Therapeutic Potential of Imvotamab, a CD20-Targeted Bispecific IgM T Cell Engager, for the Treatment of Refractory Autoimmune Disease Patients

Racquel Domingo-Gonzalez, Isabelle Baribaud, Miho Oyasu, Kevin C. Hart, Keely Burns, Sivani Pandey, Maya K. Leabman, Genevive Hernandez, Albert Candia, Stephen F. Carroll, Rebecca Kunder, Bruce A. Keyt, Maya F. Kotturi, Carrie Brodmerkel, Mary Beth Harler

IGM Biosciences, Inc. | Mountain View, CA and Doylestown, PA

Background

- B cell depletion therapy (BCDT) with conventional IgG antibodies (e.g. rituximab) has been used to treat autoimmune (AI) disease for several decades
- However, many patients do not achieve long term disease control or remission. The inability of these therapies to fully deplete tissue-resident B cells may result in persistent reservoirs of pathogenic clones that contribute to the ongoing generation of autoantibodies and disease activity
- Bispecific IgM antibody T cell engagers (TCEs) are exciting drug candidates with the potential to deplete tissue-resident target cells more effectively through T cell-dependent cellular cytotoxicity (TDCC) and complement-dependent cytotoxicity (CDC) as compared to conventional BCDT mechanisms of action, which rely predominantly upon antibody-dependent cellular cytotoxicity (ADCC)
- Imvotamab (IGM-2323) is an engineered high-affinity, high avidity bispecific anti-CD20 IgM antibody TCE
- CD20 expression varies across B cell subsets, with memory B cells (precursors to autoantibody producing cells) among the lowest expressors of CD20 in B cells. Thus, targeting low CD20 expressing cells are important in the context of autoimmunity
- Imvotamab has previously been evaluated in non-Hodgkin's lymphoma (NHL)[1]. Ninety-seven (97) patients with NHL have received imvotamab, and complete responses have been observed across all major NHL subtypes (DLBCL, FLL, MCL, MZL)[1].
- Given the preliminary clinical profile of imvotamab in NHL, which shows durable responses and a favorable safety profile, we evaluated its potential to deplete peripheral and tissue-resident B cells in preclinical studies of AI disease

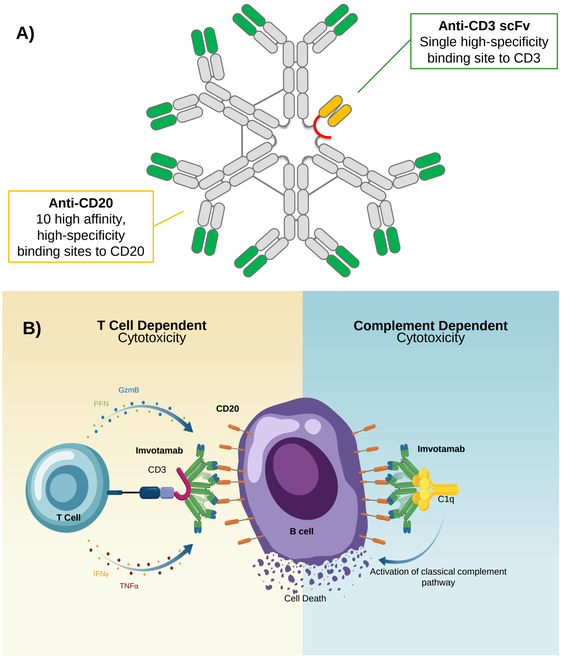


Figure 1. (A) Structure of imvotamab. Imvotamab is a fully human pentameric anti-CD20 IgM antibody with ten CD20 binding domains, and with a J-chain fused to a single chain variable fragment (scFv) targeting CD3ε. **(B)** Imvotamab has two potential mechanisms of action of killing B cells: TDCC and CDC.

CD20 receptor expression on B cells throughout B cell development

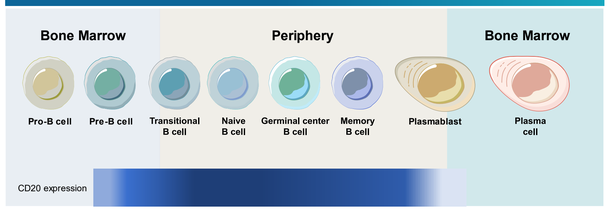


Figure 2. CD20 receptor expression on B cell subsets throughout B cell development in the bone marrow and the periphery. Schematic is modified from Crickx et al. *Kidney Int* 2020.

