Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma

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Table S1. **Comparison of cellular and humoral immunity at baseline to up to 1 year post-axi-cel.**

	Difference	Lower confidence interval	Upper confidence interval	P-value
WBC				
30-0	-2927·0	-3682·3	-2171·7	<0·001
90-0	-2048·3	-2849·4	-1247·2	<0·001
180-0	-2202·8	-3074·9	-1330·7	<0·001
270-0	-1790·1	-2743·6	-836·6	<0·001
360-0	-1618·3	-2582·3	-654·4	<0·001
CD3				
30-0	-108·5	-369·0	152·1	0·769
90-0	-187·9	-455·5	79·7	0·280
180-0	-223·9	-506·3	58·5	0·177
270-0	-287·6	-595·7	20·5	0·077
360-0	-292·0	-605·7	21·6	0·079
CD4				
30-0	-169·7	-266·1	-73·4	<0·001
90-0	-172·8	-271·8	-73·8	<0·001
180-0	-163·3	-267·7	-58·8	<0·001
270-0	-163·1	-277·1	-49·1	0·002
360-0	-160·1	-276·1	-44·0	0·002
CD8				
30-0	76·9	-133·5	287·3	0·847
90-0	-15·4	-231·5	200·7	1·000
180-0	-57·4	-285·5	170·7	0·963
270-0	-131·4	-380·2	117·5	0·566
360-0	-128·9	-382·2	124·4	0·602
CD56				
30-0	40·5	-4·4	85·4	0·094
90-0	26·5	-19·6	72·7	0·479
180-0	14·0	-34·6	62·7	0·936
270-0	22·1	-31·0	75·2	0·770
360-0	43·9	-10·2	97·9	0·160
CD19				
30-0	-23·4	-65·3	18·6	0·512
90-0	-19·4	-62·5	23·6	0·707
180-0	-4·2	-49·6	41·3	1·000
270-0	35·9	-13·7	85·5	0·252
360-0	50·4	-0·0	100·9	0·050
IgG				
30-0	-85·4	-203·4	32·6	0·255
90-0	-159·1	-277·1	-41·2	0·003
180-0	-197·4	-331·2	-63·6	0·001
270-0	-141·3	-304·5	22·0	0·118
360-0	-17·3	-164·8	130·2	0·999
N				
30-0	-2434·6	-3109·1	-1760·1	<0·001
90-0	-1604·2	-2319·6	-888·8	<0·001
180-0	-1650·4	-2429·2	-871·5	<0·001
270-0	-1396·2	-2247·7	-544·7	<0·001
360-0	-1315·5	-2176·4	-454·6	0·001

Differences between baseline (0) and day 30 (30-0), 90 (90-0), 180 (180-0) and 360 (360-0) were assessed by Dunnett's test to control for multiple comparisons. Mean peripheral blood white blood cell (WBC), neutrophil (N), IgG, NK cells (CD56), B cells (CD19) and T cell subsets (CD3, CD4 and CD8) are shown. The data in the difference column represent the raw change in the mean value. The confidence level is 95%.

***Table S2*. Details of infections experienced after axi-cel infusion**

a) Infection prior to day 30*	**Incidence, n(%)**
Clostridium Difficile	12 (14·1)
URTI	10 (11·8)
Rhinovirus	7
Influenza	2
Respiratory Syncytial Virus	1
Sepsis	6 (7·1)
Other bacterial site infections	6 (7·1)
Urinary tract infection***	4
Cellulitis	1
Acute cholecystitis	1
Fungi**	2 (2·4)
Viremia	2 (2·4)

*38 infections in 31 patients. 5 patients had multiple infections
** One case of fusariosis, one case of candidiasis
*** One case of pyelonephritis requiring IV antibiotics

b) Infection after day +30*	**Incidence, n**
Clostridium Difficile	1
URTI	19
Rhinovirus	4
Influenza	2
Parainfluenza	2
Respiratory Syncytial Virus	1
Viral infection**	10
Sepsis***	1
Other bacterial site infections	5
Neutropenic fever	1
Cellulitis	1
Abscess	1
Sinusitis	2
Pneumonia	6

