Supplemental Figure Legends

Supplemental Figure 1 Institutional management guidelines for CRS adapted from the CARTOX working group criteria.[6]

Supplemental Figure 2 Institutional management guidelines for NT adapted from the CARTOX working group criteria.[6]

Supplemental Figure 3. **A-D Validation of serum cytokine samples using the Ella with the Luminex.** We used extra vials of patient serum samples that had been prior analyzed 4 years ago with the Luminex and reported by Park et al to validate cytokine analysis using the Ella (ProteinSimple).[3] **A-D** Patient case examples are used to demonstrate correlations of IFNγ, IL6 and TNFα in the analyses conducted using the Ella (ProteinSimple) and the Luminex.

Supplemental Figure 4. A-B. Correlation of baseline IL6 levels(pg/mL) with IL6 levels collected on day of axi-cel infusion (**A**) and peak levels (**B**) using spearman's rank-order correlation.

Supplemental Figure 5. **A-D Noradrenaline levels in patients with grade 0, grade 1, grade 2 and grade 4 CRS respectively.** Samples were analyzed for catecholamine levels as previously described (Staedtke et al. Nature 2018). Black arrows denote day of onset of CRS, blue arrows denote day of peak CRS and orange arrow symbolizes day of CRS resolution.

Supplemental Figure 6. Myeloid and Tregs associated with severe CRS in patients treated with axi-cel. RNAseq was performed on an overlapping set of baseline biopsies that was prospectively snap frozen (n=5 gr.3-4, n=20 gr.0-2). **A.** Volcano plot for differentially expressed genes based on CRS severity. **B.** Enrichment plots of genes analyzed for immunologic GSEA

signatures for Tregs and Monocytes. **C.** Enrichment plots of genes analyzed for immunologic GSEA signatures for M1 and M2 macrophages.

Supplemental Figure 7. Early intervention in a patient with elevated IL6 pre-conditioning chemotherapy. A. PET CT showing pre-treatment disease in a patient with Stage IV DLBCL and **B.** post treatment response at day 30 following infusion of axi-cel. **C.** Outline of treatment interventions for CRS in relation to grading severity, IL6 and temperature for 8 days following infusion of axi-cel.

Supplemental Table 1: Univariate analysis of baseline characteristics and grade 3-5 toxicities

Variable (n)	OR (95% CI) CRS	p value CRS	OR (95% CI) NT	p value NT
Age	1.009 (0.960,1.074)	0.7492	1.022 (0.979,1.074)	0.3554
Sex Female (25) Male (50)	 1.0 (reference) 0.651 (0.185,2.434)	0.5060	 1.0 (reference) 0.911 (0.327, 2.644)	0.8595
ECOG* 0-1 (56) ≥ 2 (18)	 1.0 (reference) 3.205 (0.813,12.366)	0.0871	 1.0 (reference) 2.187 (0.715, 6.630)	0.1640
Stage I/II (13) III/IV (62)	 1.0 (reference) 1.058 (0.234,7.505)	0.9469	 1.0 (reference) 1.587 (0.429, 7.653)	0.5165
IPI at apheresis* 0-2 (23) 3-5 (51)	 1.0 (reference) 2.25(0.521, 15.636)	0.3263	 1.0 (reference) 2.820 (0.897, 10.835)	0.0954
Bridging No (27) Yes (48)	 1.0 (reference) 1.846 (0.494,8.93)	0.3914	 1.0 (reference) 0.824 (0.300, 2.318)	0.7074
Time to 1st Fever ≤24 hours (31) >24 hours (41)	 1.0 (reference) 1.039 (1.006-1.085)	0.4590	 1.0 (reference) 0.447 (0.159, 1.215)	0.1172

ECOG- Eastern Cooperative Oncology Group; IPI- International Prognostic Index * One patient had apheresis done at another institution and therefore ECOG and IPI were not available at time of apheresis.

