MANAGEMENT OF CAR T RELATED ADVERSE EVENTS

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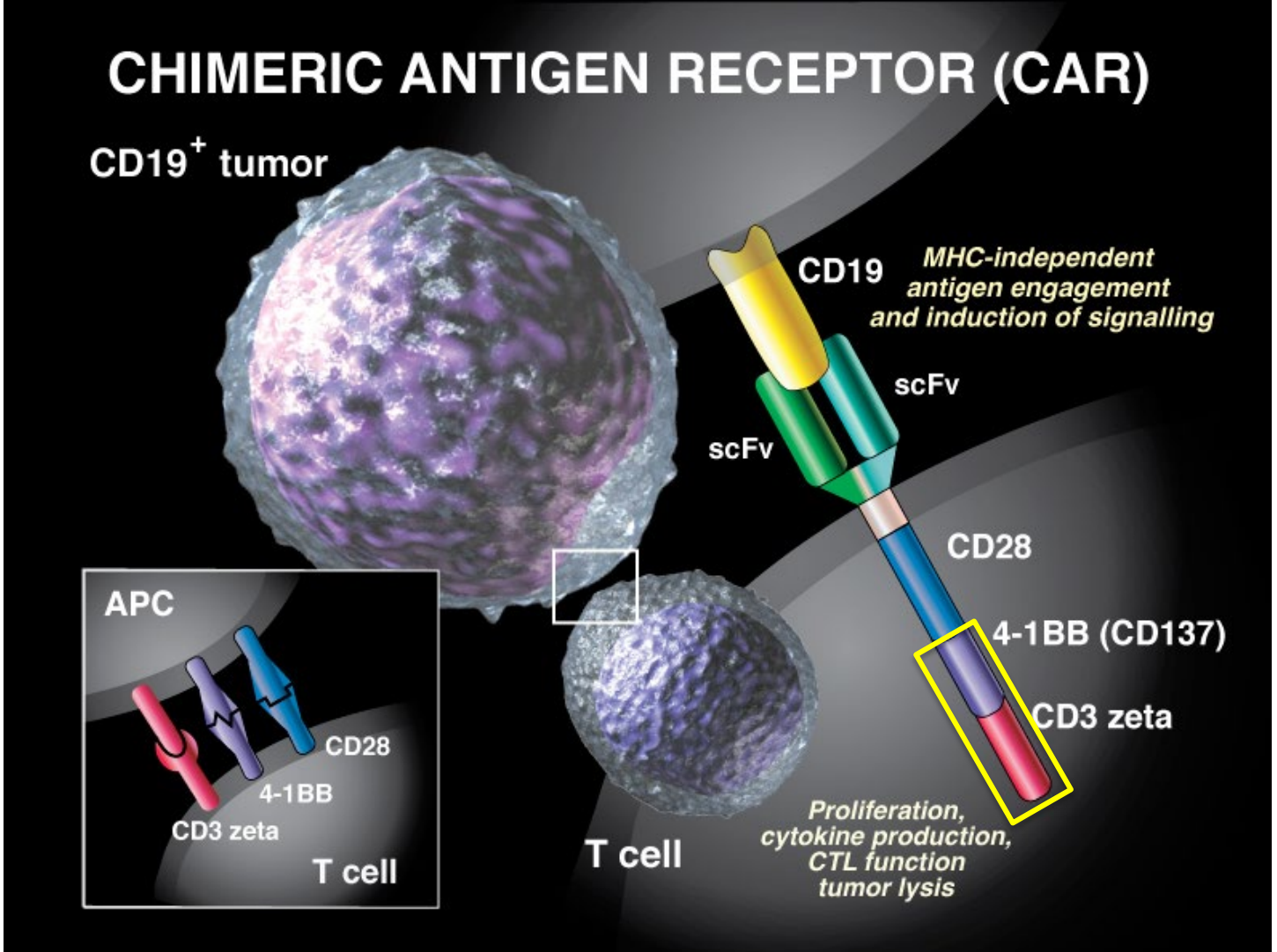
Disclosures

