



DLBCL

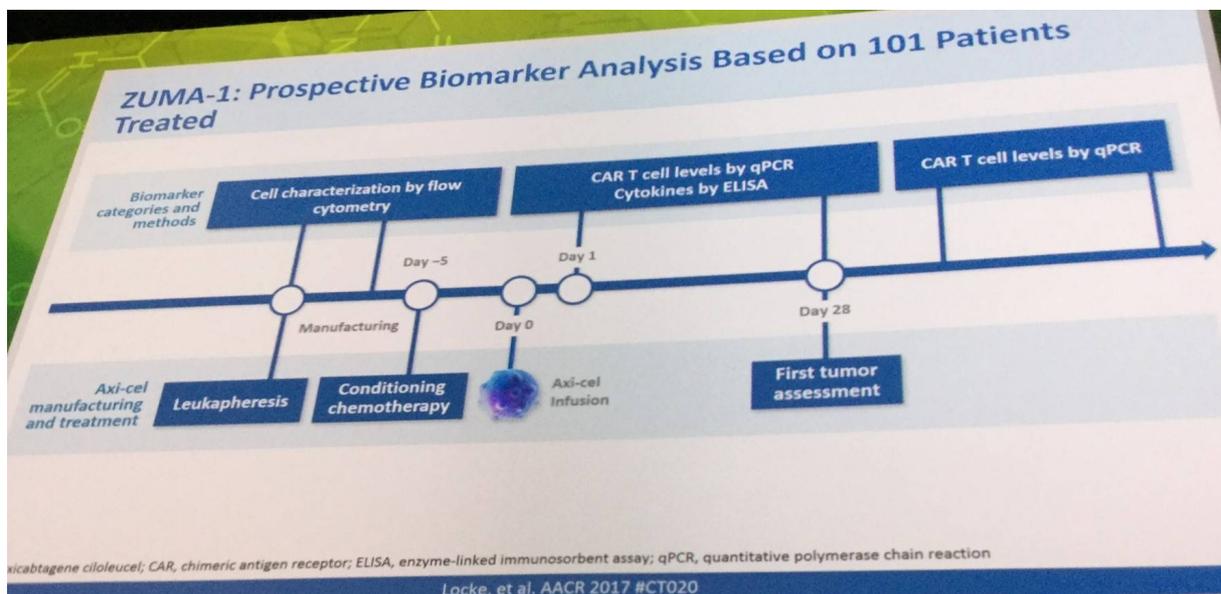
AACR 2017 | ZUMA-1 trial: immune signatures of CRS and neurologic events in subjects with refractory Diffuse Large B-Cell Lymphoma treated with KTE-C19

 Terri Penfold | Apr 12, 2017

On Sunday 2nd April, during the “[CTSY02 - Immuno-oncology Biomarkers in Clinical Trials](#)” session, [Frederick L. Locke, MD](#), of the [H. Lee Moffitt Cancer Center & Research Institute](#), Tampa, FL, gave a talk titled “[Immune signatures of cytokine release syndrome and neurologic events in a multicenter registrational trial \(ZUMA-1\) in subjects with refractory diffuse large B-cell lymphoma treated with axicabtagene ciloleucel \(KTE-C19\)](#).”

Dr. Locke began the talk by explaining what Cytokine Release Syndrome (CRS) and neurologic events are. They are two potentially serious AEs that are associated with treatment with Chimeric Antigen Receptor (CAR) T-cells. CRS is mediated by high levels of IL-6 and other inflammatory cytokines, and symptoms include hypoxia, hypotension, tachycardia, and fever. Neurologic events are linked to high levels of cytokines or CAR T-cells, and symptoms include seizures, aphasia, tremor, encephalopathy, and confusion. The anti-IL-6 receptor antagonist, tocilizumab, and/or corticosteroids to suppress the immune system are used to manage neurologic events and CRS.

Following this, a brief overview of the ZUMA-1 prospective biomarker analysis, based on 101 treated patients, was given:



The manufacturing success rate of axi-cel was 99%, despite heterogeneity in starting apheresis material (14% naïve, 15% effector, 27% central memory, and 38% effector memory).

Consistent Efficacy and Safety Across a Broad Range of CD4/8 Ratios

CD4/8 Ratio*	ORR, %	CR, %	Grade ≥3 NE, %	Grade ≥3 CRS, %
Overall	82	54	28	13
Quartile 1 (0.03–0.5)	92	67	33	17
Quartile 2 (0.5–0.9)	68	48	48	12
Quartile 3 (0.9–1.9)	83	50	21	13
Quartile 4 (1.9–5.8)	88	52	12	12

Median CD4/8 ratio was 0.9
complete response; CRS, cytokine release syndrome; NE, neurologic events; ORR, objective response rate

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Dr. Locke went on to state that levels of CAR T-cells were reported to peak within 7–14 days of treatment with Axi-cel. It was also reported that CAR T-cell expansion is associated with objective response ($P = 0.0002$) as well as \geq grade 3 neurologic events ($P = 0.0028$).

Distinct biomarkers also peaked within 7 days of treatment with Axi-cel. Analytes were elevated in $\geq 50\%$ of patients with ≥ 2 -fold induction above baseline out of a panel of 44 measured. Biomarkers found to associate with \geq grade 3 CRS and neurologic events included, but were not limited to, IL-15, IL-10, and granzyme B. However, IL-2, GM-CSF, and ferritin were found to only associate with neurologic events.

