

Management of CAR-T Toxicities

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Disclosures

- Research funding to institution
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FDA approved CAR-T cell Therapies for ALL/NHL/Myeloma

- CD19 CAR-T for Aggressive NHL
 - tisagenlecleucel
 - axicabtagene ciloleucel (axi-cel)
 - lisocabtagene maraleucel (liso-cel)
- CD19 CAR-T for Mantle Cell lymphoma
 - Brexucabtagene autoleucel
- CD19 CAR-T for Follicular lymphoma
 - axicabtagene ciloleucel (axi-cel)
- CD19 CAR-T for ALL (Ped/AYA)
 - tisagenlecleucel
- BCMA CAR-T for Myeloma
 - idecabtagene vicleucel

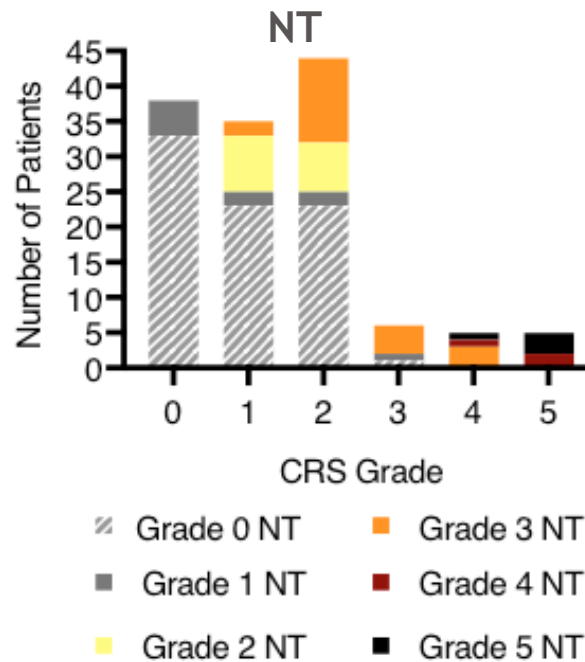
Each product associated with it's own REMS program with the FDA

Toxicities of CD19 CAR-T cell immunotherapy

CD19-independent
Chemotherapy toxicities
Infection
Anaphylaxis
RCL
Transformation

CD19-dependent
Cytokine release syndrome
Neurotoxicity
B cell depletion/infection
Tumor lysis syndrome

Overlap between CRS and



CRS grading: Lee criteria, Blood, 2014
NT grading: CTCAEv4.03

CRS spectrum

Fever
Hypotension
Capillary leak
Coagulopathy
Marrow dysfunction
Multi-organ failure
Hypoxia
HLH-like syndrome
+

Neurotoxicity

Headache
Speech disturbance
Delirium
Seizures
Focal deficits
Cerebral edema

Aggressive lymphoma: commercial CD19 CAR T cell products

Feature	Tisagenlecleucel ¹	Axi-cel ²	Liso-cel ³
Construct	FMC-63 murine scFv 4-1BB co-stimulatory domain	FMC-63 murine scFv CD28 co-stimulatory domain	FMC-63 murine scFv 4-1BB co-stimulatory domain
Viral transfer	Lentiviral	Gamma retroviral	Lentiviral
Collection	Resting state apheresis Cryopreserved Bulk cells	Resting state apheresis Fresh only Bulk cells	Resting state apheresis Fresh only Selection CD4 and CD8
Manufacture	CD3/CD28 stimulation	CD3/CD28 stimulation	CD4, CD8 selection CD3/CD28 stimulation
Dose administered	0.6-6.0 × 10 ⁸ CAR T cells CoA based on cell recovery	2 × 10 ⁶ /kg Max. 200 × 10 ⁶ No CoA	100 × 10 ⁶ (CD4/CD8) in separate vials (1:1) Dose based on recovery
Histology	DLBCL tFL	DLBCL PMBCL tFL	DLBCL, HGBCL PMBCL tIND (FL, CLL, MZL)
CNS involvement	No	No	Secondary

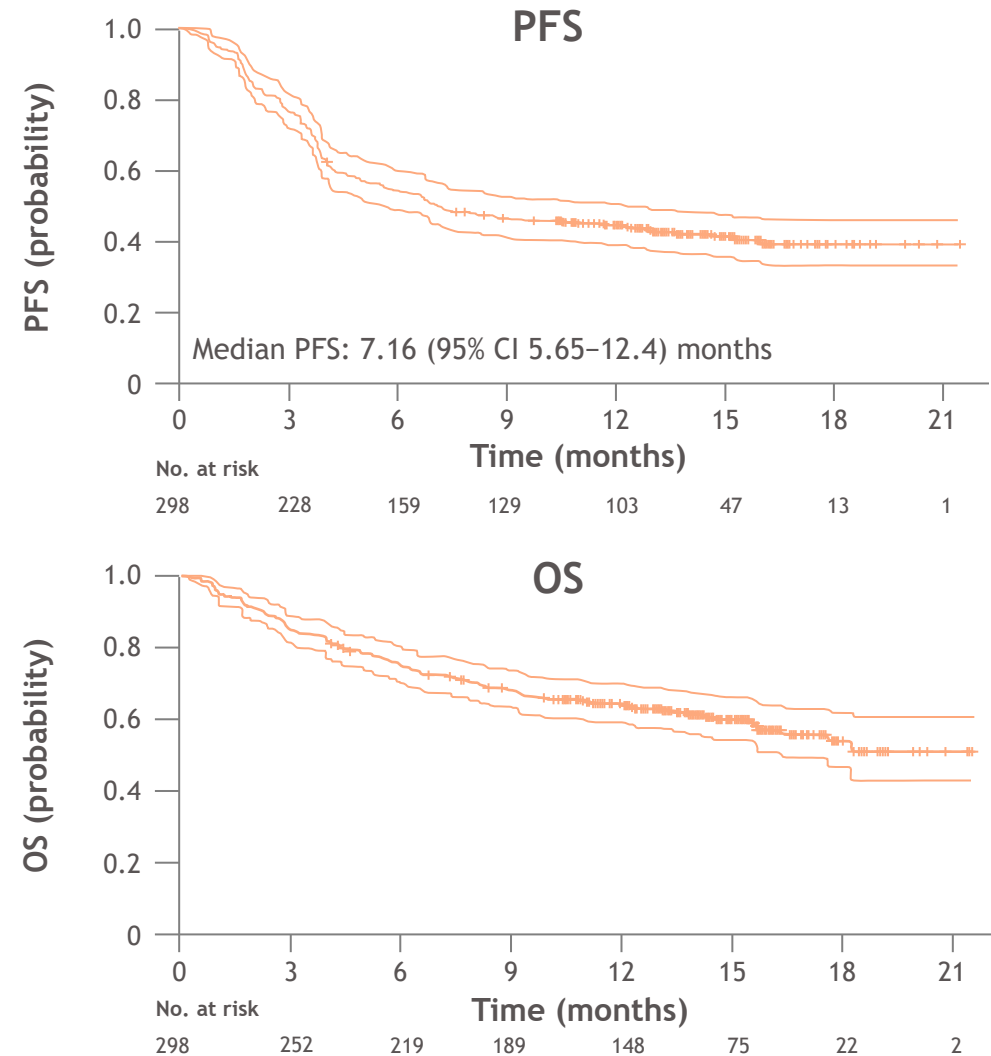
US Lymphoma CAR T Consortium: real-world efficacy of axi-cel in r/r LBCL

Characteristics	Patients (N = 298)
Age, years	
Median (range)	60 (21-83)
≥ 60, n (%)	154 (51.7)
Disease type, n (%)	
DLBCL	203 (68.1)
PMBCL	19 (6.4)
tFL	76 (25.5)
LDH > ULN at leukapheresis, ^a n (%)	157 (60.6)
LDH > ULN at conditioning chemotherapy, ^b n (%)	155 (59.4)
Bulky disease (≥ 10 cm), n (%)	68 (22.7)
Prior therapies, n (%)	
≥ 3 prior lines	222 (74.5)
Median no. of prior lines of therapy (range)	3 (2-11)
History of primary refractory disease	101 (33.9)
Outcomes	
ORR, %	82
CR, %	64
Median DOR (95% CI), months	NR (6.2-NR)
PFS at 12 months (95% CI), %	45 (39-51)
OS at 12 months (95% CI), %	64 (59-70)
CRS Grade ≥ 3, %	7
Neurologic events Grade ≥ 3, %	31

^a N = 259; does not include 39 patients in whom LDH at leukapheresis was unknown. ^b N = 261; does not include 37 patients in whom LDH before conditioning was unknown.

DOR, duration of response; LBCL, large B cell lymphoma; LDH, lactate dehydrogenase; NR, not reached; OS, overall survival; ULN, upper limit of normal.

Nastoupil LJ, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large b-cell lymphoma: results from the US lymphoma CAR T consortium. J Clin Oncol. 2020;38:3119-28.



