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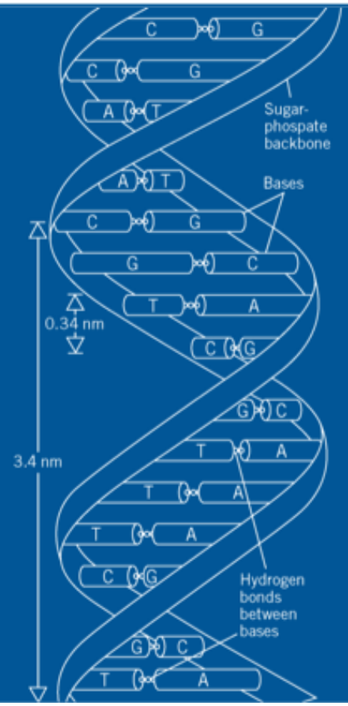
Cytokine Release Syndrome (CRS)



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Pathophysiology of CRS

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Cytokines mediate the immune response

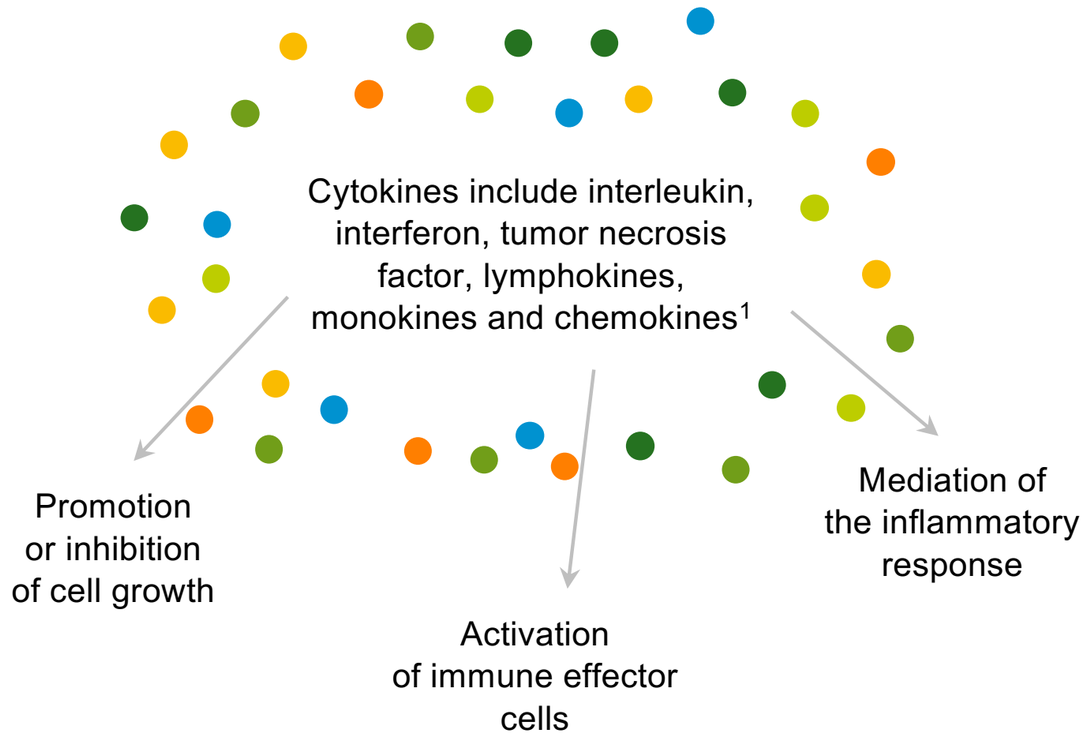
Cytokines are a diverse group of polypeptide chemical messengers that are secreted by most cells in the body[1]

Their functions include immune-cell activation and mediating the inflammatory response[1]

Cytokine activation is often associated with systemic effects, such as fever (at the onset), hypoxia, hypotension, headache, chills, nausea, fatigue and end-organ dysfunction[1–3]

CRS is a supraphysiologic response resulting from the over-activation of endogenous or infused T cells and/or other immune effector cells, which in turn leads to hypersecretion of cytokines[1–3]

CRS can be triggered by a variety of factors such as infections and certain drugs (e.g. certain antibody-based therapies and immunotherapies). CRS is a potential serious adverse event of immunotherapies, particularly some T cell-engaging immunotherapies.[3]



1. Breslin S. Clin J Oncol Nurs 2007;11(Suppl):37–42; 2. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; 3. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38

Pathophysiology of Cytokine Release Syndrome (CRS)

Immunotherapy is thought to trigger CRS via[1]

