Bispecific Antibodies in Cancer Care

WHAT THIS MEANS FOR PATIENTS AND CAREGIVERS:

“What to Know and What to Expect”

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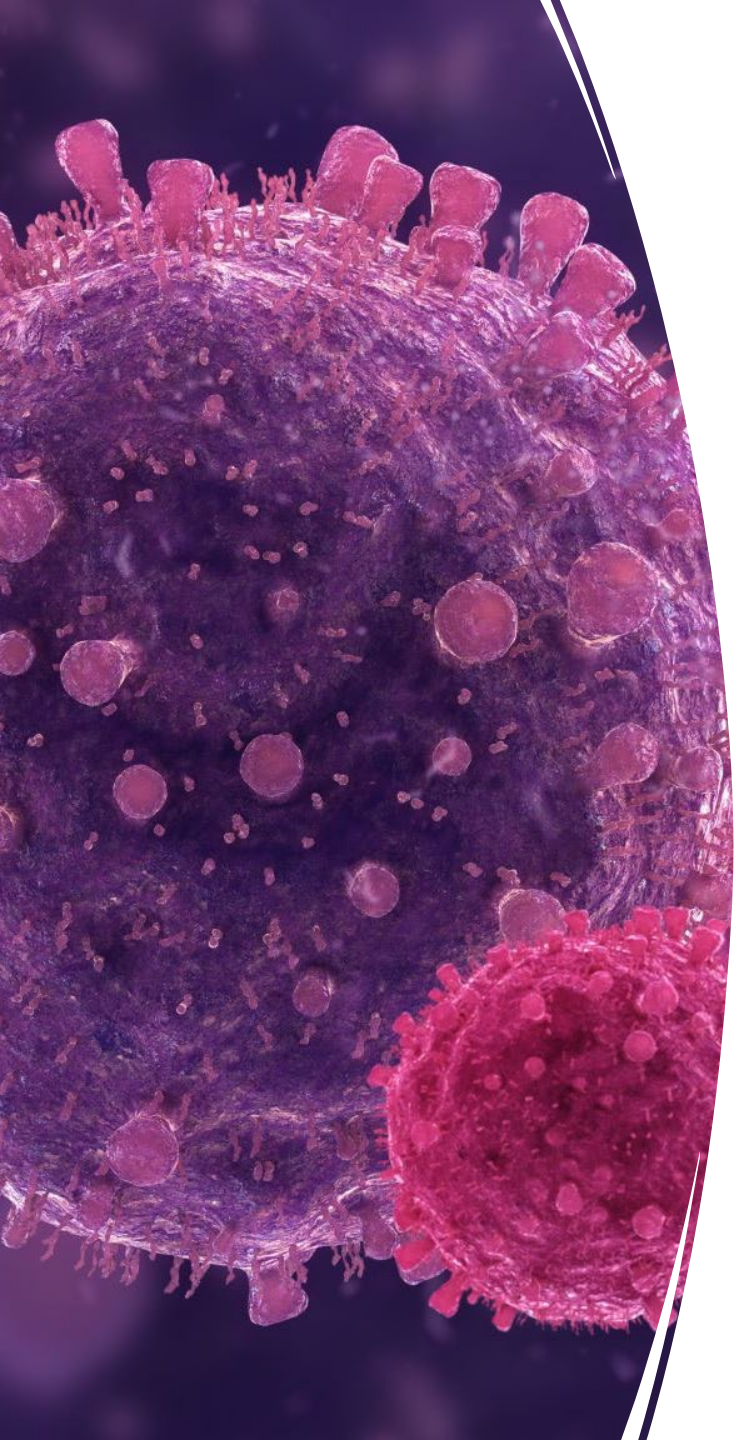
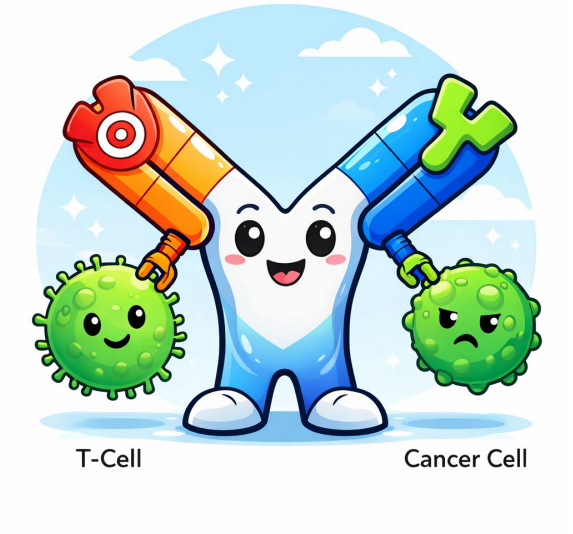
Why This Matters Now

- Changing how we treat blood cancers
  - Used in Lymphoma, Myeloma (Small Cell Lung Cancer, Uveal Melanoma)
  - Moving earlier in treatment