CIBMTR registry: real-world analysis of tisagenlecleucel in r/r DLBCL

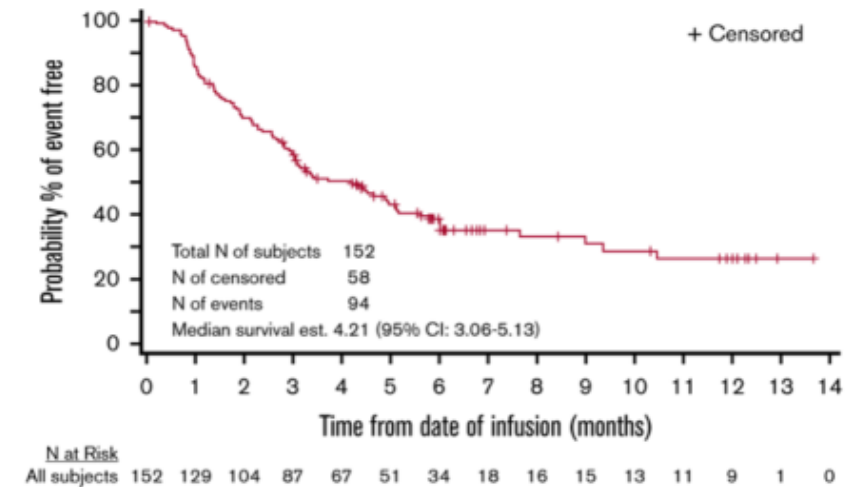
Characteristics	Patients (N = 155)
Median age (range), years	65.4 (18.45-88.99)
Lymphoma type, n (%)	
Double/triple hit	17 (11.0)
Transformed	42 (27.1)
Disease status before tisagenlecleucel, n (%)	
Primary RR	147 (94.8)
Prior HSCT, n (%)	
Autologous	40 (25.8)
Allogeneic	5 (3.2)
Median time of follow-up since CAR T cell infusion (range), months	11.9 (3.8-19)
Median time from leukapheresis acceptance to CAR T cell infusion (range), days	31.5 (22-130)

^a Fewer than 10 patients at risk at this time point.

CIBMTR, Center for International Blood and Marrow Transplant Research; HSCT, hematopoietic stem cell transplant.

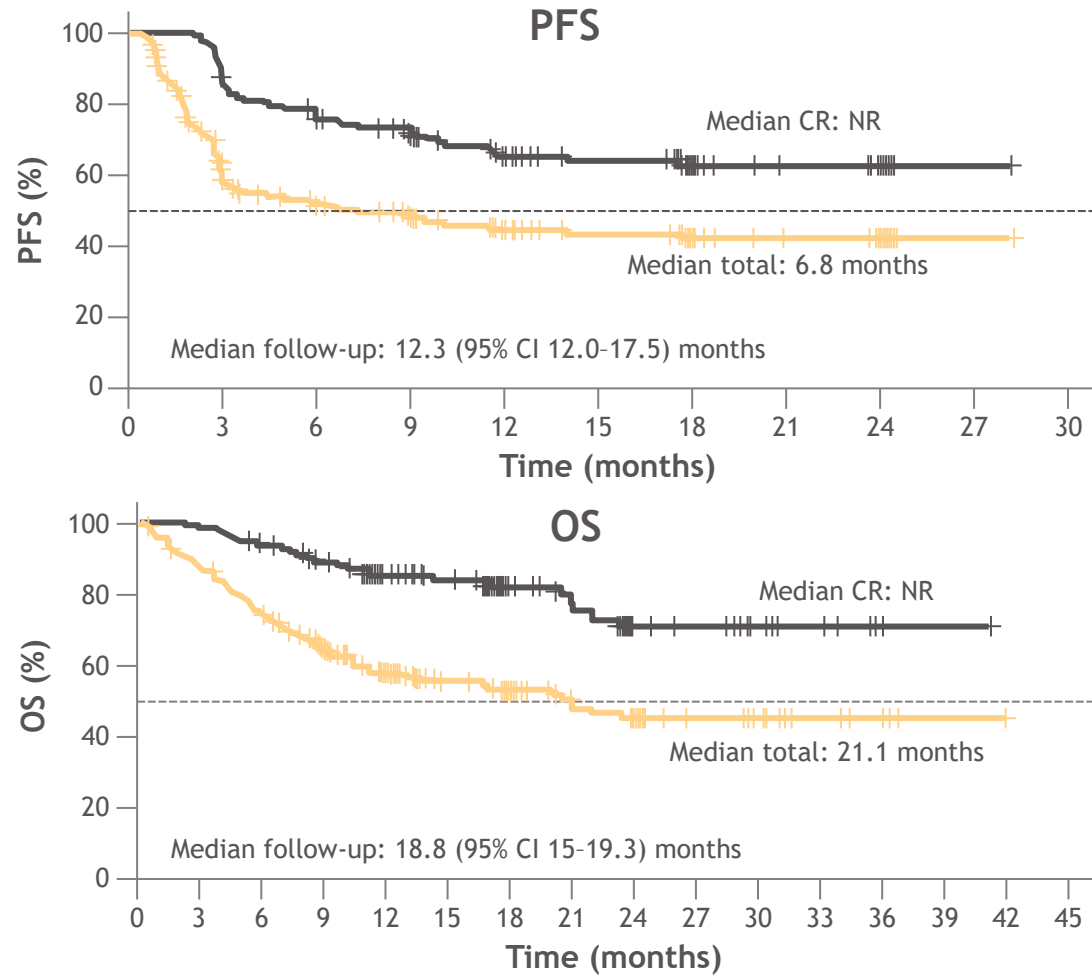
Pasquini MC, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv. 2020;4:5414-24.

PFS: real-world setting



Response	CIBMTR (n =152)	JULIET (n =115)
ORR, n (%)	61.8 (53.6-69.6)	52.2 (42.7-61.6)
12-month PFS, ^a n (%)	26.4 (17.2-36.6)	34.7 (25.7-43.9)
12-months OS, n(%)	56.3 (44.2-66.8)	48.2 (38.6-57.1)
12-month DOR, ^a n (%)	48.4 (33.9-61.5)	62.7 (48.7-73.9)
AEs	CIBMTR (n = 155)	JULIET (n =115)
CRS Grade ≥ 3, n (%)	7 (4.5)	26 (22.6)
Neurologic event Grade ≥ 3, n (%)	8 (5.1)	13 (11.3)

TRANSCEND NHL 001: efficacy and safety of liso-cel in patients with r/r LBCL



Characteristics	Patients (N = 269)
Median age, years (range)	63 (18-86)
Double-/triple-hit lymphoma, n (%)	36 (13)
CNS involvement, n (%)	7 (3)
Median prior lines of therapy, n (range)	3 (1-8)
Chemorefractory, n (%)	181 (67)
Best response	Patients (N = 256)
Best ORR, %	73
Best CR, %	53
12-month DOR, %	55
AEs	Patients (N = 269)
Any CRS, %	42
Median time to onset, days	5
CRS Grade $\geq$ 3, %	2
Any neurologic event, %	30
Neurologic event Grade $\geq$ 3, %	10

Abramson JS, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396:839-52.

Summary of CD19 CAR T cell therapies for aggressive lymphoma

Characteristics	Axi-cel ¹	tisagenlecleucel ²	Liso-cel ³
Lymphodepletion chemotherapy	Cy/Flu 500/30 mg/m ² × 3 days	Cy/Flu 250/25 mg/m ² × 3 days Bendamustine 90 mg/m ² × 2 days	Cy/Flu 300/30 mg/m ² × 3 days
Bridging therapy, %	Not allowed	92%	59%
Indication	DLBCL, High grade, PMBCL, tFL	DLBCL, High grade, tFL	DLBCL, HGBCL, PMBCL, tFL, tIND
ORR, %	82	53	73
CR, %	54	40	53
CRS overall/Grade 3/4, %	94/13	58/23 ^a	42/2
Neurologic event overall/Grade 3/4, %	87/28	21/12	30/10
Outpatient treatment	No	Yes (26%)	Yes

^a Penn grading scale. tIND, transformed indolent NHL.

1. Neelapu SS, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531-44. 2. Schuster SJ, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45-56. 3. Abramson J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396:839-52. Liso-cel PI. Available from <https://www.fda.gov/media/145711/download>. Accessed May 2021. Axi-cel PI. Available from: www.fda.gov/media/108377/download. Tisagenlecleucel PI. Available from: <https://www.fda.gov/media/107296/download>. All accessed May 2021..

Summary (1):

CRS and ICANS tend to go together. Patients with severe CRS are more likely to get severe ICANS.

The incidences and severities of toxicities appear to differ between different products (no randomized trials; different grading systems).



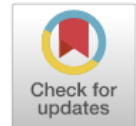
Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org



Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells



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Cytokine Release Syndrome (CRS)

- CRS (ASTST)
 - “a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.”
 - Onset at $T \geq 38.0C$
 - Resolution when signs contributing to grading (fever/hypotension/hypoxia) resolve

Cytokine release syndrome: ASTCT grading system

	Fever	Hypotension		Hypoxia
Grade 1	$\geq 38^{\circ}\text{C}$	None	AND/OR	None
Grade 2	$\geq 38^{\circ}\text{C}$	Responsive to fluids		Low flow nasal cannula ($\leq 6\text{L/minute}$) or blow-by
Grade 3	$\geq 38^{\circ}\text{C}$	Requiring one vasoactive agent ($\pm$ vasopressin)		High-flow nasal cannula ($>6\text{L/minute}$), facemask, non-rebreather mask or Venturi mask
Grade 4	$\geq 38^{\circ}\text{C}$	Requiring more than one vasoactive agent (excluding vasopressin)		Positive pressure ventilation, such as CPAP, BIPAP, intubation with mechanical ventilation

Overall grade is determined by the worst parameter

CRS grade is largely determined by supportive strategies

Immune effector Cell Associated Neurotoxicity Syndrome (ICANS)

- ICANS (ASTCT)
 - “a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.”
 - Onset at grade 1
 - Resolution when signs are no longer apparent

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) - ASTCT grading system

	ICE score	CAPD score	Depressed level of consciousness	Seizure	Motor findings	Elevated ICP/cerebral edema
Grade 1	7-9	1-8	Awakens spontaneously	None	None	None
Grade 2	3-6	1-8	Awakens to voice	None	None	None
Grade 3	0-2	≥ 9	Awakens only to tactile stimuli	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve without intervention	None	Focal/local edema on imaging
Grade 4	0	Unable to perform	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma	Life-threatening prolonged seizure (>5min); or repetitive clinical or electrical seizures without return to baseline in between	Deep focal motor weakness (e.g. hemiparesis or paraparesis)	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on imaging