*32 infections in 31 patients.
**Clinical diagnosis without microbiological confirmation
*** MRSA bacteremia

A) Details on early infections (before day +30) after axi-cel
B) Details on late infections (after day +30) after axi-cel

Table S3. **Microbiology of Blood Stream Infections***

Organism (n=11)	Incidence, n (%)
Gram Positive Bacteria	
Coagulase negative Staphylococcus species	3 (27%)
Staphylococcus aureus (MRSA)	1 (9%)
Streptococcus species	1 (9%)
Enterococcus faecalis	1 (9%)
Clostridium sporongenes	1 (9%)
Gram Negative Bacteria	
Escherichia coli (Fluoroquinolone resistant)	1 (9%)
Bacteroides species	1 (9%)
Fungi	
Candida krusei	1 (9%)
Fusarium species	1 (9%)

*Seven patients experienced a bacteremia. One patient had three bacterial isolates grow and one patient had a bacteremia and a separate fungemia.

***Table S4*. Patients with infections in the first 30 days by CRS, neurologic toxicity grade, tocilizumab use, and steroid treatment**

a)	Infection (n=31)	No infection (n=54)	P-value overall
CRS			0·486
Grade 0	3 (9·7%)	3 (5·6%)	
Grade 1-2	24 (77·4%)	47 (87·0%)	
Grade 3-4	4 (12·9%)	4 (7·4%)	
Neurotoxicity			0·161
Grade 0	7 (22·6%)	21 (38·9%)	
Grade 1-2	11 (35·5%)	20 (37·0%)	
Grade 3-4	13 (41·9%)	13 (24·1%)	
Tocilizumab use	16 (51·6%)	23 (42·6%)	0·564
Steroid use*	17 (54·8%)	22 (40·7%)	0·303
Bridging therapy	21 (67·7%)	27 (50·0%)	0·174

b)	Severe infection (n=11)	No severe infection (n=74)	P-value overall
CRS			0·007
Grade 0	1 (9·1%)	5 (6·8%)	
Grade 1-2	6 (54·5%)	65 (87·8%)	
Grade 3-4	4 (36·4%)	4 (5·4%)	
Neurotoxicity			0·007
Grade 0	1 (9·1%)	27 (36·5%)	
Grade 1-2	2 (18·2%)	29 (39·2%)	
Grade 3-4	8 (72·7%)	18 (24·3%)	
Tocilizumab use	9 (81·8%)	30 (40·5%)	0·025
Steroid use*	10 (90·9%)	29 (39·2%)	0·004
Bridging therapy	10 (90·9%)	38 (51·4%)	0·020

*** steroid use indicates the use of any dose of corticosteroids to manage CAR T-associated toxicity (CRS or neurotoxicity)**

A) Association of all patients experiencing infections in the first 30 days with cytokine release syndrome (CRS), neurotoxicity, tocilizumab use, steroid use, and bridging therapy.
B) Association of patients experiencing severe infections in the first 30 days with cytokine release syndrome (CRS), neurotoxicity, tocilizumab use, steroid use, and bridging therapy.

