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

Keylu Li, Rui Yun, Min Chai, Poonam Yakkundi, Rodnie Rosete, Gene Li, Liqiu Liu, Mandy Li, Daniel Santos, Kevin C. Hart, Dean Ng, Paul R. Hinton, Umesh Muchhal, Thomas Manley, Maya F. Kotturi, Stephen F. Carroll, Angela M. Sinclair, Bruce A. Keyt

IGM Biosciences, Inc. | Mountain View, CA

**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 current 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-CD3 scFv fused to the joining chain. IGM-2644 is capable of mediating both T cell dependent cellular cytotoxicity (TDCC) and complement dependent cytotoxicity (CDC).

**IGM-2644 Mediates Improved CDC Compared to Anti-CD38 IgG Antibodies**

- **CD38 Expression Level**
  - LP-1
  - Ramos
  - Raji
  - Normal Control IgM

- **IGM-2644**
  - Daratumumab
  - Negative Control IgM

**IGM-2644 Achieves Similar TDCC Activity with Lower Cytokine Release than a Bispecific IgG**

- **IGM-2644**
  - Polyvalent IgG
  - Carteratum
  - Daratumumab

- **Bispecific IgG Ab2**
  - Polyvalent IgG
  - Carteratum
  - Daratumumab

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

- **Bispecific IgG Ab2**
  - Polyvalent IgG
  - Carteratum
  - Daratumumab

- **Bispecific IgM Ab2**
  - Polyvalent IgG
  - Carteratum
  - Daratumumab

**IGM-2644 Suppresses CD38+ Tumor Growth in Xenograft Models**

- **IGM-2644**
  - Solvent Control
  - 1 mg/kg
  - 3 mg/kg
  - 10 mg/kg
  - 30 mg/kg

- **Daratumumab**
  - Solvent Control
  - 1 mg/kg
  - 3 mg/kg
  - 10 mg/kg
  - 30 mg/kg

- **Polyclonal IgM**
  - Solvent Control
  - 1 mg/kg
  - 3 mg/kg
  - 10 mg/kg
  - 30 mg/kg

**Summary**

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

- 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, the potential to be active in daratumumab resistant tumors. A Phase 1 clinical study evaluating the activity and safety of IGM-2644 is planned.