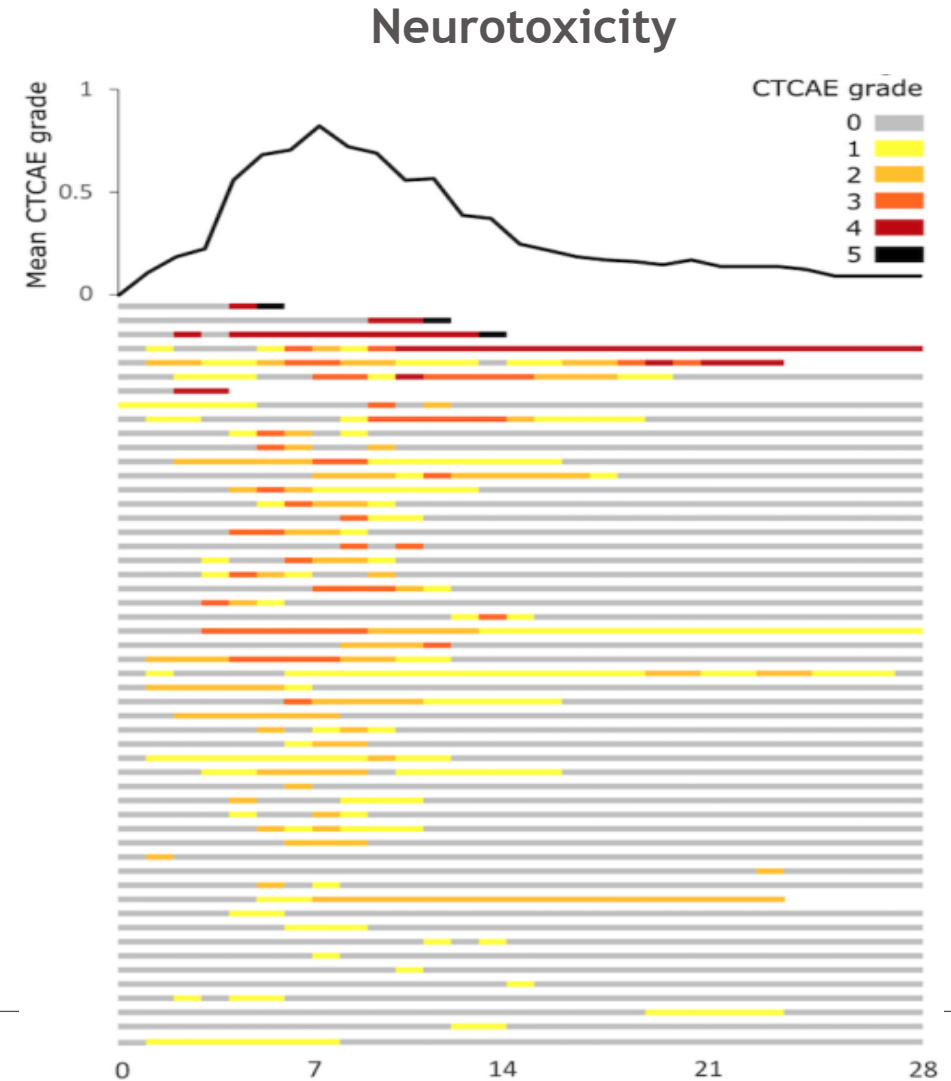
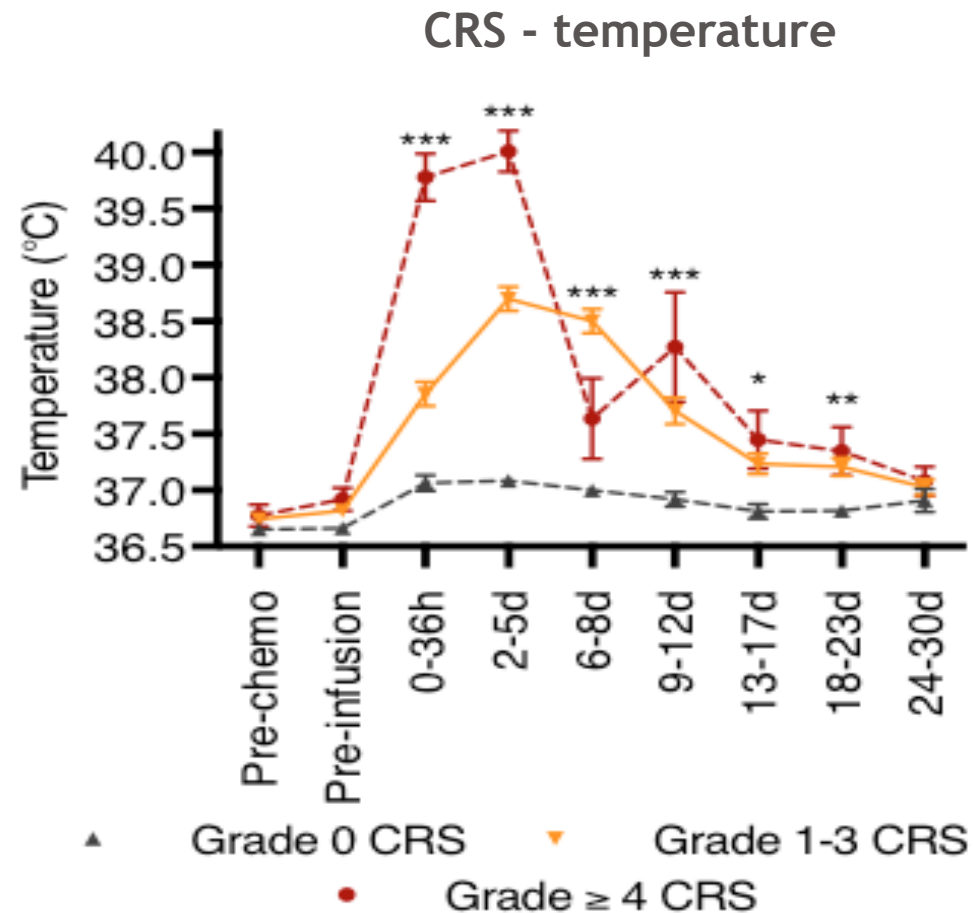
Immune Effector Cell-associated encephalopathy (ICE) score - ASTCT grading system

Parameter	Instruction	Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Name 3 objects that are indicated (e.g. point to clock, pen, button)	3
Following commands	Simple commands (e.g. “Show me 2 fingers”)	1
Writing	Write a standard sentence (e.g. “Our national bird is the bald eagle”)	1
Attention	Ability to count backwards from 100 by 10	1
Total		10

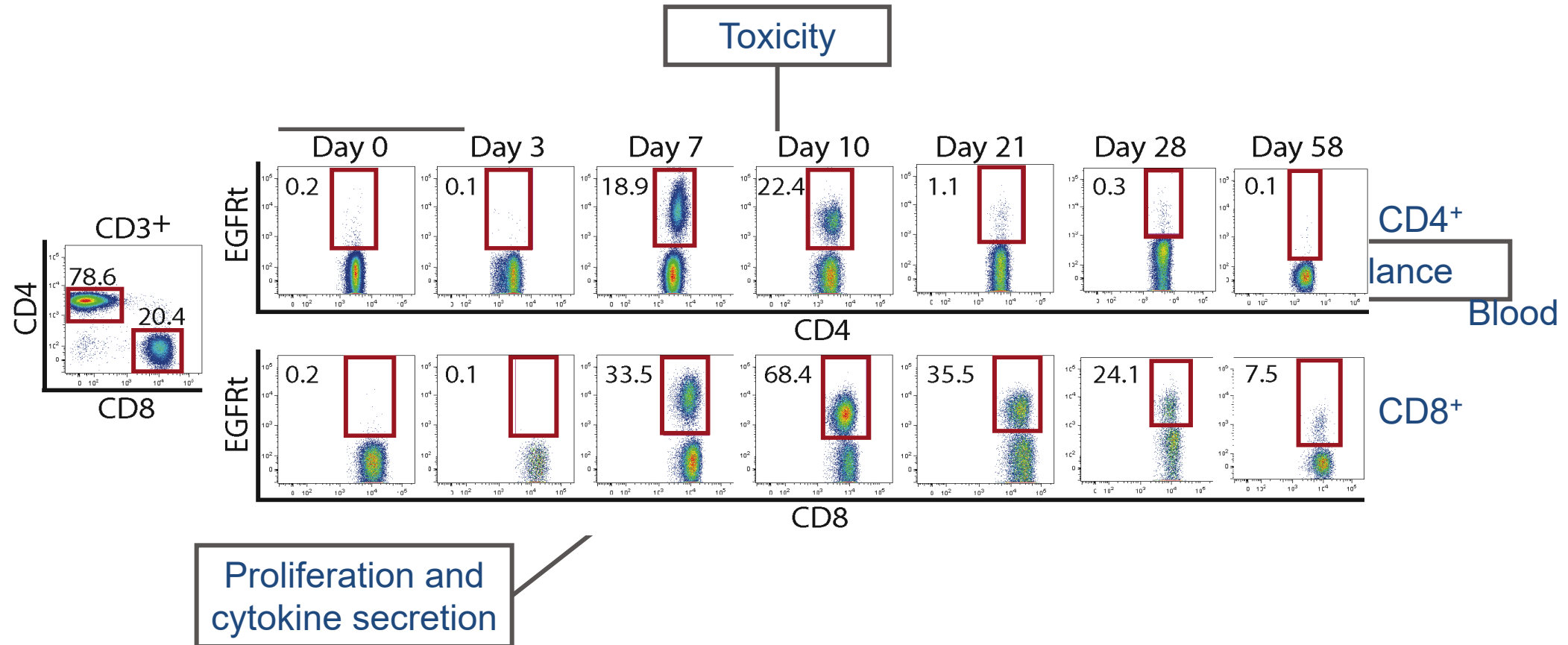
Summary (2):

Consensus toxicity grading criteria were introduced to improve standardization in CRS/ICANS toxicity assessments.