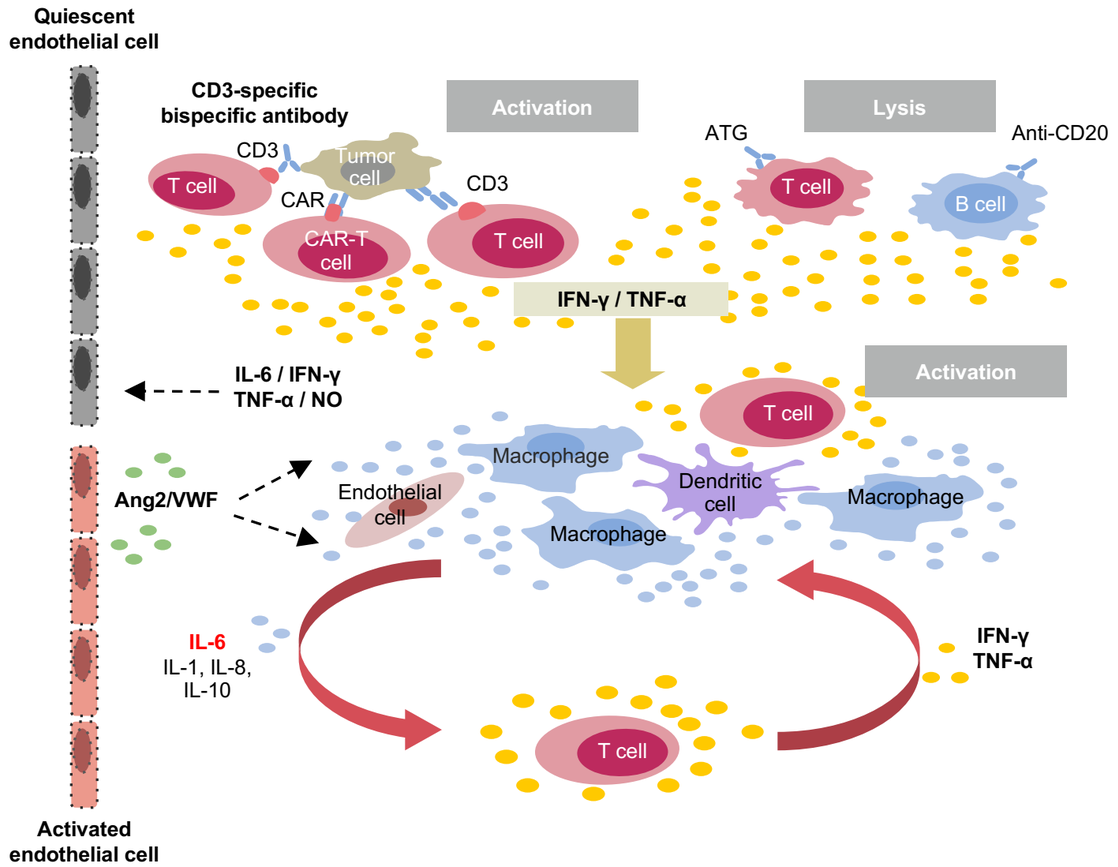
- **T-cell activation** with subsequent cytokine release (mainly IL-6, IFN-γ and TNF-α)
- **Target cell lysis** with subsequent cytokine release

These cytokines trigger a chain reaction that involves the activation of innate immune cells, such as macrophages and endothelial cells, which results in the release of additional cytokines[1]

Activated endothelial cells release stored Ang2 and VWF, while macrophages trigger the production of NO, which promotes vasodilation and hypotension[2]

Additional and uncontrolled immune cell recruitment and activation then occurs, resulting in the release of further cytokines[2]

IL-6 is considered to be a **central mediator of CRS** and is thought to contribute to many of the key symptoms[3]



1. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; 2. Cobb DA, and Lee DW. Cancer J 2021:27:119–125; 3. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; Image adapted from: Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56 and Cobb DA, and Lee DW. Cancer J 2021:27:119–125

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Clinical manifestations of CRS

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Clinical Manifestations of CRS

Mild Cases

Account for most events and often present as a febrile flu-like illness

Severe Cases

In the most severe cases, patients may have life-threatening cardiovascular, pulmonary, and renal involvement

