Understanding and Managing Immune Effector Cell Toxicities in Hematologic Malignancies

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Objectives & Disclosure

Assess the risk for immune effector toxicity associated with therapies for hematologic malignancies

Propose a strategy to manage a patient experiencing immune effector toxicity

Disclosure

- *I have no conflicts of interest to disclose*
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Immune Effector Toxicity vs Immune Related Adverse Effects

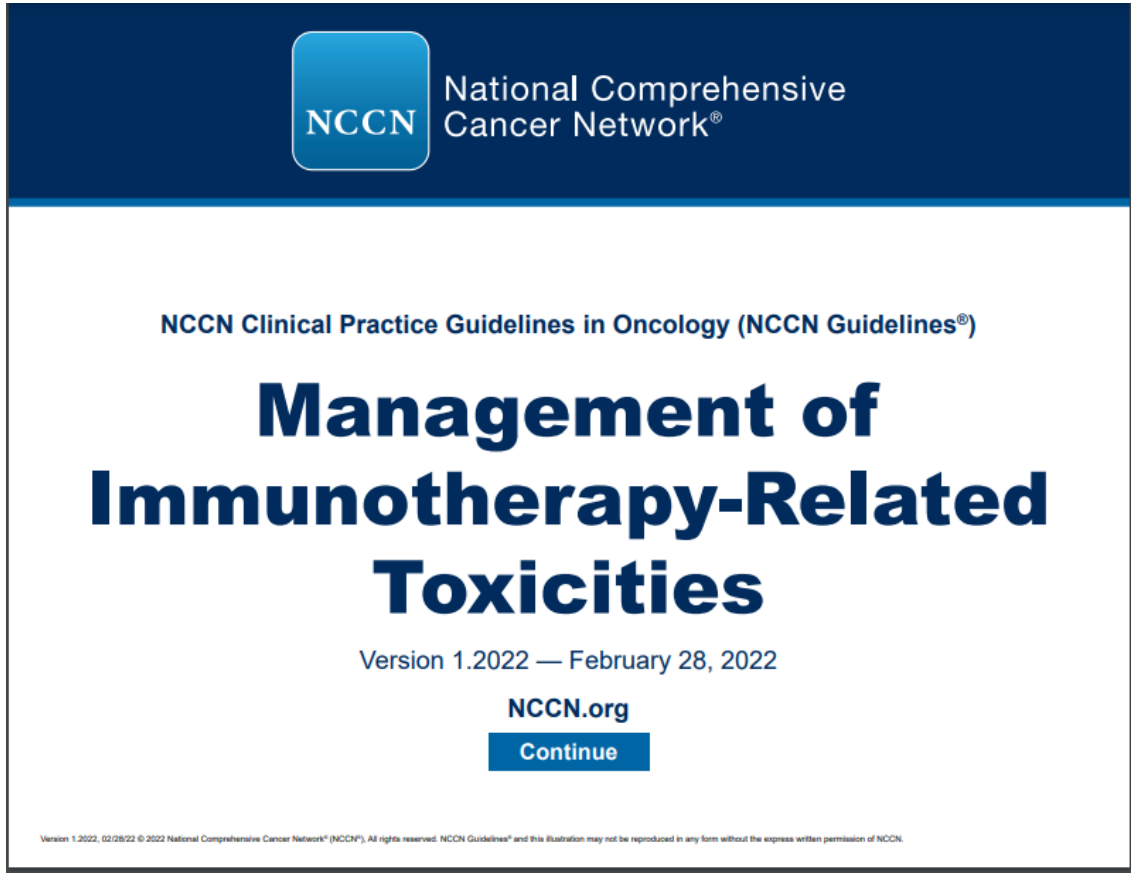
Immune system manipulation as a therapeutic strategy continues to expand

Checkpoint inhibitors

- Immune related adverse effects (iRAE)

