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

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Disclosures

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IGM-2323 is a novel engineered high-affinity, high-avidity CD20xCD3 IgM bispecific T-cell engager

Bispecific antibodies that bridge lymphoma cells to T cells have shown promise in treating B-cell malignancies1–3

However, existing T-cell engaging antibodies that lead to dense clustering and supraphysiologic T-cell signaling are associated with toxicity (especially CRS) and have a limited therapeutic window that may be related to downregulation of T-cell function.

IGM-2323 is a novel bispecific antibody, based on an engineered pentameric IgM framework, with a recombinant J-chain that is fused to an anti-CD3 scFv.

In preclinical studies, IGM-2323 has been shown to bind irreversibly to CD20-expressing cells, including cancer cells expressing very low levels of CD20, and eliminate them through cell-dependent (TDCC) and cell-independent mechanisms (CDC)4,5

Anti-CD20
10 high affinity, high-specificity binding sites to CD20

Anti-CD3
Single high-specificity binding site to CD3

Complement
IgM mediates >100x greater complement dependent killing of bound cancer cells

CD: cluster of differentiation; CDC: complement dependent cytotoxicity; CRS: cytokine release syndrome; IgG/M: immunoglobulin G/M; scFv: single-chain variable fragment; TDCC: T cell-dependent cytotoxicity

IGM-2323 is designed to enhance immune-modulation

IGM-2323 may provide more physiologic T-cell activation compared with existing bispecific T-cell engaging antibodies:
- T cells respond differently to different levels of TCR signaling
- Activation of T-cell cytotoxic mechanisms and IFNγ secretion require the lowest levels of TCR signal

Importantly, IGM-2323 may limit supraphysiologic stimulation of T cells, leading to:
- More physiologic levels of cytokines secreted, improving safety and tolerability
- More physiologic levels of T-cell stimulation, leading to a IFNγ-dominant cytokine secretion profile
- Ability to preserve or strengthen T-cell responsiveness over time, leading to further enhanced cancer cell elimination over time, and stimulation of endogenous or pre-existing anti-cancer T-cell responses

IFNγ: interferon-gamma

**Existing bispecific T-cell engaging antibodies:**
- IgG or single chain
- **Supraphysiologic T-cell stimulation**

**Novel bispecific T-cell engaging antibodies:**
- IgM
- **More-physiologic T-cell stimulation**

Primary objectives: Safety and tolerability; R2PD and schedule, MTD; Secondary objectives: PK, immunogenicity, preliminary efficacy
Patient baseline characteristics, disposition, and preliminary PK (N=16 total enrolled)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Follicular NHL/ Marginal Zone NHL (n=10)</th>
<th>DLBCL/ Mantle Cell (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>66.5 (47–75)</td>
<td>61 (46–82)</td>
</tr>
<tr>
<td>Histology</td>
<td>FL=8 MZL=2</td>
<td>DLBCL=4 MCL=2</td>
</tr>
<tr>
<td>Prior therapies, median (range)</td>
<td>4 (2–6)</td>
<td>4 (2–6)</td>
</tr>
<tr>
<td>Prior ASCT, n (%)</td>
<td>2 (20%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Prior CAR-T, n (%)</td>
<td>1 (10%)</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>

CD20-positive NHL (N=16)

- Discontinued, n (%): 3 (30%)
  - AE: 0 (0)
  - Physician's decision: 1 (10%)
  - Progressive disease: 2 (20%)

- Ongoing, n (%): 7 (70%)
  Duration: 47, 26, 25, 19, 17, 14, and 14 weeks

Follicular/ Marginal Zone NHL (n=10)

- Discontinued, n (%): 2 (33%)
  - AE: 0 (0)
  - Physician's decision: 1 (17%)
  - Progressive disease: 1 (17%)

- Ongoing, n (%): 4 (67%)
  Duration: 38, 18, 14, and 2 weeks

DLBCL/ Mantle Cell NHL (n=6)

- Discontinued, n (%): 2 (33%)
  - AE: 0 (0)
  - Physician's decision: 1 (17%)
  - Progressive disease: 1 (17%)

- Ongoing, n (%): 4 (67%)
  Duration: 38, 18, 14, and 2 weeks

Preliminary PK

- No drug-induced anti-drug antibodies detected to date
- PK is within expected range based on preclinical data

ASCT: autologous stem cell transplantation; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; LLOQ: lower limit of quantitation; NHL: non-Hodgkin lymphoma

Data cut-off: October 30, 2020
AE summary:
Treatment-emergent AEs occurring in ≥20% of patients

- Generally well tolerated
- No DLTs
- No Grade 3 or higher CRS
- No neurotoxicity

### Preferred Term (N=16* patients)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Any grade n (%)</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade ≥3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>9 (56)</td>
<td>8 (50)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>7 (44)</td>
<td>3 (19)</td>
<td>4 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6 (38)</td>
<td>4 (25)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (38)</td>
<td>4 (25)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatinine increased (^a)</td>
<td>5 (31)</td>
<td>4 (25)</td>
<td>1 (6)(^d)</td>
<td>0</td>
</tr>
<tr>
<td>CRS (^b)</td>
<td>4 (25)</td>
<td>3 (19)</td>
<td>1 (6)(^d)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion related reaction (^c)</td>
<td>4 (25)</td>
<td>1 (6)</td>
<td>3 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (25)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) out of 5 patients with creatinine increase were assessed as unrelated to study treatment, per investigator

\(^b\) CRS grading by ASTCT criteria; all CRS patients are also captured under pyrexia and/or chills.

