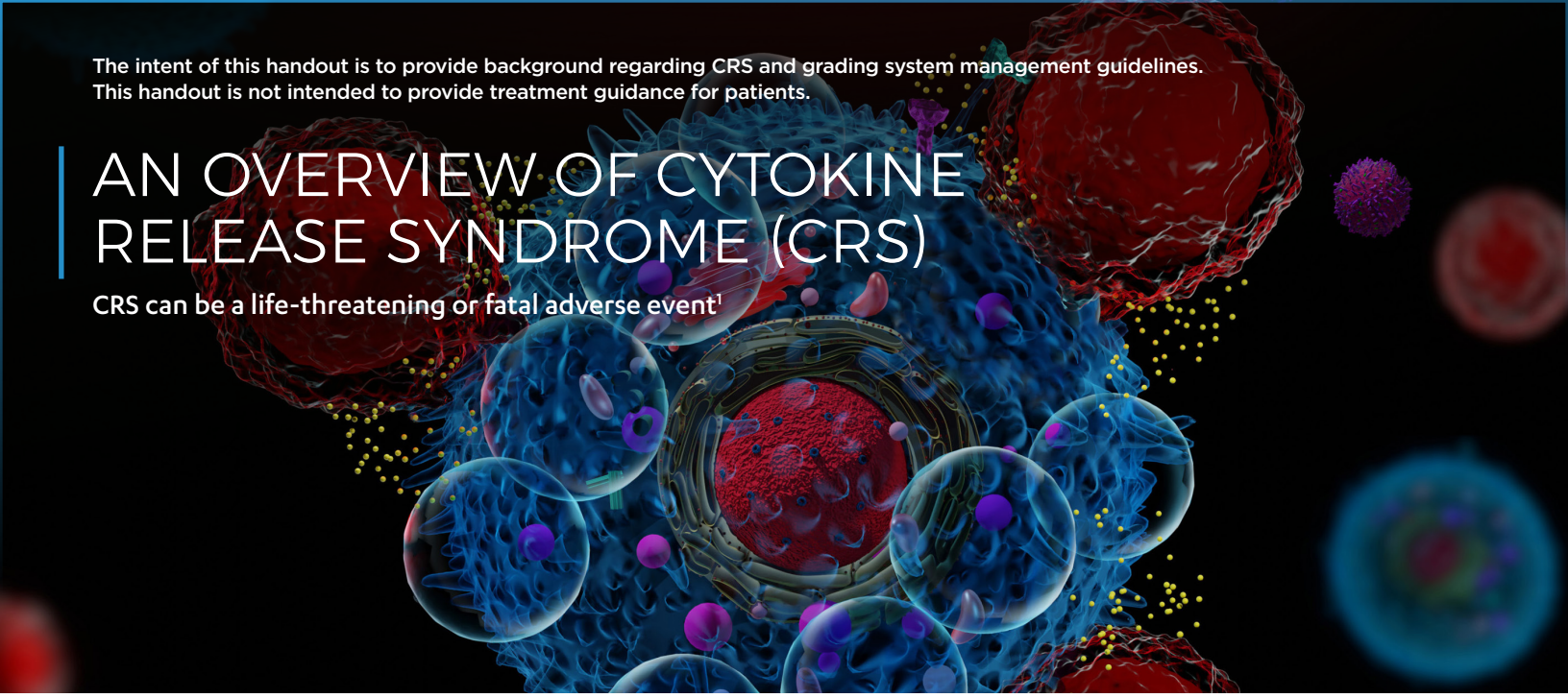
The intent of this handout is to provide background regarding CRS and grading system management guidelines. This handout is not intended to provide treatment guidance for patients.

