Management of CRS and ICANS after CD19 CAR-T cell immunotherapy

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Toxicities of CD19 CAR-T cell immunotherapy

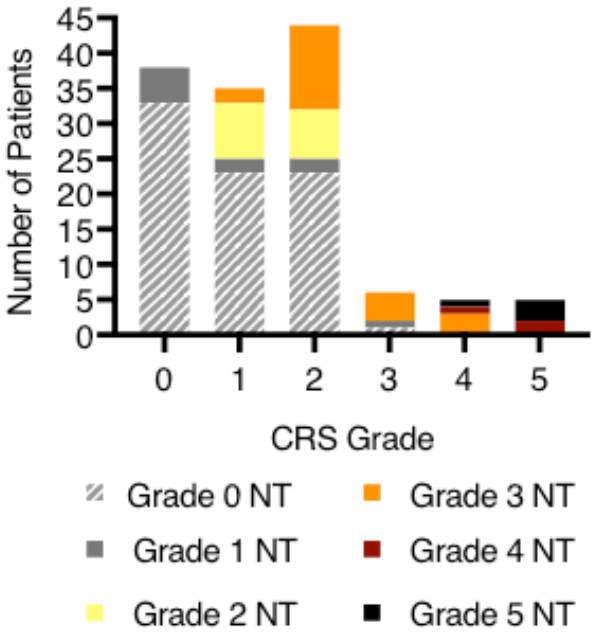
CD19-independent

Chemotherapy toxicities
Infection
Anaphylaxis
RCL
Transformation

CD19-dependent

Cytokine release syndrome
Neurotoxicity
B cell depletion/infection
Tumor lysis syndrome

Overlap between CRS and NT



CRS spectrum

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

Neurotoxicity

Headache
Speech disturbance
Delirium
Seizures
Focal deficits
Cerebral edema

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

Hay et al. Blood, 2017;
Gust et al, Cancer Discovery, 2017

Toxicities differ between CD19 CAR-T cell products for non-Hodgkin lymphoma

	Axicabtagene	Tisagenlecleucel	Lisocabtagene	1:1 CD4:CD8 (FHCRC)
Study populations	**DLBCL, TFL, PMBCL**	**DLBCL**	**DLBCL, tFL, FL3B†**	**All histologies**
CR (Best)	58% (N=108)	40% (N=81)	63% (N=27)	50% (N=20)#
Any grade CRS	94% (N=108)	58% (N=99)	24% (N=29)	62% (N=62)
Grade ≥ 3 CRS	12% (N=108)	23% (N=99)	0% (N=29)	8% (N=62)
Grade ≥ 3 NT	31% (N=108)	12% (N=99)	7% (N=29)	13% (N=62)
Grade 5 AE (CAR-related)	4% (N=108)[A]	-	-	3% (N=62)
Source	ASH 2017 (ZUMA-1; Neelapu)	ASH 2017 (JULIET; Schuster)	ASH 2017 (TRANSCEND; Abramson, Maloney)	Hay, Blood, 2017 ASCO, 102, 2016

*****DIFFERENT TRIALS USED DIFFERENT GRADING SYSTEMS*****

[A] 2 patients grade 5 CRS
[B] Press release 12.6.2016
[C] Press release 2.28.2017
*≥ 3 month follow-up.
†CORE Group (proposed pivotal population) including DLBCL, NOS tFL, FL3B, ECOG 0-1, and R/R patients.
#Cy/Flu, DL2

Toxicities differ between CD19 CAR-T cell products for B-ALL

	Axicabtagene	Tisagenlecleucel	FHCRC 1:1 CD4:CD8
Description	CD28 costim; Phase 1	4-1BB costim; Phase 2	4-1BB costim; Phase 1/2
Study populations	R/R; adult/peds	R/R; peds	R/R; adult
MRD-negative CR	82% (N=11)	81% (N=75)	89% (N=36)#
≥ Grade 3 CRS	30.8% (N=13)	47% (N=75)	17% (N=47)
≥ Grade 3 NT	38.4% (N=13)	13% (N=75)	30% (N=47)
Grade 5 AEs	8% (N=13)	0% (N=75)	4% (N=47)
Source	ASH 2016 (ZUMA-3/4; Shah)	Maude N Engl J Med 2018	Hay, Blood, 2017 Gust, Canc Disc, 2017

*****DIFFERENT TRIALS USED DIFFERENT GRADING SYSTEMS*****

#ASCO, abstract 102, 2016

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

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

Lee et al, BBMT, 2019

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≥38.0C
  - Resolution when signs contributing to grading (fever/hypotension/hypoxia) resolve

Lee et al, BBMT, 2019

Cytokine release syndrome
ASTCT grading system

	Fever	Hypotension		Hypoxia
Grade 1	≥ 38°C	None	**AND/ OR**	None
Grade 2	≥ 38°C	Responsive to fluids		Low flow nasal cannula (≤ 6L/minute) or blow-by
Grade 3	≥ 38°C	Requiring one vasoactive agent (± vasopressin)		High-flow nasal cannula (>6L/minute), facemask, non-rebreather mask or Venturi mask
Grade 4	≥ 38°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