CRS impacts multiple organ systems

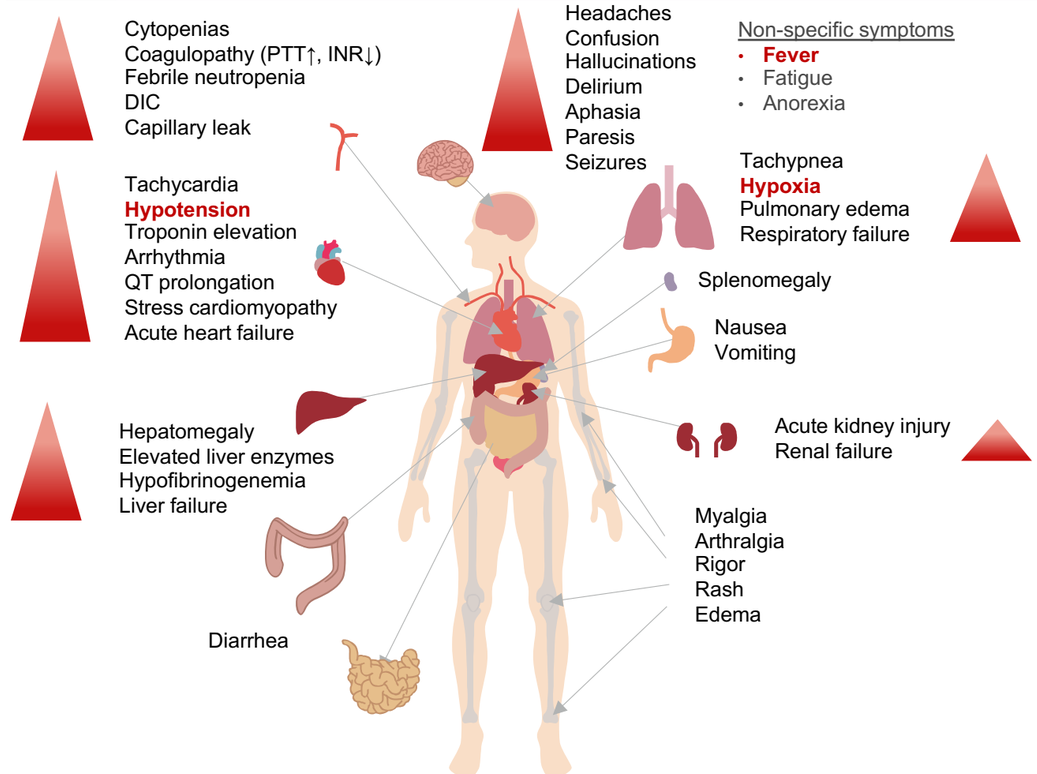

Image adapted from: Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56. CRS, cytokine release syndrome; DIC, disseminated intravascular coagulation; INR, international normalized ratio; PTT, partial thromboplastin time.

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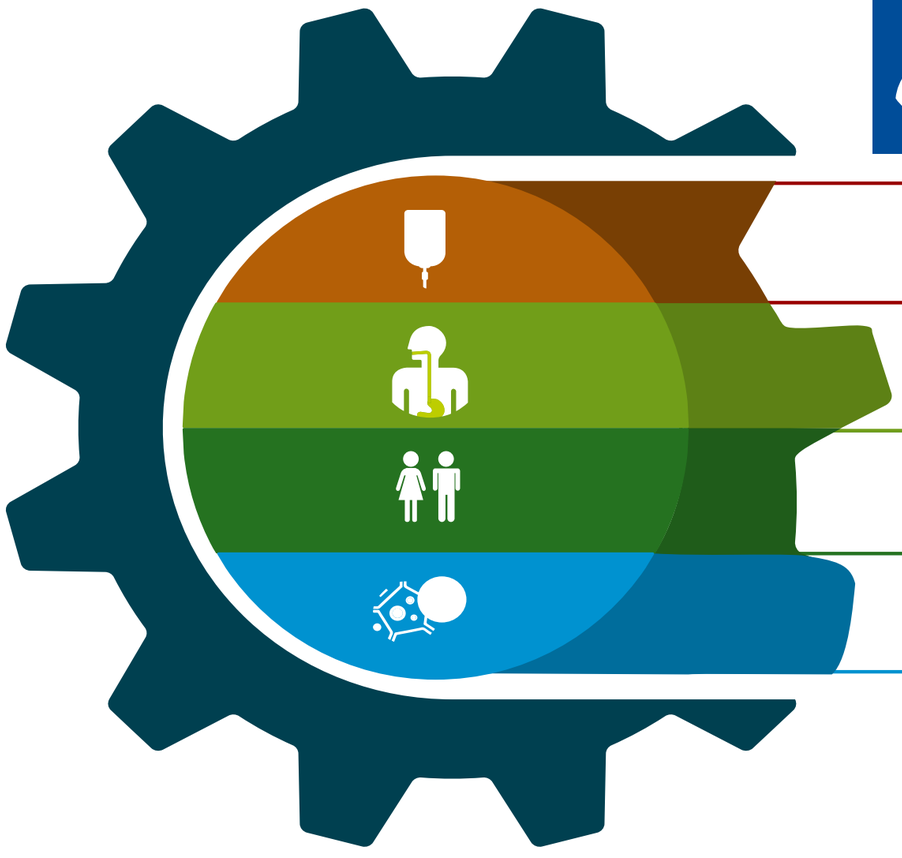
Potential predictors of CRS severity



