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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Baseline CD4 T Cells Are Associated with Improved Response to CD20-CD3 Bispecifics in Lymphoma

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Background: Mosunetuzumab (Mosun) is a CD20xCD3 T-cell engaging bispecific monoclonal antibody that redirects T cells to eliminate malignant B cells. Mosun is approved for the treatment of patients (pts) with relapsed/refractory follicular lymphoma (FL) after two or more systemic therapies and has shown activity in both aggressive non-Hodgkin lymphoma (aNHL) and indolent (iNHL). Previous reports have shown that CD20 loss is a common mechanism of resistance to Mosun (Schuster SJ, ASCO 2022). However, as the mechanism of action of Mosun is T cell mediated killing of tumor cells, we sought to characterize the immune microenvironment of tumor samples from patients with NHL treated with Mosun. Here we report integrated biomarker analysis of pt samples from the phase I/II Mosun monotherapy trial (NCT02500407).
Methods: Baseline and at-progression biopsies were collected from 240 relapsed/refractory NHL pts from the fixed dosing (arm A) and Cycle 1 step-up dosing (arm B) cohorts, including 78 DLBCL, 89 FL, 37 transformed FL (trFL), and 36 other aNHL and iNHL histologies (including MCL, MZL, SLL, & RS). A total of 265 biopsies were profiled via RNASeq, including 58 paired baseline and at-progression samples. As a proxy for immune subset prevalence, immune gene signatures were calculated using principal component analysis. Association with best overall response was calculated using limma with histology and archival status included as covariates for the pooled cross-histology analysis, or with archival status for within-histology comparisons. Significance for exploratory analysis was defined as false-discovery rate (FDR)<0.05.
Results: Pooled analysis of all baseline biopsies identified expression of 76 genes as significantly associated with response (Figure 1A). A number of immune-related genes, such as ITGAL, IL6R, and TOX2 were expressed at higher levels in responders. Gene signature analysis revealed that most of the top hits were T cell related, with T follicular helper (Tfh) signatures most strongly associated with response. Analysis of individual histologies revealed that the majority of genes identified had indication-specific associations, with significant hits in DLBCL (n=472) or trFL (n=4). No hits were found in FL after FDR correction. DLBCL hits appeared mostly tumor-specific (HLA-E, DOK1, and ITGA2), while trFL hits were more associated with CD4 T cell biology (TIGIT and FOXN3). The Tfh signature was the most strongly associated with response in trFL, and was also nominally significant in FL (Figure 1B). The signature displayed a histology-specific expression profile, with lower expression in aNHL and higher expression in iNHL. A split was observed in trFL, with responders showing signature scores similar to iNHL and non-responders like aNHL. Other CD4-but not CD8-signatures showed a similar profile.
At progression, a small number of genes showed sustained changes, with reductions in XCR1 & CLEC9A, and induction of ALOX15B seen in patients up to 2 years after the last Mosun administration, suggesting long-term changes in the immune microenvironment during the development of resistance.
Conclusions: Baseline biomarker data reveal an important role for CD4 T cells in Mosun response and suggest that higher prevalence of CD4s may be a factor in the improved response to Mosun in indolent NHL. Our data specifically point to Tfh cells as potential drivers of response, although the mechanisms by which Tfh contributes to response, as well as the implications for other bispecifics, requires more exploration.

Disclosures Bolen: *Genentech, Inc.:* Current Employment; *F Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company. **Roy:** *Genentech:* Current Employment; *F. Hoffmann-La Roche:* Current equity holder in publicly-traded company; *Amgen:* Ended employment in the past 24 months. **Huw:** *Genentech, Inc.:* Current Employment; *F. Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company. **Hatzi:** *Genentech, Inc., F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Penuel:** *Genentech, Inc. / F. Hoffman-La Roche Ltd:* Current Employment, Current holder of *stock options* in a privately-held company.

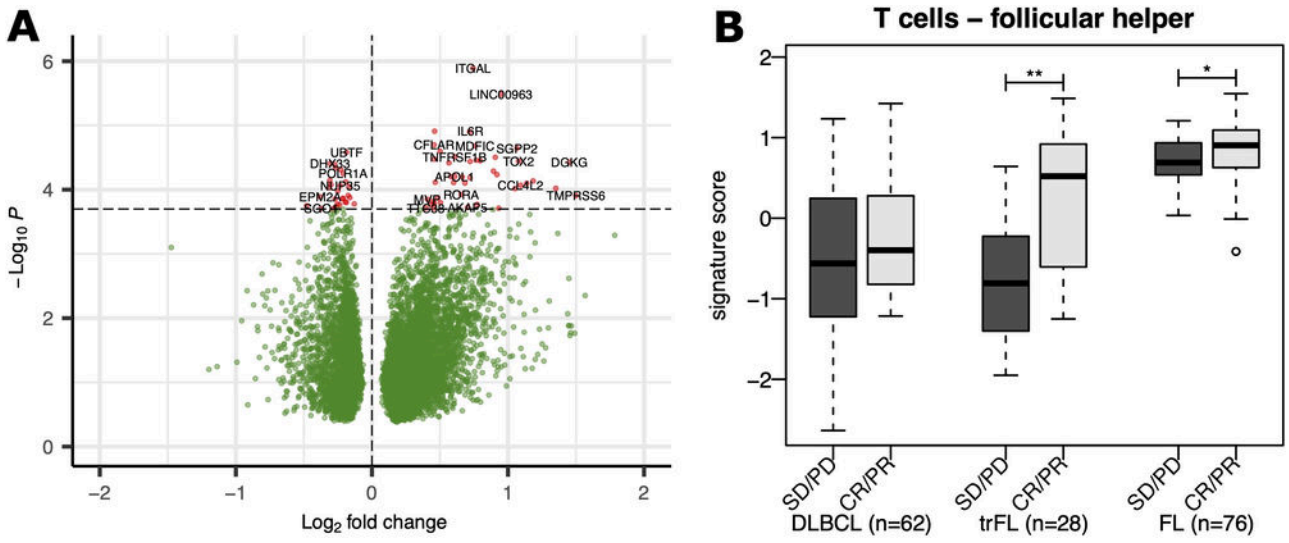

Figure 1

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