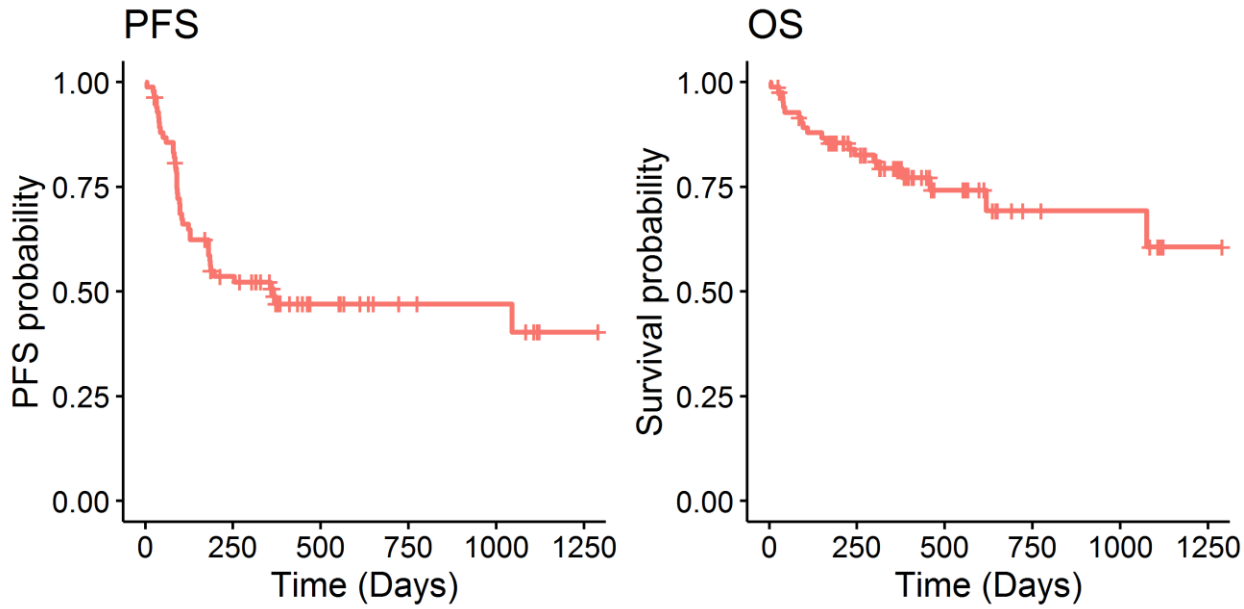
***Table S5*. Patients with infections by baseline cell counts and immunoglobulin levels**

a)	**Infection (n=31)**	**No infection (n=54)**	**P-value**
IgG	489 (305-829)	629 (302-1081)	0·153
IgA	109 (61-165)	116 (53-951)	0·631
IgM	50 (30-115)	52 (28-372)	0·541
WBC	6340 (1290-12800)	4640 (1880-14800)	0·030
Neutrophils	4300 (490-10760)	3090 (640-13480)	0·023
Lymphocytes	640 (70-2940)	635 (90-2080)	0·819
Eosinophils	60 (0-380)	100 (0-1690)	0·277
Monocytes	720 (130-1920)	650 (20-1600)	0·228
CD3	574 (199-2092)	475 (66-2250)	0·340
CD4	269 (73-609)	214 (34-1720)	0·815
CD8	293 (50-1522)	178 (22-1673)	0·304
CD56	64 (17-330)	100 (10-368)	0·225
CD19	1 (0-512)	0 (0-127)	0·242

b)	**Severe infection (n=11)**	**No severe infection (n=74)**	**P-value**
IgG	479 (305-731)	618 (302-1081)	0·170
WBC	9180 (1290-12800)	5175 (1880-14800)	0·091
Neutrophils	7390 (490-10760)	3435 (640-13480)	0·083
Lymphocytes	640 (70-1410)	655 (70-2940)	0·547
Eosinophils	40 (0-200)	100 (0-1690)	0·076
Monocytes	720 (130-1360)	660 (20-1920)	0·395
CD3	593 (231-1332)	504 (66-2250)	0·472
CD4	216 (73-459)	223 (34-1720)	0·298
CD8	320 (114-1164)	167 (22-1673)	0·130
CD56	103 (33-209)	92 (10-368)	0·577
CD19	1 (0-174)	0 (0-512)	0·414

