# PHARMACODYNAMICS AND BIOMARKER CORRELATES OF IMVOTAMAB (IGM-2323), THE FIRST-IN-CLASS CD20xCD3 BISPECIFIC IGM ANTIBODY WITH DUAL MECHANISMS OF ACTION, IN PATIENTS WITH ADVANCED B CELL MALIGNANCIES


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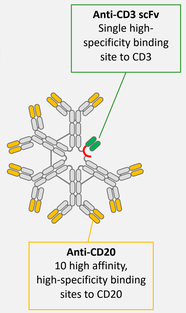
## INTRODUCTION

- Imvotamab (IGM-2323) is a novel CD20xCD3 bispecific T cell engager utilizing an engineered IgM antibody platform. Its high avidity enables irreversible target cell binding even at low CD20 levels and results in T cell dependent (TDCC) and complement dependent (CDC) mechanisms of cytotoxicity, with minimal cytokine release. Imvotamab is also designed to induce more physiologic T cell activation in order to prevent overstimulation and subsequent downregulation of immune function.



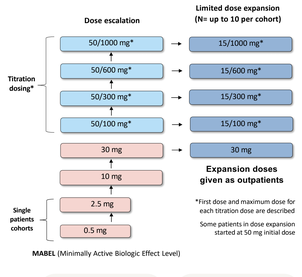

- Preliminary results from the first-in-human study of imvotamab show single-agent activity with durable complete responses as well as a favorable safety and tolerability profile up to 1000 mg dose. [1]
- We present biomarker data from the imvotamab Phase 1 dose escalation cohorts, highlighting pharmacodynamic effects and immune correlates that demonstrate mechanisms of action (MOA), inform optimal dose/schedule selection and identify potential predictors of response.

## METHODS

**Imvotamab Phase 1 Study (NCT04082936)**

**Study Design**

- Single-patient cohorts, then 3+3 design
- R/R B-cell NHL (DLBCL, FL, MCL, MZL)
- 1 cycle: 21 days
- Weekly dosing: Days 1, 8 and 15
- Dexamethasone premedication
- DLT window Cycle 1, 3 weeks
- Q3 week dosing, post complete response
- Intra-patient dose escalation allowed
- Responses assessed by Lugano criteria
- Dose escalation cohorts completed








**INTERIM DATA** [1]

***Safety***

- Low CRS (19%)
- No ICANS observed
- Limited neutropenia (4%)
- No patient discontinuation due to AEs

***Efficacy***

- **60% ORR** in r/r NHL at 100mg (10 pts)
  - **50% CR** in DLBCL (3/6 pts)
  - **66% CR** in FL (2/3 pts)

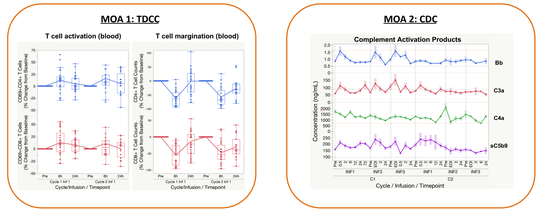
**BIOMARKER ANALYSIS**

- Immune profiling of peripheral blood was performed by flow cytometry.
- Plasma biomarker evaluation included measurement of cytokines by MSD, complement activation markers by ELISA, and ctDNA-MRD by PhasED-Seq (Foresight Dx).
- Tumor biomarkers were assessed in pre and on-tx tissue through CD20 and CD3 immunohistochemistry (IHC).

## RESULTS

### Imvotamab dual mechanisms of action (MOA)

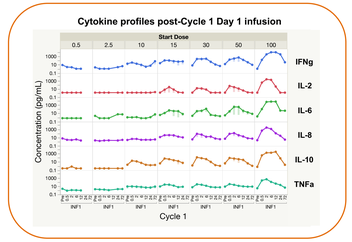
**Figure 1. Imvotamab activates T cells and complement pathway, resulting in depletion of circulating B cells**

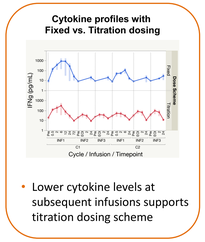



***Top Left: Left:*** *Box plots show % change from baseline from patients in titration dosing cohorts.* ***Right:*** *Mean+/- SEM of complement activation products in plasma of patients in titration dosing cohorts. Horizontal dashed lines depict lower (gray) and upper (orange) ends of normal human reference range. Vertical dashed lines (right) denote dosing days.* ***Bottom Left:*** *Plot shows B cell counts from patients in fixed and titration cohorts with measurable B cells at baseline. Data are obtained from samples collected pre-infusion at the indicated cycles. C=Cycle; EOI=end of infusion; h=hours; Inf=infusion; Pre=pre-infusion.*

### Induction of potent T cell effector cytokines while minimizing cytokines associated with CRS

**Figure 2. Dose-dependent cytokine increases after Cycle 1 Day 1 infusion**

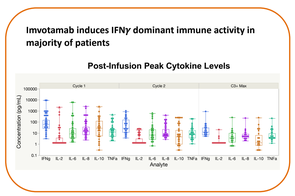


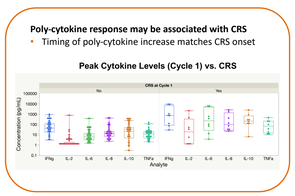




- Lower cytokine levels at subsequent infusions supports titration dosing scheme

***Left:*** *Mean+/- SEM of plasma cytokines from patients in fixed and titration dosing cohorts after Cycle 1 Day 1 infusion with the indicated starting doses.* ***Right:*** *Mean+/- SEM of IFNg in plasma of patients in fixed vs. titration dosing cohorts. Vertical dashed lines denote dosing days. C=Cycle; EOI=end of infusion; h=hours; Inf=infusion; Pre=pre-infusion.*