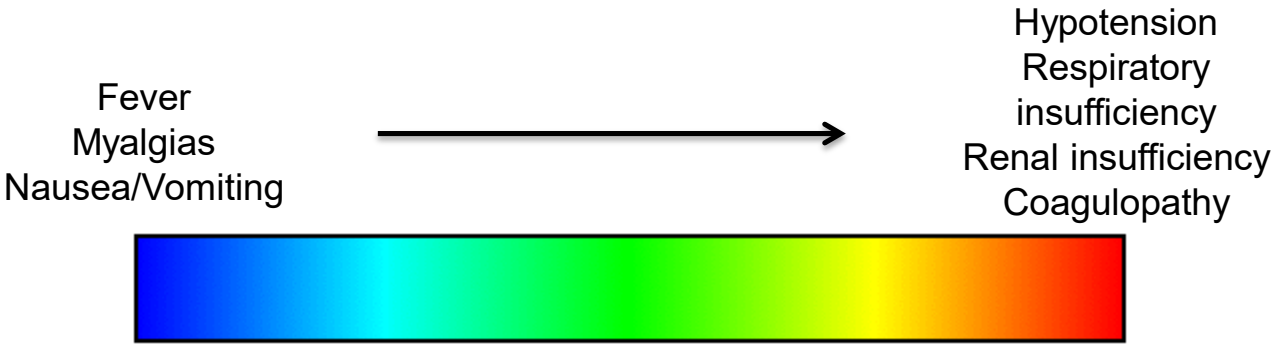
- Research and/or clinical trial support from Novartis, Servier, Vertex and Kite
- Study steering committees, consulting, or scientific advisory boards: Novartis, Adaptimmune, Eureka, TCR2, Juno, CRC Oncology, Cure Genetics, GlaxoSmithKline, Cellectis, Janssen, Vertex, Roche
- Toxicity management patent managed by U Penn policies


CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent
antigen engagement
and induction of signalling
scFv
scFv
CD28
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation,
cytokine production,
CTL function
tumor lysis

Cytokine Release Syndrome (CRS)