Chimeric antigen receptor (CAR) T-cell, Bispecific T-cell engager (BiTE) therapy

- Immune effector cell toxicity



https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

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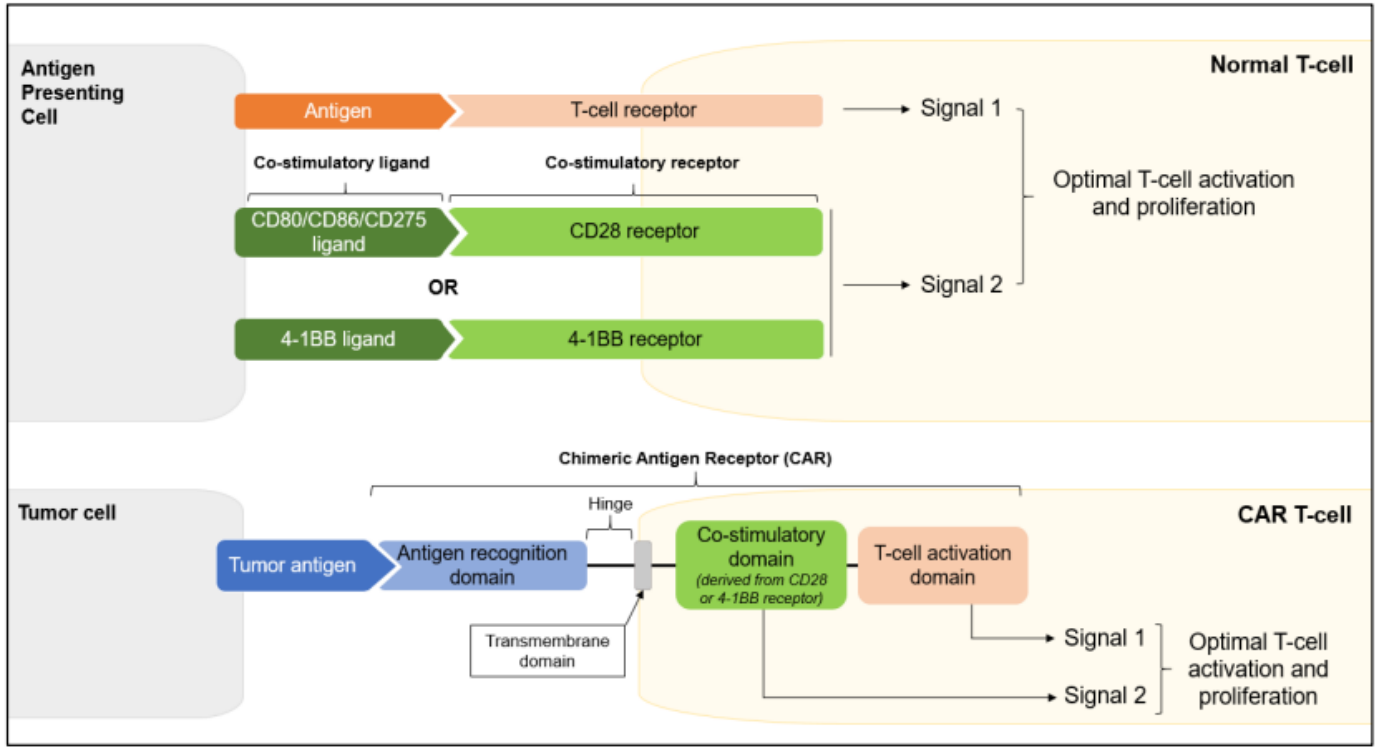
Chimeric Antigen Receptor (CAR) T-cell Therapy

Figure 1: Optimal T-cell (and CAR T-cell) activity requires two signals



https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

FDA Approved Agents	Target	Indication
Axicabtagene Ciloleucel (Axi-Cel)	CD19	r/r FL, r/r LBCL
Brexucabtagene Autoleucel (Brexu-Cel)		r/r ALL, r/r MCL
Lisocabtagene Maraleucel (Liso-Cel)		r/r LBCL
Tisagenlecleucel (Tis-Cel)		r/r ALL, r/r DLBCL, r/r FL
Ciltacabtagene Autoleucel (Cilta-Cel)	BCMA	r/r MM
Idecabtagene Vicleucel (Ide-Cel)		r/r MM

r/r: relapsed refractory

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Immune Effector Cell Toxicity

Cytokine Release Syndrome (CRS)

- Infused T-cells, host immune effector cells, and/or vascular endothelial activation result in:
  - Hyperinflammation
  - Overproduction of inflammatory cytokines (IL-6, IL-1, INFγ, TNFα)
- Typical onset 2-3 days
- Typical duration: 7-8 days

- Fevers, chills, tachycardia, hypotension, hypoxia, capillary leak, organ dysfunction, hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS)

Immune Effector Cell –Associated Neurotoxicity Syndrome (ICANS)

