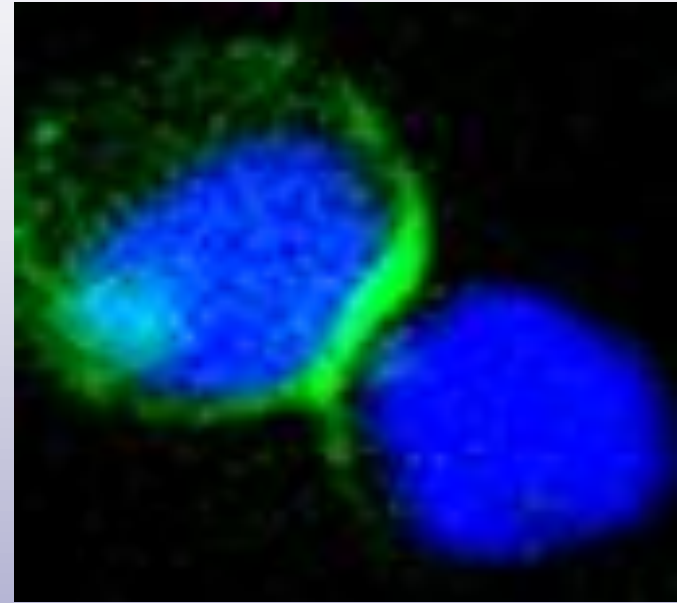
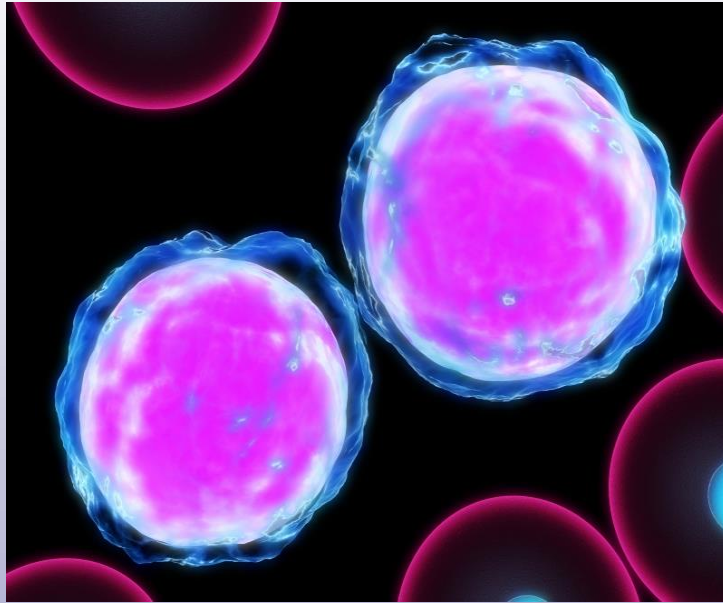


# Toxicity and Management After CTL019 Therapy

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SITC/Porter 11-9-14. Confidential

# Disclosure Information

*David L Porter*

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- Speaker and members of study team have financial interest due to potential upstream IP and patents and licensure to Novartis
- COI managed in accordance with University of Pennsylvania policy and oversight
- Funding support for trials: ACGT, LLS, NCI, Novartis

# Tasks:

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- CTL019: Anti-CD19 CAR modified T cells at the University of Pennsylvania
  - Listing of deaths, case reviews
  - Grading of CRS, MAS
  - CRS/MAS treatment algorithm
  - Safety Monitoring
- All in 10 minutes

# Summary of all cases of Grade 3/4 (life threatening) and 5 (fatal) Cytokine Release Syndrome (CRS) and Macrophage Activation Syndrome (MAS)

Disease	CART/TCR Construct	Dose	Treated (N)	Grade 3/4 (N/%)	Grade 5 (N/%)	Risk Factors
<b>ALL</b>	41bb-28	varied	60 17 adults 43 peds	52% 13/17 A 18/43 P	3 (5%)	Influenza b, infections
<b>CLL</b>	41bb-28	varied	44	30%	0	
<b>NHL</b>	41bb-28	varied	19	10%	0	
<b>MM</b>	41bb-28	varied	2	1	0	
<b>Total</b>	<b>41bb-28</b>	<b>Varied</b>	<b>125</b>	<b>38%</b>	<b>2.4%</b>	<b>Influenza b, infections</b>

# CRS: CTCAE v4

A disorder characterized by nausea, headache, tachycardia, hypotension, rash, shortness of breath; caused by the release of cytokines from cells.

