Recommended Management of Cytokine Release Syndrome

	Presenting Symptoms	Treatment Options	
		Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥38°C[c]	May be considered	Not applicable
Grade 2	Temperature ≥38°C[c] with either: Hypotension responsive to fluids and not requiring vasopressors. Or oxygen requirement of low-flow nasal cannula[d] or blow-by	Administer tocilizumabb 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per guidance below if no improvement within 24 hours of starting tocilizumab.
Grade 3	Temperature ≥38°C[c] with either: Hypotension requiring 1 vasopressor with or without vasopressin. Or, oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone (eg, 10 mg IV every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4	Temperature ≥38°C[c] with either: Hypotension requiring multiple vasopressors (excluding vasopressin). Or, oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above or administer methylprednisolone 1000 mg IV per day for 3 days per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants.[b]

a. Refer to tocilizumab prescribing information for details.
b. Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
c. Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or steroids).
d. Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

Recommended Management of ICANS

	Presenting Symptoms[a]	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7-9[b] or depressed level of consciousnessc: awakens spontaneously.	Management of CRS as appropriate per Table CRS. Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	
Grade 2	ICE score-3-6[b] or depressed level of consciousnessc: awakens to voice.	Management of CRS as appropriate per Table CRS. If no improvement after starting tocilizumab, administer dexamethasone[d] 10 mg IV every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasoned 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
Grade 3	ICE score-0-2[b] or depressed level of consciousnessc: awakens only to tactile stimulus, or seizures[c], either: any clinical seizure, focal or generalized, that resolves rapidly, Or non-convulsive seizures on EEG that resolve with intervention, Or raised ICP: focal/local edema on neuroimaging[c].	Management of CRS as appropriate per Table CRS. In addition, administer dexamethasone[d] 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg IV every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
Grade 4	ICE score-0[b] or depressed level of consciousness[c] either: ○ patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or ○ stupor or coma, or seizures[c], either: • *life-threatening prolonged seizure (>5 min), or* • *repetitive clinical or electrical seizures without return to baseline in between, or motor findingsc:* • *deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP/cerebral edemac, with signs/symptoms such as:* • *diffuse cerebral edema on neuroimaging, or* • *decerebrate or decorticate posturing, or* • *cranial nerve VI palsy, or* • *papilledema, or* • *Cushing's triad.*	Management of CRS as appropriate per Table CRS. As above, or consider administration of methylprednisolone 1000 mg IV per day with first dose of tocilizumab and continue methylprednisolone 1000 mg IV per day for 2 or more days, per physician discretion.	As above, or consider administration of methylprednisolone 1000 mg IV per day for 3 days; if improves, then manage as above.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. In case of raised ICP/cerebral edema, refer to Table 5 in the Pre-approval access treatment guidelines for Teclistamab (also available at de.heer.eu) for additional management guidelines.	

a. Management is determined by the most severe event, not attributable to any other cause
b. If patient is arousable and able to perform Mental Status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention
c. Attributable to no other cause.
d. All references to dexamethasone administration are dexamethasone or equivalent