Lee et al, BBMT, 2019

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

Lee et al, BBMT, 2019

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

Overall grade is determined by the worst parameter

Lee et al, BBMT, 2019

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

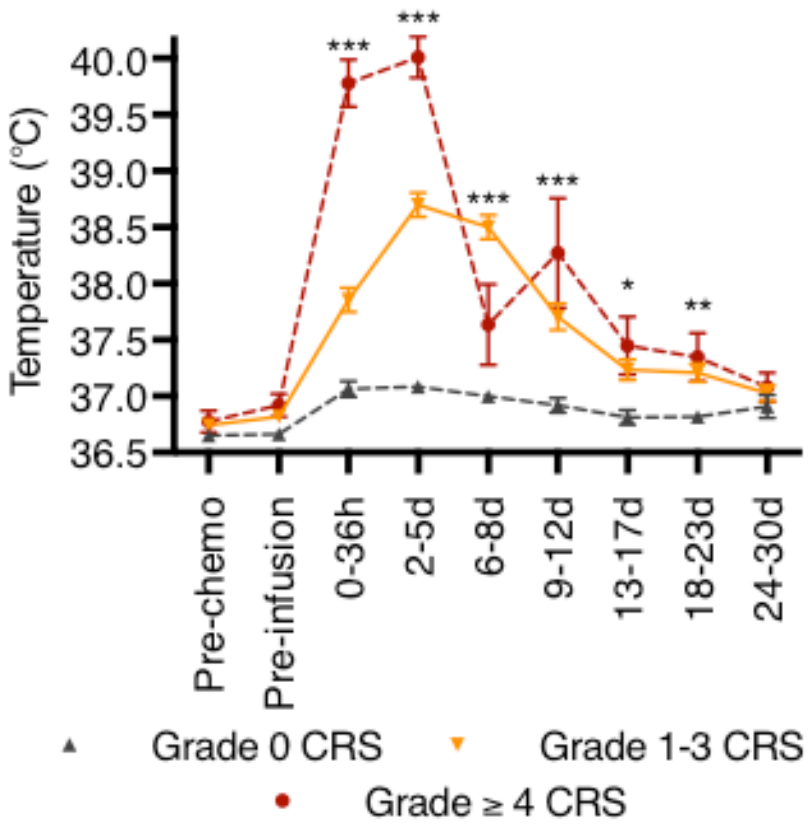
Lee et al, BBMT, 2019

Summary (2):

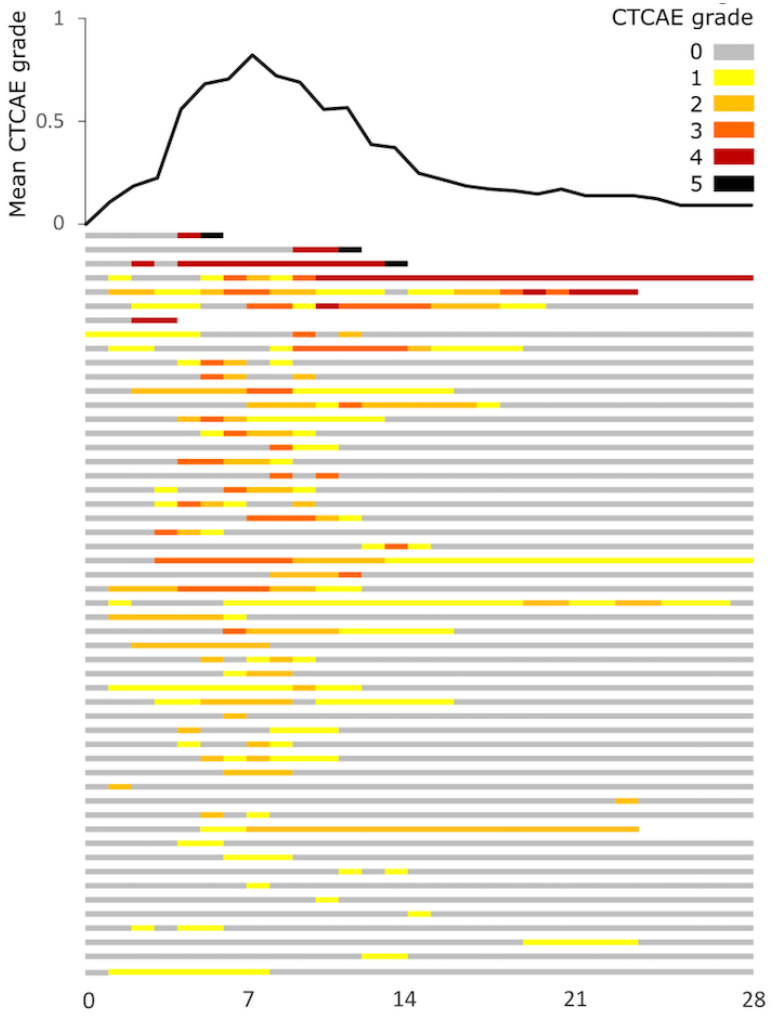
Consensus toxicity grading criteria were introduced to improve standardization in CRS/ICANS toxicity assessments.