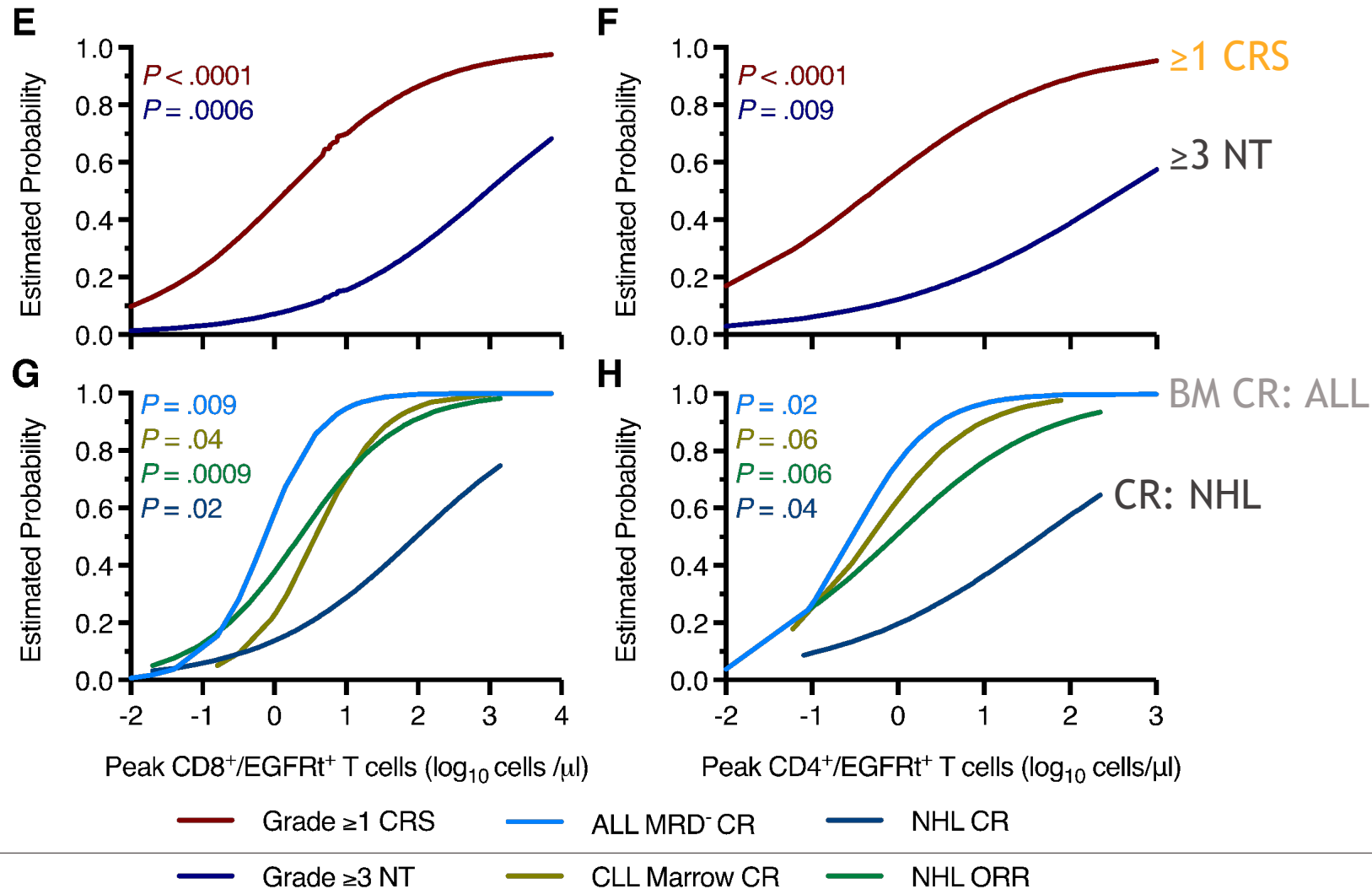
Cytokine release syndrome and neurotoxicity are almost always reversible



CAR-T cells: a living drug



In vivo CAR-T cell counts are associated with response and toxicity



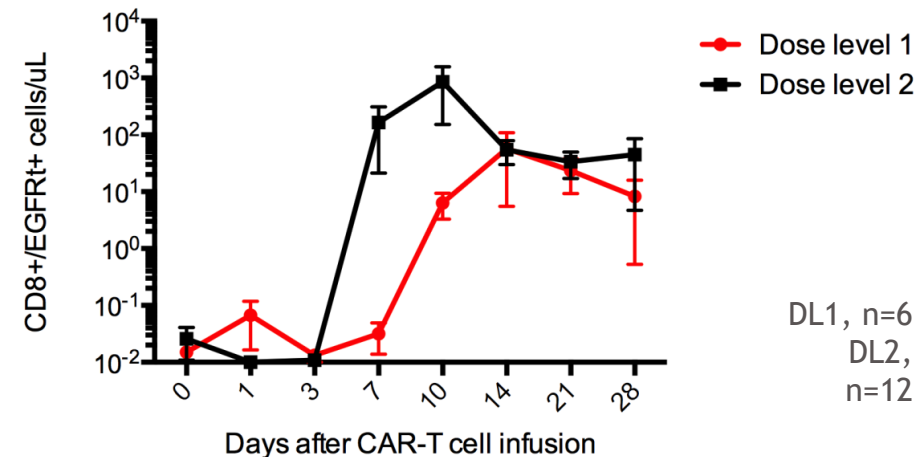
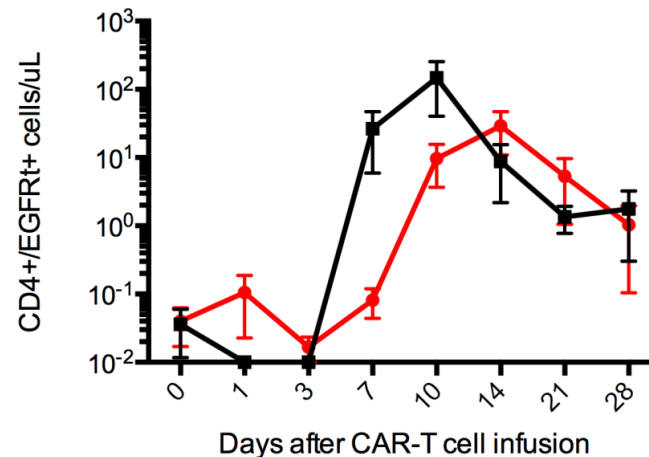
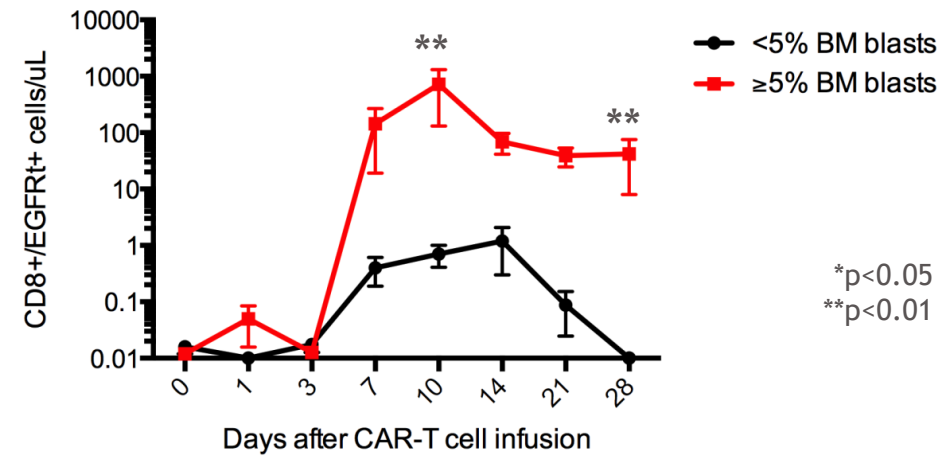
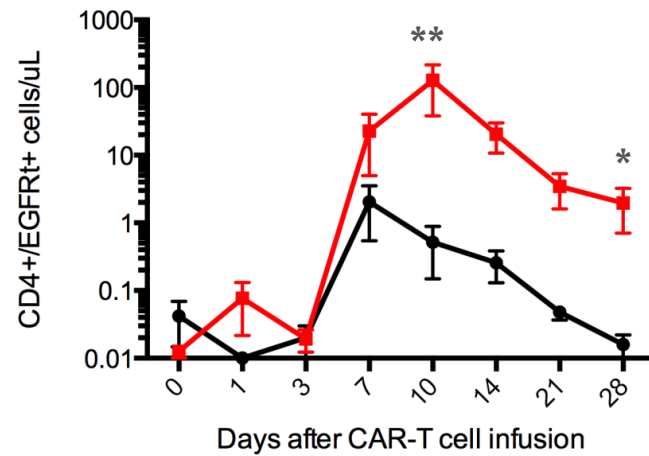
Summary (3):

CAR-T cell counts in blood follow a crescendo-decrescendo pattern.