CRS is related to T cell expansion and may be necessary for efficacy

- Symptoms typically occur 1-14 days after CTL019 cell infusion in ALL

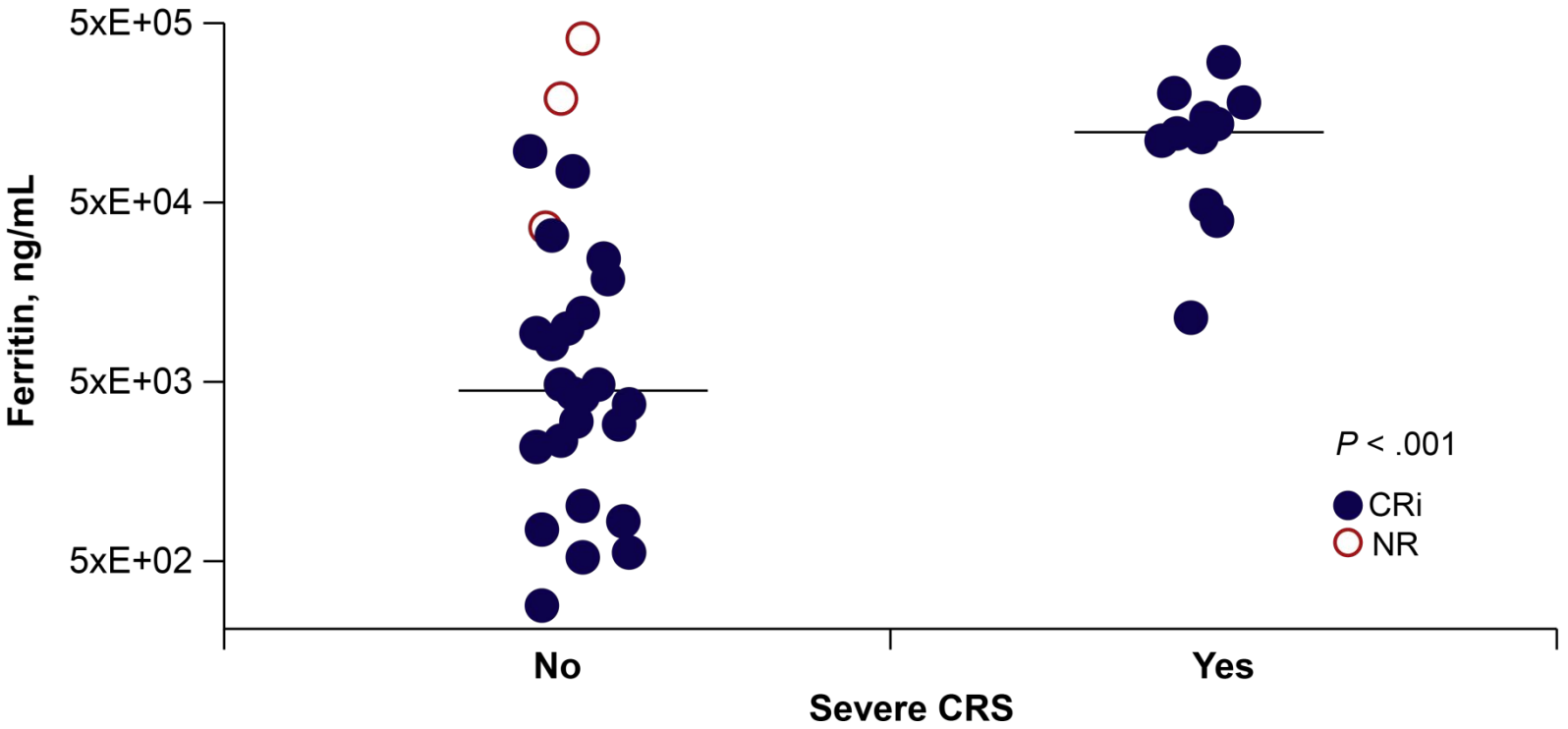


- Severity scales with disease burden

CRS definition (ASTCT consensus)

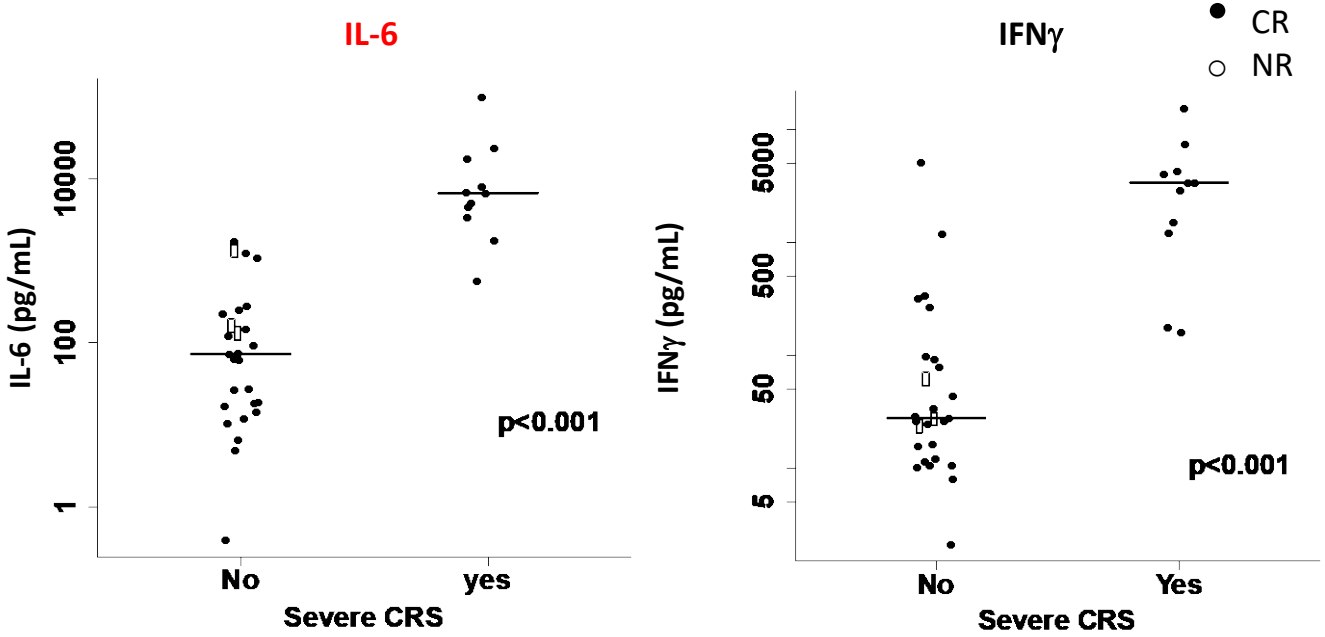
- CRS: “a supraphysiologic response following the activation or engagement of ...T cells for therapeutic intent. Symptoms can be
  - “Progressive
  - “must include fever at the onset
  - “may include hypotension, capillary leak (hypoxia) and end organ dysfunction”
- CRS should be applied to any T-cell activating/engaging therapy, not just CAR T cells
- As new, effective immunotherapies (non-T cell) are developed, the definition may need to be altered.