Gr 1	Gr 2	Gr 3	Gr 4
Mild; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for $\leq 24$ hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated

# Penn Grading System for CTL019 - associated CRS

Data from CTL019 treated patients

- Marked elevations in IL-6, interferon-gamma, and less intensely TNF-alpha.
- Symptoms occur 1-14 days after cell infusion in ALL patients.
- Symptoms may include: high fevers, rigors, myalgia/arthralgias, nausea/vomiting/anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea, hypoxia.

Grade 1	Grade 2	Grade 3	Grade 4
<b>Mild reaction:</b> <b>Treated with</b> <b>supportive care</b> <b>such as anti-</b> <b>pyretics, anti-</b> <b>emetics</b>	<b>Moderate : Requiring</b> <b>IV therapies or</b> <b>parenteral nutrition;</b> <b>some signs of organ</b> <b>dysfunction (i.e. gr 2</b> <b>Cr or gr 3 LFTs)</b> <b>related to CRS and</b> <b>not attributable to</b> <b>any other condition.</b> <b>Hospitalization for</b> <b>management of CRS</b> <b>related symptoms</b> <b>including fevers with</b> <b>associated</b> <b>neutropenia.</b>	<b>More severe reaction:</b> <b><u>Hospitalization required for management</u></b> <b><u>of symptoms related to organ</u></b> <b><u>dysfunction</u> including gr 4 LFTs or gr 3</b> <b>Cr related to CRS and not attributable to</b> <b>any other conditions; excludes</b> <b>management of fever or myalgias.</b> <b>Includes <u>hypotension treated with</u></b> <b><u>intravenous fluids* or low-dose pressors,</u></b> <b><u>coagulopathy requiring FFP or</u></b> <b><u>cryoprecipitate, and hypoxia requiring</u></b> <b><u>supplemental O2 (nasal cannula oxygen,</u></b> <b><u>high flow O2, CPAP or BiPAP).</u></b> Pts <b>admitted for management of suspected</b> <b>infection due to fevers and/or</b> <b>neutropenia may have grade 2 CRS.</b>	<b>Life-threatening</b> <b>complications such as</b> <b>hypotension requiring</b> <b>“high dose pressors” **,</b> <b>hypoxia requiring</b> <b>mechanical ventilation.</b>

\*Defined as: multiple fluid boluses for blood pressure support

\*\* See specific definition of “High dose” vasopressors

# High dose Vasopressor Use with CTL019

Definition of <b>High-Dose</b> Vasopressors	
Vasopressor	Dose for $\geq 3$ hours
Norepinephrine monotherapy	$\geq 20$ mcg/kg/min
Dopamine monotherapy	$\geq 10$ mcg/kg/min
Phenylephrine monotherapy	$\geq 200$ mcg/min
Epinephrine monotherapy	$\geq 10$ mcg/min
If on vasopressin	High-dose if vaso + NE equivalent of $\geq 10$ mcg/min (using VASST formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of $\geq 20$ mcg/min (using VASST formula)