- Systemic hyperinflammation affects blood-brain barrier + increased vascular permeability result in:
  - Accumulation of cytokines (IL-6, INFγ, TNFα) host-immune cells, and CAR T-lymphocytes in brain
- Typical onset: 4-10 days
- Typical duration: 14-17 days

- Encephalopathy, delirium, hallucinations, cognitive defects, tremors, ataxia, dysphasia, nerve palsies, focal motor or sensory deficits, myoclonus, somnolence, obtundation, seizures

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Blood Reviews. 2019;34:45-55
https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

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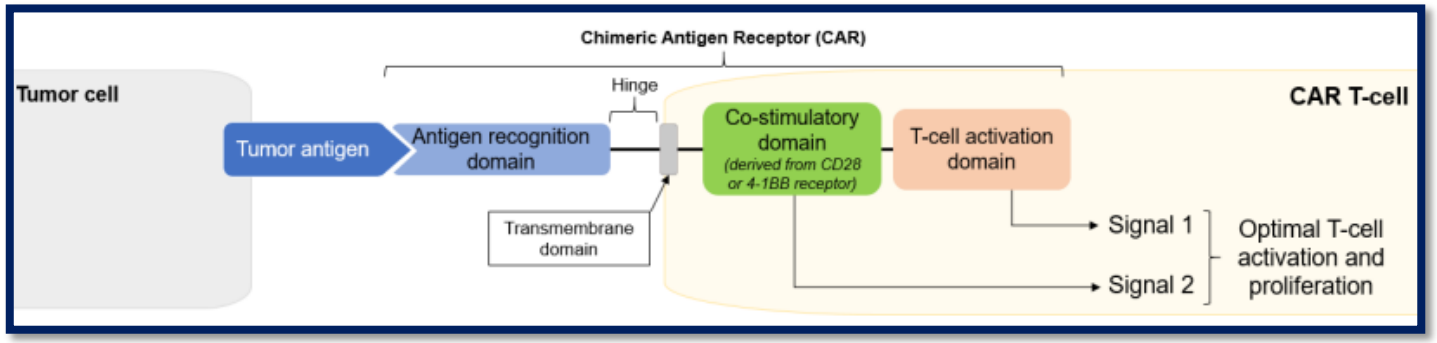
Agent Specific Toxicity

	Trial	Target	Costimulatory domain	CRS	Severe CRS	ICANS	Severe ICANS	CRS/ICANS related deaths
NHL	ZUMA-1 (Axi-Cel)	CD19	CD28	93%	13%	64%	28%	1 CRS, 1 HLH
	JULIET (Tis-Cel)		4-1BB	58%	22%	21%	12%	0
	TRANSCEND (Liso-Cel)		4-1BB	42%	2%	30%	10%	0
MCL	ZUMA2 (Brexu-Cel)		CD28	91%	15%	63%	30%	0
ALL	ELIANA (Tis-Cel)		4-1BB	77%	47%	40%	13%	0
	ZUMA 3 (Brexu-Cel)		CD28	89%	24%	60%	25%	1 ICANS
MM	KarMMa (Ide-Cel)	BCMA	4-1BB	84%	5%	18%	3%	1 CRS
	CARTITUDE (Cilta-Cel)		4-1BB	95%	4%	21%	9%	1 CRS, 1 ICANS



https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
Cancer Treatment Reviews. 2022;111:102479
Lancet. 2021;398:491-502

ASTCT Consensus Grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C
		WITH		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or		
Hypoxia	None	Requiring low-flow nasal cannula	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

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Biol Blood Marrow Transplant. 2019;25:625-638.

ASTCT Consensus Grading for ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICE Criteria	Points Possible
Orientation: year, month, city, hospital	4
Naming: name 3 objects	3
Following commands: follow simple commands	1
Writing: write a sentence	1
Attention: count backwards from 100 by 10	1