Severe CRS: High Ferritin Levels Suggest Macrophage Activation Syndrome



1. Maude SL et al. *N Engl J Med*. 2014;371:1507-1517.

CRS associated with IFN-g and IL-6



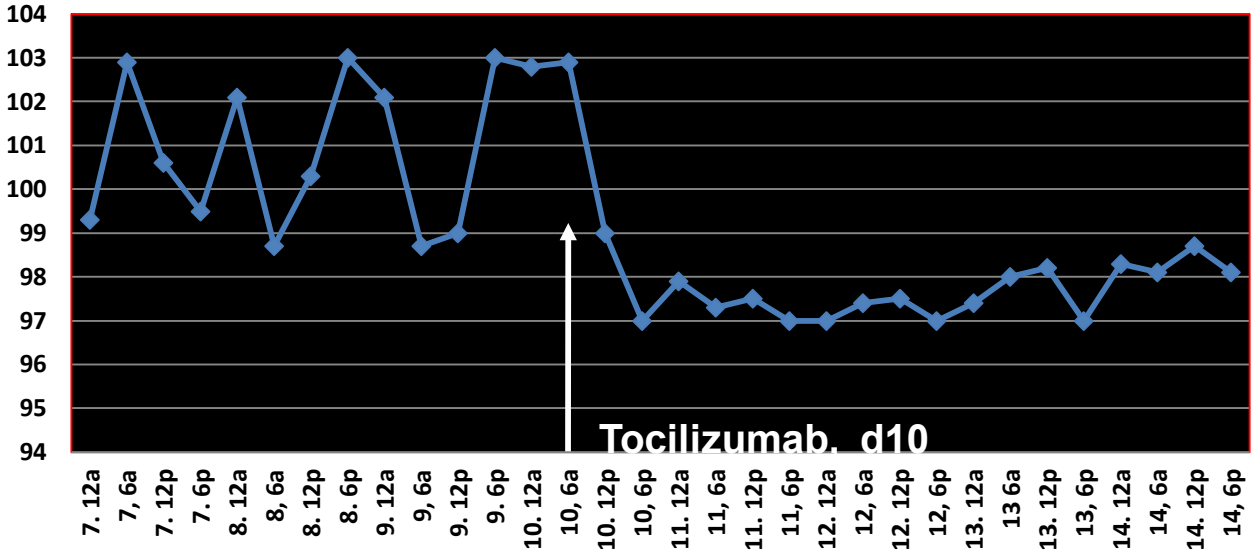
Maude et al, NEJM 2014

Tocilizumab (Actemra) aka “toci”

