POSTER: 4368

Impact of Inflammation, Tumor and Product Attributes on Clinical Outcomes in Patients with Relapsed/Refractory Follicular Lymphoma Treated with Axicabtagene Ciloleucel

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BACKGROUND

- Follicular lymphoma (FL) is the second most common subtype of adult B-cell non-Hodgkin lymphoma (NHL). The prognosis is especially poor in the 20% of patients with FL who develop progression of disease within 24 months after first-line immonochemotherapy (POD24).
- Axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, demonstrated high overall response rate (ORR; 94%), complete response rate (CRR; 79%), and durability (36-month progression-free survival [PFS] rate of 54%) in adult patients with relapsed/refractory (r/r) FL on the ZUMA-5 phase 2, multicenter, single-arm study[1].
- Identification of biomarkers associated with durable responses, resistance, and high-grade toxicity could help risk stratification and lead to development of novel approaches to further enhance therapeutic index of this therapy.

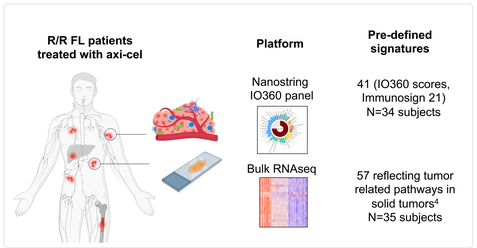
OBJECTIVE

- Analyze host, tumor, and CAR-T product attributes of r/r FL patients in ZUMA-5 study.
- Perform univariate and multivariate analyses to identify pre- and post-treatment biomarkers associated with durable responses and/or high-grade CRS and NEs

METHODS

- Product attributes, serum biomarkers, clinical features, patient characteristics and tumor characteristics separately by pre- (230 covariates) and post-infusion (66 covariates) were analyzed to identify the association with efficacy & safety outcomes which include progression-free survival (PFS), ongoing response, high-grade (grade >= 3) cytokine release syndrome (CRS) and neurologic events (NE) in 124 r/r FL patients from ZUMA-5 using 36 months data-cut.
- Wilcoxon rank sum tests were used to compare covariates between ongoing responders vs. other and for high-grade toxicities. Log-rank tests were used to compare PFS between groups. Hazard ratios along with 95% confidence interval were calculated using Cox proportional hazard models. P<0.05 was considered as significant.
- Variable importance were generated using the multivariable Random Forest model after feature selection and normalized to enable comparison across different outcomes.
- To investigate factors in the tumor microenvironment associated with outcome, we conducted gene expression profiling via Nanostring analysis of pre-treatment tumor biopsies from a subset of patients (N=34) using pre-defined PanCancer IO360™ signatures. This analysis was complemented by bulk RNA sequencing (N=35, including 30 patients overlapping with the Nanostring dataset). CD19 protein expression was measured using immunohistochemistry (IHC).

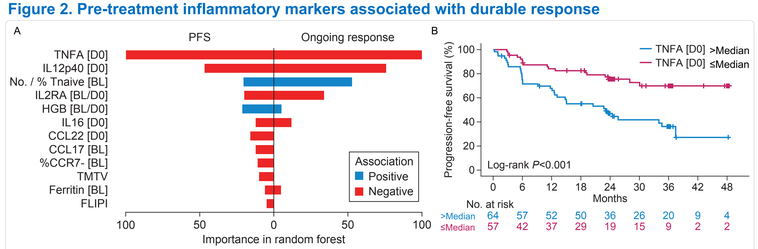
Figure 1. Gene expression of pre-treatment tumor biopsies



R/R, relapsed/refractory; 30 subjects were overlapping in nanostring and RNAseq analysis;

RESULTS

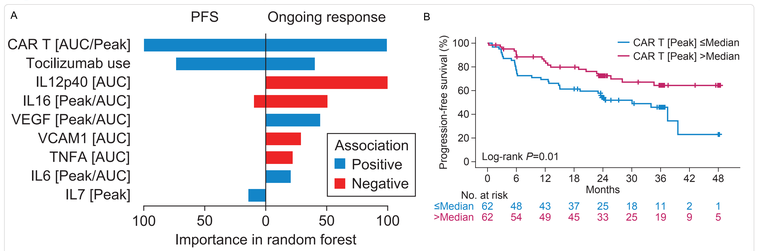
Figure 2. Pre-treatment inflammatory markers associated with durable response



FLIPI, follicular lymphoma International prognostic index; HGB, hemoglobin; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; PDL1, programmed death ligand 1; PFS, progression-free survival; TMTV, total metabolic tumor volume; Tnaive, naive T cells.