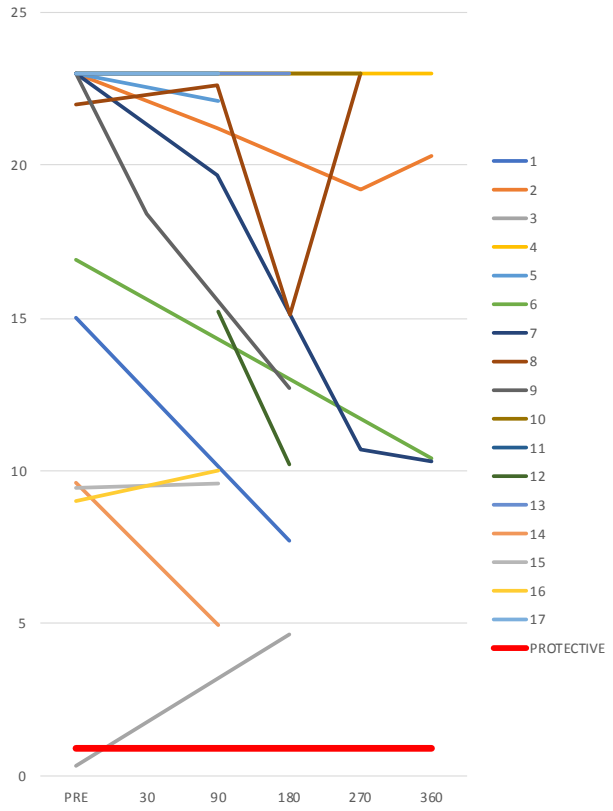
Shown is the median (range).
A) Association of any patient experiencing infection with baseline cellular and immune parameters.
B) Association of patients experiencing severe infection with baseline cellular and immune parameters.

Figure S1. **Progression free survival and overall survival for all patients**



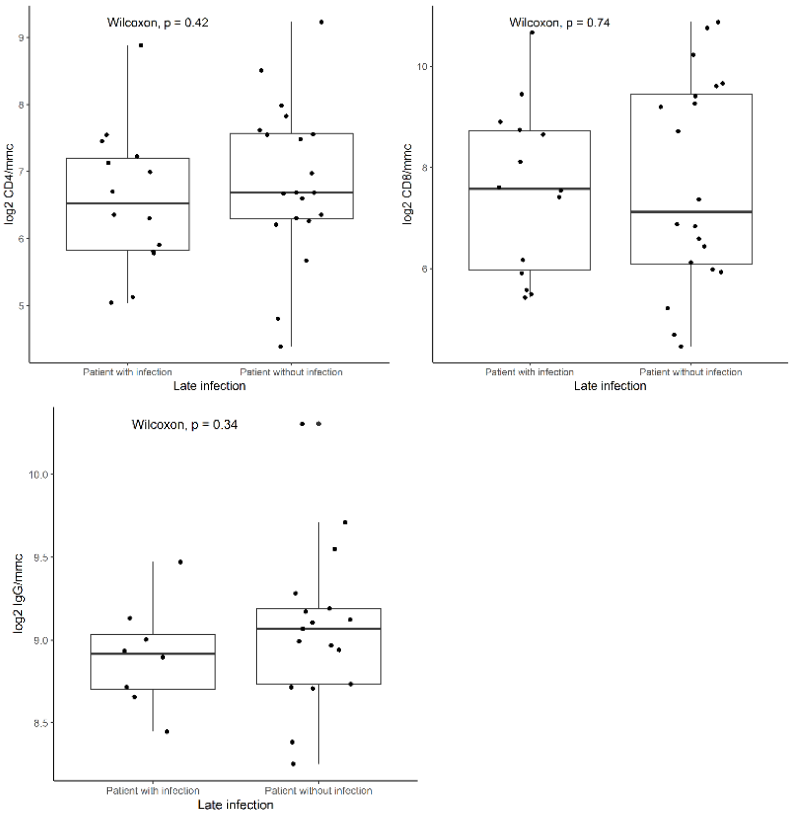
A. Progression free survival (PFS) for all 85 patients from time of axi-cel infusion. B. Overall Survival (OS) for all 85 patients.

Figure S2. **HSV titers during the first year post axi-cel.**



Changes in HSV (herpes simplex virus 1 and 2 combined IgG) titers (IV units) in 17 patients monitored during the first year following treatment with axi-cel. "Protective" indicates the minimum titre that indicates a positive test describing a history of HSV infection.

Figure S3. **Association of day 30 immune reconstitution and subsequent infection.**



Comparison of cellular and humoral immune parameters at day 30 post-axi-cel for patients with or without any infection beyond day 30 ("late infection"). Shown are day 30 CD4, CD8 and IgG levels.