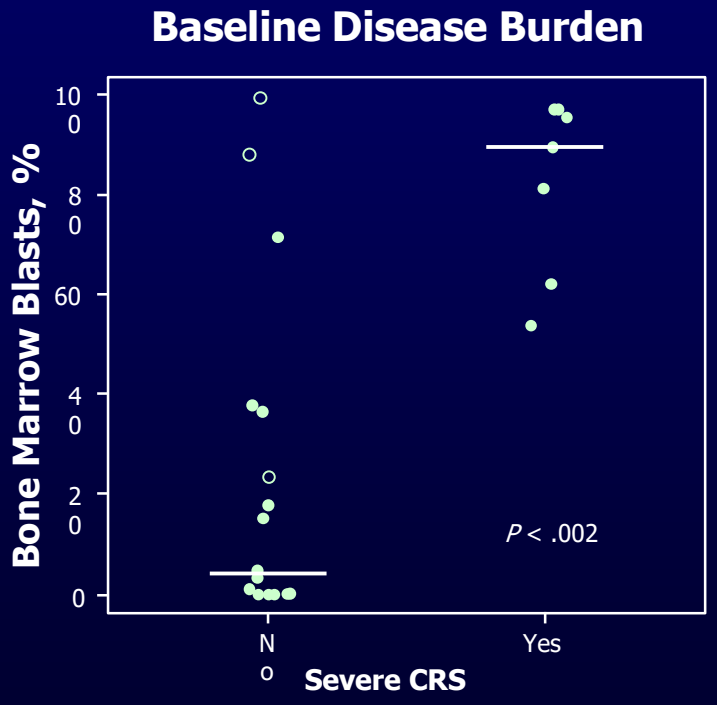
- IL-6 receptor antagonist
- Blocks IL-6 mediated effects
- Indicated in:
  - juvenile idiopathic arthritis (JIA)
  - Rheumatoid arthritis (RA)
  - In Japan, indication for Castleman’s Disease
- Given once or twice
- Rare side effects of transaminitis and neutropenia
- Now indicated for CRS treatment

Grupp et al, NEJM 2013

CRS: Treatment with Tocilizumab
Anti-Cytokine Therapy



Disease Burden Highly Predictive of Severe CRS



Maude et al. NEJM 2014

CHOP/Penn CRS management

- Response based toxicity management (not grading based)
- Step 1 – toci for unstable hypotension (most common) or other significant changes in clinical status
  - Second bolus in a short time – start of unstable hypotension
  - Trigger for toci – rapid decline, escalating single pressor, definitely 2nd pressor
- Step 2 – no change in 12-18 hrs – methylpred 2 mg/kg or equiv
  - rapid wean of steroids after hypotension resolved

Maude SL et al. *N Engl J Med*. 2014;371:1507-1517

CHOP/Penn CRS management

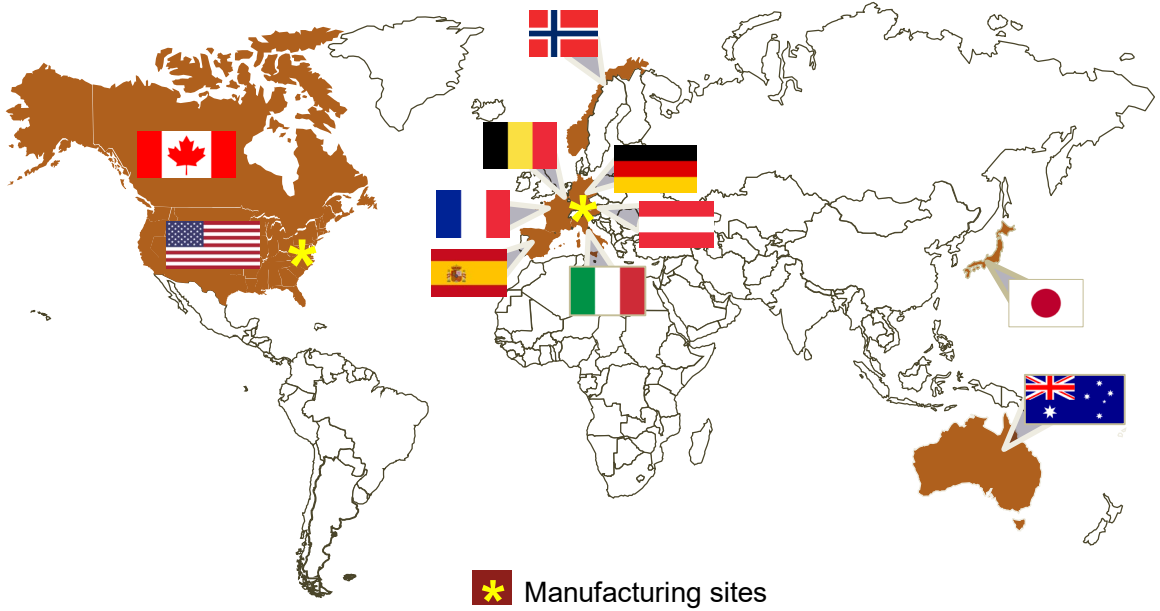
- Response based toxicity management (not grading based)
- Step 3 – no improvement in 12-18 hrs – 2nd dose of toci
- Step 4 – no improvement – consider siltuximab.
  Alternatives could include:
  - 30 mg/kg solumedrol (1 gram)
  - Cyclophosphamide?
  - Anakinra?
  - Gamifant? (UNTESTED)**
  - Cytosorb column (UNTESTED)**

