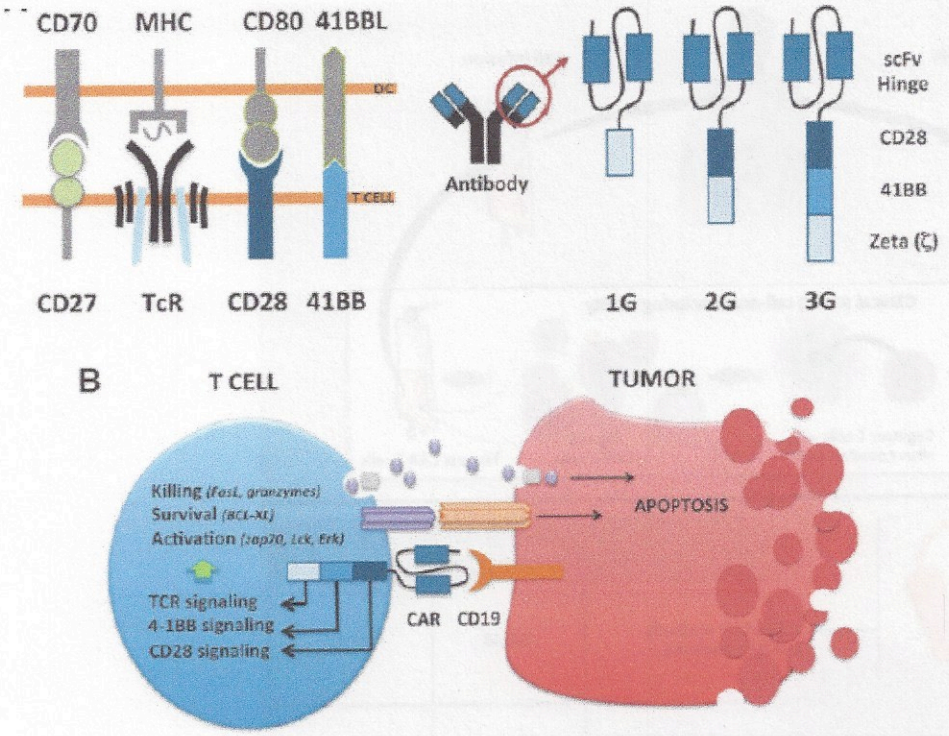

Figure 1. **(A)** T-cells interact with antigen-presenting cells such as dendritic cells (DCs) to become activated. The first signal of activation is transmitted via the T-cell receptor (TcR) that binds to major histocompatibility complex (MHC) molecules presenting antigen peptides to the T-cell. The second signal is delivered in terms of multiple interactions with co-stimulatory molecules such as CD80, 41BBL, and CD70 presented to the T-cell by mature DCs. A chimeric antigen receptor (CAR) receptor consists of an antigen-binding region such as a single chain fragment (scFv) from a tumor-targeting antibody and an intracellular signaling region. The signaling region of the first-generation (1G) CAR mimicked TcR signaling via fusing the antigen-binding region to the CD3-ζ chain. The second-generation (2G) CAR mimicked both TcR and costimulatory signaling by adding, for example, CD28 or 41BB domains to the intracellular region, while the third-generation (3G) CAR has two costimulatory domains fused with the TcR CD3-ζ chain. **(B)** The CAR gene is inserted to T-cells and expressed to produce protein CAR, which is transported to the plasma membrane. A CD19-targeting CAR interacts with CD19+ malignant B-cells to receive activation signaling leading to FasL and perforin/granzyme B-mediated cytotoxicity.