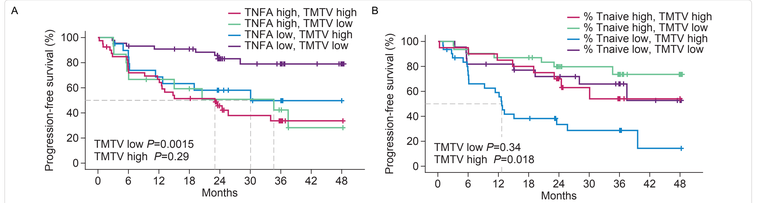
- Inflammatory marker TNF-a, IL12p40, IL2-Ra, Ferritin associated with disease progression (day 0 TNFa showed strongest association)
- Naïve T-cells associated with improved outcome, while serum chemokines CCL17, CCL22 and immune modulating IL-16 associated with disease relapse.

Figure 3. Post-infusion CAR T-cell peak and other markers associated with durable response



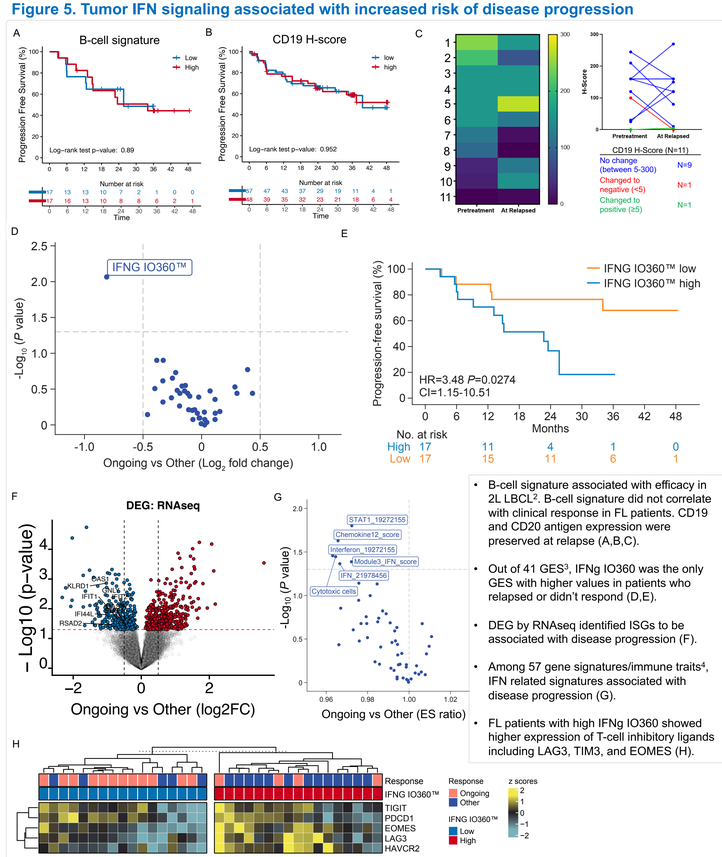
- CAR T cell peak expansion and sustained systemic inflammation associated with clinical response among post-infusion covariates.