Cytokine release syndrome and neurotoxicity are almost always reversible

CRS - temperature

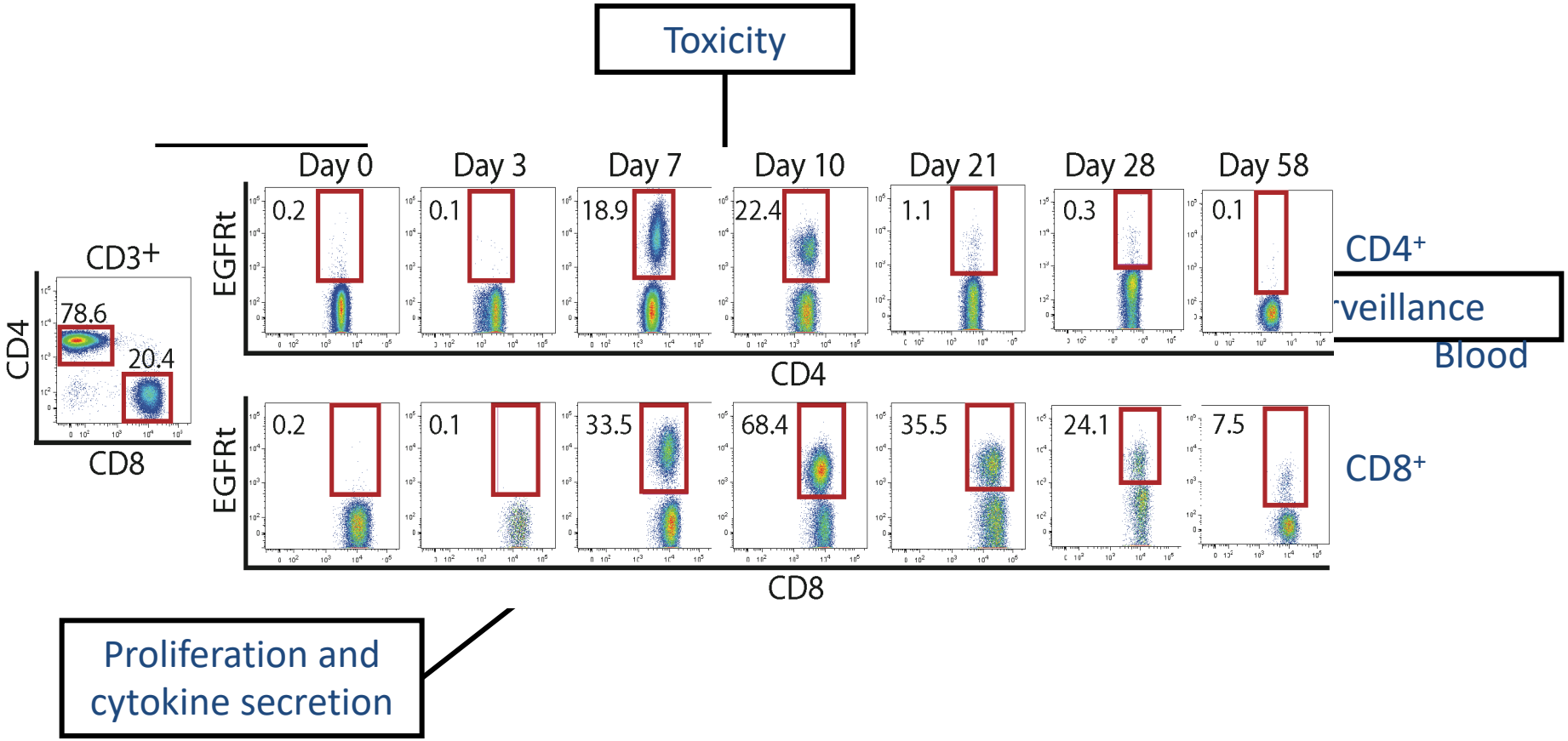


Neurotoxicity



Hay et al. Blood, 2017;
Gust, Hay, Hanafi et al, Cancer Discovery, 2017

CAR-T cells: a living drug



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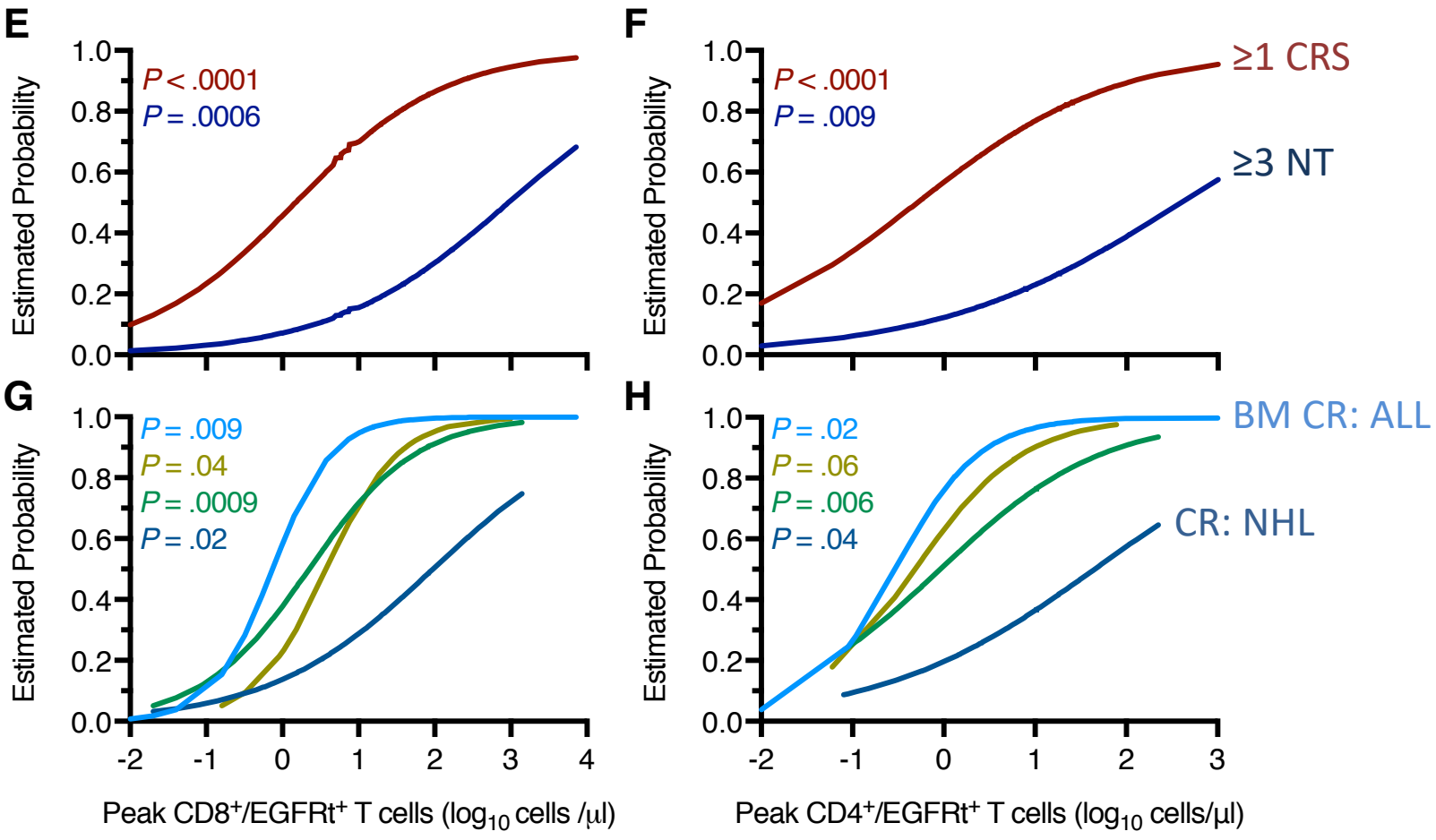
In vivo CAR-T cell counts are associated with response and toxicity