CD20 is expressed across B cell subsets from healthy donors and autoimmune patient PBMCs

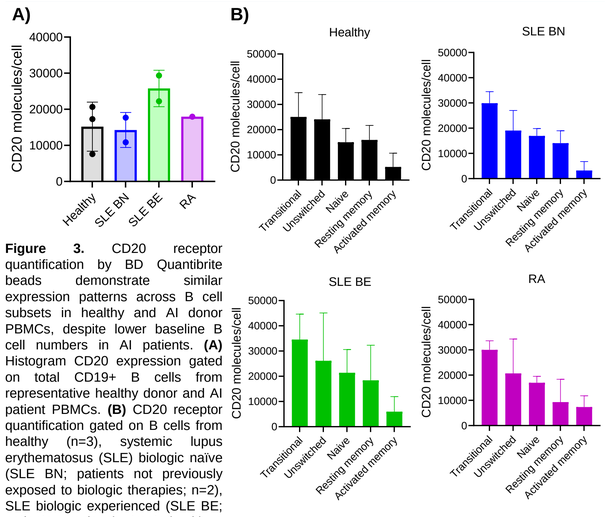


Figure 3. CD20 receptor quantification by BD Quantibrite beads demonstrate similar expression patterns across B cell subsets in healthy and AI donor PBMCs, despite lower baseline B cell numbers in AI patients. **(A)** Histogram CD20 expression gated on total CD19+ B cells from representative healthy donor and AI patient PBMCs. **(B)** CD20 receptor quantification gated on B cells from healthy (n=3), systemic lupus erythematosus (SLE) biologic naïve (SLE BN; patients not previously exposed to biologic therapies; n=2), SLE biologic experienced (SLE BE; patients previously treated with a biologic such as anti-TNF or anti-CD20 therapy n=2), and rheumatoid arthritis (RA, n=1). **(C)** CD20 molecules per cell quantified on baseline B cell subsets including transitional, unswitched, naïve, resting memory, and activated memory from PBMCs of n=4 healthy donor (black), n=6 SLE biologic naïve (blue, 2 donors assayed twice), n=4 SLE biologic experienced (green, 2 donors assayed twice), and n=3 RA (purple, 1 donor assayed twice). Bars represent mean ± SD

Imvotamab depletes peripheral B cells from healthy donors and autoimmune patients

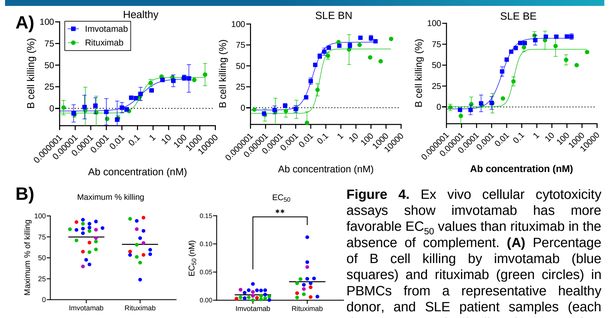


Figure 4. Ex vivo cellular cytotoxicity assays show imvotamab has more favorable EC_{50} values than rituximab in the absence of complement. **(A)** Percentage of B cell killing by imvotamab (blue squares) and rituximab (green circles) in PBMCs from a representative healthy donor, and SLE patient samples (each donor was run in duplicate). Data points are represented as mean ± SD.

(B) Maximum percentage (%) B cell killing and EC_{50} values by 200 nM imvotamab versus 1400 or 2200 nM rituximab in PBMCs from n=3 MS (red), n=10 SLE biologic naïve (blue), n=7 SLE biologic experienced (green), and n=3 RA (purple). Black horizontal bars represent either mean percent killing or EC_{50} values in nanomolar (nM). EC_{50} values were calculated based on the fitting results. If a curve did not reach plateau, EC_{50} was unavailable and excluded from the calculation of average B cell killing EC_{50} between different donors.

Imvotamab exhibits greater killing activity against Ramos cells expressing low CD20

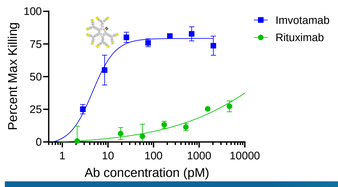


Figure 5. Cellular cytotoxicity of Ramos cells expressing low CD20 show imvotamab exhibits greater killing activity. Percent maximum killing of low CD20-expressing Ramos cells is shown following treatment with imvotamab and rituximab.

Imvotamab does not induce excessive T cell activation in AI vs healthy PBMCs

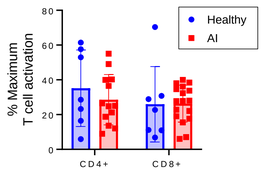
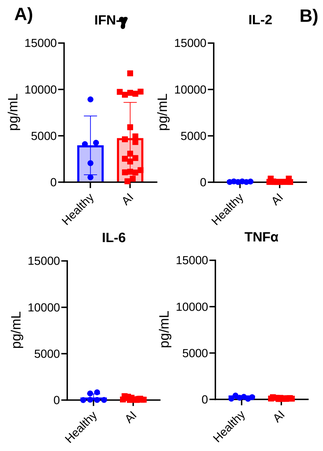


Figure 6. Flow cytometric analyses demonstrate comparable T cell activation following treatment with imvotamab. Maximum frequencies of activated (CD69+) CD4+ and CD8+ T cells from n=7 healthy and n=17 autoimmune donors. No significant difference between healthy and AI groups. Bars represent mean ± SD.