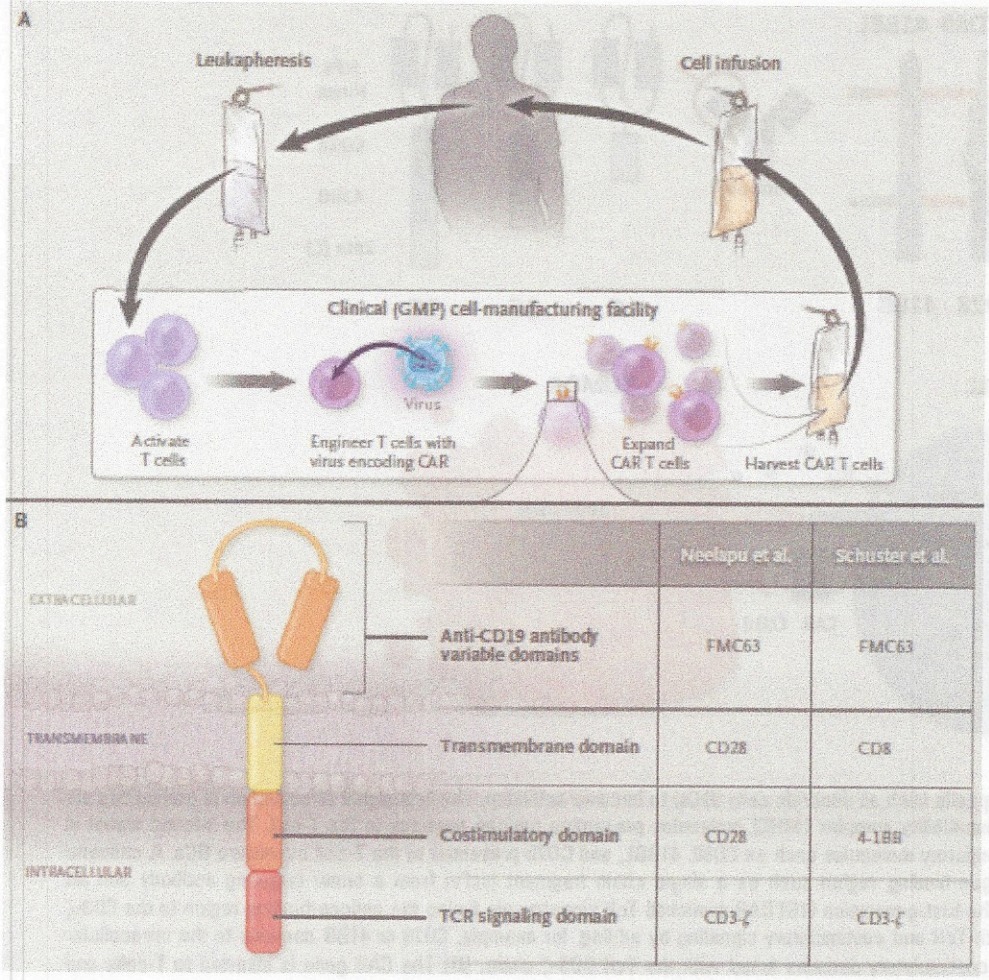

Table 1. Clinical signs and symptoms associated with CRS

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

TABLE 1. Cytokine Release Syndrome Grading and Treatment[a]