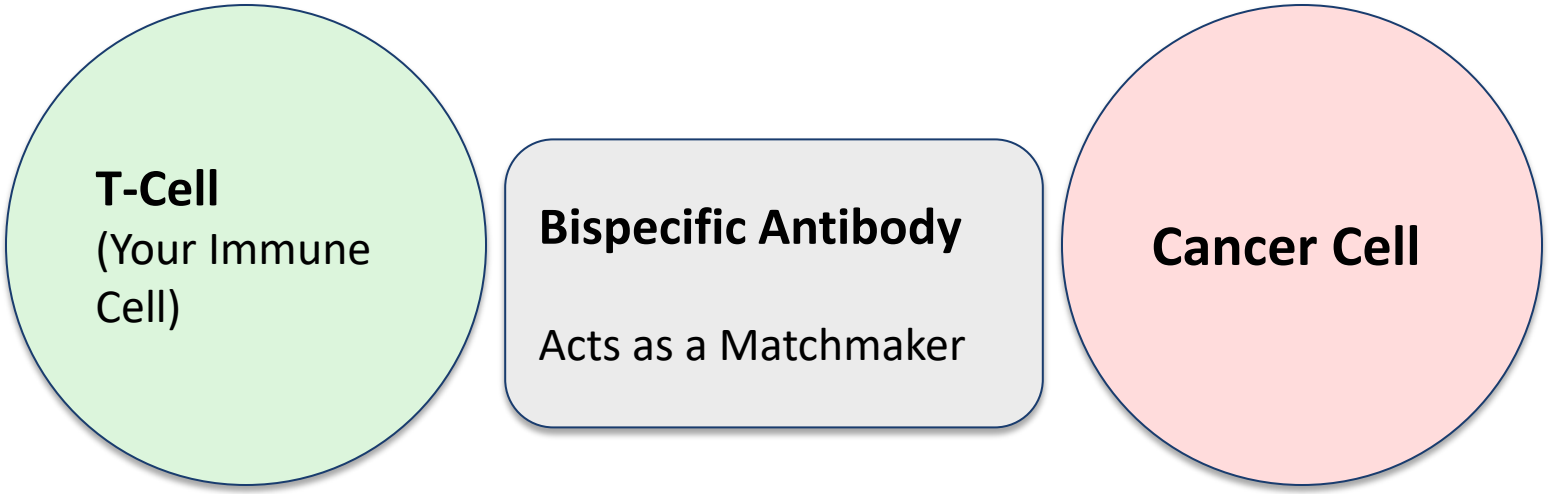


What Are Bispecific Antibodies?

- A type of immunotherapy
  - Connects your immune system to cancer
  - Helps T-cells attack cancer cells



Bispecific Antibodies: The Matchmaker



It connects your immune system to the cancer cell so your body can attack it.

How Is This Different?

- Not chemotherapy
  - Not a stem cell transplant
  - Not engineered cells like CAR-T
  - Ready-made immune therapy

When Are Bispecifics Used?

Relapsed disease 2L and 3L

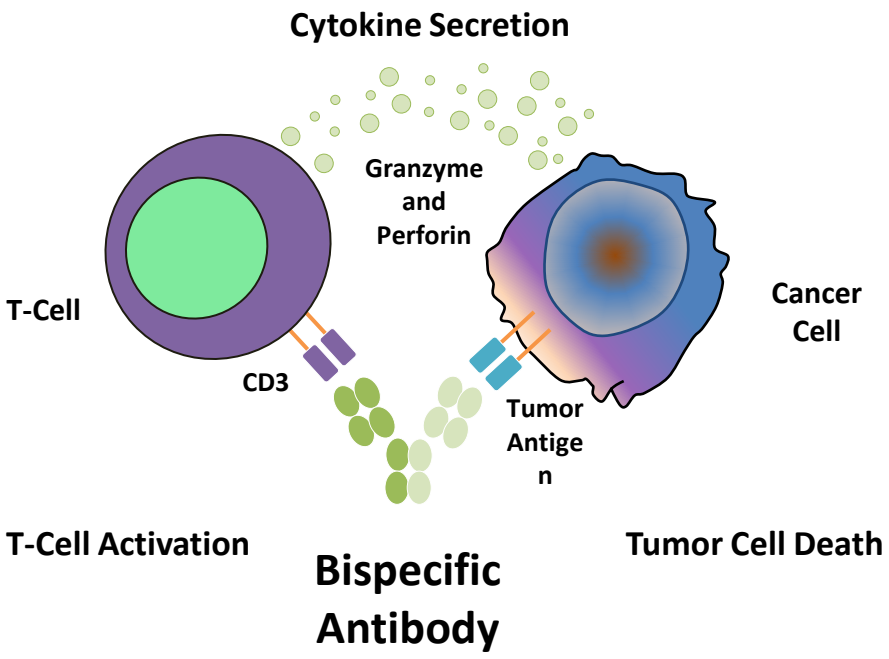
Clinical Trials Earlier

Wave of future, expanding role in treatment

Bispecifics in Lymphoma

- Target CD20 currently
  - Used in relapsed lymphoma (DLBCL and FL)
  - Monotherapy or combination
  - Newly diagnosed pts in clinical trials
  - CD19 Bispecifics in clinical trials

CD20xCD3 Bispecific Antibodies: Mechanism of Action

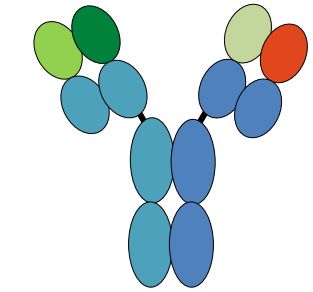


- Bivalent IgG-like, full-length Ab cotargeting CD20 (B-cells) and CD3 (pan T-cell marker)
- Off-the-shelf availability
- Target different epitopes on CD20 (potential for co-administration with anti-CD20 antibodies)
- Fc mutations to avoid ADCC, CDC, or fratricidal killing of antitumor T-cells
- Preserved neonatal FcR binding for prolonged half-life
- Cytotoxicity occurs in an MHC-independent manner
- Share pharmacokinetic properties with mAbs

Falchi. Blood. 2023;141:467.