Hay et al. Blood, 2017

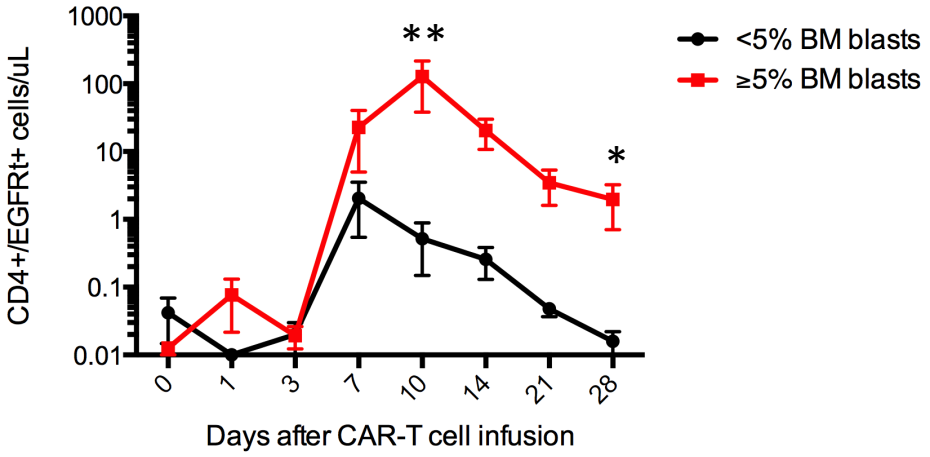
Summary (3):

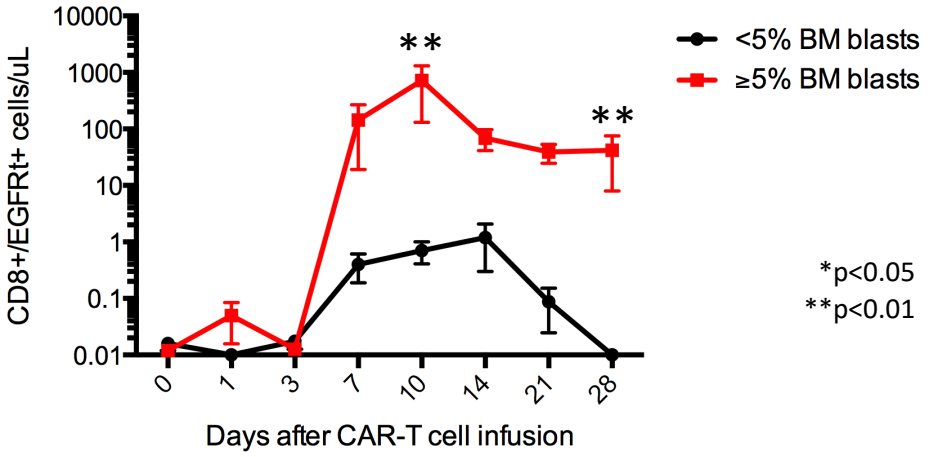
CAR-T cell counts in blood follow a crescendo-decrescendo pattern.

ICANS usually presents later than CRS.

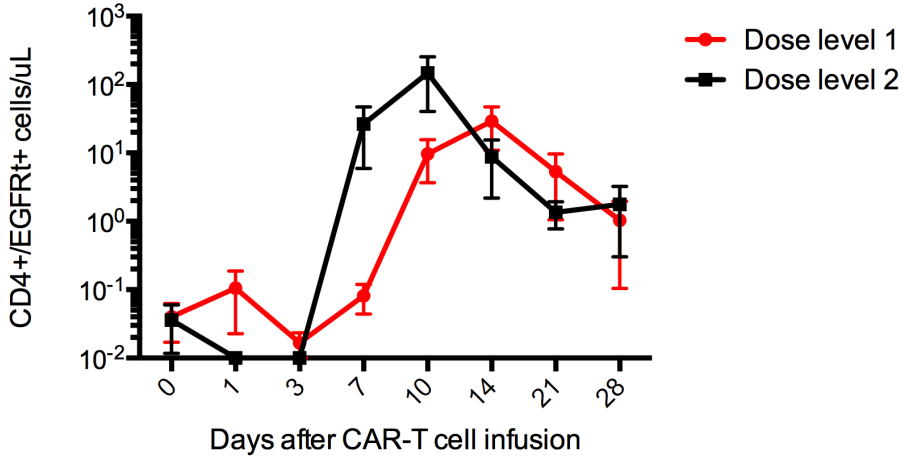
CAR-T cell proliferation and peak count are associated with both response and toxicity.

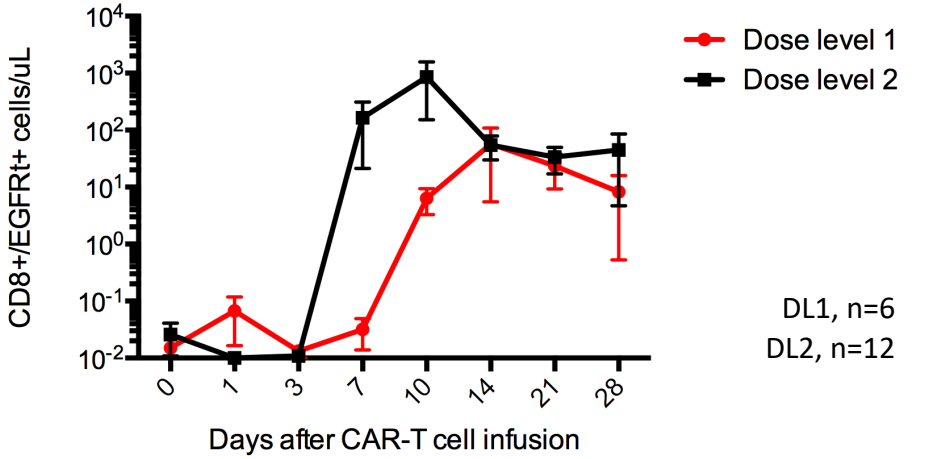
CAR-T cell expansion in B-ALL is impacted by tumor burden and infused CAR-T cell dose