**active in HLH

ELIANA: Pivotal Phase 2 Study

ELIANA is the first global, multicenter trial of CAR T cell therapy

- Tisagenlecleucel (CTL019) produced at a central manufacturing site with global distribution
- 25 sites across 11 countries in North America, Europe, and Asia-Pacific



Maude et al. NEJM 2018
Updated ASH 2018

Overall Safety and AEs of Special Interest Within 8 Weeks After Infusion

AESI[a]	Patients (N = 79)		
	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	77	22	27
Infections	43	20	4
Cytopenias not resolved by day 28	42	18	18
Neurological events	39	13	0
Tumor lysis syndrome	5	5	0

- Majority of AEs occurred in the first 8 weeks after tisagenlecleucel infusion
- No cases of cerebral edema reported

[a] Occurring within 8 weeks of tisagenlecleucel infusion.
[b] Cytokine release syndrome was graded using the Penn scale.
AESI, adverse events of special interest.

Cytokine Release Syndrome

	Patients Infused (N = 79)
Patients developed CRS, n (%)	**61 (77)**
Time to onset, median (range), days	3.0 (1-22)
Duration of CRS, median (range), days	8.0 (1-36)
ICU admission, n (%)	38 (48)
Anticytokine therapy, %	31 (39)
Tocilizumab, %	31 (39)
1 dose	18 (23)
2 doses	10 (13)
3 doses	3 (4)
Corticosteroids, %	16 (20)
Hypotension that required intervention, %	42 (53)
High-dose vasopressors, %	19 (24)
Intubation, %	12 (15)
Dialysis, %	8 (10)

CRS was graded using the Penn scale and managed by a protocol-specific algorithm[1]

CRS, cytokine release syndrome; ICU, intensive care unit.

1. Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139.

Positive Association of CRS Grade and Neurological Event Grade

CRS	N	Any-Grade Neurological Events, n (%)	Grade 3 Neurological Events, n (%)
None	18	4 (22)	1 (6)
Grade 1/2	23	7 (30)	1 (4)
Grade 3	17	7 (41)	2 (12)
Grade 4	21	13 (62)	6 (29)

- Grade 3 neurological events were more frequent with grade 4 CRS compared with grade 0-3 CRS (95% CI, –2% to 45%)
- Median onset of any-grade CRS (day 3) preceded median onset of neurological events (day 7)
- Grade 3 or 4 CRS and grde 3 neurological events occur earlier than grade 1 or 2

CRS, cytokine release syndrome.

CRS: Grading Schemes

- Difficult to compare CRS across studies

- 24 yo w/ ALL develops hypotension requiring low dose pressors after CD19 CAR

  - Grade 2 on 2014 Consensus (“Lee”) scale
  - Grade 3 on PENN/CHOP scale
  - Grade 4 on CTCAE scale

CRS: Grading Schemes

- CTCAE Versions 4.03 & Version 5.0
- Lee Criteria
- Penn Criteria
- MSKCC Criteria
- CARTOX (Neelapu, et al)

Cellular Therapy: CRS Grading Scales

Consensus 2014[1]

Grade	Toxicity
1	Mild Reaction: symptomatic treatment only
2	O_2 requirement<40% or hypotension req low dose pressors
3	O_2 requirement≥40% or req high dose pressors
4	Life threatening; mechanical ventilation, Gr 4 organ toxicity
5	Death

