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Biomarker analysis to unravel mechanisms of resistance to glofitamab monotherapy in large B cell lymphoma

M. Nowicka[5], W. Leung[1], C. Carlo-Stella[2], M. Dickinson[3], M. Hutchings[4], E. Mulvihill[5], L. Lundberg[5], H. Hamidi[1], **A. Bottos**[5]

[1] *Genentech, San Francisco, United States of America*
[2] *Humanitas University and IRCCS Humanitas Research Hospita, Milan, Italy*
[3] *Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia*
[4] *Rigshospitalet, Copenhagen, Denmark*
[5] *F. Hoffmann-La Roche, Basel, Switzerland*

Background: Glofitamab, a CD20-CD3 T-cell bispecific, has demonstrated high and durable complete responses (CR) in patients (pts) with aggressive Non-Hodgkin Lymphoma (NHL). This study aimed to investigate the correlation between baseline molecular tumor characteristics and treatment outcomes in pts with R/R large B-cell lymphoma (LBCL) receiving glofitamab monotherapy in the Phase I/II study NP30179 (NCT03075696).

Results: In baseline tumor biopsies Hallmark gene sets indicative of high tumor proliferation, protein synthesis and DNA repair – MYC targets, G2M checkpoints, and E2F targets, oxidative phosphorylation, unfolded protein response and DNA repair – were enriched in pts who did not achieve a CR. These signatures were also associated with shorter progression-free survival (PFS) and duration of CR (DoCR; all GSEA p<0.0001). B-cell and memory B-cell signatures from xCell were significantly up-regulated in CR pts compared to non-CR pts (p=0.0012 for both). High expression of these signatures was associated with longer PFS (HR [95%CI] = 0.58 [0.4-0.85], 0.63 [0.43-0.91]) but showed no association with DoCR (HR [95%CI] = 0.84 [0.4-1.79], 0.99 [0.45-2.17]).

Analysis of CD4 and CD8 T-cell signatures from xCell demonstrated a trend for increased expression of CD4+ memory T-cells, CD4+ T central memory (cm) and CD8+ Tcm in CR as compared to non-CR pts. High expression of CD4+ memory T-cells, CD4+ Tcm and CD8+ Tcm signatures was associated with longer DoCR (HR [95%CI] = 0.3 [0.14-0.64], 0.3 [0.12-0.74], 0.5 [0.24-1.04]) and PFS (HR [95%CI] = 0.6 [0.41-0.88], 0.57 [0.36-0.88], 0.6 [0.41-0.88]).

To gain more insights in the biological features of pts not responding to glofitamab we further characterized pts exhibiting a high proliferation signature, defined by high MYC targets, G2M checkpoints and E2F targets. Those pts showed a significant enrichment in the Dark Zone (DZ) signature (p<0.0001), indicating a highly active germinal center B-cell like (GCB) phenotype. A negative correlation was observed between the proliferation phenotype and CD4+ and CD8+ T-cell related signatures from xCell.

Conclusions: This analysis reveals distinct roles for tumor-intrinsic and tumor microenvironment features for response to glofitamab in pts with R/R LBCL. While characteristics related to B-cell phenotype and high proliferation strongly influence the likelihood of achieving an initial response, features of T cells appear to be more critical for a durable response.

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