There does not appear to be a direct association between the incidence and severity of CRS and response to immunotherapy[1]

Immunotherapies
CRS is a potential adverse event with T-cell engaging immunotherapies[1]

Underlying disease
Disease burden can be a predictor of severe CRS[2,3]

Patient characteristics (basal inflammatory state) and comorbidities
High baseline serum ferritin, CRP or cytokine levels can be associated with increased CRS risk[4,5]

Degree of T-cell activation and expansion
Onset of clinical symptoms of CRS may correlate with T-cell activation[6]

1. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; 2. Maude SL, et al. NEJM 2014;371:1507–17; 3. Park JH, et al. NEJM 2018;378:449–59; 4. Teachey DT, et al. Cancer Discov 2016;6:664–79
5. Davila ML, et al. Sci Transl Med 2014;6:224–5; 6. Frey N, and Porter D. Biol Blood Marrow Transpl 2019;25:e123–7

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Diagnosis of CRS

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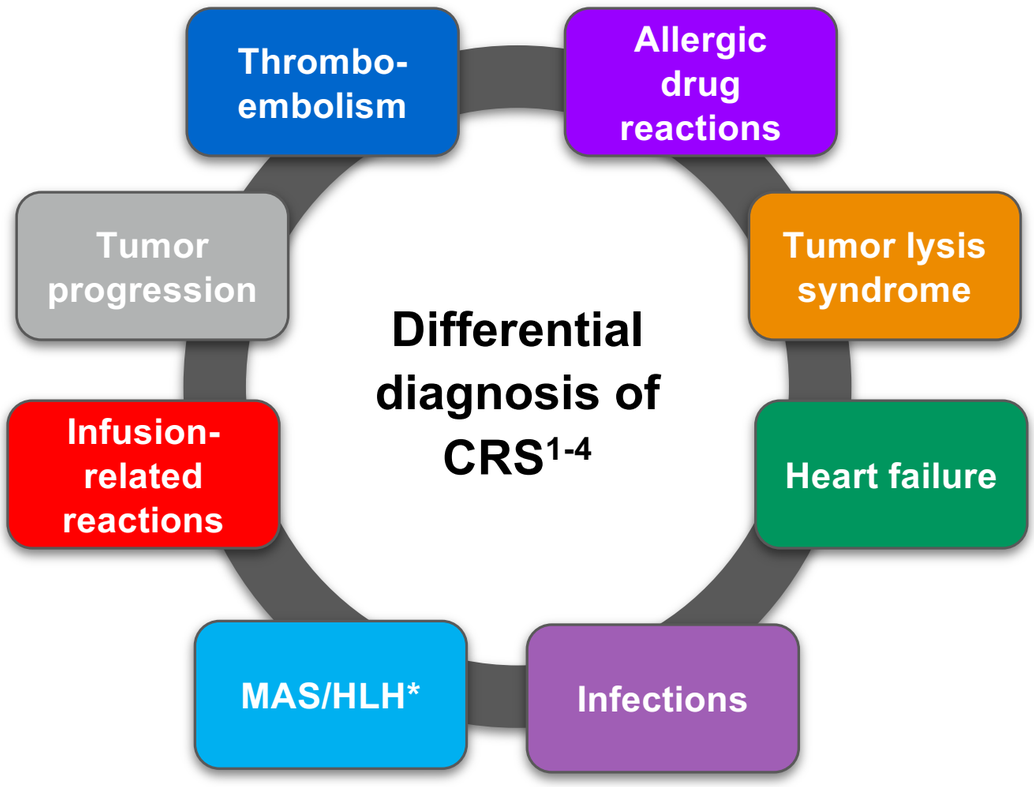
Differential diagnosis of CRS can be challenging

As patients with CRS present with a wide range of signs and symptoms, accurate diagnosis can be challenging[1]