Supplemental Table 2: Multivariable model of baseline patient characteristics and cytokines with grade 3-5 toxicities

Variable	OR (95% CI) CRS	P value CRS	OR (95% CI) NT	P value NT
Age	1.007 (0.934,1.101)	0.8546	0.997 (0.926,1.080)	0.9361
ECOG 0-1 ≥ 2	5.655 (0.894,39.925)	0.0663	2.337 (0.314,17.270)	0.3920
Stage I/II III/IV	0.679 (0.058,16.654)	0.771	3.323 (0.319,91.276)	0.3718
Bridging Chemotherapy No Yes	0.778 (0.099,7.044)	0.8077	0.448 (0.080,2398)	0.3433
IL6	1.037 (1.006,1.082)	0.0389	n/a	n/a
Log2 ANG2/ANG1	n/a	n/a	3.636 (1.436,2.167)	0.0154

ECOG- Eastern Cooperative Oncology Group; L-6 Interleukin 6; Ang2/ANG1- Angiopoietin 2/ Angiopoietin

Supplemental Table 3: Comparison of baseline characteristics for patients with elevated baseline IL6

	Baseline IL6 < 40 pg/mL (n=43)	**Baseline IL6 ≥ 40 pg/mL (n=9)**
Age - Median (Range) yrs	63 (24-76)	64.5 (32-79)
Male Sex – no. (%)	30 (70)	6 (67)
Histology – no. (%) de Novo DLBCL Transformed Indolent lymphoma	 28 (65) 15 (35)	 6 (67) 3 (33)
Bulky Disease ≥10cm – no. (%)	6 (14)	2 (22)
Ann Arbor Stage III/IV – no. (%)	35 (81)	9 (100)
IPI ≥ 3 at apheresis – no. (%)	27 (63)	9 (100)
Lines of therapy ≥ 3 — no. (%)	26 (60)	7 (78)
Bridging therapy – no. (%)	26 (60)	9 (100)
Prior autologous HSCT– no. (%)	9 (21)	1 (11)
Not eligible for Zuma 1* – no. (%)	18 (42)	5 (56)

DLBCL- Diffuse Large B Cell lymphoma; HSCT- Hematopoietic Stem Cell Transplantation ; IPI- International Prognostic Index, * based upon co-morbidities at apheresis

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Supplemental Table 4: Comparison of clinical endpoints for patients with elevated baseline IL6

	Baseline IL6 < 40 pg/mL (n=43)	Baseline IL6 ≥ 40 pg/mL (n=9)
CRS		
Median time to CRS	2 days	1 days
Median time to max CRS	4 days	5 days
CRS all grades – no. (%)	41 (95)	8 (89)
Grade ≥ 3 CRS – no. (%)	5 (12)	5 (56)
Grade 5 CRS—no. (%)	1 (2)	2 (22)
Use of tocilizumab – no. (%)	20 (47)	8 (89)
Use of steroids – no. (%)	18 (42)	7 (78)
Neurotoxicity		
Median time to NT	5 days	4 days
Median time to max NT	7 days	6 days
NT all grades– no. (%)	27 (63)	7 (78)
Grade ≥3 NT– no. (%)	8 (19)	6 (67)
D90 Response* (47)	**N=39**	**N=8**
CR + PR –no. (%)	26 (67)	0
Complete Response – no. (%)	18 (46)	0
NRM – no. (%)	1 (3)	3**(38)
Disease related mortality– no. (%)	1 (3)	5 (62.5)

Cytokine Release Syndrome (CRS) and Neurotoxicity (NT) were graded prospectively. CRS was defined and graded using the ASTCT grading guidelines.[4] Neurologic toxicity was graded using the CAR T cell therapy associated (CARTOX) working group guidelines.[6] Tumor response was determined at day 90 by the treating physician per Lugano 2014 classification.[20] CR- Complete Response; PR- Partial Response; NRM- non-relapse mortality. * Five patients did not have data available for day 90 clinical response assessment either due to data cutoff date or they were lost to follow up. ** One patient died as result as disseminated candidemia in the setting of grade 4 CRS.