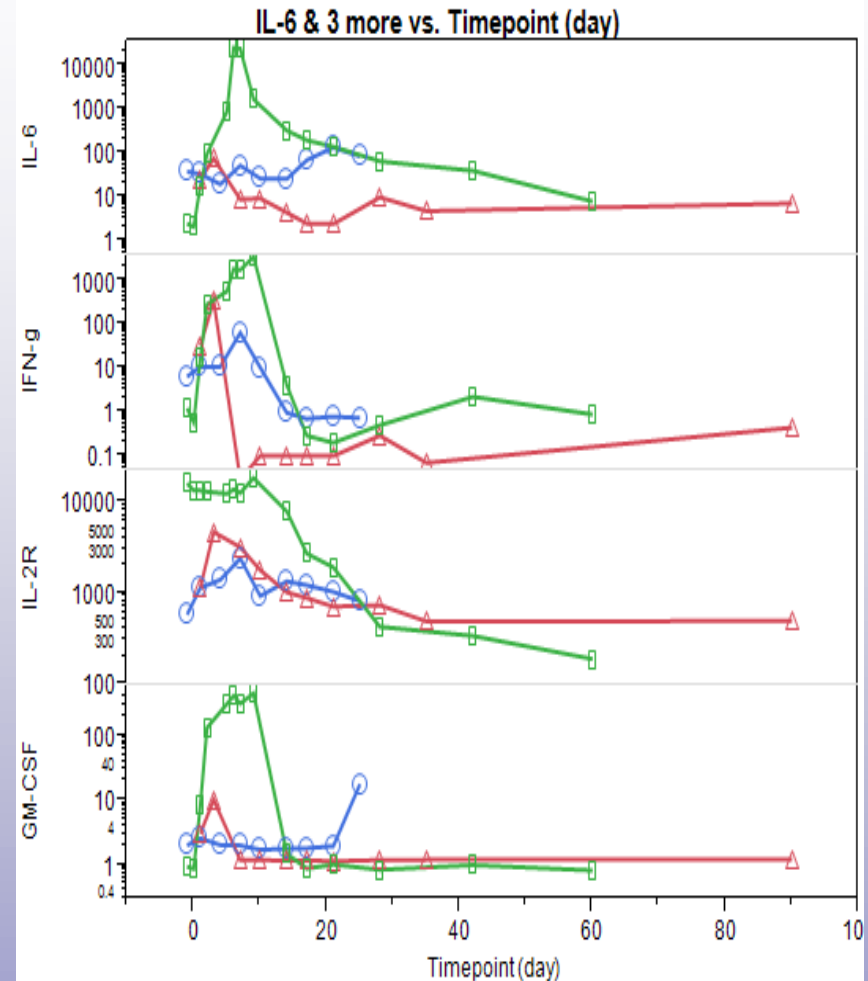
## **VASST Trial Vasopressor Equivalent Equation:**

Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min)  $\div$  2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min)  $\div$  10]

*Fuchs and colleagues, adapted from Russel et al, NEJM 2008*

# Massive Elevations in IL-6 After CTL019 in Responding Patients

- Almost all responding patients developed a CRS
  - High fevers, myalgias, nausea, hypotension, hypoxia, etc.
  - Very high levels of IL6
  - IFN-g, modest TNF- $\alpha$
  - Mild increases in IL-2