*p<0.05
**p<0.01

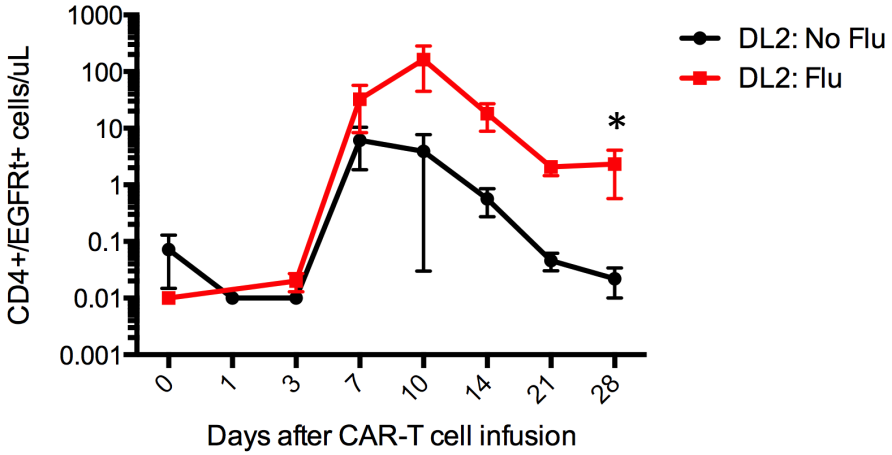


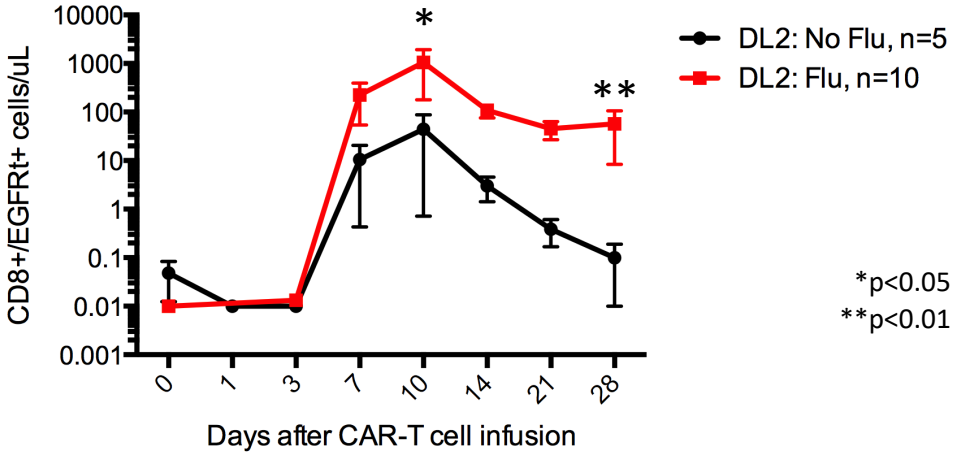


DL1, n=6
DL2, n=12

Turtle et al, J Clin Invest, 2016

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





Turtle et al, J Clin Invest, 2016

Factors impacting the risk of CRS

CRS Grade	0	1-3	4-5	Total	Univariate Analysis *P* value [a]	Multivariable Analysis *P* value [b]
Number of Patients, n	40	83	10	133		
Marrow Disease Burden by Flow Cytometry, %					**<.0001**	**<.0001**
Median [IQR]	0 [0, 1.3]	20 [0, 65]	21 [3.6, 40]	1.3 [0, 42]		
Range	0, 79	0, 97	0, 89.8	0, 97		
Not involved, n (%)	23 (47)	25 (51)	1 (2)	49 (37)		
CD19+ Cells in Marrow by Flow Cytometry, %					**.0001** [d]	-
Median [IQR]	3.6 [1.3, 6.6]	22 [3.0, 66]	22 [11, 40]	8.8 [2.2, 48]		
Range	0, 79	0, 99	0.3, 90	0, 99		
Platelet Count, 1000/μl					**.002**	**.05**
Median [IQR]	98 [58, 159]	69 [38, 119]	32 [19, 85]	77 [40, 133]		
Range	11, 265	1, 553	5, 162	1, 553		
$CD8^+$ Selection Method, n (%)					**.001**	**.03**
Bulk $CD8^+$	9 (15)	47 (77)	5 (8)	61 (46)		
Central Memory Enriched	31 (43)	36 (50)	5 (7)	72 (54)		
Lymphodepletion, n (%)					.67	**.02**
Cy/Flu based	30 (29)	65 (62)	9 (9)	104 (78)		
Non-Cy/Flu based	10 (35)	18 (62)	1 (3)	29 (22)		
CAR-T Cell Dose, n (%)					**.002**	**.003**
2 x 10^5 $EGFRt^+$ cells/kg	10 (29)	25 (71)	0 (0)	35 (26)		
2 x 10^6 $EGFRt^+$ cells/kg	27 (31)	54 (63)	5 (6)	86 (65)		
2 x 10^7 $EGFRt^+$ cells/kg	3 (25)	4 (33)	5 (42)	12 (9)		
Lymphodepletion/CAR-T Cell Dose Interaction Effect [e]					**.03**	**.009**

Age, sex, Karnofsky, disease, prior therapy, prior HCT were not significant in univariate analyses