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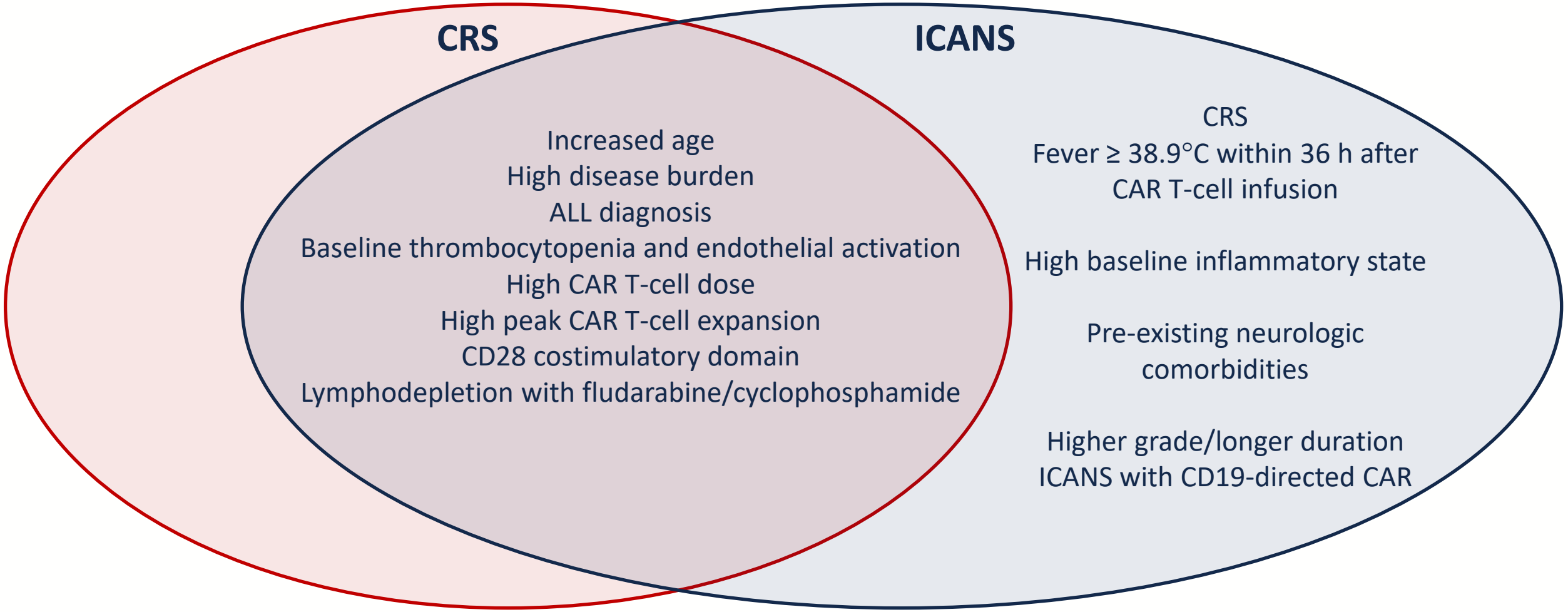
Biol Blood Marrow Transplant. 2019;25:625-638.

Immune Effector Toxicity Risk Factors



https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Cancer Treatment Reviews. 2022;111:102479
Front Pharmacol. 2022;13:950923
Ann Oncol. 2021;32:34-48

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Immune Effector Toxicity Management Overview

- Immunosuppression to counter overactive immune effector cells and increased cytokine levels

Tocilizumab	Corticosteroids	Supportive Care
• Humanized IgG1κ anti-IL6R antibody • Binds both soluble and membrane-bound IL-6R • Insufficient CNS penetration • May increase CSF IL-6 levels • Generally limited to 2 doses during a CRS episode	• CONCERN – higher doses could suppress CAR T-cell expansion and persistence • Detrimental impact on efficacy not supported in most studies • Dexamethasone may be preferred for ICANS due to better CNS penetration • Rapid taper once symptoms begin to improve	• Antipyretics • IV hydration • Vasopressors • Seizure prophylaxis (i.e., levetiracetam)

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https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

J Clin Oncol. 2021;39:3978-92

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Alternative Therapies for Immune Effector Toxicity

- Limited data with alternative therapies

Siltuximab (IL-6 antagonist)	Ruxolitinib (JAK 1 and 2 inhibitor)	Anakinra (IL-1Ra antagonist)	Cyclophosphamide

Intravenous Immune Globulin	Anti-thymocyte Globulin	Extracorporeal cytokine adsorption with CRRT (no additional immune suppression)

Cancer Treatment Reviews. 2022;111:102479
Annals Oncol. 2021;32:34-48
https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Management of CAR-T Associated CRS