CHP959-117 NR

CHP959-118 CR mild CRS

CHP959-120 CR severe CRS



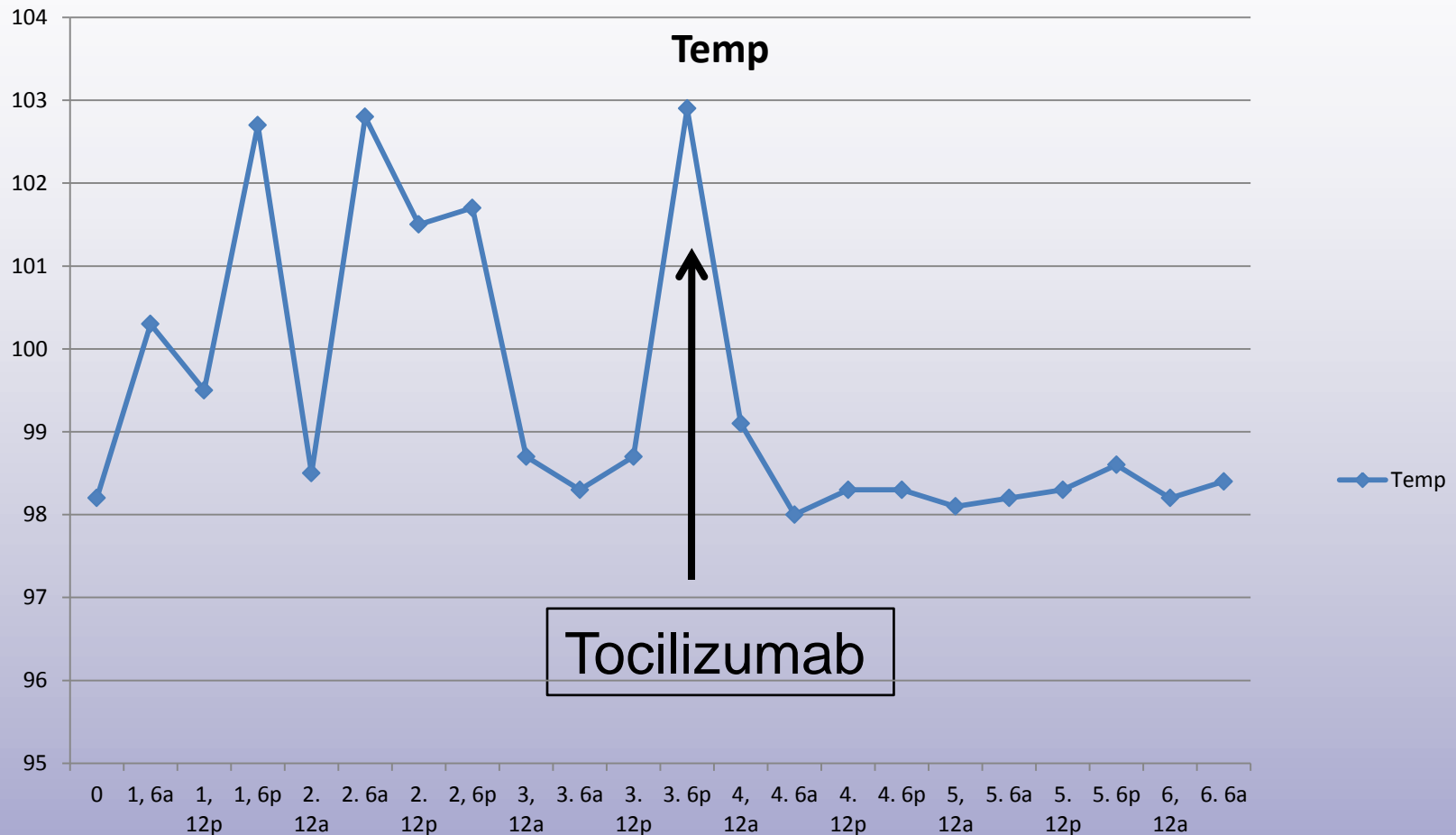
# IL-6 mediates CTL019 Associated CRS

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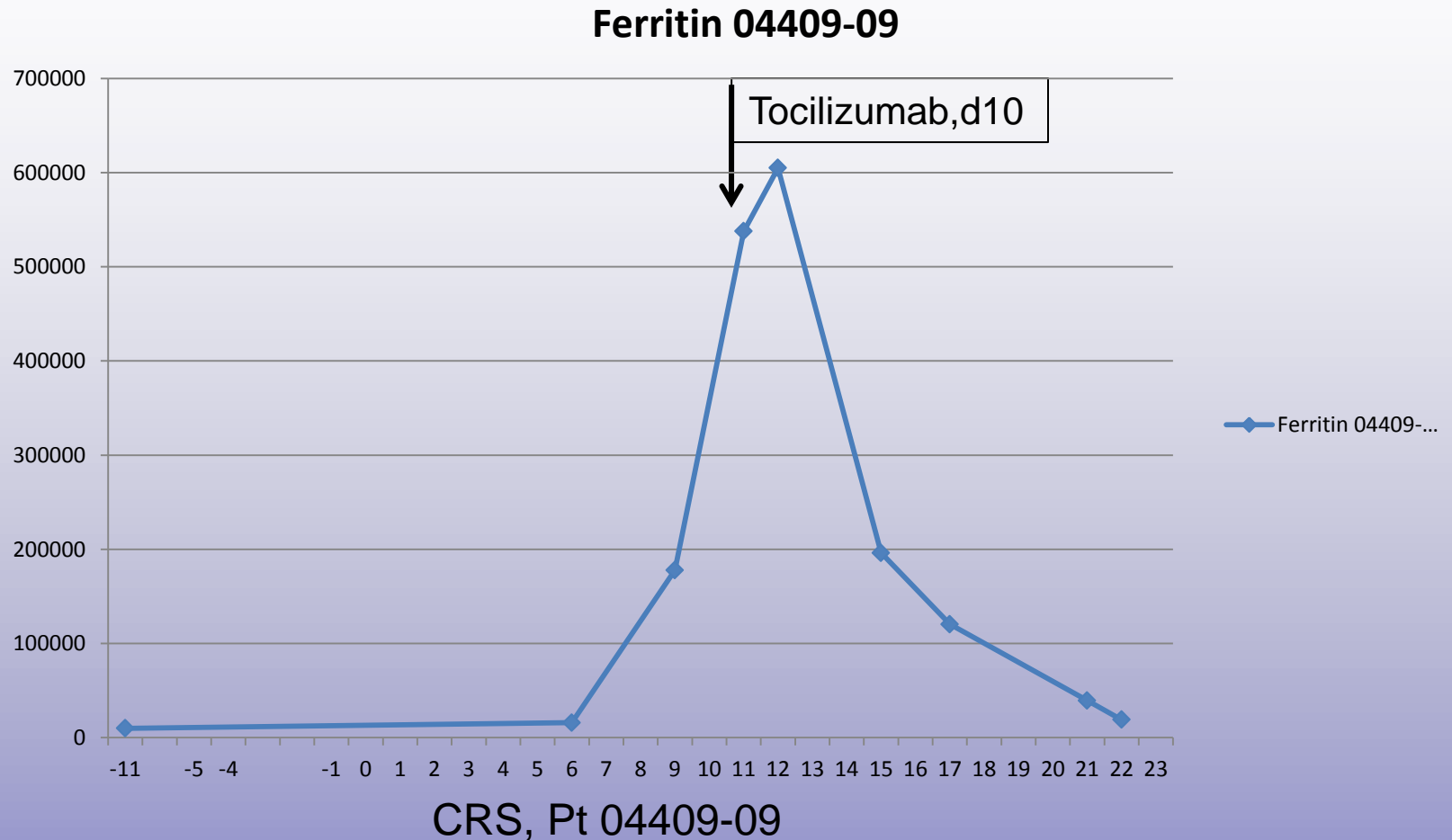
- Tocilizumab
  - IL-6 receptor antagonist
  - Blocks IL-6 mediated effects
- CRS rapidly reversed with tocilizumab when needed in most cases
  - Tocilizumab administered on day 2 to 11
  - Will early treatment for CRS abrogate response?
- CRS associated with HLH/MAS
  - Hemophagocytosis, ferritin >500,000, hemolysis, DIC, altered mental status
  - Ferritin level does not correlate with response or guide intervention

