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A Phase 1/2 Randomized Study of IGM-2323 in Relapsed/Refractory Non-Hodgkin Lymphomas

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INTRODUCTION

IGM-2323 is a novel CD20-directed bispecific T cell engager (TCE) that utilizes an IgM antibody backbone. The key properties of IGM-2323 include:

- 10 high-affinity binding sites for CD20 to facilitate high-avidity binding to CD20-expressing cells (Figure 1)
- 1 binding site for CD3 allows for monovalent engagement of T cells to generate T-cell-dependent cellular cytotoxicity (TDCC)
- Dual mechanism of action with TDCC as well as complement-dependent cytotoxicity (CDC; Figure 2)
- B-cell/cancer cell lysis without supraphysiologic cytokine release (Figure 3)

Figure 1: Structure of IGM-2323-001

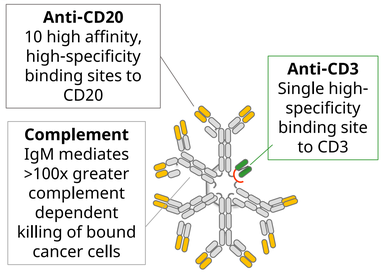


Figure 2: Dual mechanisms of action

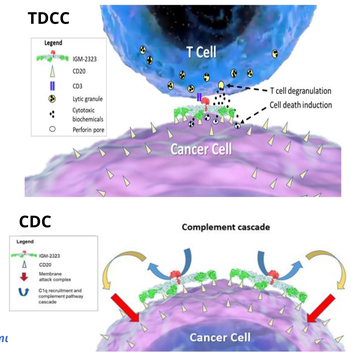
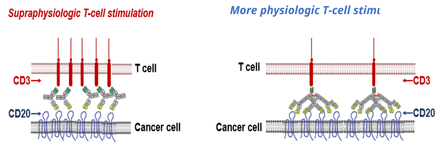


Figure 3: T cell stimulation



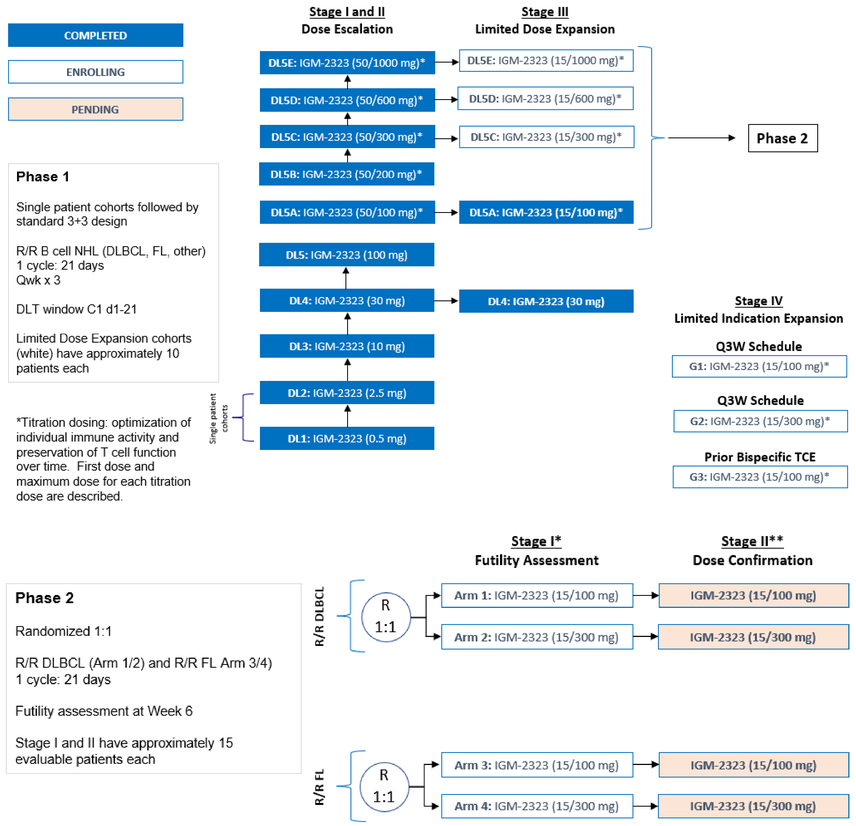
Unmet Need for Patients

- CD20 is a well-validated target, and CD20-directed antibody therapy (e.g., rituximab) has provided benefit both as a single agent and particularly in combination with chemotherapy
- New bispecific antibodies show promise by simultaneously binding CD20 on malignant cells and CD3 on T cells and provide a potent new mechanism for eliminating CD20-expressing cancer cells
- Cytokine release syndrome (CRS) is a safety concern for bispecific antibody-based TCE immunotherapeutic approaches
- Novel agents that can promote an anti-tumor immune response more safely, practically, and effectively are needed