\(^c\) 3 of 4 IRR patients are also captured under CRS

\(^d\) Single patient with pre-existing severe hypertension on four anti-hypertensive medications treated at 100 mg Cycle 1 Day 1 dose experienced Grade 2: CRS, chills, increased creatinine and Grade 1: pyrexia, fatigue, hypophosphatemia after the first infusion. No CRS symptoms were observed at subsequent infusions of study drug up to 100 mg, with or without dexamethasone pre-medication. This patient had cytokine elevation after Cycle 1 Day 1 dose and had a best response of SD (+6%), but is not included in further analyses.

\(^*\) One patient enrolled 2 weeks prior to data cut-off is also included here, but is not included in further analyses.

### Example: patient treated with IGM-2323 30 mg dosing

- Generally well tolerated
- No Grade 3 or higher CRS
- No neurotoxicity

- Some patients experience post-infusion chills and/or fever:
  - Transient (≤3 hours), low grade; majority limited to first cycle; acetaminophen is most common treatment;
  - No ICANS symptoms (Immune Cell Associated Neurotoxicity)
  - Associated with CRP elevation at 24 hours
  - Easily prevented with low dose dexamethasone premedication on subsequent infusions if desired

- No CRS observed in the 3 patients treated in 50/100 cohort

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Best overall response (PET-CT scans):
9 of 14 patients showing evidence of tumor size reduction

- B-cell depletion/reduction observed in 6/6 patients with circulating B cells at baseline

Assigned dose level noted.

PR cut-off, Lugano 2014 criteria, local reads. *100 mg indicates 50/100 mg dose level

PR lymph node size decreased to below normal size with marked decrease in PET activity
CAR-T: chimeric antigen receptor T-cell; FL: follicular lymphoma; IHC: immunohistochemistry; Mantle: mantle cell lymphoma; MZL: marginal zone lymphoma; PET-CT: positron emission tomography-computerized tomography; PR: partial response; SPD: sum of the products of diameters.

Example: 63 year old Post-CAR-T patient with R/R DLBCL treated with IGM-2323 (30 mg)

- Biopsy of new PET-avid lesion at 8 weeks shows intense T-cell infiltration with only scant lymphoma cells, >95% CD3+ T-cell infiltrates by flow cytometry post-treatment
- Lesion completely resolved by PET-CT at 12 weeks

Data cut-off: October 30, 2020. Pathology Images courtesy of MD Anderson Pathology

Immunity, pseudoprogression, and response
DLBCL/mantle cell NHL, change in SPD over time

- Plus new PET-avid lesion
- New lesion resolved

B-cell depletion/reduction observed in 6/6 patients with circulating B cells at baseline

Pre-treatment (CD3 IHC)

Biopsy of new PET-avid lesion

8 weeks post-treatment (CD3 IHC)
IGM-2323 leads to repeatable IFN$_{\gamma}$-dominant immune activity

- Transient, repeatable cytokine elevations, with peak levels 6-12 hours post-infusion
- IFN$_{\gamma}$ detectable above baseline levels in 12/12 patients treated at $\geq$10mg
- IFN$_{\gamma}$ levels $>>$ IL-6 and TNF$_{\alpha}$ levels in vast majority of patients treated
- For patients dosed with $\geq$30 mg, 9/9 show repeatable IFN$_{\gamma}$ spikes; 4/9 show higher IFN$_{\gamma}$ spikes at later infusions

**IFN$_{\gamma}$ levels pre/post-IGM-2323 treatment**

**Post-infusion peak cytokine levels**

Cytokine levels in frozen plasma were assessed on a batched basis at a central lab. Plots are from n=14 patients and show the highest concentrations obtained during the sampling period: 2, 6, 12, 24, and 72 hours for Infusions 1 and 4, and only 24 hours for Infusions 2, 3, 5, 6. Box plots show 1st and 3rd quartile, blue line connects mean values.

IFN$_{\gamma}$: interferon-gamma; IL-6: interleukin-6; TNF$_{\alpha}$: tumor necrosis factor alpha

Data cut-off: October 30, 2020
Conclusions

Interim Phase I data on the first 16 patients treated (as of October 30, 2020) demonstrates:

- IGM-2323 is generally well tolerated, with no DLTs, no Grade 3 or higher CRS and no evidence of neurotoxicity, despite less steroid pretreatment than for other T-cell engagers
  - Transient fever and CRS in a subset of patients easily suppressed with low dose dexamethasone pre-medication, allowing for control over level of immune-activation and function obtained with each dose
  - IFNγ-dominant cytokine secretion with little to no measurable circulating IL-6 or TNFα in most patients differs from other T-cell engagers
- No drug-induced anti-drug antibodies; preliminary PK consistent with preclinical modeling
- Evidence for anticancer efficacy and responses, despite low to moderate doses tested
- Case of pseudoprogression and subsequent clinical response in a post CAR-T patient with DLBCL is consistent with repeatable and potent IFNγ-dominant immune activation

IGM-2323 Phase I immune activation profile supports a more physiologic immune modulation

- Evidence for preservation of T-cell activation in the majority of patients, which contrasts with step-dosing effect seen with other T-cell engagers that may be associated with global reduction in T-cell function

Phase I dose escalation continues, with expected RP2D between 100–1000mg dose

- Application of titration dosing regimen may allow opportunity to provide NHL patients with optimal and repeatable synthetic and pre-existing immune activity and durable antitumor efficacy
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