CD20xCD3 Bispecific Antibodies: Structure and Function

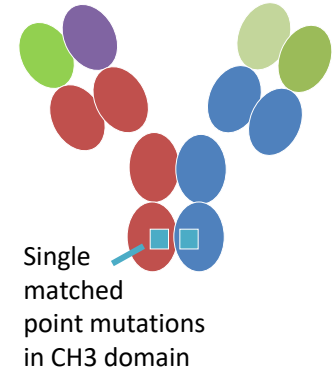
Humanized mouse IgG1-based mAbs



Mosunetuzumab (IV*)

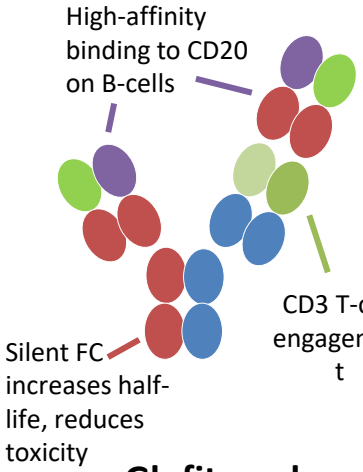
*SC formula under investigation.

FDA accelerated approval: 2L+ R/R FL



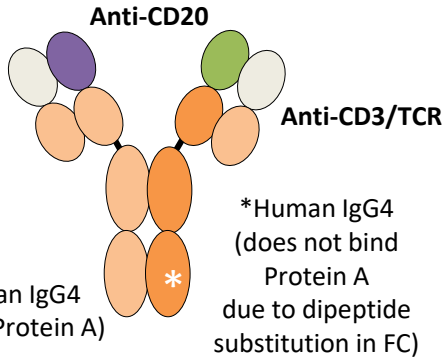
Epcoritamab (SC)

FDA accelerated approval: 2L+ R/R FL and 2L+ R/R DLBCL



Glofitamab (IV)

FDA accelerated approval: 2L+ R/R DLBCL and 2L+ LBCL arising from FL



Phase III OLYMPIA-1 trial on going, EU approval: 2L+ R/R FL and DLBCL

Mosunetuzumab PI. Epcoritamab PI. Glofitamab PI. Falchi. Blood. 2023;141:467. NCT06091254.

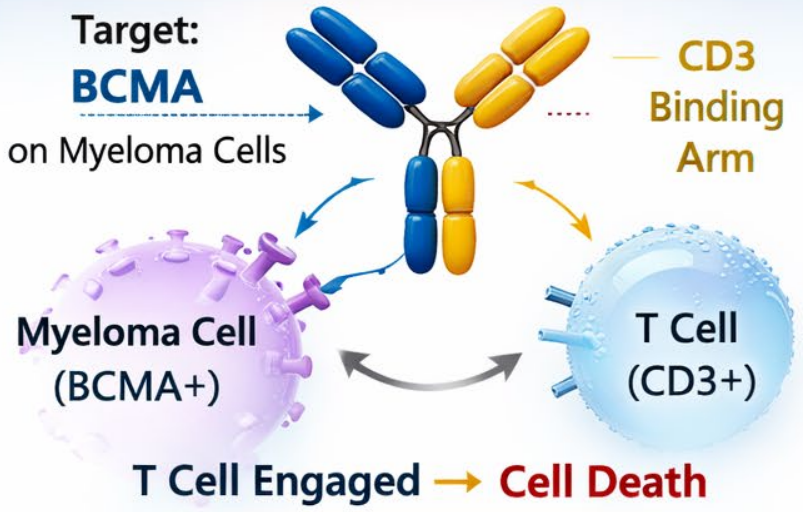
Bispecifics in Myeloma

- Target BCMA or GPRC5D
  - Used when myeloma returns
  - Newly diagnosed pts in clinical trials
  - Can lead to deep responses
  - New targets and combinations being studied

Myeloma Bispecific Antibody Platforms

Re-engaging T Cells to Destroy Myeloma

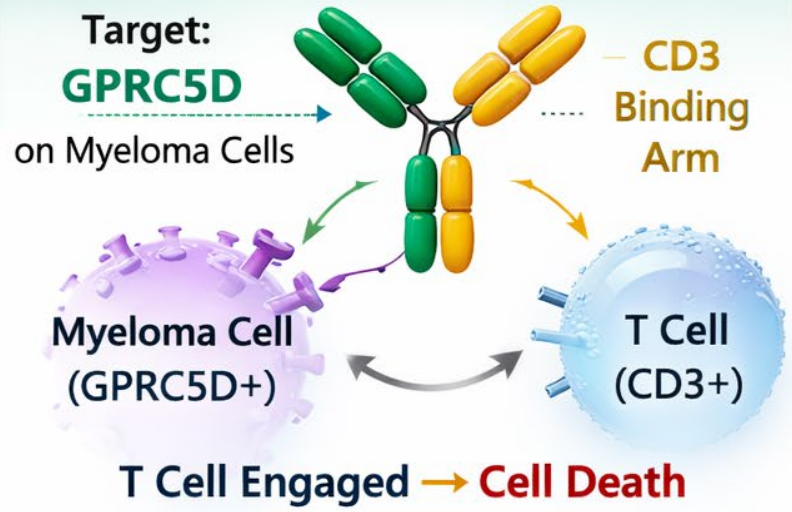
BCMA × CD3 Bispecifics



T Cell Engaged → **Cell Death**

- **Teclistamab**
- **Elranatamab** *(and others)*

GPRC5D × CD3 Bispecifics



T Cell Engaged → **Cell Death**

- **Talquetamab**

(next-gen agents)

