A Phase 1 Dose Escalation Study of IGM-2323, A Novel Anti-CD20 x Anti-CD3 IgM T Cell Engager (TCE) in Patients with Advanced B-Cell Malignancies

Elizabeth Budde, MD PhD[1], *Ajay K. Gopal, MD*[2], *Won Seog Kim, MD PhD*[3], *Ian Flinn, MD PhD*[4], *Chan Y. Cheah, MBBS*[5], *Loretta Nastoupil, MD*[6], *Matthew Matasar, MD*[7], *Catherine Diefenbach, MD*[8], *Gareth P. Gregory, MBBS PhD*[9], *Ibrahim Qazi, PharmD*[10], *Ching-Fai Pang, PhD*[11], *Maya Leabman, PhD*[10], *Genevive Hernandez, PhD*[10], *Iris Sison*[10], *Bruce Keyt, PhD*[10], *Daniel Chen, MD PhD*[10], *and Philippe Armand, MD PhD*[12]

[1]*T Cell Therapeutics Research Laboratory, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA*

[2]*University of Washington/Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Seattle, WA*

[3]*Samsung Medical Center, Seoul, South Korea*

[4]*Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

[5]*Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia*

[6]*The University of Texas MD Anderson Cancer Center, Houston, TX*

[7]*Memorial Sloan Kettering Cancer Center, New York, NY*

[8]*Perlmutter Cancer Center at NYU Langone Health, New York, NY*

[9]*School of Clinical Sciences at Monash Health, Monash University, Melbourne, Australia*

[10]*IGM Biosciences, Mountain View, CA*

[11]*Phi Consulting Group, Bellevue, WA*

[12]*Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA*

Introduction:

IGM-2323 is the first engineered high-affinity, high-avidity bispecific IgM monoclonal antibody TCE to be tested in the clinic. It has 10 binding domains for CD20 and a single binding domain for CD3 and is designed to bind irreversibly to CD20-high and low-expressing cells with more physiologic stimulation to T cells, which may mitigate cytokine release syndrome (CRS)-related toxicity and broaden the therapeutic window. IGM-2323 may act by multiple mechanisms: T-cell dependent cytotoxicity, complement dependent cytotoxicity, and enhanced immune modulation via IFNγ-dominant cytokine

stimulation. This phase 1 study is exploring the safety and activity of IGM-2323 using a dose titration schedule intended to optimize repeatable immune stimulation while minimizing toxicity.

Methods:
This first-in-human Phase 1 study is a global, multicenter, open-label, dose escalation evaluating safety, tolerability, PK, and preliminary efficacy (NCT04082936). Adults with relapsed or refractory $CD20^+$ B-cell NHL with ≥ 2 prior systemic therapies, adequate organ function, and ECOG 0-1 are eligible. IGM-2323 is given IV on Days 1, 8, and 15 of 21-day cycles until disease progression or unacceptable toxicity. Treatment can continue beyond progression if the patient (pt) has benefitted from treatment and intra-patient dose escalation is allowed. This study also utilizes a dose titration scheme where a starting dose is given on Day 1, then higher subsequent doses are given up to a plateau dose. If a pt has symptoms of CRS, the same dose may be repeated, and a higher dose is not given until the dose is well tolerated.

Results:

As of April 30, 2021, 29 pts have been enrolled: 12 at 5 fixed dose levels (0.5, 2.5, 10, 30, 100 mg) and 17 at 5 dose titration levels (50/100, 50/200, 50/300, 50/600, 50/1000 mg)*.

NHL subtypes include: 13 follicular (FL), 11 diffuse large B-cell (DLBCL), 3 mantle cell (MCL), and 2 marginal zone (MZL). Median age is 66 (range, 36-84) and median prior therapies is 3 (range, 2-7). 2 pts had prior autologous transplant and 7 had prior CAR-T.

All 29 pts received at least one dose and are safety evaluable. There were no DLTs and no neurotoxicity AEs. No pts discontinued due to AE. There were 3 drug-related SAEs (1 each Gr1/2/3 CRS by ASTCT). 16 pts discontinued treatment: 2 pt/investigator decision and 14 PD. The 13 pts still on treatment have received a median of 9 doses (range, 1-42).

At fixed dose levels, 5 of 12 pts had a CRS event, primarily grade 1 (fever). Only 1 of 17 titration pts had CRS (Gr3 in a pt with prior experimental CAR-T and baseline circulating B-cells). The most common drug-related AEs in titration pts

were hypophosphatemia (29%), IRR (29%; the distinction between IRR and CRS was determined by the investigator), and nausea (24%).

23 pts were evaluable for efficacy; there were 8 responses (5 CR, 3 PR). 5 responses were in FL/MZL and 3 in DLBCL/MCL. Response kinetics varied, with some CRs at the first scan (Week 6) and others after biopsy-confirmed pseudo-progression or prolonged SD (up to 69 weeks). 7 of 8 responses were ongoing as of the data cut. 5 of 11 evaluable patients in dose titration cohorts responded (3 CR, 2 PR), with a median time to response of 6 weeks. In the titration cohort with the longest follow-up (50/100), there were 2 CR and 1 PR in 4 evaluable pts.

Repeatable IFNγ stimulation is detectable in nearly all pts with measurable cytokine elevations, while polycytokine response was observed in CRS cases (Table). Preliminary IHC data in matched baseline and on-treatment biopsies (n=3) shows decrease of $CD20^+$ tumor cells and increase of $CD3^+$ T cells in tumor tissue upon treatment, regardless of clinical response.

Conclusions:

Preliminary results from this first-in-human study of IGM-2323 show an excellent safety and tolerability profile at up to 1000 mg, with reduced CRS when IGM-2323 was given using a dose titration scheme. Response patterns included rapid responses, deepening responses and pseudo-progression. IGM-2323 also has evidence of an IFNγ-dominant repeatable T-cell activation and preservation of T cell function over time. The MTD of IGM-2323 has not been reached. Clinical activity was observed across multiple histologies. Updated safety, PK, biomarker, and efficacy data, including complete dose escalation data, will be presented at the meeting.

* starting and plateau dose referenced

Peak Cytokine Levels Post-infusion (Cycle 1)

Cytokine *Median (IQR) pg/mL*	**No CRS** *(n=22)*	**CRS** *(n=6)*
IFN-γ	37 (101)	756 (3841)
IL-6	6 (9)	346 (2550)
TNF-α	12 (15)	68 (192)

Cytokine levels in frozen plasma were assessed on a batched basis at a central lab. The table shows median values and interquartile range (in parenthesis) of the highest concentrations obtained in each patient during the sampling period: 30 min to 72 hours for Infusion 1 and end of infusion to 24 hours for Infusions 2 and 3.