IGM-2323

- Preclinical data and *ex vivo* human studies show that IGM-2323 is able to effectively engage T cells for targeted cancer cell removal without the high level of cytokine release associated with other CD3-based agents
- In human *in vitro* cell cultures and *in vivo* in cynomolgus monkey studies, IGM-2323 has demonstrated potent killing of B-cell cancer cell lines and depletion of peripheral B cells, respectively, with minimal accumulation of cytokines in supernatants or blood
- The IgM format enables more potent CDC compared with CD20-directed antibodies with an IgG format (e.g., rituximab)
- The mechanism of action and encouraging Phase 1 data support the development of the IGM-2323 bispecific antibody to enable the potent elimination of malignant B cells in patients with minimal CRS

STUDY DESIGN



*At the end of Stage I, an interim futility analysis will be conducted.
**At the end of Stage II, efficacy and safety analysis will be conducted to select the optimally efficacious dose.

STUDY COMPONENTS

- The Phase 1 component consists of dose escalation and limited dose expansion evaluating multiple titration (or step up) dose levels. Intra-patient dose escalation is allowed for patients in Phase 1.
- The Phase 2 component randomizes patients to 2 different dose levels (100 mg and 300 mg plateau dose) in 2 separate indications (R/R DLBCL and R/R FL). This evaluation of multiple dose levels is in line with FDA guidelines (Project Optimus) and is designed to select the optimal dose for continued enrollment. A formal efficacy/safety analysis will be performed at or before 30 subjects per arm are evaluable, and the best dose for each indication will be selected for further evaluation.
- Patients receive weekly IV dosing on Days 1, 8, and 15 of each 21-day cycle. Dosing in the 15/100 mg cohorts is 15 mg on Day 1, 50 mg on Day 8, and 100 mg on Day 15 (patients in the 15/300 mg cohort will receive an additional step at 300 mg on Day 1 of Cycle 2). Patients then stay at the plateau dose until disease progression or unacceptable toxicity.
- Patients who achieve a response at Week 12 or later may switch to a less frequent dosing interval of every 3 weeks.
- Hospitalization is not required.

STUDY COMPONENTS

- Premedication regimen includes dexamethasone, paracetamol, and diphenhydramine during the first cycle.
- Response assessments are based on Lugano criteria with tumor scans by PET/CT at Weeks 6, 12, and 24, and then every 3 months while on treatment.
- Blood and tissue samples for correlative biomarker studies will evaluate the association of clinical benefit with blood and tissue biomarkers.

STUDY OBJECTIVES

Phase 1

- To evaluate the safety and tolerability of IGM-2323 in subjects with R/R NHL
- To determine a maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) and schedule of IGM-2323 as a single agent in subjects with R/R NHL

Phase 2

- To select the optimally efficacious dose of IGM-2323 in subjects with R/R DLBCL and R/R FL

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria	
• ≥18 years of age	• ECOG PS 0 or 1
• Relapsed or refractory follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, marginal zone lymphoma (MZL) in dose escalation	• Relapsed or refractory to at least 2 prior systemic treatment regimens (must include anti-CD20 chemo-immunotherapy regimen). FL/MZL may be enrolled with a least 2 prior systemic regimens, which must include an anti-CD20, without the need for a prior chemotherapy regimen
• At least 1 bi-dimensionally measurable lesion (>1.5 cm in its longest dimension by CT scan)	• Not eligible for autologous stem cell transplant (DLBCL subjects), due to chemoresistant disease, medically unfit (organ function), or unwilling
• Pre-treatment and on-treatment biopsies, where medically feasible (Phase 2 only)	
Key Exclusion Criteria	
• Prior allogeneic transplant	• ASCT within 100 days prior to the first IGM-2323 administration

STUDY INFORMATION

- Both phases of the study are currently open and enrolling in the US, South Korea, and Australia. Expansion into additional global regions is ongoing
- Phase 1 dose escalation (Stages I and II) is complete. Limited Dose Expansion (Stage III) and Limited Indication Expansion (Stage IV) are ongoing.
- Phase 2 initiated in February 2022.
- Clinical trial information: NCT04082936.

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