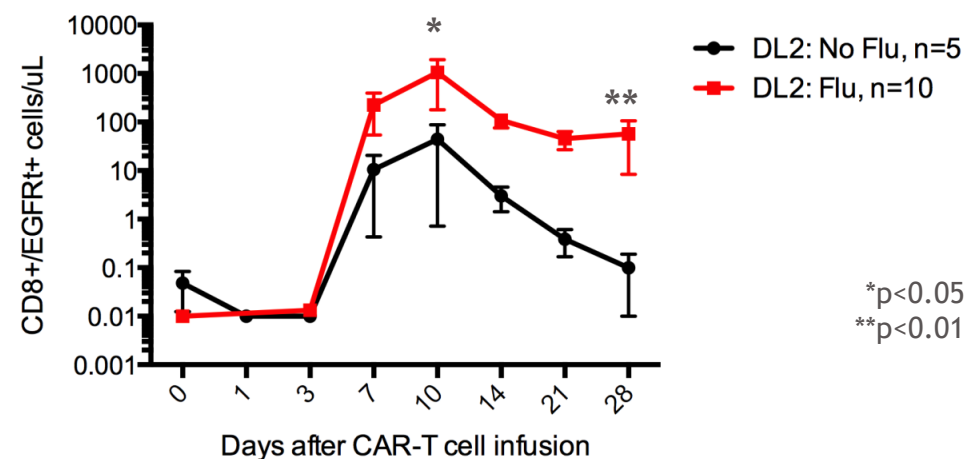
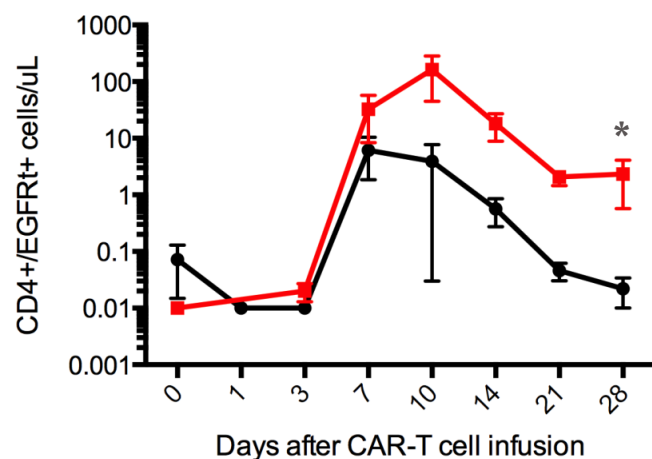
ICANS usually presents later than CRS.

CAR-T cell proliferation and peak count are associated with both response and toxicity.

CAR-T cell expansion in B-ALL is impacted by tumor burden and infused CAR-T cell dose

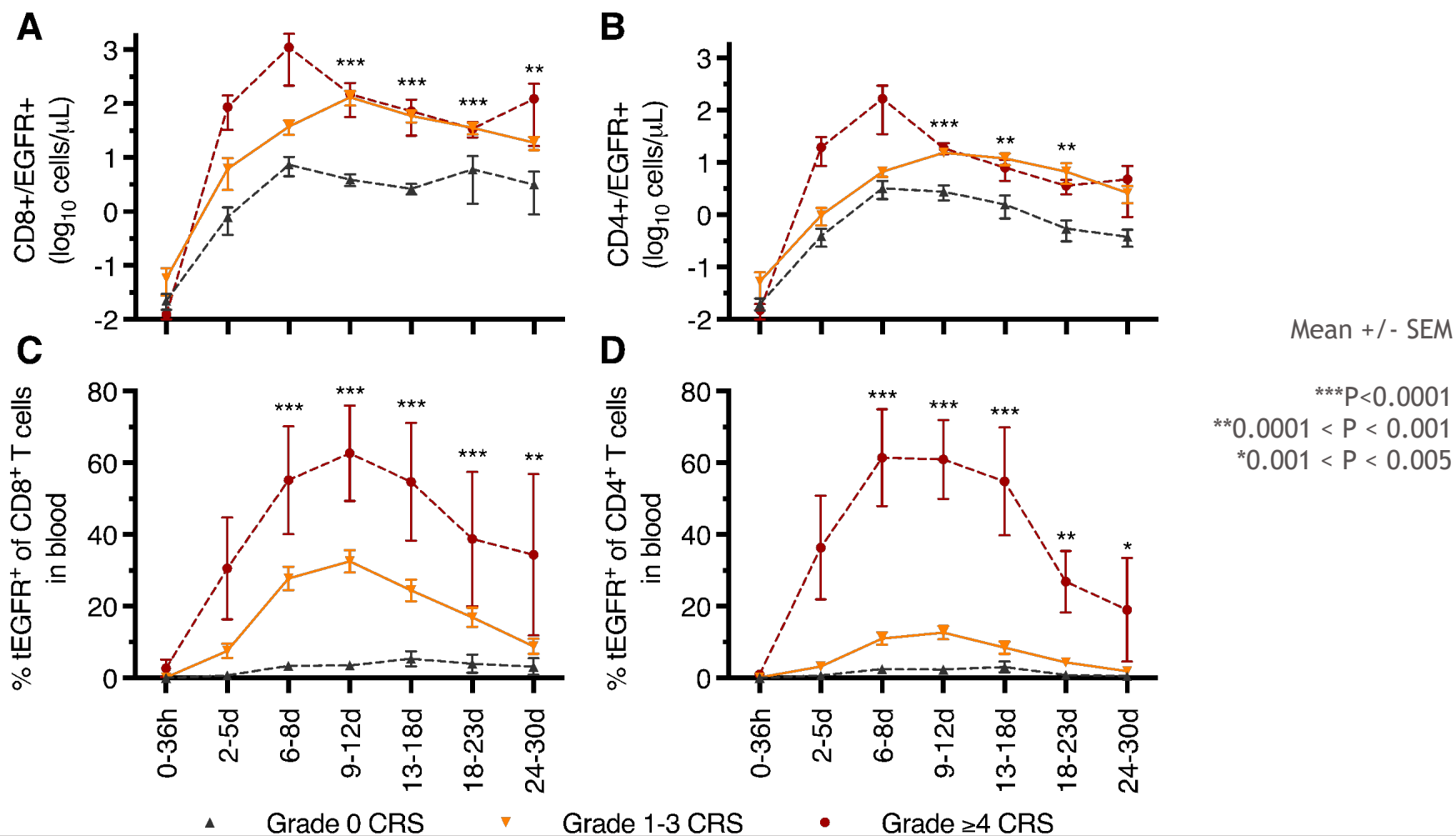


Addition of Flu to Cy-based lymphodepletion improves CAR-T cell proliferation in B-ALL



*p<0.05
**p<0.01

Severe CRS is associated with robust in vivo CAR-T cell expansion



Summary (4):

Tumor burden, CAR-T cell dose, the lymphodepletion regimen and CAR construct/manufacturing impact in vivo CAR-T cell proliferation...

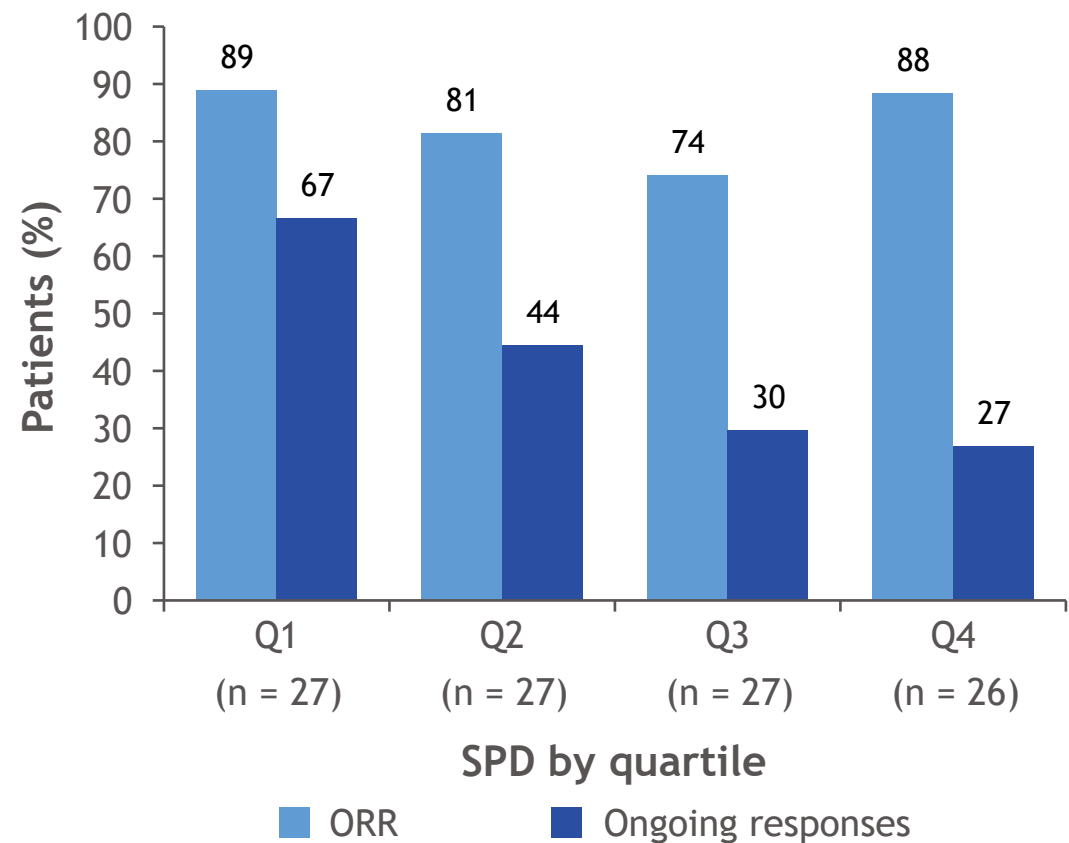
These variables and a pre-existing “inflammatory” state (e.g. high CRP) may allow an estimate of the “pre-treatment risk” of severe CRS/ICANS.

Earlier intervention is often considered in patients with high pre-treatment risk AND in frail patients with pre-existing comorbidities.