CAR-T	Grade 1	Grade 2	Grade 3	Grade 4
Axi-Cel	Tocilizumab if lasts > 24 h	Tocilizumab Dex 10 mg IV daily	Tocilizumab Dex 10 mg IV q8h*	Tocilizumab MP 1g/d IV
Brexu-Cel	Tocilizumab if lasts > 24 h	Tocilizumab Consider Dex if unresponsive to tocilizumab	Tocilizumab MP 1 mg/kg IV q12h or Dex 10 mg IV q6h	Tocilizumab MP 1g/d IV
Liso-Cel	Tocilizumab if <72 h after inf. Dex 10 mg IV q24h if < 72 h after inf.	Tocilizumab Dex 10 mg IV q 12-24h if < 72 h after inf. (consider if > 72h)	Tocilizumab Dex 10 mg IV q6h	Tocilizumab Dex 20 mg IV q6h*
Tis-Cel	Tocilizumab if lasts > 72 h	Tocilizumab Consider Dex if unresponsive to tocilizumab	Tocilizumab MP 2 mg/kg/d IV or equivalent*	Tocilizumab MP 1g 1-2 times/day
Cilta-Cel	Consider Tocilizumab	Tocilizumab Consider Dex IV q12-24h	Tocilizumab Dex 10 mg IV q12h*	Tocilizumab Dex 20 mg IV q6h*
Ide-Cel	Tocilizumab if < 72 h after inf. Consider Dex 10 mg IV q24h	Tocilizumab Consider Dex 10 IV q12-24h	Tocilizumab Dex 10 mg IV q12h*	Tocilizumab Dex 20 mg IV q6h*

h: hours; Dex: dexamethasone, inf: infusion; IV: Intravenously; MP: methylprednisolone
*NCCN guidelines recommend dexamethasone 10 mg IV q6 hours

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Recommendations based toxicity management included in Prescribing Information for each medication as of 1/2023

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Management of CAR-T Associated ICANS

CAR-T	Grade 1	Grade 2	Grade 3	Grade 4
Axi-Cel	Dex 10 mg IV x 1 Seizure prophylaxis	Dex 10 mg IV q6h* Seizure prophylaxis	MP 1g/d IV Seizure prophylaxis	MP 1g IV q12h Seizure prophylaxis
Brexu-Cel		Dex 10 mg IV q6h* Seizure prophylaxis	Dex 10 mg IV q6h Seizure prophylaxis	MP 1g/d IV Seizure prophylaxis
Liso-Cel	Dex 10 mg IV q12-24 hours if occurring < 72hrs after inf Seizure prophylaxis	Dex 10 mg IV q12h* Seizure prophylaxis	Dex 10-20 mg IV q8-12h Seizure prophylaxis	Dex 20 mg IV q6h Seizure prophylaxis
			If cerebral edema: MP 1-2g IV q24h + cyclophosphamide 1.5g/m^2	
Tis-Cel	Seizure prophylaxis if at risk	Consider Dex 10 mg IV q6-12h8 or MP 1 mg/kg IV q12h Seizure prophylaxis if at risk	Dex 10 mg IV q6-12h or MP 1 mg/kg q12h Seizure prophylaxis if at risk	MP 1g 1-2 x/d Seizure prophylaxis if at risk
Cilta-Cel	Dex 10 mg IV q12-24h Seizure prophylaxis	Dex 10 mg IV q12h* Seizure prophylaxis	Dex 10-20 mg IV q6h Seizure prophylaxis	Dex 20 mg IV q6h Seizure prophylaxis
			If cerebral edema: MP 1-2g IV q24h	
Ide-Cel	Dex 10 mg IV q 12-24 h if occurring < 72h after inf Seizure prophylaxis	Dex 10 mg IV q12h* Seizure prophylaxis	Dex 10-20 mg IV q6-12h Seizure prophylaxis	Dex 20 mg IV q6h Seizure prophylaxis
			If cerebral edema: MP 1-2g q24h + cyclophosphamide 1.5 g/m^2	

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h: hours; Dex: dexamethasone, inf: infusion; IV: Intravenously; MP: methylprednisolone

*NCCN recommends 1 dose of dexamethasone 10 mg IV, then reassess

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Recommendations based toxicity management included in Prescribing Information for each medication as of 1/2023