Hay et al. Blood, 2017

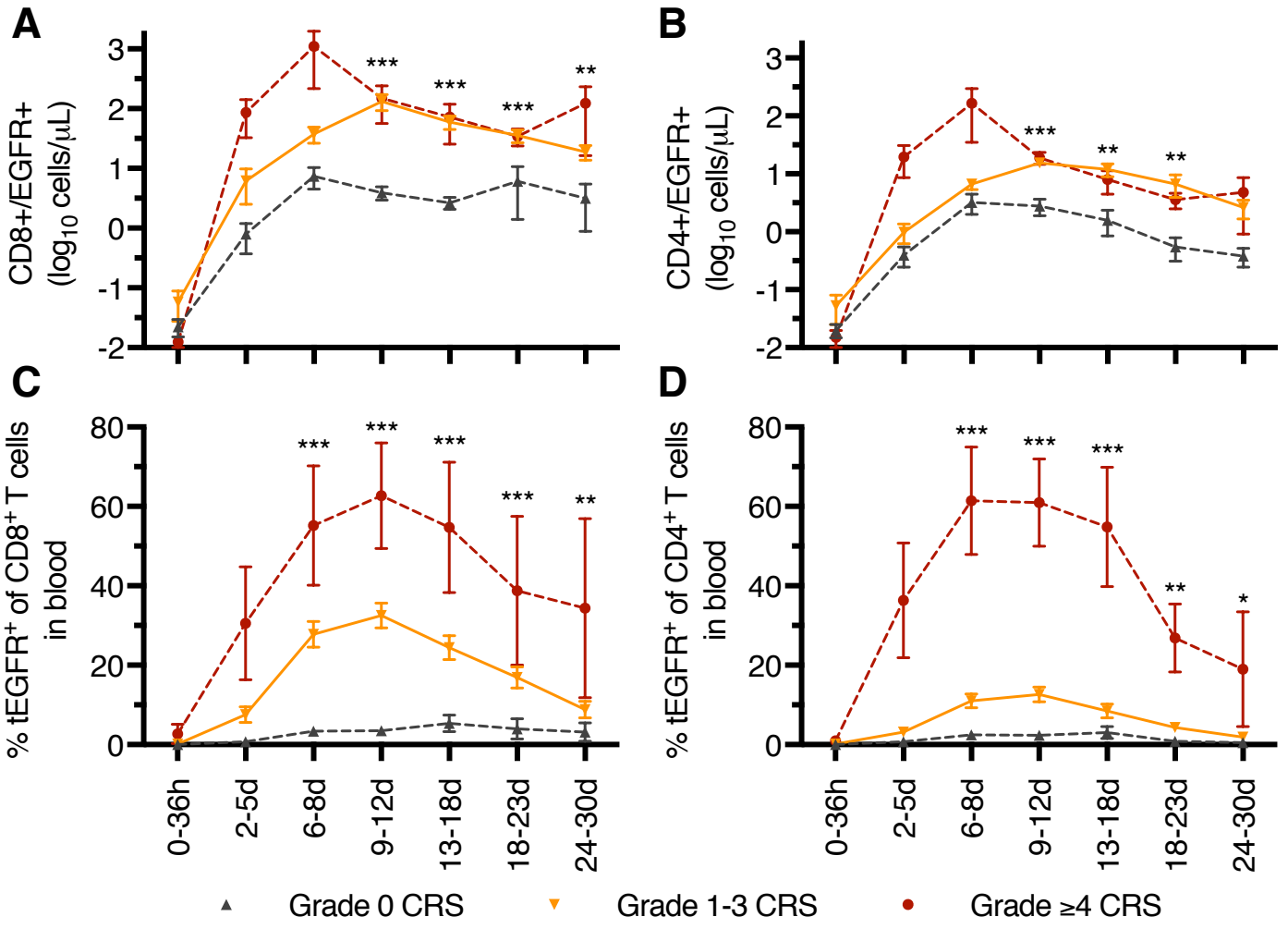
Factors impacting the risk of neurotoxicity

Neurotoxicity CTCAE grade		Grade 0[a]	Grade 1–2[a]	Grade 3–5[a]	Total	Univariate[b]	Multivariable[c]
Preexisting neurologic comorbidities, *n* (%)	Any	26 (45)	16 (28)	16 (28)	58	0.0059[g]	0.0023[g]
	PN[f]	14 (47)	7 (23)	9 (30)	30	0.2	
	CNS involvement	6 (43)	5 (36)	3 (21)	14	0.2	
	Headache disorder	6 (43)	5 (36)	3 (21)	14	0.2	
	Other	5 (50)	2 (20)	3 (30)	10	0.7	
	ICH[h]	4 (67)	1 (17)	1 (17)	6	1	
	Seizures	2 (33)	2 (33)	2 (33)	6	0.3	
	Cog impairment[i]	1 (25)	2 (50)	1 (25)	4	0.1	
	MTX CNS toxicity[j]	1 (50)	1 (50)	0	2	0.4	
Marrow disease, %	Median (range)	0.6 (0–97)	0.4 (0–93)	25.8 (0–97)	1.3 (0–97)	0.072	0.0165
Total $CD19^+$ cells in marrow, %	Median (range)	5.3 (0–99)	12.4 (0–93)	29.1 (0–97)	8.8 (0–99)	0.062	
$CD8^+$ central memory enriched CAR-T cells[k], *n* (%)	Selected	48 (67)	11 (15)	13 (18)	72 (54)	0.242	
Lymphodepletion regimen[l], *n* (%)	Cy/Flu	58 (56)	23 (22)	23 (22)	104	0.11	0.0259
	Non-Cy/Flu	22 (76)	2 (7)	5 (17)	29		
CAR-T cell dose, *n* (%)	2×10^5 cells/kg	20 (57)	10 (29)	5 (14)	35	<0.0001	0.0009
	2×10^6 cells/kg	55 (64)	15 (17)	16 (19)	86		
	2×10^7 cells/kg	5 (42)	0	7 (58)	12		
Cytokine release syndrome, *n* (%)	None (G 0)	35 (88)	5 (13)	0	40	<0.0001	n/a
	Mild (G 1–2)	44 (57)	19 (25)	14 (18)	77		
	Severe (G 3–5)	1 (6)	1 (6)	14 (88)	16		

CD19+ burden (P=0.062), diagnosis (P=0.084), age (P=0.094), lymphodepletion (P=0.11), race (P=0.17), CD8 subset (P=0.24), sex (P=0.4), prior therapies (P=0.5), prior transplant (P=0.5), Karnofsky score (P=0.5) - not significant in univariate analyses.

Gust, Hay, Hanafi et al. Cancer Discovery, 2017

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



Mean +/- SEM

***P<0.0001
**0.0001 < P < 0.001
*0.001 < P < 0.005

Hay et al. Blood, 2017

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.

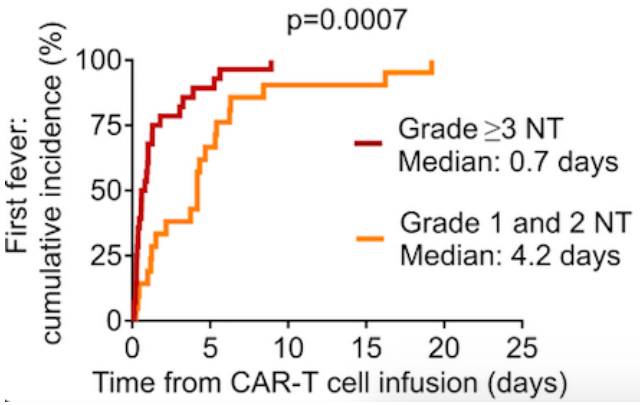
Earlier intervention is often considered in patients with high pre-treatment risk AND in frail patients with pre-existing comorbidities.