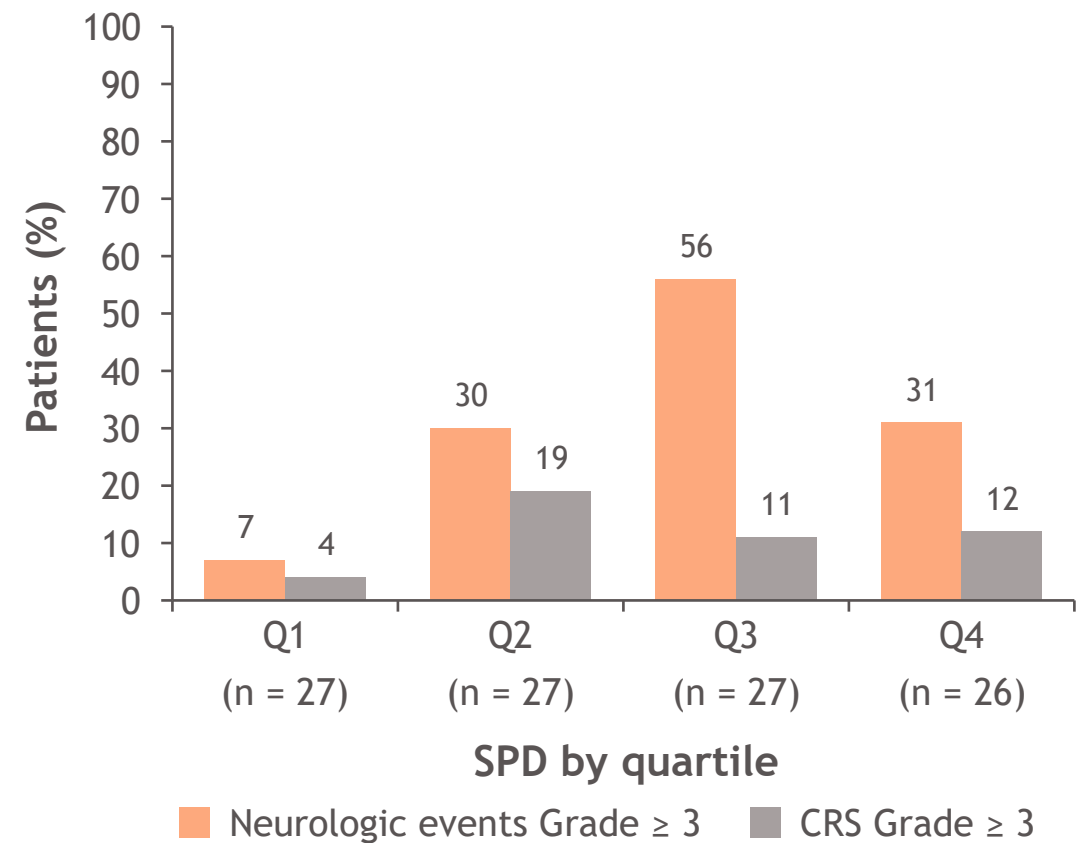
ZUMA-1 predictors: baseline tumor burden

Efficacy and safety

ORR and response at 1 year



Adverse Events



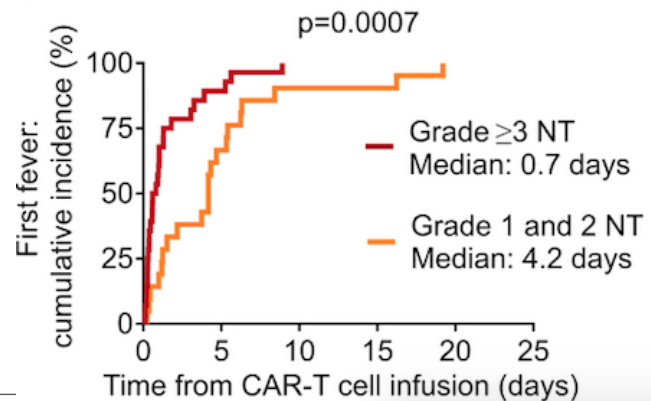
CRS, cytokine release syndrome; ORR, overall response rate; Q, quartile; SPD, sum of product diameters.
Locke FL, et al. Outcomes by prior lines of therapy (LoT) in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B cell lymphoma. J Clin Oncol. 2018;36 Suppl 15:3039-3039.

Severe CRS/ICANS are associated with early onset fever

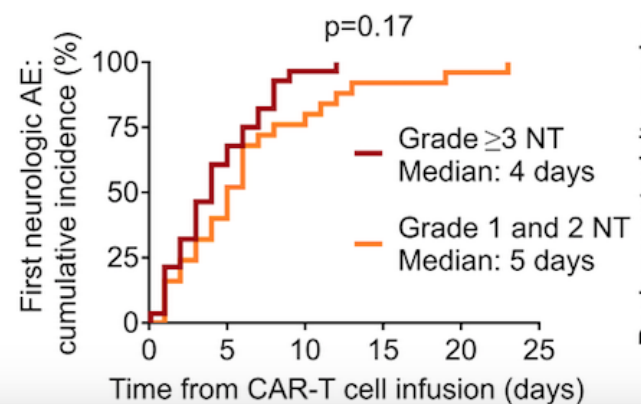
CRS Grade	1-3	4-5	Total	P value ^a
Number of Patients, n	82 ^b	10	92	
Fever Onset (days)				<.0001
Median [IQR]	3.9 [0.8, 5.6]	0.35 [0.3, 0.9]	2.2 [0.9, 5.6]	
Time to Peak Temperature (days)				.001
Median [IQR]	5.7 [4.3, 7.6]	2.8 [1.3, 3.2]		
Maximum Temperature (°C)				<.0001
Median [IQR]	39.4 [39.2, 30.6]	40.4 [40.1, 40.6]		
Fever Duration (days)				.032
Median, [IQR]	2.5 [1.2, 4.7]	4.4 [3.6, 5.4]	3.0 [1.2, 4.8]	

^aTwo-sided *P*-values calculated based on Kruskal-Wallis test. ^bOne patient with grade 2 CRS did not develop fever; and, therefore, was not included in this analysis.