Prophylaxis and Early Treatment

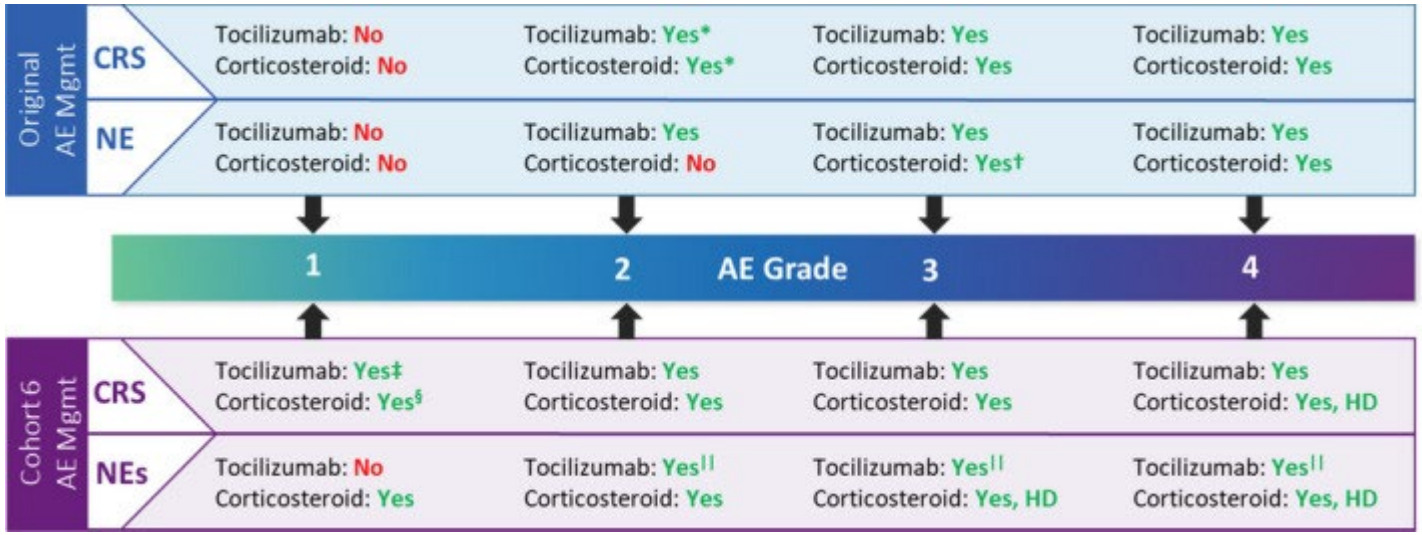
- Corticosteroid prophylaxis
- Anakinra prophylaxis
- JAK1 inhibition
- Lenzilumab (GM-CSF inhibitor)
- Fractionation of CAR T-cell dose
- Simvastatin
- Early tocilizumab

Cancer Treatment Reviews. 2022;111:102479
Annals Oncol. 2021;32:34-48
https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Steroid Prophylaxis

- Concern: Higher cumulative dose/longer duration steroid → decreased survival

- ZUMA-1, cohort 6: Axi-cel + dexamethasone 10 mg/d on days 0-2
  - Also included earlier CRS/ICANS management



CRS	
Any grade	80%
≥ Grade 3	0%
Time to onset of CRS	5 days
Duration of CRS	4 days
ICANS	
Any grade	58%
≥ Grade 3	13%
Median time to onset	6 days

- 2 yr update: ORR 95%; CR 80%; DOR: 25.9 mo; PFS 26.8 mo

- Use of lower doses up front to prevent need for higher doses to treat CRS/ICANS?

Blood. 2021;137:3273-3276
Br J Haemtol. 2021;194:690-700
Blood. 2022;140:10399–10401

Anakinra Prophylaxis and Treatment

Systematic review of anakinra treatment

- N=132 patients with aggressive B-cell lymphoma and grade 3-4 steroid-refractory ICANS
- Grade 5 ICANS: 4.7% (historical 16-27%)
- Amelioration of neurological status: 46-100%
- Higher response rate and lower early mortality with doses > 200 mg/d

Prophylactic anakinra: Open label, prospective pilot study in LBCL

- 100 mg daily or 100 mg twice daily x 7 days starting day 0

	Anakinra	TMTV matched historical cohort
CRS any grade	95%	100%
CRS grade 2-4	40%	70%
ICANS any grade	35%	70%
ICANS grade 3-4	20%	50%
ICANS duration	2 days	10 days
Day 30 CR rate	65%	55%

TMTV: total metabolic tumor volume

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Blood. 2022;140:5056–5057
Blood. 2022;140:7493–7495