Severe CRS/ICANS are associated with early onset fever

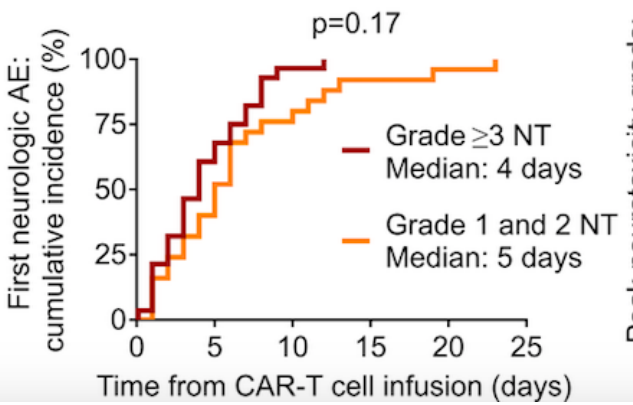
CRS Grade	1-3	4-5	Total	*P* value[a]
Number of Patients, n	82[b]	10	92	
Fever Onset (days)				<.0001
Median [IQR]	3.9 [0.8, 5.6]	0.35 [0.3, 0.9]	2.2 [0.9, 5.6]	
Time to Peak Temperature (days)				.001
Median [IQR]	5.7 [4.3, 7.6]	2.8 [1.3, 3.2]		
Maximum Temperature (°C)				<.0001
Median [IQR]	39.4 [39.2, 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]	

[a]Two-sided *P*-values calculated based on Kruskal-Wallis test. [b]One patient with grade 2 CRS did not develop fever; and, therefore, was not included in this analysis.

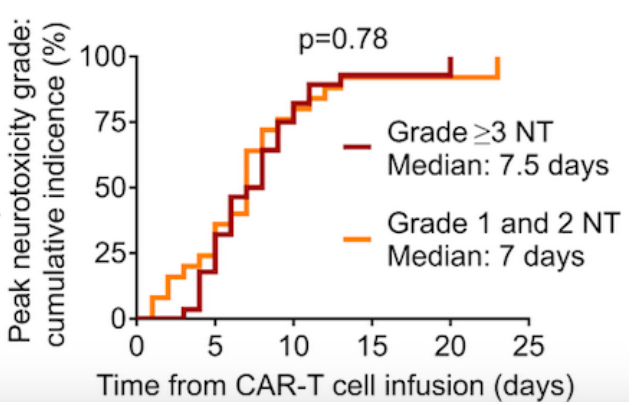
Time to first fever



Time to the first neurologic adverse event



Time to the maximum grade of neurotoxicity



Hay et al. Blood, 2017

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, cryoprecipiate if needed), fluids, O_2, 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
  - Other strategies

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

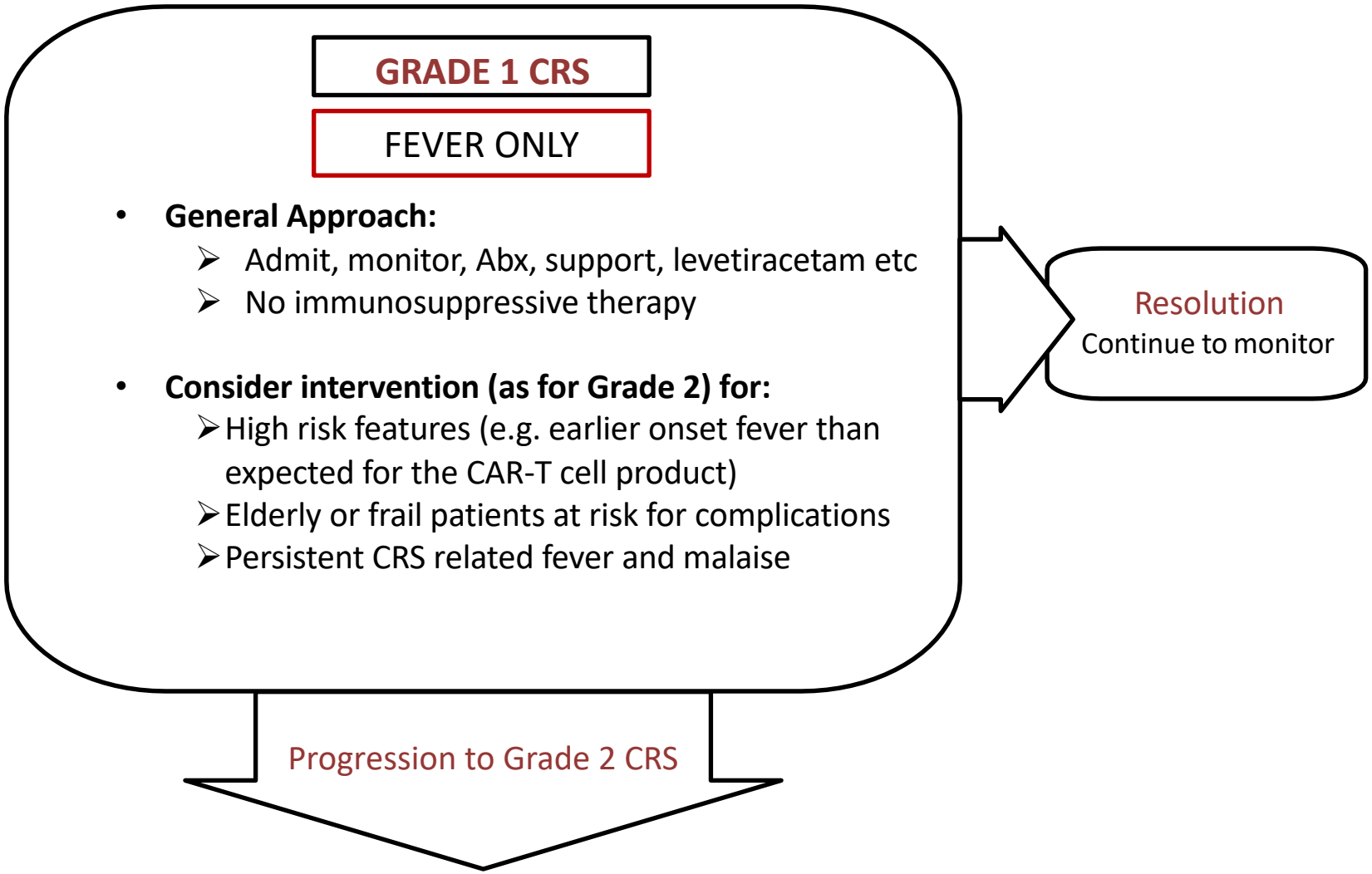
- Consider:
  - High-risk (high-dose, high-burden, frail) versus low risk patients before infusion
  - High-risk (early fever, organ dysfunction, rapid progression) versus low risk patients after infusion
  - Stable versus unstable components of CRS grading (e.g. unstable hypotension)