Common Features

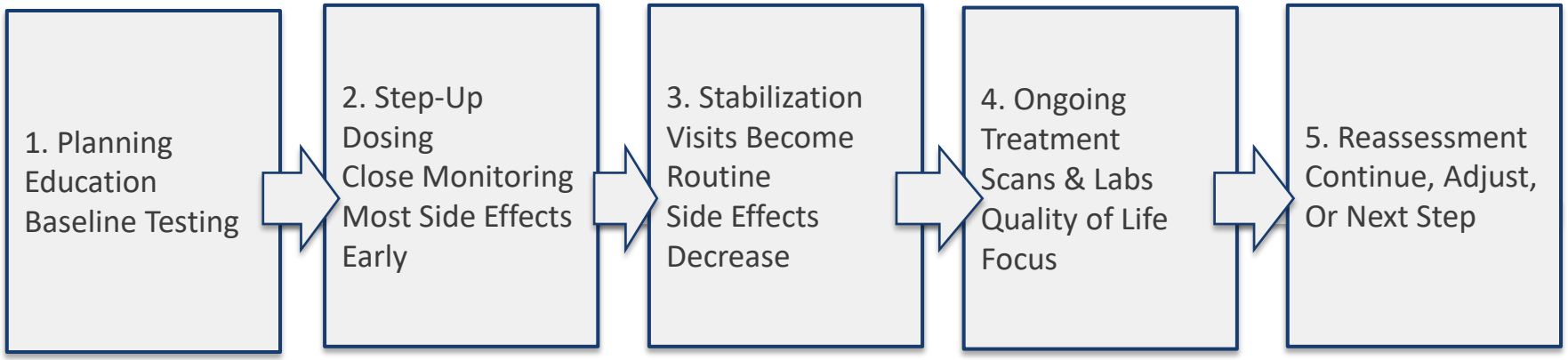
- T-Cell Redirecting
- Tumor-Specific Killing
- Engineered Fc = Safer
- CRS & ICANS Risk → Managed with Step-Up Dosing

Where are the Bispecifics?

Academic Centers

Community Oncology Offices

Your Journey on a Bispecific Antibody



This is a structured, monitored process — you are never navigating it alone.

National Expert Safety Guidance

WHAT THIS MEANS FOR YOU

- We plan before treatment starts
- We watch closely during early doses
- We expect fever and treat early
- We monitor for confusion
- We adjust safely if needed

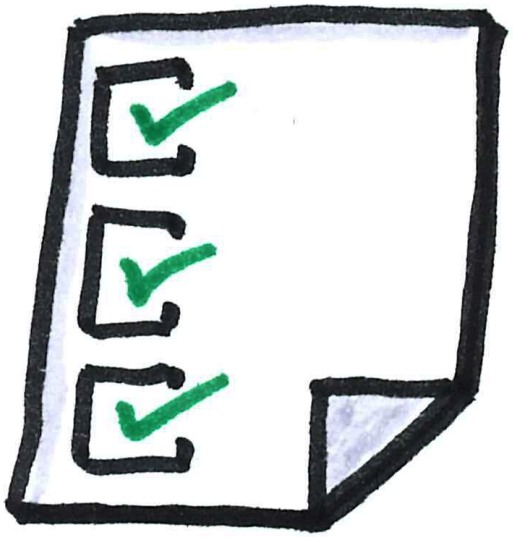
There is a structured safety plan.

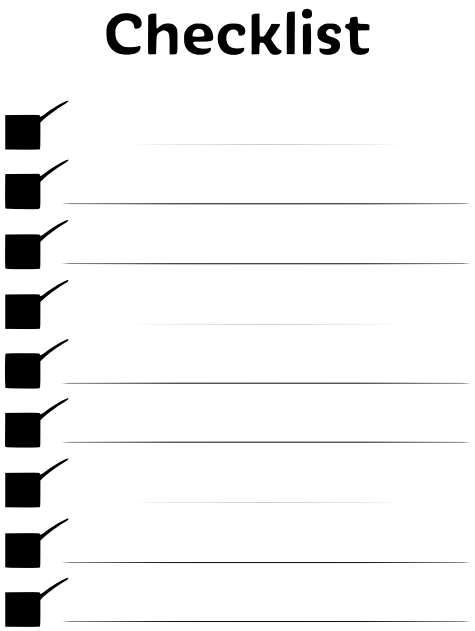
WHAT THE CONSENSUS GUIDELINES RECOMMEND

- Baseline clinical evaluation
- Step-up dosing strategy
- Structured CRS grading & management
- Neurologic monitoring protocols
- Early use of tocilizumab or steroids when indicated

Guidance developed by national experts.

What do you do when you start a patient?