JAK Pathway Inhibition

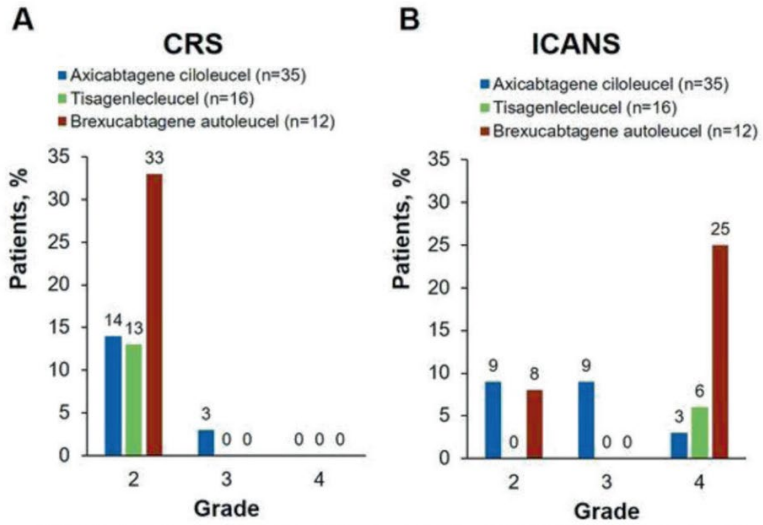
Ruxolitinib

- Treatment of steroid refractory CRS may result in rapid resolution
- *In vitro* data: reduced cytokine release and temporary inhibition of CAR-T proliferation without damaging viability
  - Cytotoxic activity of CAR-T cells restored after ruxolitinib removed
  - Cytokine inhibition maintained

Itacitinib prophylaxis

- Phase 2 trial, n=63 with B-cell malignancies
- Itacitinib 200 mg PO daily from day -3 to day 26
- Onset/duration: CRS – 4d/3d, ICANS 5d/2d
- Promising activity at prevention of grade 2+ CRS/severe ICANS
- Expanded to Phase 3 trial

Figure 1. Incidence of **a** CRS and **b** ICANS grade ≥2 by CAR-T therapy.



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, IEC-associated neurotoxicity syndrome; IEC, immune effector cell.

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J Cell Mol Med. 2021;24:1089-1099
Biochem Biophys Res Commun. 2022;595:54-61
Bone Marrow Transplant. 2022;57:11015

