P1210

Immune correlations of response to glofitamab: biomarker findings from a pivotal Phase II expansion study in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)

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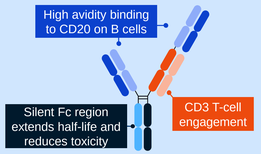
Summary

Glofitamab: a T-cell engaging bispecific monoclonal antibody with a unique 2:1 format



We evaluated tumor and peripheral blood biomarkers of glofitamab response in patients with R/R DLBCL in a pivotal Phase II expansion study (NCT03075696)

Novel response-associated biomarkers were identified in peripheral blood, and circulating tumor DNA (ctDNA) showed prognostic value

Clinical activity of glofitamab may depend on the immune environment within peripheral blood and the tumor

Background

- Glofitamab is a T-cell engaging bispecific monoclonal antibody with a unique 2:1 configuration that confers bivalency for CD20 (B cells) and monovalency for CD3 (T cells).[1]
- In an ongoing Phase I/II study (NCT03075696), glofitamab demonstrated durable complete responses and a favorable safety profile in patients with R/R B-cell lymphomas (Phase I dose-escalation part)[2]; and in patients with R/R DLBCL (pivotal Phase II expansion).[3]
- We evaluated tumor and peripheral blood (PB) biomarkers associated with clinical response to glofitamab in the pivotal Phase II expansion.

Methods

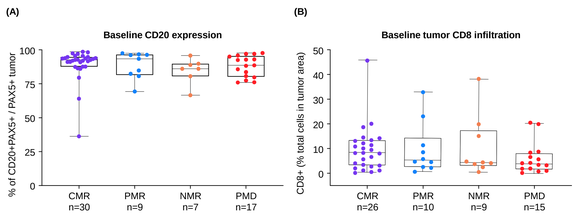
- Patients with DLBCL (DLBCL, not otherwise specified, high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma; n=107) and ≥2 prior therapies received intravenous (IV) obinutuzumab pretreatment (1000mg) 7 days before the first glofitamab dose on Day (D)1. IV glofitamab was then given as step-up doses on D8 (2.5mg) and D15 (10mg) of Cycle (C)1 and at the target dose (30mg) on D1 of C2–12 (21-day cycles). Response was assessed by Independent Review Committee (Lugano 2014 criteria).[4]
- Biopsy samples (archival or fresh) were collected at baseline, prior to obinutuzumab pretreatment.
- Baseline tumor biopsies were assessed by CD20/PAX5 immunohistochemistry (n=64) and CD8/Ki67 immunofluorescence (n=61).
- PB biomarkers were evaluated by flow cytometry (n=87) and plasma cytokines by enzyme-linked immunosorbent assay (ELISA; n=70).
- Immune and stromal cell type were inferred from bulk tumor RNA sequencing (RNAseq) samples (n=55) using xCell cell type enrichment analysis.
- ctDNA was measured using a customized panel of recurrently mutated genes in DLBCL. Mutant molecules per mL (MMPM) and changes in ctDNA levels from baseline to C3 D1 were analyzed to determine whether they were associated with response using the methodology previously described by Herrera et al.[5]

Results

Glofitamab efficacy was independent of baseline CD20 or CD8 T-cell levels

- Immunohistochemistry/immunofluorescence analysis of baseline tumor biopsies revealed that clinical responses were achieved irrespective of baseline CD20 expression levels or the amount of tumor T-cell infiltration (**Figure 1A**); no significant differences were found between response categories.
- A trend was observed towards higher CD8+ T cells at baseline in patients with a complete metabolic response (CMR) (**Figure 1B**; CMR median=8.18 versus partial metabolic response [PMR]/no metabolic response [NMR]/progressive metabolic disease [PMD] median=4.49, Wilcoxon p-value=0.34), consistent with observations from the dose escalation phase.[6] Similar results were observed with CD8+Ki67+ T cells (data not shown).

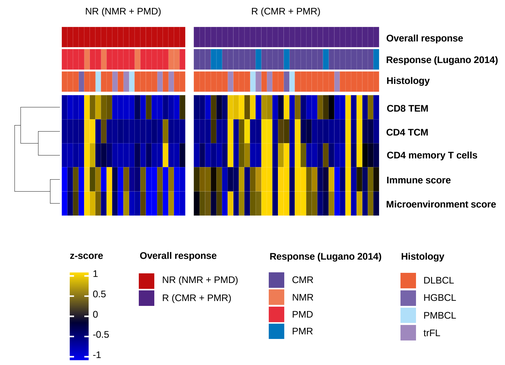
Figure 1. Association of baseline tissue biomarkers with response to glofitamab.



Transcriptomic based signatures associated with response to glofitamab

- Gene expression analysis was performed by applying the xCell algorithm to bulk RNAseq from baseline tumor biopsies to assess tumor microenvironment (TME) cell type enrichment.
- Responders had a significantly higher (p-value<0.05) overall TME abundance score which was driven by the immune subset as measured by the immune score which include the CD4 and CD8 T-cell subset scores (**Figure 2**).

Figure 2. Association between transcriptomic based signatures and response to glofitamab.