PENN/CHOP[2]

Grade	Toxicity
1	Mild Reaction: symptomatic treatment only
2	Moderate Reaction: IVF required. Mild signs organ dysfunction
3	Moderate organ dysfunction, low dose pressors, hypoxia
4	Life threatening; mechanical ventilation, high dose pressors
5	Death

[1]Adapted from: Lee et al. Blood. 2014
[2]Adated from: Porter et al. SciTranslMed. 2015

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CRS grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever not attributable to any other cause	Temperature ≥38°C with or without constitutional symptoms	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension not attributable to any other cause	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia not attributable to any other cause	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

CRS grading – specific comments

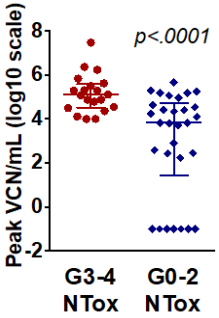
- Fever = ≥38°C
- After Rx, fever is no longer required.
  In this case, CRS grading is driven by hypotension and/or hypoxia
- CRS grade is determined by the more severe event: hypotension or hypoxia
- Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

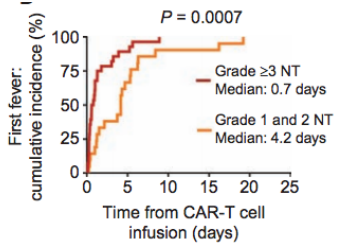
Neurotoxicity (ICANS)

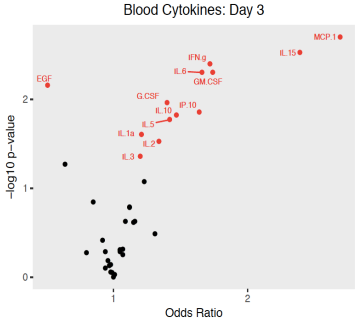
- –Seen across CD19 immunotherapy trials with CAR T cells (NCI, CHOP/UPENN, MSKCC, Seattle) as well as blinatumomab
- –Delirium, confusion, encephalopathy, rare seizures
- –In our experience: generally untreated, fully resolves
- –No cerebral edema seen in our studies
- – Cerebral edema was a major toxicity seen in one study (Juno ROCKET trial)

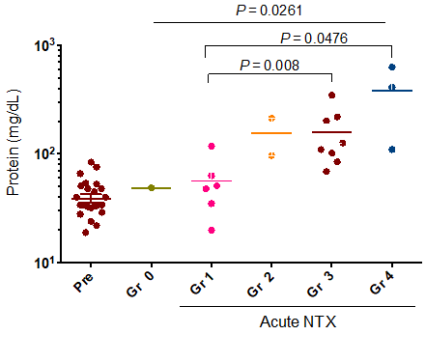
Correlates of severe Neurotoxicity

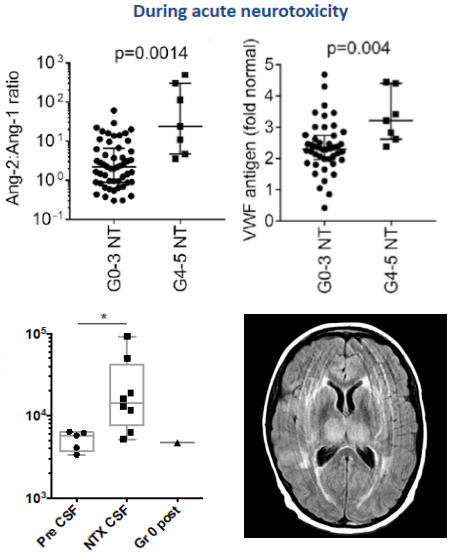
- Higher peak CAR expansion in blood
- Earlier onset of fever
- Elevated serum cytokines
- Endothelial activation
- Blood-CSF barrier breakdown
- Excitotoxicity











Santomasso B & Park J et al. Cancer Discovery 2018

Gust J et al. Cancer Discovery 2017

ASTCT Neurotoxicity (ICANS) Consensus Grading for Adults

NT Domain	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Assessment ICE Score	7-9	3-6	0-2	0 **AND** One of the events below
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP / Cerebral edema	N/A	N/A	Focal/local edema with or without hemorrhage on neuroimaging	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