Lenzilumab

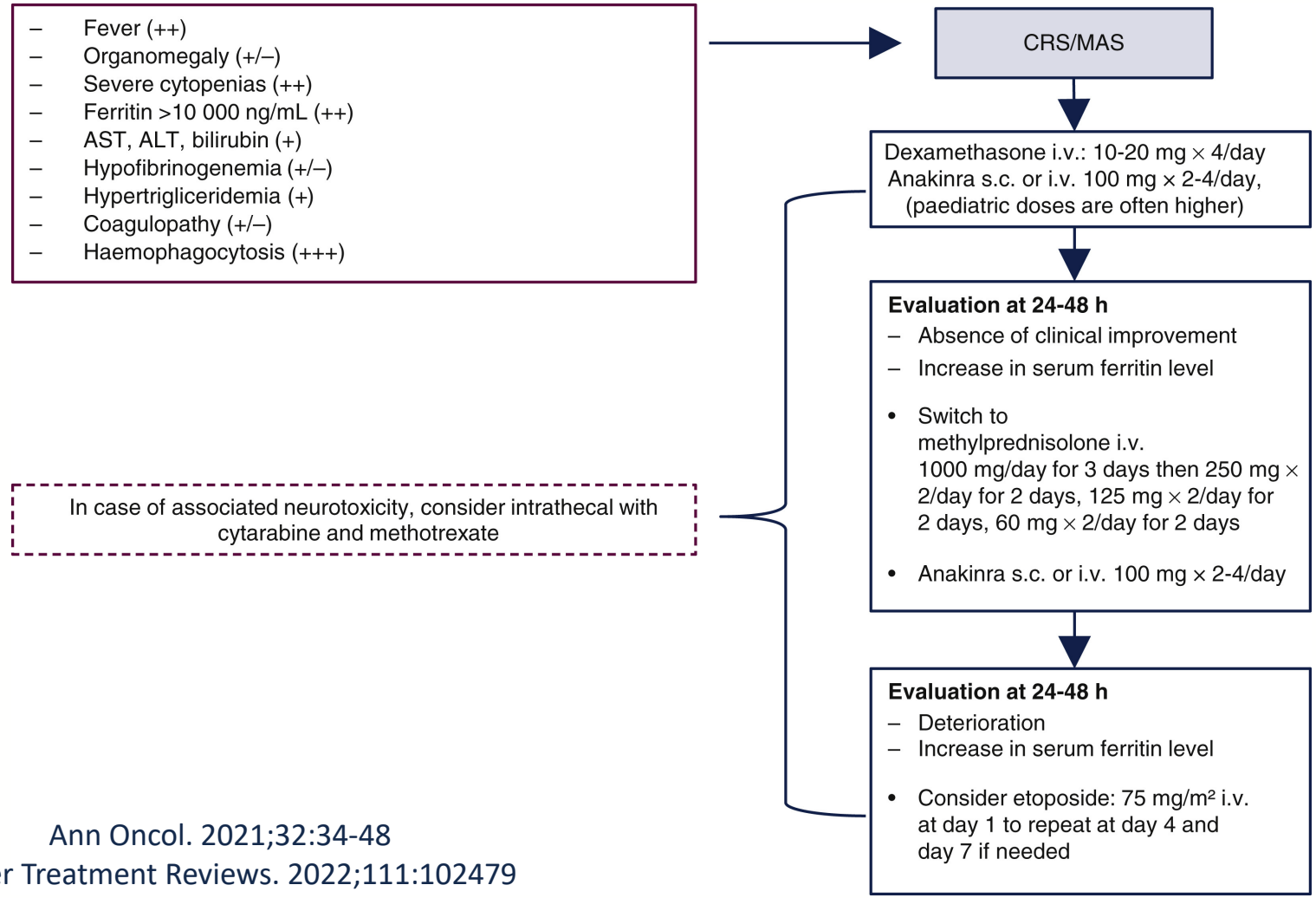
- Granulocyte-macrophage-colony-stimulating factor (GM-CSF) levels associated with grade ≥ 3 ICANS and CRS
- Lenzilumab – Humanized anti-GM-CSF monoclonal antibody
- Phase 1, ZUMA-19: n=6 with LBCL
  - 600 mg or 1,800 mg 6 hours prior to Axi-cel

	Lenzilumab 600 mg (n=3)	Lenzilumab 1,800 mg (n=3)	Overall (n=6)
Any grade CRS	67%	67%	67%
Grade ≥ 3 CRS	0%	0%	0%
Any grade neurotoxicity event	100%	67%	83%
Grade ≥ 3 neurotoxicity event	33%	0%	17%

Blood. 2022;140:10318-10320

Hemagophagocytic Lymphohistiocytosis (HLH)/Macrophage-Activation Syndrome (MAS)

- Severe immunological syndrome caused by uncontrolled immune activation
- 1 – 3.5% of those receiving CAR T-cell therapy
  - Overlap with severe CRS
- Most cases resolve with clinical management and resolution of CRS



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J clin Oncol. 2021;39:3978-3992
Ann Oncol. 2022;33:259-75
https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

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Bispecific T-cell Engager: Blinatumomab

CRS

- All grade: 16%; grade ≥ 3: 5%
- Onset day 2

- Prevention
  - Cytoreduction: BM blast > 50%, peripheral blast > 15,000/µL, extramedullary tumor load, or rapid increase in LDH
  - Premedication with dexamethasone
  - Dose step

- Treatment
  - Grade 1/2: consider steroid
  - Grade 3/4: Dexamethasone 8 mg IV q8hours and hold or discontinue therapy
  - May consider steroids in earlier grade
  - Tocilizumab may be considered for grades 3 or 4

Neurotoxicity

- All grade: 52%; grade ≥ 3: 13%
- Onset day 9, duration 5d

- Prevention: seizure prophylaxis?

- Treatment
  - Grade 1/2: hydration, consider dexamethasone, antiseizure medication
  - Grade 3/4: Dexamethasone 8mg IV q8h and hold or discontinue therapy
  - May restart those with grade 3 when <grade 1 x 3 days

Conclusions

- Immune effector cell toxicities (CRS/ICAN) occur commonly and require prompt recognition and grading
- Early, grade-based management with tocilizumab and/or steroids is necessary to prevent progression
- Most respond to guideline/grade driven management
- Novel therapeutic and prophylactic approaches under investigation to decrease the impact of toxicity as number of FDA approved agents and indications continue to increase

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