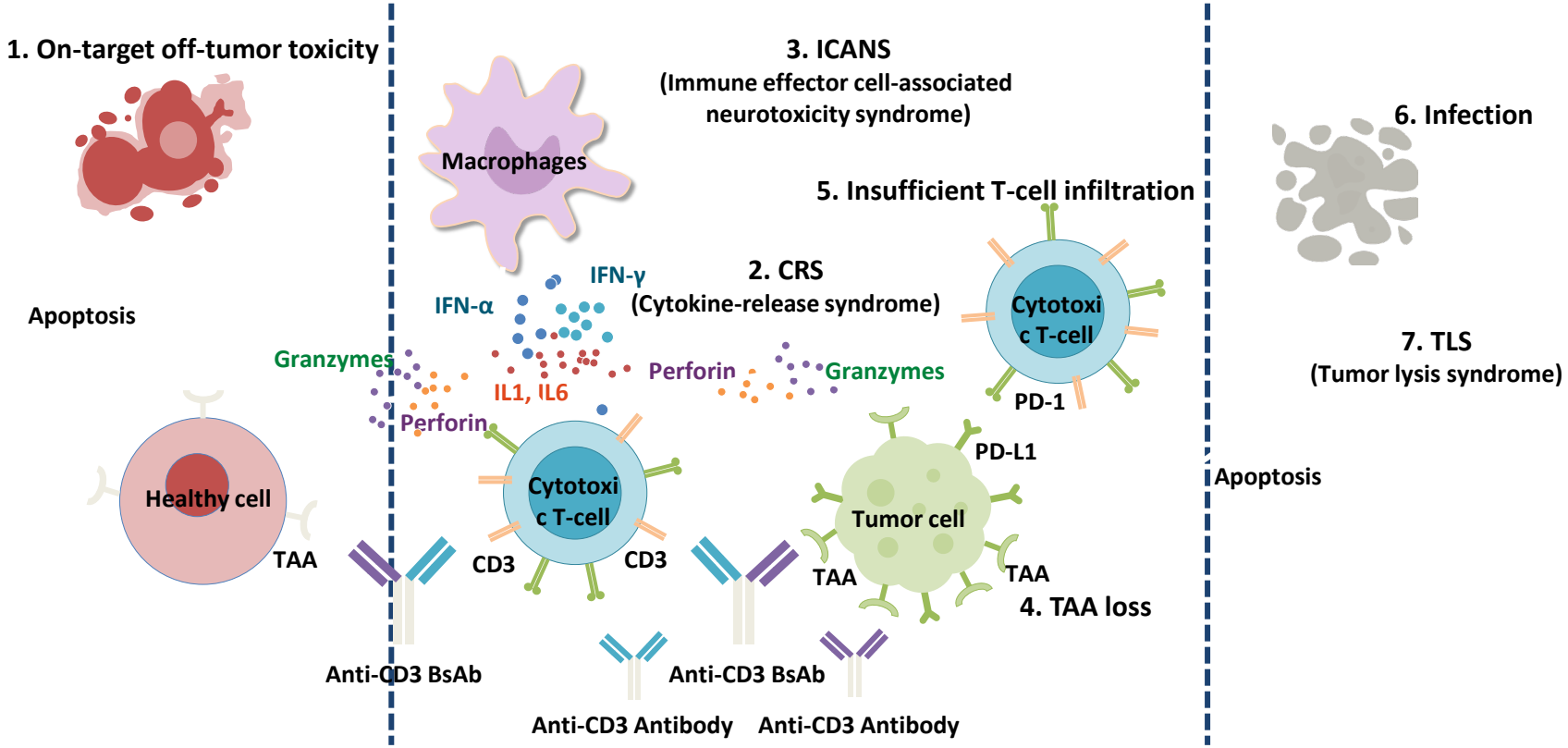
- [ ] Bispecific Team Notified: Patient's Name, DOB, Drug and requested start date (prefer 7 days' notice)
- [ ] APP performing teach; has the individual been trained and do they have the necessary documents including ICE questionnaire for patient/caregiver
- [ ] Patients have a caregiver and if they do not arrangements must be made. **Patients are excluded from outpatient observation and must be admitted if they are unable to provide a caregiver**
- [ ] If patient lives >60 min from the treatment center, it is preferred that the patient stay at hotel** during observation period. Inpatient admission for observation is last resort.
  **Hotel stays for patients who are on trial will be covered by the sponsor **please contact Dr. Graff for potential costs that could be covered by the sponsor.
  **Patients who are on commercial treatment can use the MCB Foundation for hotel stay coverage
- [ ] Verify all patient and caregivers' numbers. Let caregiver know they will be called if patient does not answer
- [ ] Drug, Cycle # and day of step-up dosing must be updated in patient banner with each treatment
- [ ] Medical equipment must be purchased (or provided if cannot afford) and brought to first treatment appointment.
  **Equipment for patients who are on trial will be covered by the sponsor **please contact Dr. Graff for potential costs that could be covered by the sponsor.
- [ ] Patient and caregiver to demonstrate proper use and vitals to be taken on MCB equipment and patient's before leaving chemo suite
- [ ] If the patient is to be inpatient, then all medical equipment must be in the room before discharge and set of vitals to be done on patient equipment and hospitals before discharge
- [ ] Those set of vitals (2 sets) must be the first email on Maddie's patient thread (ALWAYS use Maddie's thread)
- [ ] 10am and 4pm calls by doctor team; 10pm and 5am calls by bispecific team. Any additional calls also stay on thread