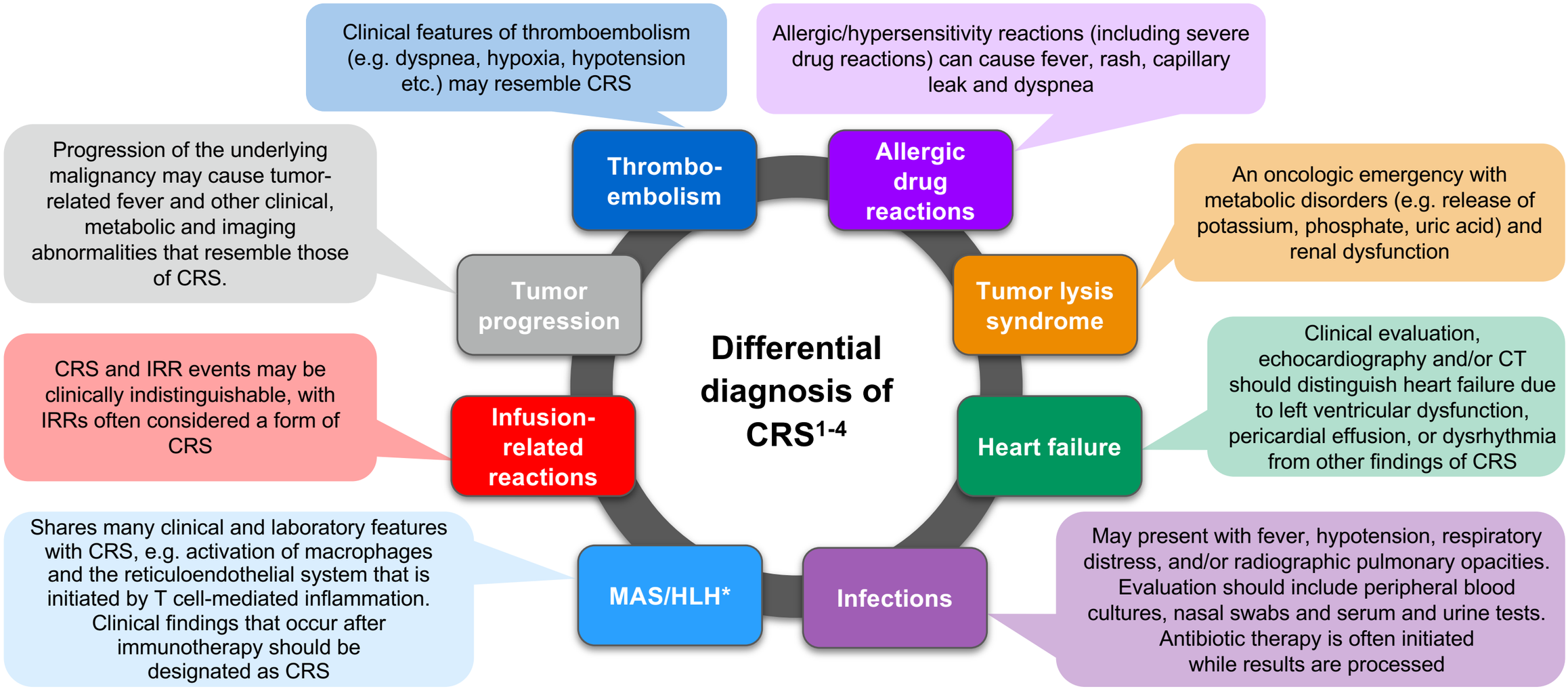
Neurologic AEs, such as headaches, confusion, dysphasia and ataxia, can occur alongside CRS in the context of T-cell targeted immunotherapy[2,3]



Recognizing whether symptoms are related to CRS or another condition is key to optimal management

*Familial or secondary MAS/HLH; 1. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; 2. Chavez JC, et al. Hematol Oncol Stem Cell Ther 2020;13:1–6; 3. Brudno N, and Kochenderfer JN. Blood 2016;127:3321–30; 4. Doessegger L & Banholzer ML. Clin Transl Immunol 2015;4:e39

Diagnosis of CRS



*Familial or secondary MAS/HLH; 1. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; 2. Chavez JC, et al. Hematol Oncol Stem Cell Ther 2020;13:1–6; 3. Brudno N, and Kochenderfer JN. Blood 2016;127:3321–30; 4. Doessegger L & Banholzer ML. Clin Transl Immunol 2015;4:e39

