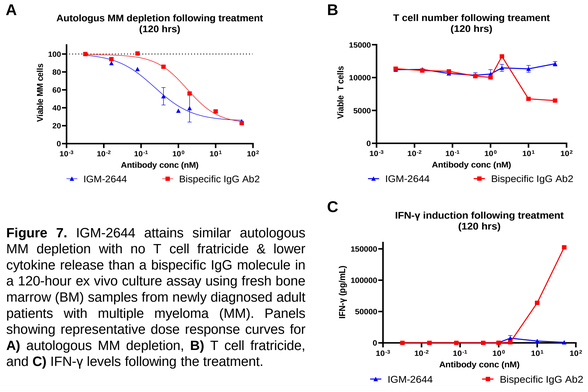


Figure 7. IGM-2644 attains similar autologous MM depletion with no T cell fratricide & lower cytokine release than a bispecific IgG molecule in a 120-hour ex vivo culture assay using fresh bone marrow (BM) samples from newly diagnosed adult patients with multiple myeloma (MM). Panels showing representative dose response curves for **A)** autologous MM depletion, **B)** T cell fratricide, and **C)** IFN-γ levels following the treatment.

IGM-2644 Eliminates MM Cells but Spares Normal Hematopoietic Progenitor Cells in CFU Assay

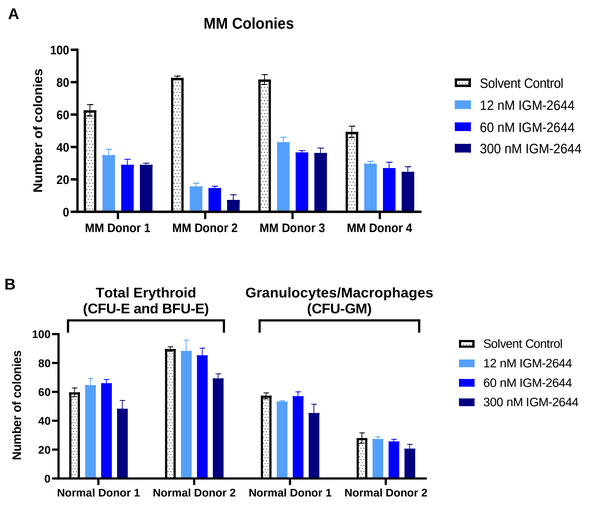


Figure 8. IGM-2644 was tested in a colony forming unit (CFU) assay using primary bone marrow samples. (5-day liquid culture in optimal conditioned media with various concentrations of IGM-2644, followed by CFU assay. Data presented as Mean ± SD). IGM-2644 was able to **A)** reduce MM colonies using primary 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.

Summary

- IGM-2644 is a novel CD38xCD3 bispecific IgM T cell engager that:
  - ✓ Has improved CDC activity compared to marketed anti-CD38 mAbs.
  - ✓ Achieves potent TDCC activity on daratumumab resistant cell lines.
  - ✓ Induces lower cytokine release than CD38 x CD3 bispecific IgG antibodies.
  - ✓ Inhibits CD38+ tumor growth in humanized xenograft models.
  - ✓ Shows minimal binding to human RBCs and platelets.
  - ✓ Shows in vitro activity in liquid culture and CFU assays using MM patient samples.
  - ✓ Preserves immune cell viability with minimal fratricide effect in preclinical studies.
- 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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