Figure 4. Improved risk stratification using pre-treatment covariates



- Risk stratification is improved using the pre-treatment covariates in combination with FLIPI score (data not shown)
- Notably, naïve product T cells associated (P < 0.05) with improved outcome only in patients with relatively high (> median) TMTV. Conversely, low levels of TNFa at day 0 associated with improved outcome only in patients with lower TMTV

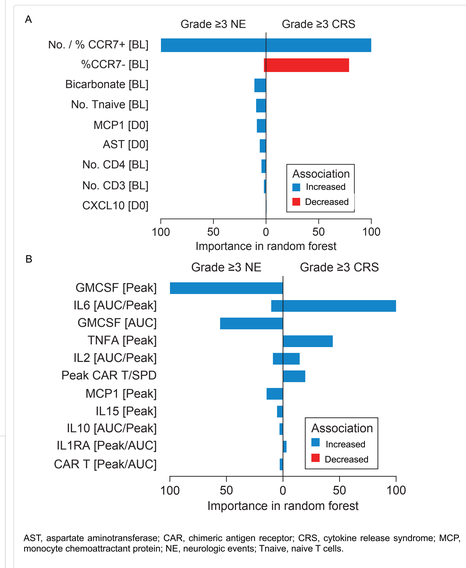
Figure 5. Tumor IFN signaling associated with increased risk of disease progression



- B-cell signature associated with efficacy in 2L LBCL[2]. B-cell signature did not correlate with clinical response in FL patients. CD19 and CD20 antigen expression were preserved at relapse (A,B,C).
- Out of 41 GES[3], IFNg IO360 was the only GES with higher values in patients who relapsed or didn't respond (D,E).
- DEG by RNAseq identified ISGs to be associated with disease progression (F).
- Among 57 gene signatures/immune traits[4], IFN related signatures associated with disease progression (G).
- FL patients with high IFNg IO360 showed higher expression of T-cell inhibitory ligands including LAG3, TIM3, and EOMES (H).

Wilcoxon tests were done to compare expression between ongoing responder vs others, with the following P values, ***P<0.001; **P<0.01; *P<0.05; P<0.1.
KM, Kaplan-Meier; PFS, progression-free survival; EFS, event-free survival; GES, gene expression signature; DEG, differentially expressed genes; IS21, Immunosign 21
B-cell signature is derived using gene expression of BLK, CD19, MS4A1, TNFRSF17, FCRL2, FAM30A, PNOC, SPIB, and TCL1A

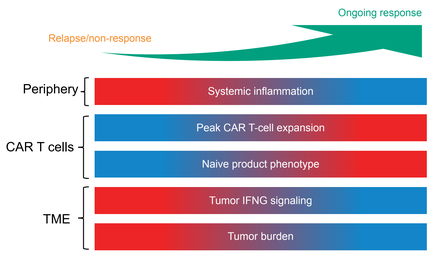
Figure 6. Multivariate analysis of covariates associated with high-grade CRS and NE



AST, aspartate aminotransferase; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; MCP, monocyte chemoattractant protein; NE, neurologic events; Tnaive, naive T cells.

- Product CCR7+ T cells (naïve and central memory T cell phenotype) associated with both grade ≥3 NE and CRS, while effector and effector memory T-cell phenotypes (CCR7-) exhibited negative association with grade≥3 CRS (A)
- GM-CSF peak/AUC serum levels emerged as foremost analyte associated with grade≥3 NE (B)
- IL-6 peak/AUC and TNFa peak in serum were identified as the primary analytes associated with grade≥3 CRS (B)
- TNFa associated with disease progression and occurrence of high-grade cytokine release syndrome or neurologic events, presenting targets to improve the therapeutic index of axi-cel in FL.

CONCLUSIONS



- Systemic inflammation (e.g. TNFa) associated negatively with clinical response and high-grade toxicity.
- Naïve product phenotype and CAR T peak expansion associated with durable response.
- Tumor IFN signaling and tumor burden were associated with increased risk of disease progression.
- Analysis of paired biopsies, at pre-treatment and relapse, showed preservation of CD19 and CD20 expression, suggesting pre-treatment antigen levels and loss of CD19 expression are not major drivers of CAR T-cell resistance.

Data not shown:
- Combined analysis of pre- and post-infusion variables with response ranked pre-treatment covariates higher than post-infusion covariates

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