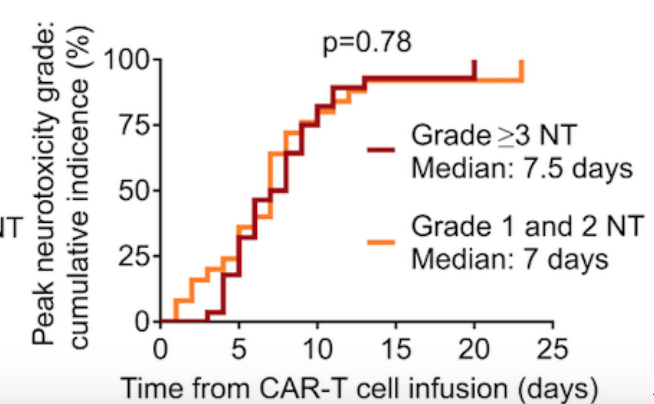
Time to first fever



Time to the first neurologic adverse event

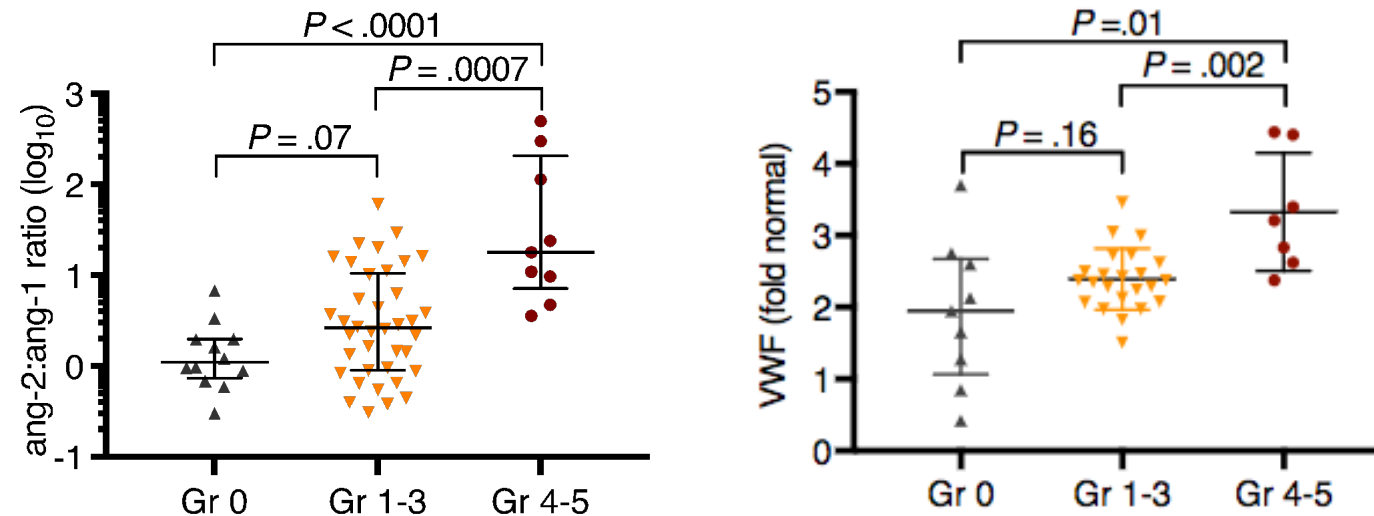


Time to the maximum grade of neurotoxicity



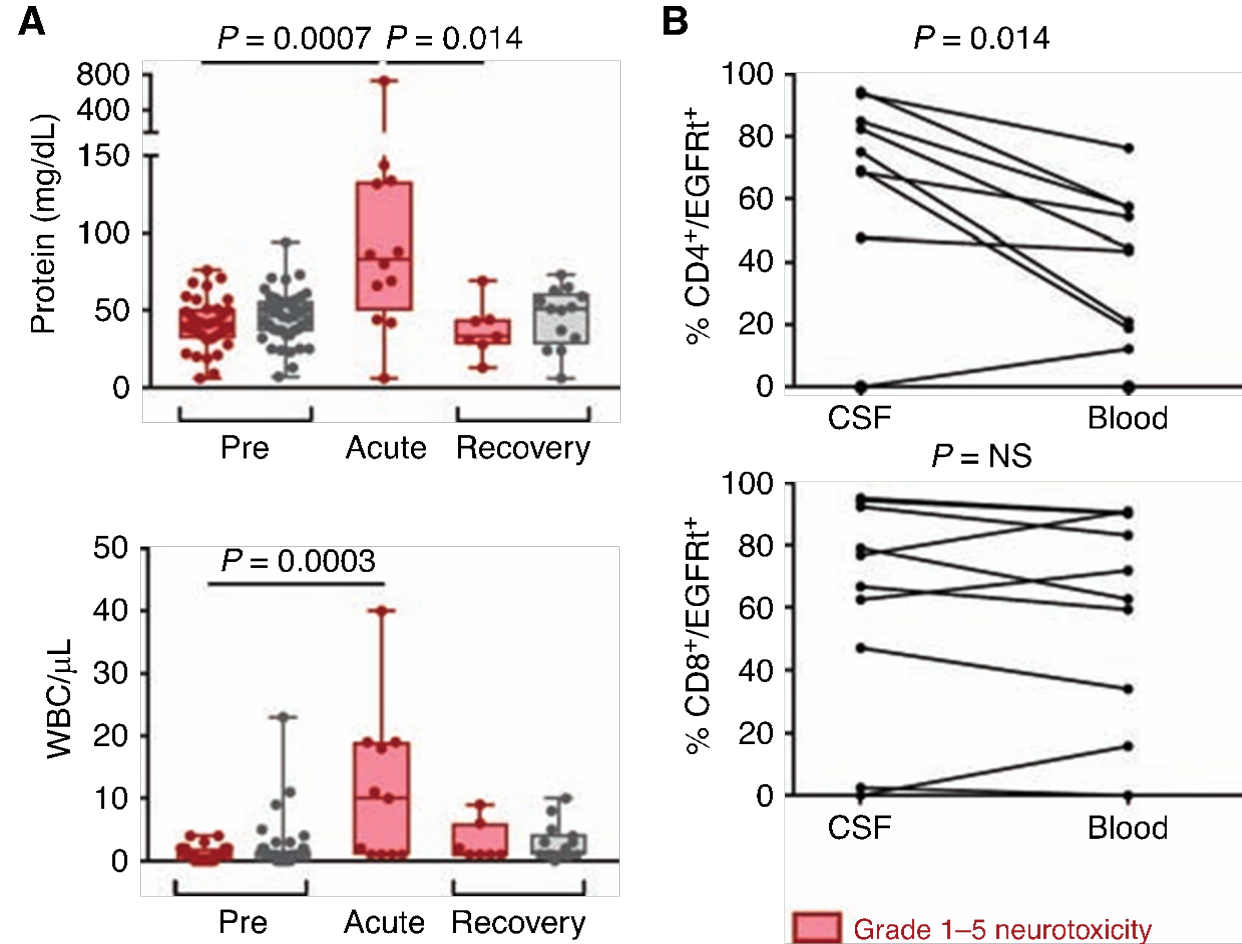
Endothelial activation in severe CRS

- Angiopoietin-1 (ang-1) and angiopoietin-2 (ang-2) have opposing roles in endothelial integrity
 - Ang-1 promotes endothelial quiescence and suppresses inflammation
 - Ang-2 increases endothelial permeability
- Ang-2 and VWF are secreted from Weibel-Palade bodies on endothelial activation

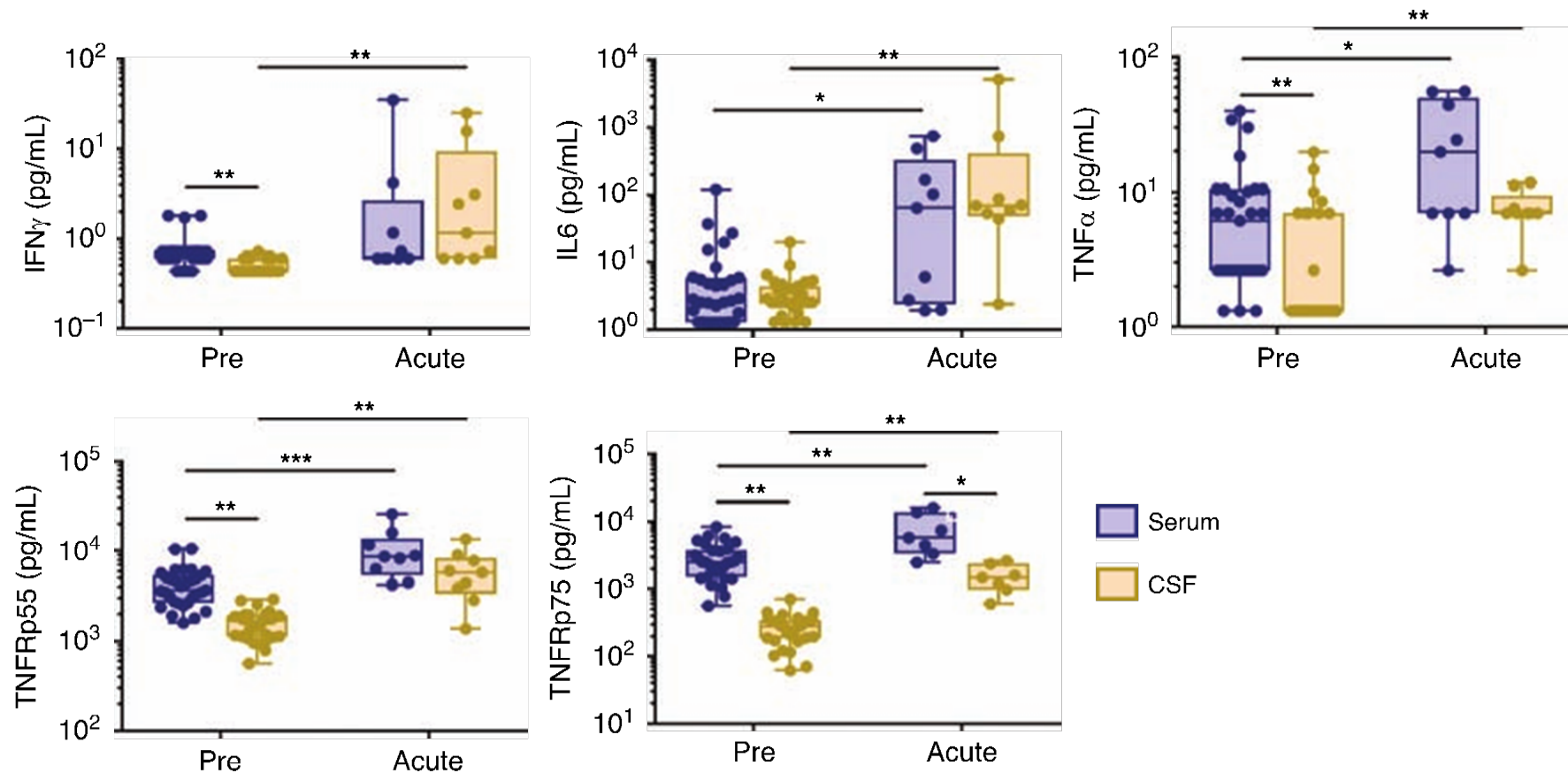


Severe CRS and neurotoxicity can be associated with a TTP-like coagulopathy

Increased permeability of the blood-brain barrier after CD19 CAR-T cell immunotherapy



Permeability of the blood-brain barrier allows transition of systemic cytokines into the CSF



Does not exclude local production of cytokines within the CNS

Summary (5):

Early/rapid progression of clinical toxicity (“post-infusion risk”) is associated with subsequently more severe CRS and ICANS.

Earlier intervention is often considered in patients with high post-infusion risk.

GENERAL MANAGEMENT STRATEGIES

Note: Institutional practices vary widely

Goals of treatment of CRS and ICANS

- Control severe acute toxicities and prevent persistent toxicities while waiting for resolution of CRS and ICANS
- Avoid impairment of anti-tumor efficacy

General management strategies; not an exhaustive list...

- Admit for any grade of CRS or ICANS
- Investigate/exclude other etiologies (cultures, CXR etc)
- Monitoring/investigations
 - Vitals, ICE score
 - Daily labs incl CBC, BMP, LFT, DIC screen, Ua, ferritin/CRP/IL6
 - EKG, telemetry, imaging, EEG, LP etc if indicated
- Supportive care
 - Cooling, acetaminophen, antibiotics, GCSF, transfusions (RBC, platelets, cryoprecipitate if needed), fluids, O₂, seizure prophylaxis, pressors, airway protection, ventilation etc
- Immune modulation
 - Interruption of the cytokine cascade
 - Tocilizumab: anti-IL-6R Ab - first line; FDA-approved
 - Siltuximab: anti-IL-6 Ab - limited data
 - Anakinra: IL-1R antagonist - limited data
 - Corticosteroids

CRS is not the only cause of fever and ICANS is not the only cause of encephalopathy in patients receiving CAR-T cells...

...always consider the differential diagnoses, especially in patients with severe or refractory toxicity on a lot of immune suppression...

