675 GENOMIC DRIVERS OF LARGE B-CELL LYMPHOMA RESISTANCE TO CD19 CAR-T THERAPY

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Background CD19-directed chimeric antigen receptor-reprogrammed autologous T cells are breakthrough immunotherapies for heavily pretreated patients with diffuse large B-cell lymphoma (DLBCL), but across CAR-19 products, ~60% of patients fail to respond or relapse. Inflammatory markers and clinical factors associate with impaired responses, but tumor-intrinsic resistance drivers are largely undefined.

Methods To characterize the genomic mechanisms involved resistance to CAR-19, we interrogated whole genome sequencing (WGS) from 28 relapsed/refractory (r/r) aggressive lymphoma patients uniformly treated with axicabtagene ciloleucel (axi-cel).

Results Because prognostic factors defined in the frontline treatment setting are largely inapplicable to CAR-19, we leveraged the WGS data, including comparative analyses with untreated DLBCL cases in the Pan-Cancer Analysis of Whole Genomes (PCAWG) (figure 1). In analyses of individual mutated genes, TP53 was significantly enriched (p=0.002) in CAR-19 patients, but did not predict outcome. However, mutations in either NFKBIA or MYC associated with worse PFS after CAR-19 (p=0.04, p=0.025 respectively). We next identified 12 single base substitution (SBS) mutational signatures in our cohort and found presence of APOBEC (SBS2 and SBS13) signatures associated with worse PFS, with 4/5 patients progressing (p=0.03). Copy number analysis by GISTIC2.0 revealed focal deletions of RHOA and RB1 to be significantly enriched in our cohort and independently predicted poor outcome (p=0.0007, p=0.05 respectively). WGS identifies structural variants and complex events. We found chromothripsis, a catastrophic shattering and reassembly of chromosomes, in 39.3% of r/r DLBCL, which was strongly associated with poor CAR-19 outcome, with 9/11 affected cases progressing (p=0.041). Finally, reduced expression (n=3) or genomic alteration (n=3) of CD19 did not associate with poor outcome. One case with durable response contained a sub-clonal CD19 mutation (L174V) previously reported as associated with CAR-19 resistance. These findings demonstrate predominance of CD19-independent resistance and indicate antigen-mediated tumor killing is not the only mechanism of tumor eradication. Genomic complexity appears to promote an immunosuppressive tumor microenvironment (TME), limiting CAR-19 efficacy.

Conclusions Leveraging the resolution of WGS, we observed that markers of genomic complexity (chromothripsis and APOBEC) and specific genomic alterations (RHOA and RB1 deletions) associate with resistance to CAR-19 immunotherapy for aggressive B-cell lymphomas (figure 1). 93.8% of CAR-19 relapsed patients contained at least one or these genomic alterations. Recent patient data demonstrate that an immunosuppressed TME leads to CAR-19 failure. Combining these findings with our genomics findings, successful CAR-19 therapy must overcome the immune-exhausted TME to mobilize the host immune system and eliminate the tumor.

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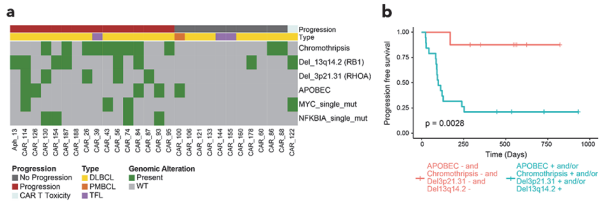

Abstract 675 Figure 1 Genomic alterations associated with disease progression. (a) The heatmap shows the significant genomic alteration present in at least 4 patients associated with progression after CD19 CAR-T cell therapy. (b) Kaplan-Meier curve of progression free survival with the combination of statistically significant genomic anomalies