# Temperature Response to Tocilizumab

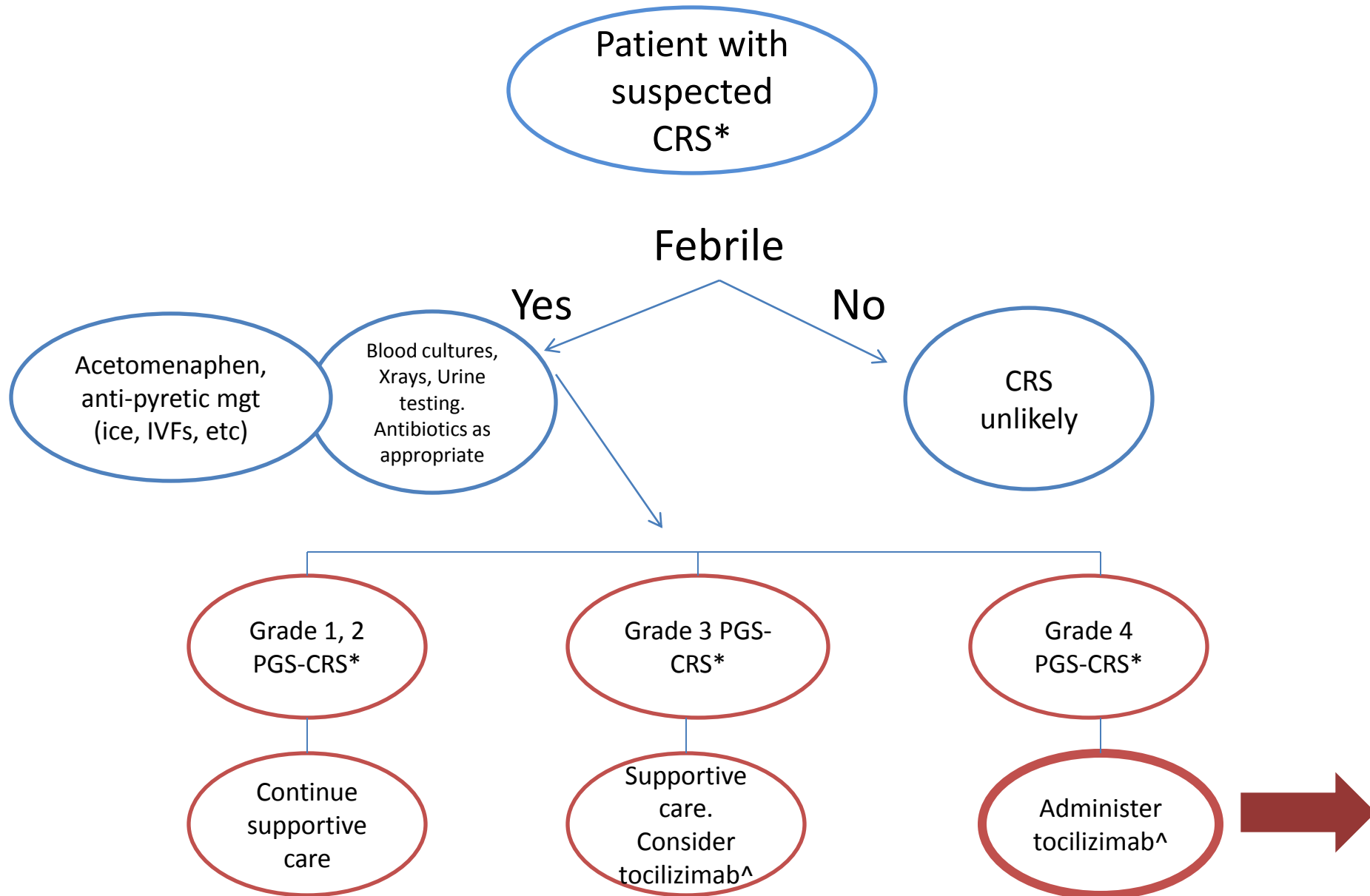
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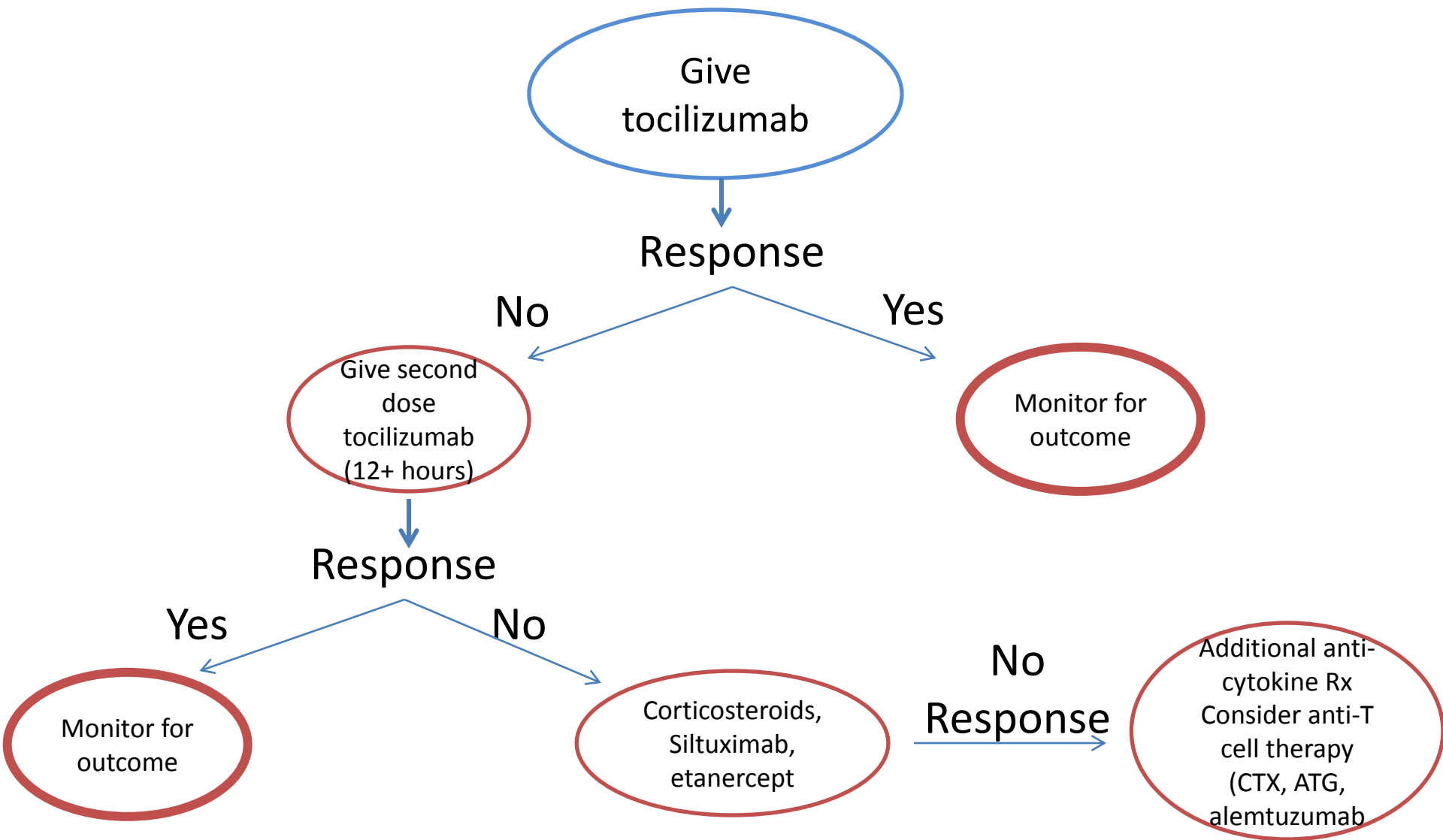
# MAS: Treatment with Anti-cytokine therapy