blood®
Special Report

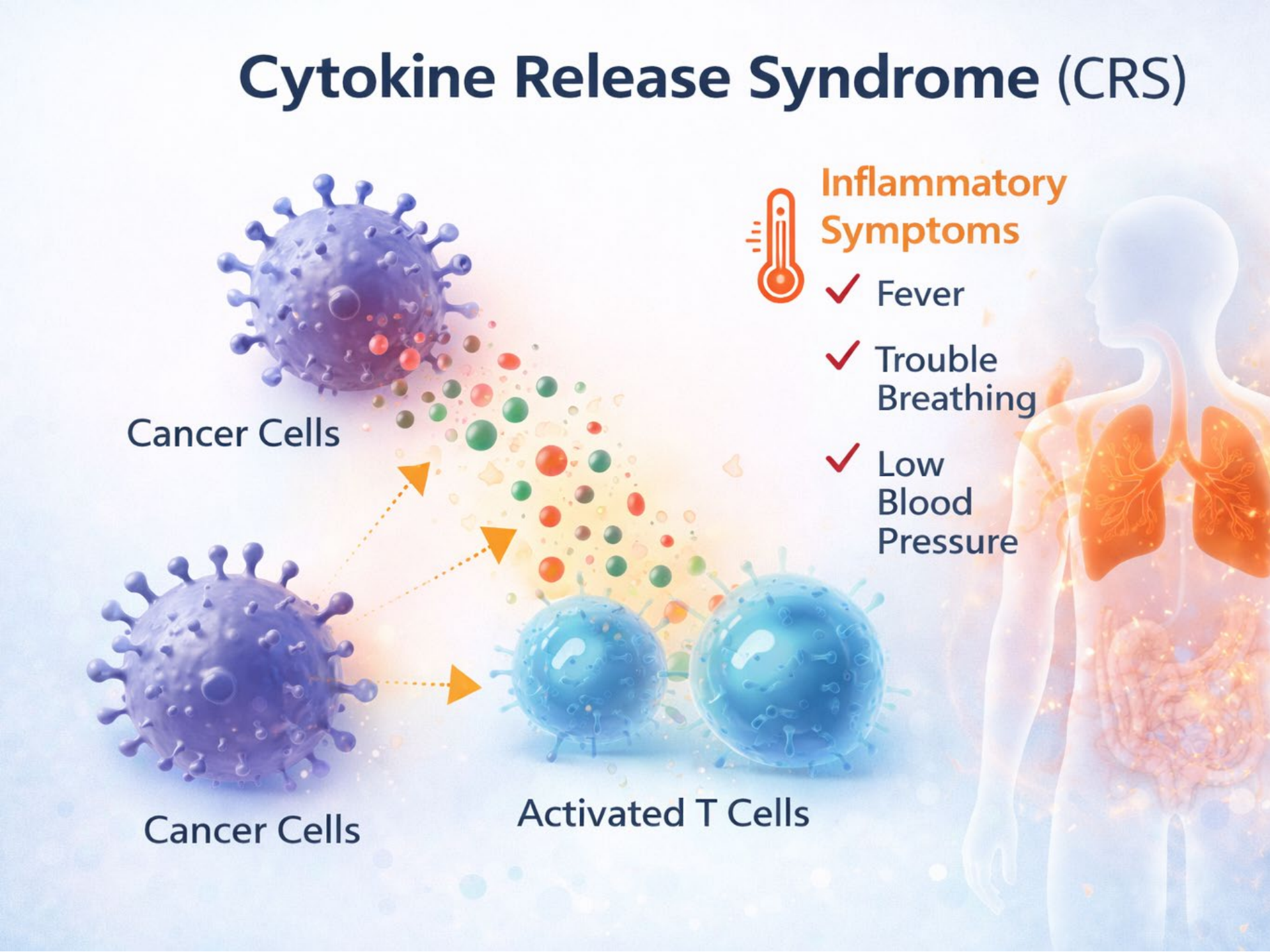
Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy

Jennifer L. Crombie,[1,*] Tara Graff,[2,*] Lorenzo Falchi,[3,*] Yasmin H. Karimi,[4,*] Rajat Bannerji,[5] Loretta Nastoupil,[6] Catherine Thieblemont,[7] Renata Ursu,[8] Nancy Bartlett,[9] Victoria Nachar,[4] Jonathan Weiss,[4] Jane Osterson,[2] Krish Patel,[10] Joshua Brody,[11] Jeremy S. Abramson,[12] Matthew Lunning,[13] Nirav N. Shah,[14] Ayed Ayed,[15] Manali Kamdar,[16] Benjamin Parsons,[17] Paolo Caimi,[18] Ian Flinn,[19] Alex Herrera,[20] Jeffrey Sharman,[21] Marshall McKenna,[5] Philippe Armand,[1] Brad Kahl,[9] Sonali Smith,[5,22] Andrew Zelenetz,[3] Lihua Elizabeth Budde,[20,†] Martin Hutchings,[23,†] Tycel Phillips,[4,†] and Michael Dickinson[24,†]

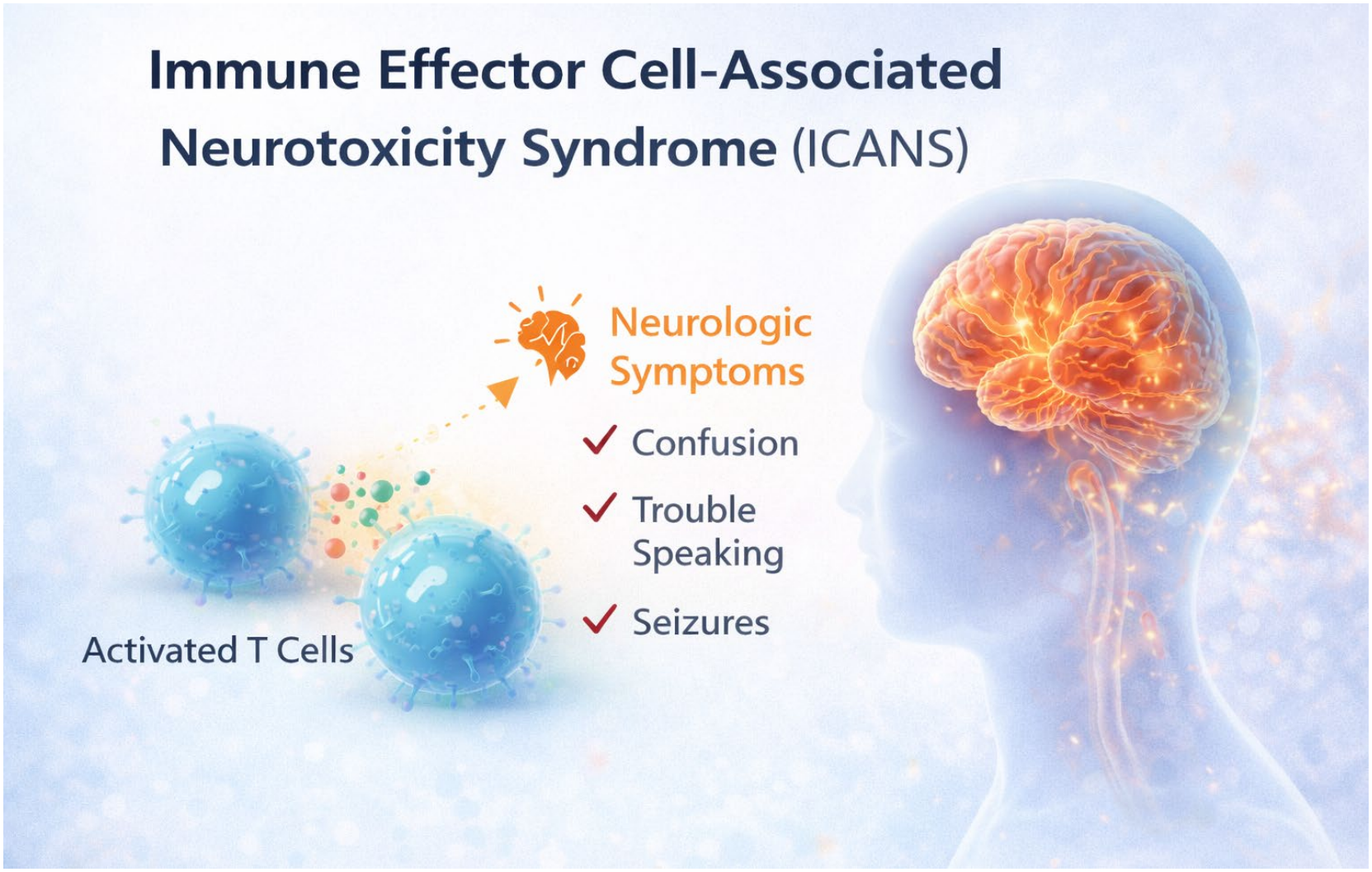
Bispecific Antibody Therapy–Associated Toxicity