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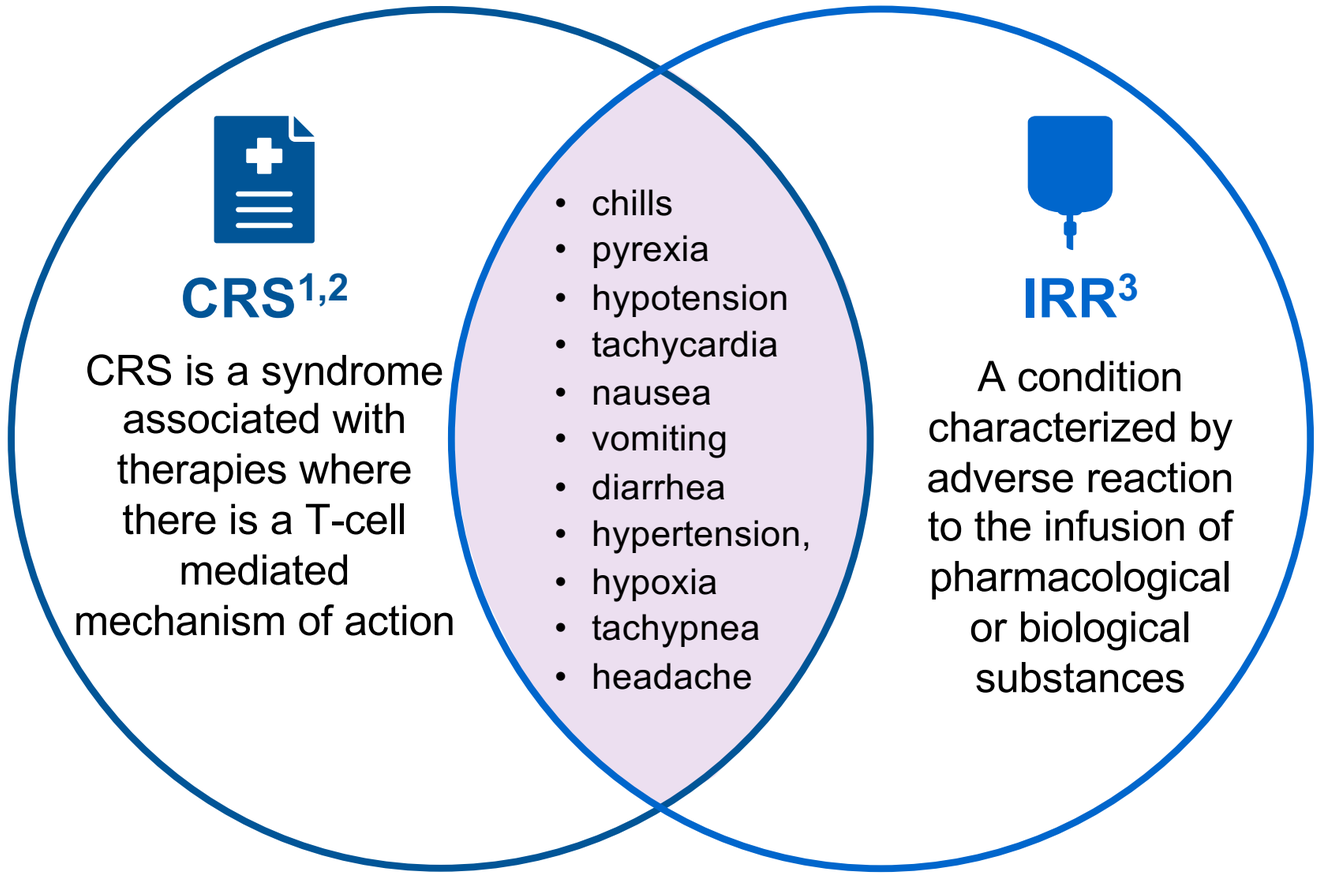
CRS vs Infusion Related Reactions (IRR)

Clinical presentations of CRS and IRR may be similar



AE, adverse event; CRS, cytokine release syndrome; IRR, infusion-related reaction. 1. Gutierrez C, et al. Crit Care Med. 2020;48(1):10-21. 2. Kroschinsky F, et al. Crit Care. 2017;21:89. 3. Doessegger L and Banholzer ML. Clin Transl Immunology. 2015;4(7):e39

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CRS may be diagnosed by process of exclusion

Exclude anaphylactic reaction
Prior exposure?
Response to antihistamines?

Exclude systemic infection
Positive blood culture, X-ray, etc?
Response to anti-infective treatment?

Exclude TLS
Hyperuricemia, hyperkalemia?
Hyperphosphatemia, hypocalcemia?

Exclude MAS/HLH
Family history of MAS/HLH?
Associated genetic aberrations with MAS/HLH?