Factors impacting interpretation of CRS management guidelines

- Consider:
 - High-risk (high-dose, high-burden, frail) versus low risk patients before infusion
 - High-risk (early fever, organ dysfunction, rapid progression) versus low risk patients after infusion
 - Stable versus unstable components of CRS grading (e.g. unstable hypotension)
- Pediatric versus adult
- Variations in clinical trial design
- Differences in CAR-T cell construct
- Variations in institutional practice

GRADE 1 CRS

FEVER ONLY

- **General Approach:**
 - Admit, monitor, Abx, support, levetiracetam etc
 - No immunosuppressive therapy
- **Consider intervention (as for Grade 2) for:**
 - High risk features (e.g. earlier onset fever than expected for the CAR-T cell product)
 - Elderly or frail patients at risk for complications
 - Persistent CRS related fever and malaise

Resolution
Continue to monitor

Progression to Grade 2
CRS

GRADE 2 CRS

STABLE HYPOTENSION AND/OR LOW O2 NEEDS

- **General Approach:**
 - Continue monitoring and supportive care
- **Consider tocilizumab/dex for pts:**
 - At high risk for complications from sustained fevers
 - At high risk for subsequent development of severe CRS
 - Development of significant end organ toxicity
 - Prolonged/persistent CRS-related fever

UNSTABLE HYPOTENSION AND/OR LOW O2 NEEDS

- **General Approach:**
 - Give tocilizumab + standard dose corticosteroids e.g dex 10 mg bid x 2
 - ICU vs try to keep them out of ICU (institutional variation)

Failure to improve/progression
8-12 hrs after 1st toci/steroids

- Consider 2nd tocilizumab and continue corticosteroids
- Talk to IMTX Attending if not responding

Progression to Grade 3
CRS

Resolution

- Continue to monitor
- If corticosteroids were started for isolated CRS, rapidly taper or stop
- No further anti-cytokine directed therapy

GRADE 3 CRS

HYPOTENSION REQUIRING VASOPRESSOR (+/- vasopressin)
HYPOXIA REQUIRING HIGH-FLOW NASAL CANNULAE ETC

GENERAL APPROACH: ICU

- Tocilizumab x 1 with dex 10 mg bid

Failure to improve/progression
8-24 hrs after 1st toci /dex

- Give 2nd dose of toci
- Consider higher dose corticosteroids e.g. dex 10 mg qid

Failure to improve/progression
8-24 hrs after 2nd toci/dex

- Axi-cel label recommends toci up to q8h x3 over 24 h, max 4 doses
- However, we would consider alternative anti-cytokine agents (e.g. anakinra) if refractory after 2 toci doses

Improved status

- Continue to monitor
- Stop corticosteroids

Progression to Grade 4 CRS

Adapted from draft ASTCT
CRS/ICANS Management
Guidelines, 2019

HYPOTENSION REQUIRING MULTIPLE
VASOPRESSORS (excluding vasopressin)
HYPOXIA REQUIRING PPV ETC

• **GENERAL APPROACH: ICU**

- Give tocilizumab X 1 and dex 10 mg qid

Failure to improve/progression
8-24 hrs after 1st toci/steroids

- Give 2nd dose of toci 8-24 hrs after prior dose
- Consider escalating to higher dose steroids

Failure to improve/progression
8-24 hrs after 2nd toci/steroids

- Axi-cel label recommends toci up to q8h x3 over 24 h, max 4 doses
- However, we would consider alternative anti-cytokine agents (e.g. anakinra) if refractory after 2 toci doses
- Other strategies in dire cases

Improved status

- Continue to monitor
- Consider corticosteroid taper

Considerations for antibiotic management in different scenarios among patients with CRS/ICANS

- Initial presentation of grade 1-2 stable CRS
 - Usually neutropenic, so use cefepime/ceftaz
 - Be careful not to stop too soon after defervescence
- Prolonged grade 1-2 CRS (if no toci/dex needed)
 - After ~3 days on cefepime, consider broadening to cover anaerobes/gram pos
- Grade ≥ 2 CRS
 - Regardless of speed of progression: consider broad cover (anaerobes/gram pos)
- Refractory CRS after the patient has received anti-cytokine therapy and is on steroids
 - Broad cover
 - Consider that signs of infection might be masked
- Ongoing severe ICANS without active CRS
 - Often on high-dose steroids for a prolonged time: consider surveillance cultures and be cautious about antibiotic withdrawal

GRADE 1 ICANS

ICE SCORE	7-9
CONFUSION	Mild disorientation/confusion
SOMNOLENCE	Mild lethargy, easily awakened
HEADACHE	Headache which resolves with supportive care for fever/pain
DYSPHASIA	Mild intermittent word finding difficulty or slowness of speech, stuttering; mild difficulty or delay following complex commands
ABNORMAL MOVEMENT	None or mild tremor not interfering with activity

IMMUNOSUPPRESSIVE THERAPY

Not generally recommended.

However, if concurrent CRS, consider anti-cytokine therapy and standard dose steroids.

SUPPORTIVE CARE

- Admit
- NT obs (ICE, motor, LOC) q12 hours
- Aspiration precautions and IV hydration if needed
- Neurology consult if concerning features
- Levetiracetam 500 mg bid
- Consider noncontrast head CT or brain MRI
- Consider other etiologies (e.g. infection, thiamine def etc)

Improved
status
Continue
monitoring

Progression to Grade 2 ICANS

Adapted from draft ASTCT
CRS/ICANS Management
Guidelines, 2019

GRADE 2 ICANS

ICE SCORE	3-6
CONFUSION	Moderate disorientation (e.g. oriented to self but disoriented to time, place), difficulty following complex commands
LEVEL OF CONSCIOUSNESS	Moderate lethargy; responds to voice

IMMUNOSUPPRESSIVE THERAPY

Observe or dex 10 mg bid x 2.

If concurrent CRS, consider anti-cytokine therapy and standard dose steroids.

SUPPORTIVE CARE

In addition to Grade 1:

- NT obs (ICE, motor, LOC) q8 hours
- Consider increasing monitoring as indicated
- Head CT or MRI brain if no contraindications
- Consider lumbar puncture if no contraindications
- EEG

**Persistent
signs**

Consider
standard dose
corticosteroids

**Improved
status**
Continue
monitoring

Progression to Grade 3 ICANS

Adapted from draft ASTCT
CRS/ICANS Management
Guidelines, 2019

GRADE 3 ICANS

ICE SCORE	0-2
DYSPHASIA	Global aphasia. Mute or not following commands, not waxing waning
SEIZURE	Any clinical seizure, focal or generalized that resolves rapidly to baseline mental status

IMMUNOSUPPRESSIVE THERAPY

Dexamethasone 10 mg IV bid-qid

If concurrent CRS, consider anti-cytokine therapy

SUPPORTIVE CARE

In addition to Grade 2:

- Consider ICU
- Head CT or MRI brain
- LP if feasible
- Increase anti-seizure meds if seizure activity
- Repeated re-evaluation to exclude additional pathologies

Progression to Grade 4 ICANS

Persistent signs

Continue
dex 10mg qid;
consider higher dose
steroids or anakinra
if prolonged or
deteriorating

Improved status

Stop
steroids or
rapid
steroid
taper

Adapted from draft ASTCT
CRS/ICANS Management
Guidelines, 2019

GRADE 4 ICANS

ICE SCORE	Unable to participate in screening
LEVEL OF CONSCIOUSNESS	Stupor/coma
SEIZURES	Life-threatening: Prolonged seizure (> 5 min); or repetitive clinical or electrographic seizures without return to baseline in between
MOTOR WEAKNESS	Deep hemiparesis or paraparesis
CEREBRAL EDEMA	Posturing, CN 6 palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

IMMUNOSUPPRESSIVE THERAPY

Dex. 10 mg qid

Pulse dose corticosteroids (e.g. methylprednisolone 1 gram q 24h x 3) if no rapid improvement

SUPPORTIVE CARE

In addition to Grade 3:

ICU

Consider intubation +/- mechanical ventilation

Evaluation for status epilepticus

Repeated re-evaluation for new pathologies

Persistent signs
Consider
anakinra and other
T cell-directed
therapies

**Improved
status**
Consider steroid
taper

Adapted from draft ASTCT
CRS/ICANS Management
Guidelines, 2019

PROLONGED CYTOPENIAS (> 30 days post infusion)

- Frequently observed in > 30% of patients with all products
- More frequent and more severe in patients with high grade CRS
- Correlated with marrow quality at time of treatment and intensity of lymphodepletion
- Transfusion support
 - Fibrinogen > 100 (during acute CRS)
 - HCT and PLTS
 - Growth factors as needed
- Consider auto-immune process in some cases
- Usually this improves and resolves over time
- Rare patients may need HCT to recover (BCMA in MM)

HYPOGAMMAGLOBULINEMIA

- On target toxicity due to the ongoing elimination of CD19 B cells as long as functional CAR-T cells are present
- Persistence varies between CD28 (shorter) and 41BB (longer) CAR constructs
- Persistent hypogammaglobulinemia often in patients with low IgG at start
- Minority of patients (with normal IgG at infusion) require ongoing IVIG
- IVIG support suggested for patients with IgG < 400 mg/dl -especially those with recurrent infections

Management of CAR-T Toxicity: Conclusions

- Real world data suggests that we have improved toxicity management from the original clinical trials.
 - Earlier treatment?
 - Patient selection?
- Fortunately, most toxicity resolves.
- Product selection associated with different rates of toxicity
- Prolonged cytopenias observed in all trials and may require prolonged transfusion support
- Hypogammaglobulinemia is an "on target" toxicity and may persist as long as functioning CAR-T cells are present.
 - Managed by IVIG support (generally to keep IgG level > 400 mg/dl)
- Patients need ongoing follow-up for second malignancies and potential genetic risks from therapy

Immunotherapy is
changing the way
cancer is treated!

BEZOS FAMILY
IMMUNOTHERAPY
CLINIC



Photograph courtesy of Ron hood, Fred Hutch