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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Molecular Mechanisms Underlying Response and Resistance to Glofitamab

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The prognosis for patients with relapsed or refractory Diffuse Large B-cell Lymphoma (r/rDLBCL) is poor. Glofitamab (a CD20xCD3 T-cell-engaging bispecific antibody) demonstrated high and durable complete response rates and a manageable safety profile in patients with relapsed/refractory (R/R) Large B-cell lymphoma (LBCL). Despite its clinical efficacy and a rapid achievement of complete responses, some patients are refractory to glofitamab treatment, prompting us to investigate the mechanisms underlying response and resistance to glofitamab.

To gain insight into these mechanisms, we performed molecular (single cell RNA and TCR sequencing data) and functional (ex-vivo assessment of cytotoxicity, cytokine and cytotoxic granules secretion, activation) characterisation of PBMCs from glofitamab-treated patients who achieved complete response (CR, n=18) or progressed (progressive disease, PD, n=13) by cycle 3, collected in a Phase I/II study (NCT03075696). All patients received glofitamab in a step-up-dose regimen of 2.5/10/30 mg following obinutuzumab pre-treatment (1000 mg) administered 7 days prior to the first glofitamab dose. The PBMC samples were analyzed at baseline (cycle 1 day 1 pre-dose) and on treatment (cycle 2 day 1 pre-dose).

The assessment of PBMCs using single cell RNA sequencing did not reveal major differences in abundance of the main immune cell subsets between patients who achieved CR or PD. Paired analysis of on-treatment samples (compared to respective baseline) pointed to a tendency towards decreased frequency of CD8 T cells in patients with CRs and increased frequency of the same in patients with PDs (consisting mainly of an increase of proliferating CD8). Glofitamab treatment further increased the frequency of monocytes and DCs in patients with CRs, and of NKs in both CRs and PDs. Within the DC population, we observed a significant decrease of cDC1 population and increase of the AXL+SIGLEC6+ DC population with high capability of driving T cell activation and proliferation upon treatment in both CR and PD patients.

Complementary to changes in cell proportions, we identified gene expression programs associated with response, of which some were shared between two or more cell types while others were cell type-specific. Using established gene expression programs of naiveness, cytotoxicity, and exhaustion, we found that CD8 T cells of CR patients maintain their naive phenotype on treatment, whereas the naiveness of CD8 T cells of PD patients decreases upon treatment. Subsequently, we observed a higher naiveness of CD8 T cells in patients with CRs compared to PDs on treatment. Moreover, CD4 T cells increase their naiveness upon treatment in patients with CRs and decrease in patients with PDs, resulting in higher overall naiveness of CD4 T cells on treatment in CR patients compared to PD patients. In line with the expected mode of action, glofitamab treatment led to an increase of the cytotoxicity and exhaustion scores in CD8 T cells, and of the exhaustion score in CD4 T cells, of both CR and PD patients, reflective of T cell engagement in both patient groups. However, CD8 T cells of PD patients display overall a higher cytotoxicity and exhaustion level compared to CR patients.

TCR sequencing data showed a higher clonal diversity in CD4 T cells compared to CD8 T cellsand and enrichment of hyper-expanded clonotypes in the CD8 T cell compared to CD4 T cell compartment . However, we neither detected an increase in the proportion of clonal cells, nor a change in clonal diversity upon treatment, regardless of the patient response group.

In addition, we did not find any association between the percent of TCR repertoire occupied by clones of a given size and response or treatment time point.
In agreement with the molecular analysis, T cells from CR patients (collected at baseline and on treatment) displayed a tendency towards higher cytotoxicity, cytokine secretion and T cell activation compared to PD patients upon ex vivo re-stimulation with glofitamab, suggestive of a better functional state of T cells from patients with CR compared to PD.
Taken together, our work provides a thorough characterization of peripheral blood immune cells from CR and PD patients treated with glofitamab, and provides evidence that T cells from CR patients maintain a fresher/naive and more functional state compared to PD patients, which display T cells in a more advanced differentiation state with lower functionality.

Disclosures Nassiri: *Roche:* Current Employment. **Schmeing:** *Roche:* Current Employment. **Leclercq:** *Roche:* Current Employment, Current holder of *stock options* in a privately-held company. **Herter:** *ROCHE:* Current Employment, Current equity holder in publicly-traded company. **Servera:** *Roche:* Current Employment. **Hüsser:** *Roche:* Current Employment. **Yángüez:** *Roche:* Current Employment. **Dunshee:** *F. Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company; *Genentech, Inc.:* Current Employment. **Korfi:** *Roche:* Current Employment. **Umana:** *Roche/Genentech:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties. **Bröske:** *F. Hoffmann La Roche Ltd:* Current Employment. **Bottos:** *F. Hoffmann La Roche Ltd:* Current Employment, Current holder of *stock options* in a privately-held company. **Bacac:** *Roche:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties.

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