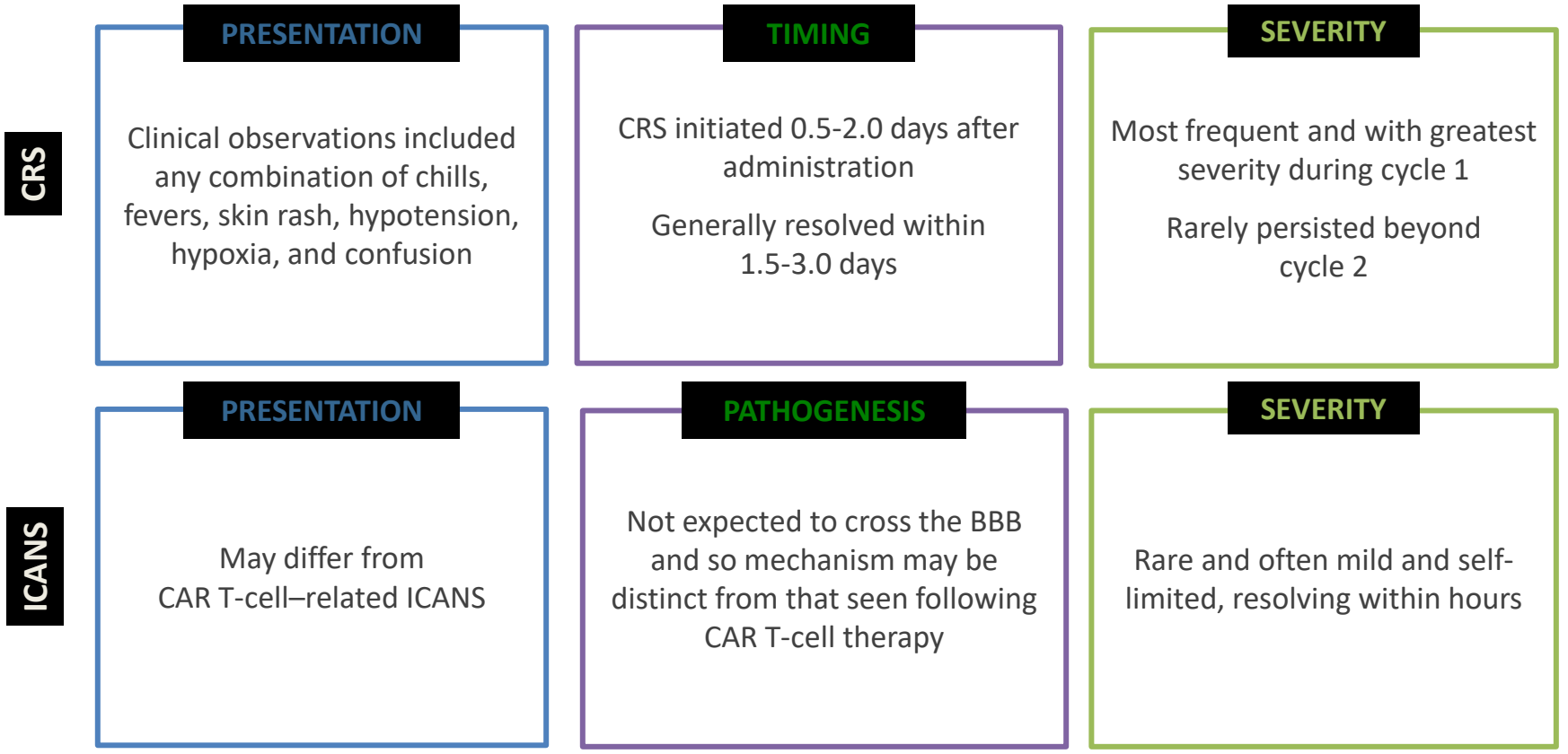
Cytokine Release Syndrome (CRS)



Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)



Bispecific Antibody–Related CRS and ICANS



CRS Mitigation Nuts and Bolts

- Education (BsAb teaching)
- Medical equipment purchased and in hand
- Importance of hydration
- Pre-medications
- Dexamethasone 4 mg tablets x 4 (16 mg) as “pill in the pocket” for home
- Tylenol and NSAIDs (in date and in house)
- Drug Bracelet
- Pocket Cards

CRS Mitigation

- Step Up Dosing
- Hospitalization if needed
- Slower Infusion
- SQ vs IV

- Introduce BsAb into the immune system
- Decrease risk of CRS and ICANS

Safety: What Patients Feel vs. What We Are Doing

- **WHAT PATIENTS MAY FEEL**

- • Fever
- • Fatigue
- • Chills
- • Confusion
- • Dizziness

- This can feel sudden or scary.