**Figure 3. IFNg-dominant immune activity with reduced elevation of IL-6 and other inflammatory cytokines**

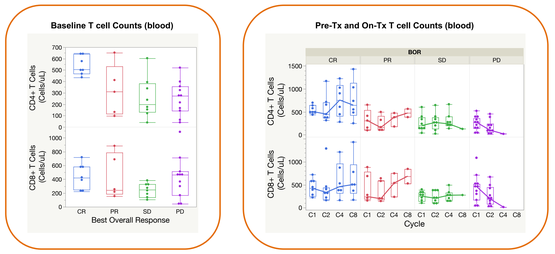



*Box plots show highest concentration of plasma cytokines at the indicated cycles from patients in fixed and titration dosing cohorts. CRS=cytokine release syndrome.*

### Higher T cell counts at baseline and on-treatment in patients with complete response (CR)

**Figure 4. Baseline and on-treatment T cell counts by response category**

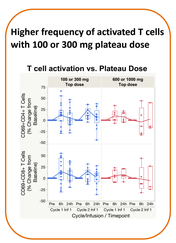



*Plots shows T cell counts from patients in titration dosing cohorts. Data are obtained from samples collected pre-infusion at the indicated cycles. BOR=best overall response; C=Cycle; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.*

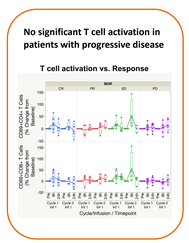
### T cell functional state may be associated with response

**Figure 5. T cell activation and PD1 expression by dose and response category**

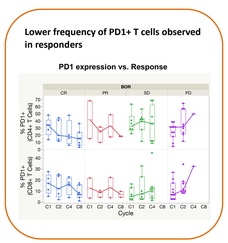
**Higher frequency of activated T cells with 100 or 300 mg plateau dose**




**No significant T cell activation in patients with progressive disease**



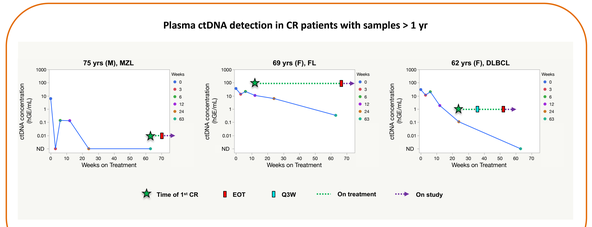

**Lower frequency of PD1+ T cells observed in responders**




*Box plots show data from patients in titration dosing cohorts. Subjects receive highest doses by Cycle 2 Inf 1. Data on the right panel are obtained from samples collected pre-infusion or at the indicated cycles. BOR=best overall response; C=Cycle; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.*

### Sustained molecular response with imvotamab treatment

**Figure 6. ctDNA kinetics in a subset of CR patients**

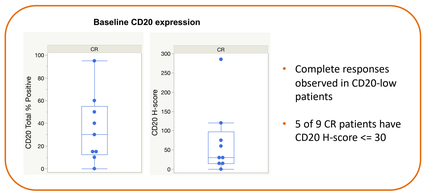



- Imvotamab-induced objective responses are sustained even after transitioning to less frequent Q3W dosing.

*Plasma ctDNA detection to evaluate molecular response was performed using PhasED-Seq platform from Foresight Dx. Response assessment for each patient is shown under the respective ctDNA plots. ctDNA=circulating tumor DNA; CR=complete response; EOT=end of treatment; F=female; M=male; ND=not detectable; Q3W=every 3wk dosing.*

### Efficacy observed in patients with CD20-low tumors

**Figure 7. CD20 expression in baseline tumor tissue of complete responders**

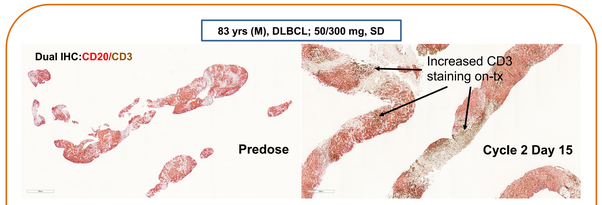



- Complete responses observed in CD20-low patients
- 5 of 9 CR patients have CD20 H-score <= 30

*Box plots shows CD20 IHC data from pre-treatment tumor tissue of patients with complete response. CR=complete response.*

### CD3+ tumor infiltrating T cells (TILs) increase on-treatment

**Figure 8. CD20 decrease and CD3+ TIL increase observed on-treatment**




- CD3+ TIL increase on-treatment is observed irrespective of response
- Baseline levels of CD3+ TILs are not predictive of response

*Representative images obtained from CD20/CD3 dual IHC in a patient with paired pre and on-treatment tumor tissue. CD3+ TIL increase on-treatment is observed irrespective of response. M=male; SD=stable disease.*

## CONCLUSIONS

- Acute pharmacodynamic changes confirm the dual TDCC and CDC MOA of imvotamab and inform selection of titration dose/schedule for safety and efficacy.
- Overall, the data suggest a model whereby an optimal number of sufficiently activated and functional T cells may be required to elicit strong and durable clinical responses with this novel bispecific IgM T cell engager.

## REFERENCE


1. Budde LE, et al. ASH 2021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