Progression of the underlying malignancy should be considered if symptoms are mild

Gödel P, et al. Intensive Care Med 2018; 44:371–73

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Grading of CRS

Various CRS Grading Systems Have Been Developed Based on Different Assessment Criteria

2010: CTCAE version 4.03[1]

2014: **Lee criteria**[2]

2018:
- CTCAE version 5.0[3]
- Penn criteria[4]
- MSKCC criteria[5]
- CARTOX criteria[6]

2019: **ASTCT Consensus Criteria**[7]

- New **ASTCT consensus criteria** (2019) are now more commonly used†

ASTCT, American Society for Transplantation and Cellular Therapy; CARTOX, CAR-T-cell-therapy-associated TOXicity; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MSKCC, Memorial Sloan Kettering Cancer Center. †The newly updated ASTCT criteria have specific differences compared with the previous guidelines. 1. CTCAE v4.03. 2. Lee DW, et al. Blood 2014;124:188–95. 3. CTCAE v5.0. 4. Porter D, et al. J Hematol Oncol 2018;11:35. 5. Park JH, et al. Clin Infect Dis 2018;67:533–40. 6. Neelapu SS, et al. Nat Rev Clin Oncol 2018;15:47–62. 7. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38. 8. Palomba ML, et al. EHA 2020 #EP1236 [poster presentation]. 9. Schuster S, et al. N Eng J Med 2019;380:45–56. 10. Neelapu SS, et al. N Eng J Med 2017;377:2531–445. *Studies GO29781 (mosunetuzumab) and NP30179 (glofitamab).

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ASTCT Consensus Definition of CRS[1]

A supraphysiologic response following the activation or engagement of T cells and other immune effector cells for therapeutic intent.
Symptoms MUST include fever at the onset and:

- May include hypotension, capillary leak (hypoxia) and end organ dysfunction
- Symptoms must occur within a reasonable timeframe to the therapy
- **CRS is NOT defined by cytokine levels or laboratory tests**
- **CRS applies to any immune effector cell activating/engaging therapy, not just CAR-T cells**

ASTCT, American Society for Transplantation and Cellular Therapy; CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome. 1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

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Lee Criteria vs ASTCT Consensus Criteria

CRS Grade*†	Lee Criteria (2014)[1]	ASTCT Consensus Criteria (2019)[2]				
		Fever‡	+	Hypotension	+/-	O_2 Hypoxia
1	**Symptoms are not life threatening** and require symptomatic treatment only, e.g. fever, nausea, fatigue, headache, myalgias, malaise	≥ 38°C		None		None
2	**Symptoms require and respond to moderate intervention;** oxygen requirement <40% OR hypotension responsive to fluids or low dose of one **vasopressor** OR grade 2 organ toxicity	≥ 38°C		**Not requiring vasopressors**		Requiring low-flow nasal cannula¶ or blow-by
3	**Symptoms require and respond to aggressive intervention**; oxygen requirement ≥40% OR hypotension requiring high-dose or multiple vasopressors OR grade 3 organ toxicity or grade 4 transaminitis	≥ 38°C		Requiring a vasopressor +/- vasopressin		Requiring high-flow nasal cannula#, facemask, nonrebreather mask, or Venturi mask
4	**Life-threatening symptoms**; requirement for ventilator support OR grade 4 organ toxicity (excluding transaminitis)	≥ 38°C		Requiring multiple vasopressors (excluding vasopressin)		Requiring positive pressure (CPAP, BiPAP, intubation and MV)
5	**Death**	N/A				

ASTCT, American Society for Transplantation and Cellular Therapy; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MV, mechanical ventilation. *For the Lee Criteria, grades 2–4 refer to CTCAE version 4.0 grading. †For the ASTCT Criteria, organ toxicities associated with CRS may be graded according to CTCAE version 5.0, but they do not influence CRS grading; 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 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. ‡Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. ¶Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. #High-flow nasal cannula is defined as oxygen delivered at >6 L/min. 1. Lee DW, et al. Blood 2014;124:188–95; 2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

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ASTCT Consensus Criteria: Grade of CRS Defined by Management Intervention[1]

	Grade 1	Grade 2	Grade 3	Grade 4
Fever (≥38°C)	✓	✓	✓	✓
Low blood pressure	✗	Yes, treatment needed but no vasopressors required	Yes, treatment needed, including vasopressors	Yes, aggressive treatment needed*
		And/or		
Low oxygen levels	✗	Yes, minimal intervention needed (low flow, <6L O_2)	Yes, moderate intervention needed (high flow, >6L O_2)	Yes, aggressive/life-saving intervention needed†

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome. 1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25(4):625–38. * Multiple blood pressure raising therapies (vasopressors) required; † e.g. mechanical ventilation.