- NT grade is determined by the most severe event not attributable to any other cause.
- A patient with a neuro-assessment score of 3 who has a generalized seizure is classified as having Grade 3 NT.
- A patient with a neuro-assessment score of 0 may be classified as having Grade 3 NT if the patient is awake with global aphasia. But a patient with a neuro-assessment score of 0 may be classified as having Grade 4 NT if the patient is unarousable.
- Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)
- Tremors and myoclonus associated with NT may be graded according to CTCAE v5.0 but they do not influence NT grading.

Toxicity reporting in the commercial setting

- Large effect sizes have meant that CAR T indications are FDA approved on <100 patients
- Further data collection is paramount
- Data will not be collected in a research setting with research budgets and direct regulatory mandates on the centers

- Excessive, inconsistent, or conflicting data requests from companies or health authorities in the commercial setting may interfere with getting necessary data #Askforeverythinggetnothing

Toxicity reporting in the commercial setting

- Large reporting mandates (all grade 4 and especially grade 3 tox, grade 1 or 2 CRS) will bury the signal in noise and are not feasible
- A registry approach is likely to be the best method of providing consistency and as complete data as possible.
- CIBMTR reporting should achieve this

What is are the current labeled indications for Kymriah?

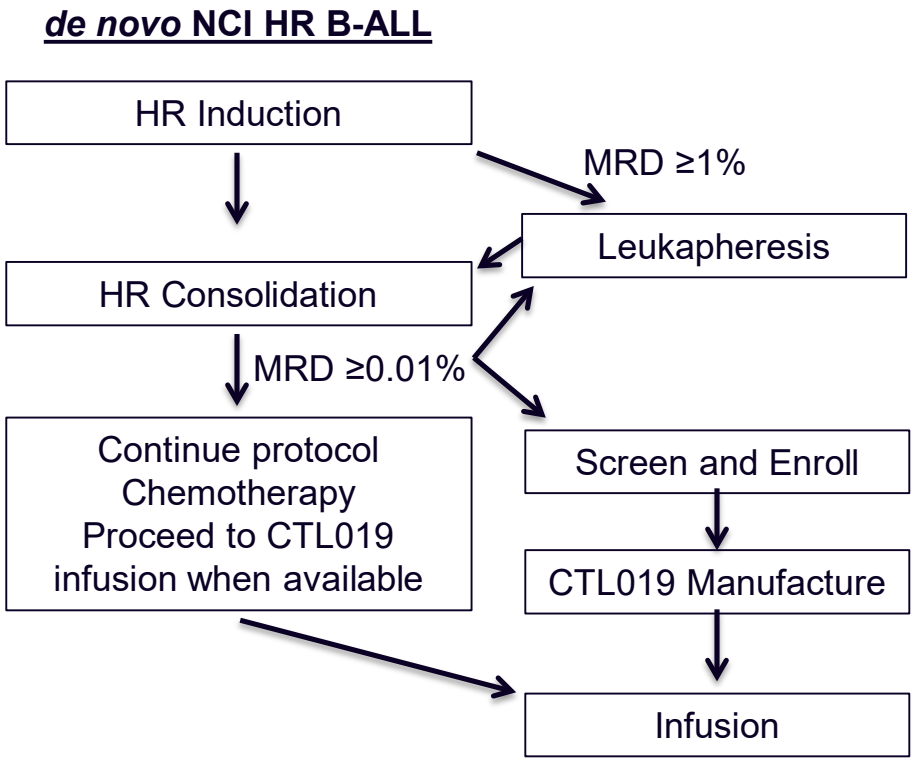
ALL up to age 25
(CHOP treats to 29, but not w/ commercial product)

- Refractory, second relapse OR post-SCT relapse

Other key points:

- Patients do not need to be in remission
- No donor is required
- Contraindications:
  - Rapidly progressing refractory disease
  - Active infection
  - Inadequate organ function suggesting inability to tolerate CRS (risk adjusted)

AALL1721 Trial Design



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The world's childhood cancer experts

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