Preliminary Results of a Phase 1 Dose Escalation Study of the First-in-Class IgM Based Bispecific Antibody Igm–2323 (anti-CD20 x anti-CD3) in Patients with Advanced B–Cell Malignancies

Introduction:

Bispecific antibodies that bridge lymphoma cells to T–cells have shown promise in treating B–cell malignancies. However, existing T cell engaging antibodies are associated with toxicity, especially cytokine release syndrome (CRS), which may limit dose intensity and efficacy. CRS results from overstimulation of T cells, which can also lead to subsequent downregulation of T cell function. IGM–2323 is a novel type of bispecific antibody, based on an engineered pentameric IgM framework, with a recombinant J–chain that is fused to an anti–CD3 scfv. The resulting construct has 10 high–affinity binding domains for CD20 and one binding domain for CD3. In preclinical studies, IGM–2323 has been shown to bind irreversibly to CD20–expressing cells and deplete them in human PBMC cell cultures with limited cytokine secretion. This first–in–human Phase 1, open–label, multicenter, dose escalation study was designed to evaluate the safety, tolerability, biomarkers and preliminary anti–tumor activity of IGM–2323 in adults with B–cell malignancies.
**Methods:**

Patients with relapsed or refractory CD20-positive B-cell NHL who had received $\geq 2$ prior systemic therapies, acceptable organ function and ECOG 0–1 are eligible for enrollment. IGM–2323 is administered as an IV infusion on Days 1, 8, and 15 of a 21-day cycle, for up to 8 cycles, or longer if there is evidence of clinical benefit. The study utilized an accelerated titration design, with single patient cohorts for the first two dose levels, followed by traditional 3+3 design with further dose levels. The primary objectives are to evaluate the safety and tolerability of IGM–2323, and to determine a recommended phase 2 dose and schedule.

**Results:**

As of June 12, 2020, 8 patients have been treated at 4 dose levels (0.5, 2.5, 10, and 30 mg).

NHL subtypes include 3 follicular lymphoma (FL), 2 mantle cell lymphoma, 2 marginal zone lymphoma, and 1 diffuse large B-cell lymphoma. Median age is 65 (range 47–81), median number of prior therapies is 4 (range 2–6). 2 patients had prior autologous transplant (ASCT).

All 8 patients have completed at least one cycle and are evaluable for safety and dose limiting toxicities (DLT). 6/8 patients remain on active treatment at the time of the database cutoff. Two patients have discontinued at 25 and 7 weeks, due to patient and investigator decision. Six patients remain on study at 37, 27, 18, 9, 6, and 5 weeks ongoing. Median number of doses is 14. There were no DLT observed and no drug-related SAE. Two patients experienced Grade 3–4 treatment-emergent adverse events of transient neutropenia (0.5 mg cohort G4 <3 days on day 76; 30 mg cohort G3 <7 days on day 8). Neither experienced fever or required antibiotic treatment. No patient discontinued due to toxicity, and no patient required dose reductions.

Two patients in the 30 mg cohort experienced transient low-grade fever (one grade 1, one grade 2), with neither requiring treatment with steroids. Analysis of pharmacodynamic biomarkers shows measurable levels of circulating B cells at baseline in 1/8 patients, where B cell depletion was observed with treatment. Furthermore, there is evidence of cytokine secretion consistent with repeatable T cell responses over successive doses in both 10 mg and 30 mg cohorts. When cytokines were detectable following dosing, they were transient and were mostly gone at less than 6–12 hours. Interferon–gamma (IFNg) was the primary cytokine observed, with significant levels of IL–6 detected in only one patient.

**Conclusions:**

IGM–2323 is the first engineered high-affinity, high-avidity bispecific IgM monoclonal antibody to be tested in the clinic, and is designed to bind irreversibly to CD20–expressing cells while providing a more physiologic stimulation to T cells. Preliminary results from this first in human T–cell engaging antibody study show an improved safety and tolerability profile at higher doses. There is also evidence of a novel mechanism of action based on repeatable T cell activation and preservation of T cell function compared with other T cell engaging antibodies. The study continues to enroll patients in dose escalation. Updated safety, pharmacokinetic, biomarker, and efficacy data will be presented at the meeting. This study is registered with clinicaltrials.gov identifier NCT04082936.
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