Organ Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Constitutional	Fever, malaise, fatigue, myalgia, arthralgia	Fever, malaise, fatigue, myalgia, arthralgia	Fever, malaise, fatigue, myalgia, arthralgia	Fever, malaise, fatigue, myalgia, arthralgia
Respiratory		Hypoxemia requiring < 40% FiO_2 to maintain O_2 saturation > 92%	Hypoxemia requiring > 40% FiO_2 (high-flow nasal cannula or noninvasive ventilation) to maintain O_2 saturation > 92%	Hypoxemia requiring mechanical ventilation
Cardiac	Tachycardia	Stable dysrhythmias Hypotension/shock: responsive to fluid resuscitation or requiring low dose vasopressors for < 24 hr Cardiomyopathy: EF > 40% or 10% drop in EF from baseline	Unstable dysrhythmias Shock: requiring high dose vasopressors or multiple vasopressors, low dose vasopressors for > 24 hr, or showing signs of hypoperfusion independent of dose Cardiomyopathy: EF 20–39% or > 10% drop in EF from baseline	Life-threatening dysrhythmias Shock: refractory requiring multiple vasopressors Cardiomyopathy: EF < 20%
Gastrointestinal[b]	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea
Hepatic	AST/ALT < 3 normal limits, T Bili <1.5 normal limits	AST/ALT 3–5 normal limits, T Bili 1.5–3 normal limits	AST/ALT 5–20 normal limits, T Bili 3–10 normal limits	AST/ALT > 20 normal limits, T Bili > 10 normal limits
Renal	Creatinine < 2 × baseline with normal urine output	Creatinine 2–3 × baseline with normal urine output	Creatinine > 3 × baseline with oliguria	Anuria and indications for dialysis
Hematologic		Coagulopathy without bleeding	Coagulopathy with bleeding	Coagulopathy with life-threatening bleeding
Electrolytes	Low PO^4, Mg, Na, K	Low PO^4, Mg, Na, K	Low PO^4, Mg, Na, K	Low PO^4, Mg, Na, K
Treatment	Monitoring and supportive care[d]	Tocilizumab or consider Siltuximab[c] Corticosteroids can be considered if symptoms are persistent	Tocilizumab or Siltuximab if not dosed yet. Corticosteroids: dexamethasone 10 mg IV q6 hr or equivalent dosing[e]	Tocilizumab or Siltuximab if not dosed yet. Corticosteroids: methylprednisolone 1 g/d Consider suicide gene activation for refractory symptoms

TABLE 2. Neurotoxicity Grading and Treatment[a]

Clinical Presentation	Grade 1	Grade 2	Grade 3	Grade 4
Disorientation[b]	Mild	Moderate	Severe	Severe
Dysgraphia[b]	Present	Present	Limited assessment	Limited assessment
Aphasia[b]	Word finding difficulty	Moderate aphasia	Severe global aphasia	Severe global aphasia
Dyskinesia	Mild tremor	Intermittent facial twitching, tremors, or myoclonus	Continuous facial twitching and myoclonus	Continuous facial twitching and myoclonus requiring airway protection
Attention and consciousness[b]	Inattentive or mild delirium	Lethargic or moderate delirium	Obtundation/stupor or severe delirium	Coma or severe delirium requiring airway protection
Seizure	None	None	Partial seizures, nonconvulsive or convulsive seizures	Convulsive or nonconvulsive status epilepticus
Cerebral edema	None	None	Grades 1–2 papilledema and associated headache, nausea, and vomiting	Grades 3–5 papilledema, or clinical signs of herniation such as Cushing's triad, posturing, cranial nerve VI palsy, and diabetes insipidus
Motor strength	5/5	5/5	3–4/5	0–2/5
Supportive care	Imaging (CT or MRI brain) and EEG Frequent neurologic examination Consider seizure prophylaxis Consider and treat other causes of encephalopathy as needed Lumbar puncture if no contraindication	Imaging (CT brain or MRI) and EEG Frequent neurologic examination Consider seizure prophylaxis Consider and treat other causes of encephalopathy as needed Lumbar puncture if no contraindication	Imaging (CT or MRI brain) and EEG Frequent neurologic examination Treatment of seizures including benzodiazepines, levetiracetam, or other antiepileptic drugs Consider and treat other causes of encephalopathy as needed Lumbar puncture if no contraindication	Imaging (CT or MRI brain) and continuous EEG Frequent neurologic examination Management of status epilepticus as per institutional guidelines Consider and treat other causes of encephalopathy as needed
Treatment	Supportive care and close monitoring for progression[c]	Supportive care and close monitoring for progression[c] Consider corticosteroids if symptoms are persistent or if the CAR construct is known to cause severe neurotoxicity	Corticosteroids: dexamethasone 10 mg IV q 6 hr or equivalent to methylprednisolone[d]	Corticosteroids: methylprednisolone IV 1 g/d[d] Consider suicide gene activation for refractory symptoms