AN OVERVIEW OF CYTOKINE RELEASE SYNDROME (CRS)

CRS can be a life-threatening or fatal adverse event[1]



CRS is characterized by high levels of serum cytokines and inflammatory markers[2,3]

- Activation and proliferation of T cells initiates a cytokine cascade from lymphocytes and other immune cells
- A range of symptoms can appear within hours/days after initiation of certain T-cell-engaging therapies

Symptoms[1,3]

Flu-like symptoms*

- Fever ≥100.4°F (≥38°C)
- Fatigue
- Headache
- Rash
- Diarrhea
- Arthralgia
- Myalgia

*Including but not limited to

Severe life-threatening manifestations*

- Hypotension
- Hypoxia
- Seizures
- Disseminated intravascular coagulation
- Multiorgan dysfunction
- Fatality

Conditions associated with CRS[2]

CRS has clinical signs similar to those of infection, HLH/MAS, TLS, and sepsis. Appropriate differential diagnosis should be considered for CRS diagnosis and management.

Clinical factors associated with CRS[2,4-7]

Patient-related factors:

- Age
- Preexisting inflammation
- Comorbidities (ie, prior infection)
- Thrombocytopenia prior to lymphodepletion (administration of therapy to deplete normal lymphocytes)

Therapy-related factors:

- Immune therapy modality construct (CAR-T therapies and other immunotherapies, such as bispecific antibody-based approaches)
- Dosing schedule

Disease-related factors:

- Disease type (high burden of disease prior to treatment)

Patients and caregivers should be counseled to look out for the symptoms of CRS (as listed in the product labeling of their current treatment) and to contact you immediately if any should emerge.

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CRS Grading Systems[8-11]

Multiple grading criteria have been defined, including CTCAE, CARTOX, and MSKCC guidelines. ASTCT (below) is a broadly used grading system that harmonizes other guidelines into a consensus framework.

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever* *with*	≥100.4°F (≥38°C)			
Hypotension *and/or*†	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring >1 vasopressor (excluding vasopressin)
Hypoxia	None	Requiring a low-flow nasal cannula‡ or blow-by	Requiring a high-flow nasal cannula,‡ facemask, nonbreather mask or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

*Fever is defined as temperature ≥100.4°F (≥38°C) not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as anti–IL-6R or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. †CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 103.1°F (39.5°C), hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. ‡Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute. Reproduced from Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. With permission from Elsevier.

Mitigation Strategies[4,6,12,13]

To reduce the risk of CRS and other side effects associated with therapy, clinical trials include the following for consideration for therapy modality:

- Step-Up Dosing
- Antipyretics
- Antimicrobials
- Corticosteroids
- Antihistamines

Monitoring[3,8,14]

Monitor early for signs and symptoms of CRS:

- Fever
- Disseminated intravascular coagulation
- CBC with differential, CMP, coag panels, ferritin, CRP, hepatic function
- Assess pulmonary and cardiac status

Management Considerations[7,14-17]

Shown below are select pharmacological management strategies for CRS from established guidelines.

Established CRS management guidelines are available for CAR-T and immune checkpoint therapies. For more comprehensive guidance on supportive care related to CRS management, refer to your institutional guidelines and established guidelines (eg, ASCO, CARTOX, SITC, and NCCN).

Consider administration of:

- Anti-IL-6R
- Corticosteroids

Operational considerations for therapy modalities[3,15]

1. Potential requirements of clinical interventions and specific site training on CRS.
2. Implementation of a dedicated clinical and safety monitoring plan for outpatient and inpatient settings.
3. Logistical considerations for the transition of care: outpatient to inpatient and vice versa.
4. Patient and caregiver education on signs and symptoms of CRS.

Consult individual product labeling to familiarize yourself with what to expect when CRS occurs and continue treatment in accordance with the guidance provided within.

ASCO, American Society of Clinical Oncology; ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CAR-T, chimeric antigen receptor T cells; CARTOX, CAR-T cell therapy–associated toxicity; CBC, complete blood count; CMP, comprehensive metabolic panel; CPAP, continuous positive airway pressure; CRP, C-reactive proteins; CRS, cytokine release syndrome; CTCAE, common terminology criteria for adverse events; HLH, hemophagocytic lymphohistiocytosis; IL-6R, interleukin 6 receptor; MAS, macrophage activation syndrome; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; SITC, Society for Immunotherapy of Cancer; TLS, tumor lysis syndrome.

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