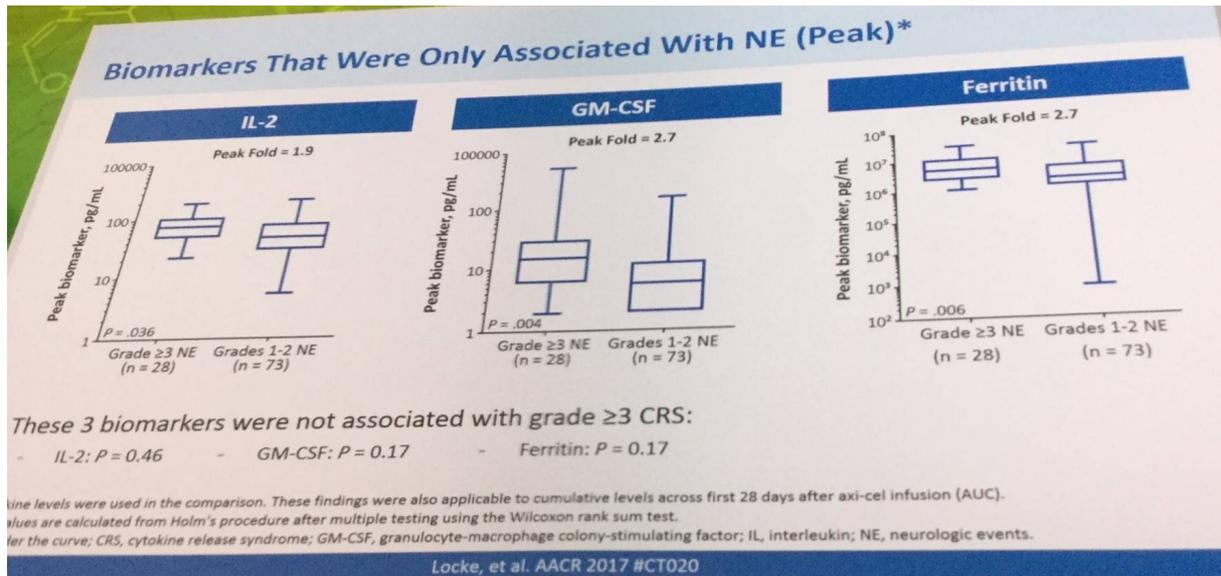
Biomarkers Associated With Both Grade ≥3 CRS and Grade ≥3 NE*

Function	Analyte	CRS Grade ≥3 vs Grades 0-2	NE Grade ≥3 vs Grades 0-2
Homeostatic	IL-15		
	IL-6		
Inflammatory	IL-1Ra		
	IL-2Ra		
Immune-modulating	IFN-γ		
	IL-10		
Chemokine	IL-8		
	MCP-1		
Effector	Granzyme B		

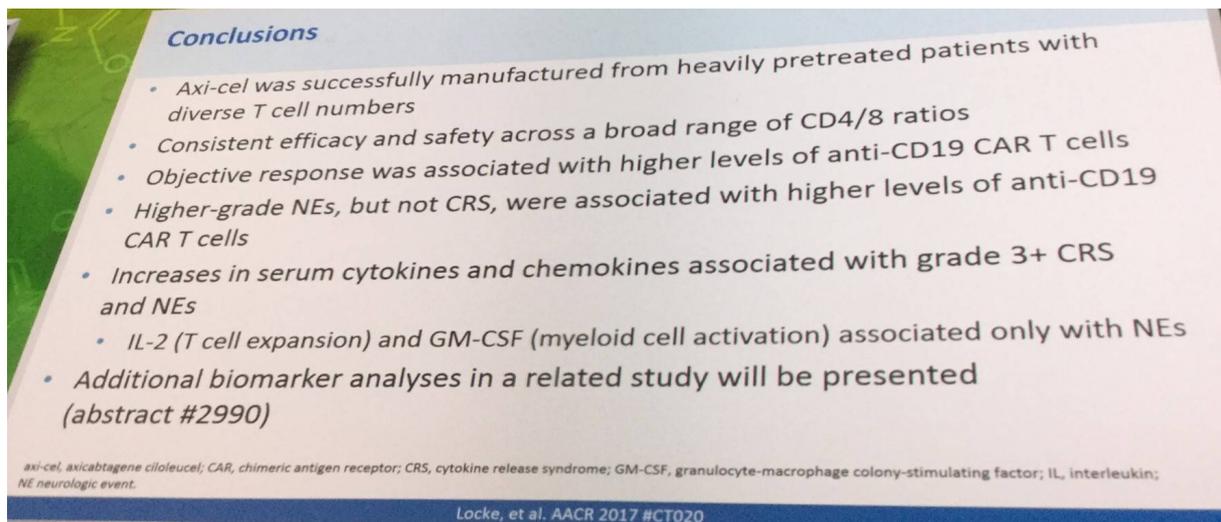
Adjusted P values are calculated from Holm's procedure after multiple testing using the Wilcoxon rank sum test

*Peak levels after axi-cel infusion were used in the comparison.
AUC, area under the curve; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; NE, neurologic events.

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Dr. Locke concluded the talk with a concise summary slide:



Reference:

1. [Locke F.L.](#) Immune signatures of cytokine release syndrome and neurologic events in a multicenter registrational trial (ZUMA-1) in subjects with refractory diffuse large B-cell lymphoma treated with axicabtagene ciloleucel (KTE-C19) [Presentation]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; 2017. Abstract nr [CT020](#).

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