# CTL019 Symptom Management Algorithm



# CTL019 Symptom Management Algorithm



# Early Mortality after CTL019

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- 3 of 60 ALL pts (3/17 adults) died of refractory CRS.
  - 03 tested + for influenza B on admission for fever (early CRS).
  - 06 received anti-cytokine therapy and developed pseudomonas pneumonia
  - 11 received anti-cytokine therapy and developed stenotrophomonas sepsis (abx resistant)
  - All with slightly higher dose of CTL019 on new protocol
    - Median cell dose in previous trial:  $1.16 \times 10^8$  (range 0.0.65-15.5).
    - Median CTL019 cell dose  $5.0 \times 10^8$  (range 0.42–5.0) for patients on new trial (UPCC 21413).
  - No other obvious characteristics predict refractory CRS (i.e. pre-chemotherapy tumor burden)

# Clinical Management: CTL019

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- Because of unique therapy and toxicity, pts required to be within ~20 min of HUP for 30-60 days.
- Outpatient care:
  - Visits day -1, 0, 1, 2, 4, 7, 10, 14, 21, 28
  - Visits month 2, 3, 4, 5, 6, 9, 12, +/- 15, 18, 21, 24
- Multicenter protocols being planned which will allow therapy to be given at limited outside institutions.

# Lessons and Take Home Messages

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- Key Points

- CRS may be dependent on tumor burden and disease (ALL > CLL/NHL)
- Refractory CRS can lead to mortality.
  - TRM may be expected
- CRS may be exacerbated by infection
- CRS can be managed in most but not all cases with anti-cytokine therapy
- Timing of anti-cytokine therapy unclear and may abrogate anti-tumor response
- Is there a dose:toxicity or dose:response relationship?
  - Not obvious in CLL
  - Possibly in ALL



# Lessons and Take Home Messages

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- Lessons learned
  - Response rates in CLL, NHL and ALL to CTL019 are high
    - Remissions sustained >2 yrs (ALL) and >4 yrs (CLL)
  - CRS is major complication of CTL019 therapy managed in most but not all cases with anti-cytokine therapy
- Potential impact on field
  - Continue to test and learn about CRS management
    - Tocilizumab vs siltuximab
    - Role for anti-TNF therapy?
    - Role for anti-IL1 therapy
    - Impact of steroids
    - Suicide switches and conditional expression
    - Timing of intervention
    - Responses without CRS? (low tumor burden, etc)

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