- Pediatric versus adult

- Variations in clinical trial design

- Differences in CAR-T cell construct

- Variations in institutional practice



Adapted from draft ASTCT CRS/ICANS Management Guidelines, 2019

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

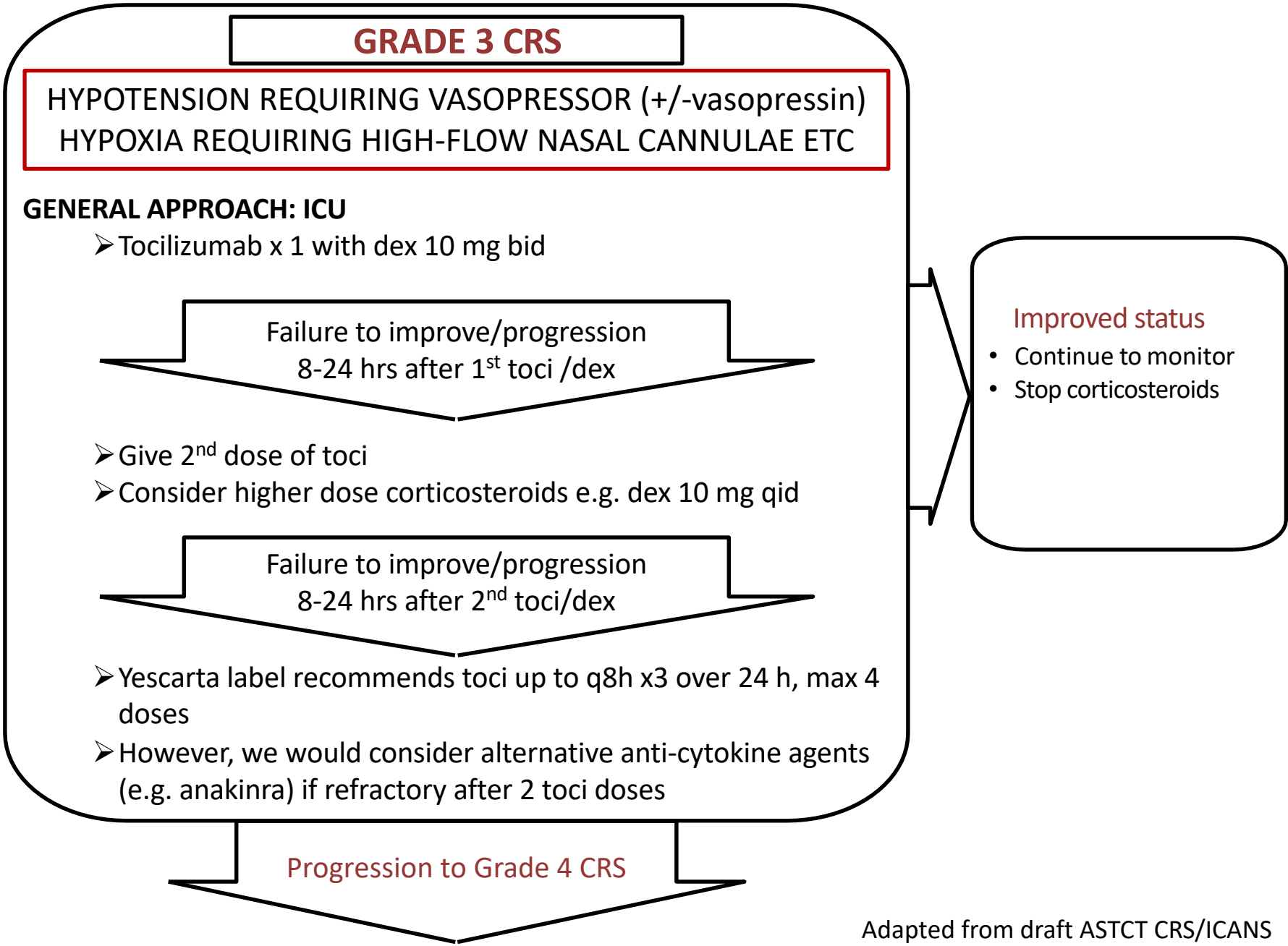
- Consider 2nd tocilizumab and continue corticosteroids
- **Talk to IMTX Attending if not responding**

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

Adapted from draft ASTCT CRS/ICANS Management Guidelines, 2019



Adapted from draft ASTCT CRS/ICANS Management Guidelines, 2019

GRADE 4 CRS

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

- Yescarta 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

Adapted from draft ASTCT CRS/ICANS Management Guidelines, 2019

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 lots of steroid 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
LEVEL OF CONSCIOUSNESS	Moderate somnolence, awakens to tactile stimulus
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

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

Improved status
Stop steroids or rapid steroid taper

Progression to Grade 4 ICANS

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

Persistent signs
Consider anakinra and other T cell-directed therapies

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

Improved status
Consider steroid taper

Adapted from draft ASTCT CRS/ICANS Management Guidelines, 2019