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Lee Criteria 2014: CRS Grading Assessment and Management[1]

GRADING		Management
Grade 1 Fever, constitutional symptoms		• Vigilant supportive care • Assess for infection - Treat fever and neutropenia - Monitor fluid balance - Antipyretics, analgesics as needed
Grade 2 Hypotension: responds to fluids or one low dose pressor Hypoxia: responds to <40% O_2 Organ toxicity: grade 2	*Extensive co-morbidities or older age?* No	• Vigilant supportive care (Monitor cardiac and other organ function)
Grade 3 Hypotension: requires multiple pressors or high dose pressors Hypoxia: requires ≥ 40% O_2 Organ toxicity: grade 3, grade 4 transaminitis	Yes	• Vigilant supportive care • Tocilizumab ± corticosteroids
Grade 4 Mechanical ventilation Organ toxicity: grade 4, excluding transaminitis		

1. Lee DW, et al. Blood 2014;124:188–95

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Management of CRS

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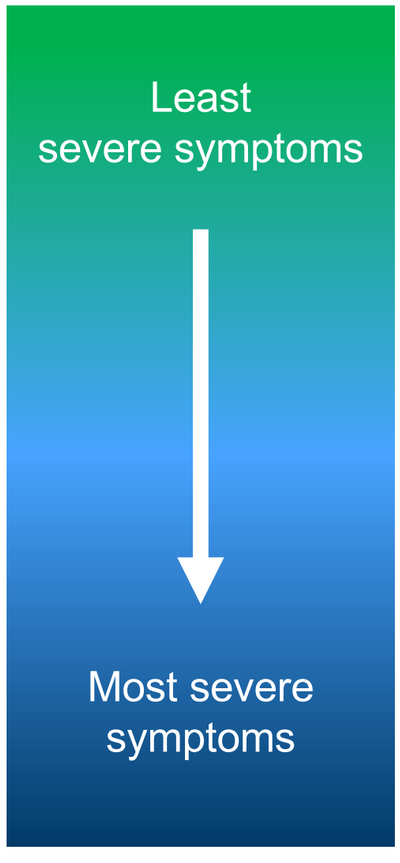
Therapies To Consider for Management of CRS Symptoms Depending on Severity



Potential symptom management

- Antipyretics, antihistamines, antiemetics, analgesics
- Corticosteroids
- Antibiotics/anti-infectives (infection)
- Fluid resuscitation (for mild hypotension)
- Hemodynamic support
- O_2 (for hypoxia)
- Vasopressors (for severe hypotension)
- Anti-cytokine therapy +/- corticosteroids (for severe or life-threatening CRS)
- CPAP, mechanical ventilation (for respiratory distress)

CPAP, continuous positive airway pressure; CRS, cytokine release syndrome. Lee DW, et al. Blood 2014;124:188–95. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Monitoring and resolution of CRS

- The duration and degree of monitoring of CRS should reflect the severity of the illness

Mild to moderate CRS (Grade 1–2)
Clinical and laboratory monitoring should be performed daily initially, then tapered as the symptoms improve

Moderate to severe CRS (Grade 3–4)
May require monitoring in an intensive care setting with daily clinical and laboratory monitoring.
Patients should not be discharged until clinically stable.

Clinical monitoring (every 1–4 hours)	Laboratory monitoring (once or twice daily)
• Body temperature • Respiratory rate • Blood pressure • Heart rate • O_2 levels • Neurological exam	• Blood counts • Electrolytes • Kidney and liver function tests • Cytokine profile

CRS is considered resolved when there is a sustained resolution of fever and no further need for oxygen supplementation or vasopressors

Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–3
Brudno JN, and Kochenderfer JN. Blood 2016;127:3321–30

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Summary

Summary

CRS is thought to result from **over-activation of endogenous or infused T cells** and/or other immune effector cells, leading to **hypersecretion of cytokines** [1-3]

A variety of factors may trigger CRS such as infections and certain drugs[2]

CRS can be triggered by T-cell activation and direct target cell lysis, leading to subsequent **cytokine release** and an exaggerated or excessive **systemic inflammatory response**[3,4]

Symptoms and severity vary, ranging from mild flu-like symptoms with fever (most common) to very rare, severe life-threatening manifestations of systemic inflammation (e.g. hypotension, hypoxia, capillary leak, coagulopathy, multi-organ failure)[2,3]

Early recognition and treatment of symptoms is important to reduce the severity of CRS[5]

Treatment algorithms can be used to guide diagnosis and management of mild to severe CRS[6]

1. Breslin S. Clin J Oncol Nurs 2007;11(Suppl):37–42; 2. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56; 3. Lee DW, et al. Blood 2014;124:188–95; 4. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–3; 5. Gardner RA, et al. Blood 2019;134:2149–58; 6. Yakoub-Agha I, et al. Haematologica 2020;105:297–316