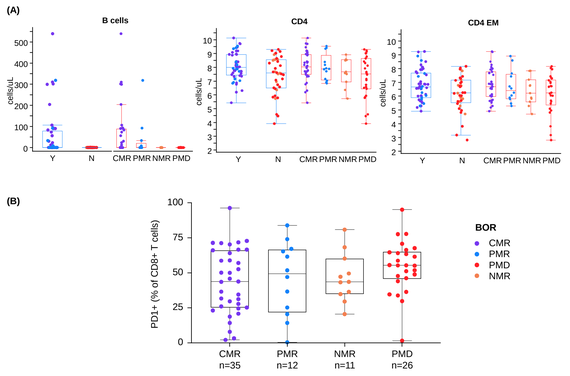


HGBCL, high-grade B-cell lymphoma; NR, non-responders; PMBCL, primary mediastinal B-cell lymphoma; R, responders; TCM, T-cell central memory; TEM, T-cell effector memory; trFL, transformed follicular lymphoma.

Peripheral blood biomarkers associated with response to glofitamab

- Immune cell subsets were assessed by flow cytometry at baseline (**Figure 3A**). Significance probabilities were assessed by Chi-square Wald test in a logistic regression model that predicts best overall response (BOR) by baseline biomarker value.
- A positive association with response was observed for B cells (p=0.006), CD4 T cells (p=0.019) and CD4 effector memory (EM) cells (p=0.033). Other cell types of interest were not associated with response: CD8 T cells (p=0.332), regulatory T cells (p=0.140), natural killer cells (p=0.286), and monocytes (p=0.760).
- A trend was observed towards higher expression of the checkpoint marker PD1 on CD8 cells for patients with PMD (association with progressive disease: p=0.05; **Figure 3B**).

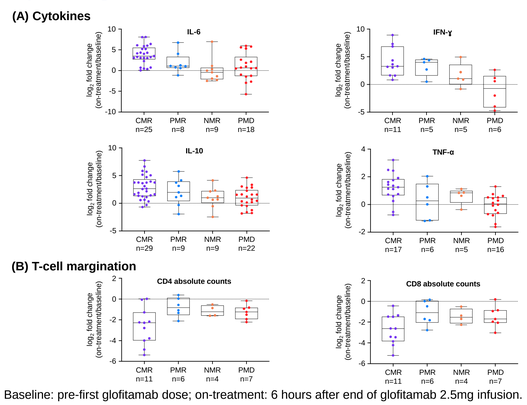
Figure 3. Association between PB biomarkers at baseline and response to glofitamab.



Responder groups: Yes = CMR + PMR; No = NMR + PMD. Many patients with R/R DLBCL had low B-cell counts at study entry. All values below LLOQ (1 cell/μL) were imputed as zero. LLOQ, lower limit of quantitation; N, no; Y, yes.

- Induction of interleukin (IL)-6, interferon (IFN)-γ, IL-10 and tumor necrosis factor (TNF)-α 6 hours after the first glofitamab dose was strongest in patients with a CMR (IL-6, IFNγ, IL-10: 6- to 16-fold induction; TNFα: 1.5-fold induction; **Figure 4A**).
- Transient margination of CD4 and CD8 T cells was strongest in patients with a CMR (**Figure 4B**).

Figure 4. Association between early on-treatment PB changes and response to glofitamab.

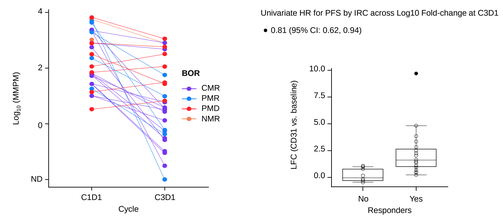


Baseline: pre-first glofitamab dose; on-treatment: 6 hours after end of glofitamab 2.5mg infusion.

ctDNA reduction associated with response to glofitamab

- ctDNA levels were assessed at baseline (C1 D1, pre-obinutuzumab pretreatment) and after two cycles of glofitamab (C3 D1) in 30 patients.
- Log10-fold change in ctDNA MMPM at C3 D1 was greatest in responders and was associated with progression-free survival (**Figure 5**).
- Median log10-fold change in ctDNA MMPM at C3 D1 was associated with BOR (p≤0.001).

Figure 5. Association between ctDNA reduction and response to glofitamab.



Responder groups: No = NMR + PMD; Yes = CMR + PMR. CI, confidence interval; HR, hazard ratio; IRC, independent review committee; LFC, log fold-change; ND, not detected; PFS, progression-free survival.

Conclusions

- Biomarker results from the expansion cohort in patients with R/R DLBCL were consistent with those from the dose-escalation phase.[6]
- Several novel response-associated biomarkers were identified in PB including higher baseline B cell, CD4 cell, and CD4 EM cell counts in responders, and higher PD1 expression on CD8 in patients with progressive disease.
- These data suggest a model where the clinical activity of glofitamab may be dependent upon immune context in the tumor and PB at the start of treatment.
- The prognostic value of ctDNA in R/R DLBCL, previously demonstrated with polatuzumab vedotin and bendamustine plus rituximab[5] and axicabtagene ciloleucel,[7] extends to glofitamab monotherapy, highlighting the value of ctDNA as a monitoring tool for characterizing response to therapy.

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