Imvotamab induces IFNγ release consistent with TCE mechanism of action



	Range		Median	
Cytokine	**Healthy**	**AI**	**Healthy**	**AI**
IL-2	60 ± 33	90 ± 115	57	53
IL-6	276 ± 395	143 ± 137	34	99
TNFα	212 ± 132	124 ± 57	211	127

Figure 7. Imvotamab induces strong IFNγ but low cytokine release syndrome (CRS)-associated cytokines (IL-6, TNFα). **(A)** IFNγ, IL-2, IL-6 and TNFα quantification within supernatants from a 72 hr TDCC assay using PBMCs from healthy donor (n=6) and AI (n=17) patient samples in response to 200 nM of imvotamab. Data points are represented as mean ± SD. **(B)** Mean +/- SD and median of IL-2, IL-6, and TNFα of healthy and AI donors (as shown in (**A**)) described in table format. IL-6 and TNFα are within range of peak cytokine levels observed in non-Hodkin's lymphoma patients that did not develop cytokine release syndrome following Cycle 1 of imvotamab[2].

Imvotamab demonstrates higher CDC compared to rituximab

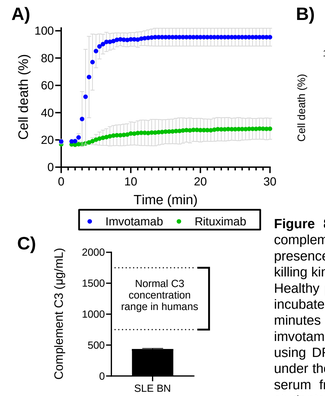
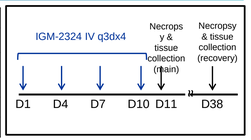


Figure 8. Live cell imaging and kinetic analysis of complement dependent cytotoxicity (CDC) in the presence of SLE BN patient serum demonstrates faster killing kinetics by imvotamab compared to rituximab. **(A)** Healthy primary B cells labeled in Oregon Green are incubated with 50% serum from a SLE BN patient for 5 minutes before the addition of 1 µg/mL of either imvotamab or rituximab. Cell death was quantified using DRAQ7. **(B)** The maximum cell death and area under the curve (AUC). **(C)** The C3 level in the SLE BN serum from the patient was assessed by ELISA. A students T test was used for statistical analysis, **p<0.001.

IGM-2324 penetrates lymphoid tissues and depletes > 90% resident CD20+ B cells in cynomolgus monkeys

Group No.	Test Material	Dose Level (mg/kg)	No. of Animals	
			Main Study	
			Male	Female
1	Vehicle	0	3	3
2	IGM-2324	5	3	3
3	IGM-2324	25	3	3



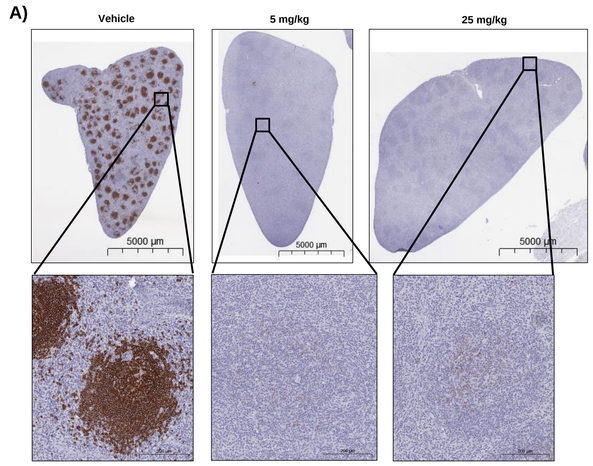


Figure 9. Cynomolgus monkeys were administered vehicle or a surrogate CD20xCD3 bispecific IgM TCE, IGM-2324, at 5 mg/kg or 25 mg/kg through intravenous (IV) infusion twice weekly for a total of four doses on days 1, 4, 7, and 10. Depletion of tissue-resident B cells was evaluated in the spleen, mesenteric lymph node (MLN) and bone marrow (BM) of monkeys at 24 hours post the last dose of vehicle or IGM-2324 on day 11. **(A)** Markedly reduced intensity of CD20 immunoreactivity was observed in the spleens by IHC in the 5 mg/kg and 25 mg/kg IGM-2324 treated monkeys compared to vehicle on day 11. **(B)** Quantitative analysis revealed significant reduction of the frequency of CD20 expressing B cells in tissues by IGM-2324 treatment. Error bars represent mean ± SD. Statistical analyses (Unpaired t-test) represent comparisons to vehicle control groups (ns: p > 0.05, *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001).

Summary

- Imvotamab induced killing of B cells from both AI patients and healthy donors
- Imvotamab demonstrated greater cytotoxicity vs rituximab in the absence of complement
- Imvotamab demonstrated greater complement-dependent cytoxicity vs rituximab
- Imvotamab targets and kills low CD20-expressing Ramos cells
- Imvotamab does not induce excessive T cell activation in autoimmune versus heathy PBMCs
- Deep depletion of tissue-resident B cells was observed in cynomolgus monkeys following treatment with IGM-2324 (imvotamab surrogate)
- Phase 1b studies have been initiated and are ongoing in lupus [NCT06041568] and RA [pending]

[1]Budde et al. *American Society of Hematology Annual Congress* 2021

[2]Hernandez et al. *American Society of Hematology Annual Congress* 2022