WHAT WE ARE DOING BEHIND THE SCENES

• Following national expert guidelines

• Monitoring closely during early doses

• Checking labs and vital signs

• Treating early with medications if needed

• Adjusting dosing safely

There is a clear plan.

When Should You Call Your Doctor?

- Fever 100.4°F or higher
- Confusion or speech changes
- Severe dizziness
- Nausea and extreme body aches
- Anything that worries you

CRS Management

Definition: CRS is an acute systemic inflammatory syndrome characterized by fever and organ dysfunction
Symptoms: fever (required) with possible hypoxia, hypotension, tachypnea, nausea, headache, fatigue, myalgias, or malaise
Workup and evaluation:
- Pertinent history and physical examination including vital sign evaluation and evaluation of respiratory symptoms
- Review medications including BsAb received, last dose of antipyretic therapy, steroids, or anticytokine administration
- Assess for concurrent symptoms of neurotoxicity
- Assess for alternate diagnosis including infection (including neutropenic fever), venous thromboembolism, respiratory infection (including COVID-19 and influenza), volume overload or dehydration, and exacerbation of underlying cardiopulmonary condition. Treat as appropriate.
- For duration of symptoms over 1 week, consider excluding HLH/MAS[12]

Monitoring: consider monitoring patient for 1-2 h after infusion if outpatient administration of BsAb on day of step-up dosing
Next dose: follow prescribing label

Grade and definition	Management
Grade 1: Fever* of ≥100.4°F with/without constitutional symptoms requiring symptomatic treatment, no hypotension or hypoxia	Home: • A/P 650-1000 mg orally, can repeat, if recurrent fever, ≥6-8 h later if clinically stable • Recommend aggressive oral hydration • Continue to check temperature every 1-2 h and other vitals if able. Patients should recontact the clinic urgently or present to ED if BP goes <10 mm Hg below baseline AND <90 mm Hg systolic, new orthostatic symptoms, weakness, confusion, dizziness, or new hypoxia (<90%). Home vs outpatient/ED evaluation: • If refractory or recurrent fever (<6-8 h) consider dexamethasone 10 mg once. Home management may be appropriate if vital signs remain stable and no other concerning symptoms. Otherwise, patients should be evaluated in a health care facility. • Consider earlier administration of steroids and immediate in-person evaluation for patients with multiple disease risk factors or comorbidities (see text) • Consider daily dexamethasone with persistent symptoms Additional management: • Consider anticytokine therapy (eg, tocilizumab) in cases of protracted fever (eg, >48 h despite corticosteroids) • Early tocilizumab after trial of dexamethasone should be considered for patients with multiple medical risk factors (eg, comorbidities)
Grade 2: Fever of ≥100.4°F with either hypotension not requiring pressors and/or hypoxia managed with low-flow nasal canula or blow-by.	• All patients should be urgently evaluated in person. Recommend inpatient management for most cases of grade 2 CRS unless qualified outpatient day hospital/infusion center and no hypoxia. • If after hours without access to appropriate outpatient treatment area or if clinical scenario dictates, recommend ED evaluation • A/P 650-1000 mg as needed, up to 3-4 times daily • Dexamethasone 10 mg every 12 h • Administer IV fluids/supplemental oxygen as appropriate • Administer tocilizumab† if symptoms persist despite IV fluids and dexamethasone (~4-6 h after dosing) or if clinically unstable. Consider alternative agent (eg, anakinra or siltuximab) if persistent symptoms despite maximal dosing.
Grade 3: Fever of ≥100.4°F with either hypotension (BP <90/60 or <10 mmHg below, not responsive to fluids and/or hypoxia requiring high-flow nasal canula, face mask, or venturi mask)	• Emergent inpatient admission (floor or ICU) for hemodynamic monitoring, IV fluids, oxygen therapy, and vasopressors • A/P 1000 mg IV as needed up to 3-4 times daily when safe • Dexamethasone (eg, 10 mg IV Q 6 h), until resolution to grade ≤1, followed by dexamethasone taper • Evaluate for sepsis and consider empiric antibiotics • Administer tocilizumab† and consider alternative agent (eg, anakinra or siltuximab) if persistent grade 3 CRS despite maximal dosing • If refractory hypotension/hypoxia, admit to ICU
Grade 4: Fever of ≥100.4°F with any of the following: Life-threatening consequences, urgent intervention required; requiring multiple pressors and/or positive pressure respiratory support or mechanical intubation	• Inpatient admission to ICU for hemodynamic monitoring, IV fluids, oxygen therapy, and vasopressors • A/P 1000 mg IV as needed up to 3-4 times daily when safe • Dexamethasone (eg, 20 mg IV every 6 h), until resolution to grade ≤1, followed by dexamethasone taper • Administer tocilizumab and if repeated doses of tocilizumab have been used, consider alternative agent (eg, anakinra or siltuximab) if persistent grade 4 CRS despite maximal dosing of first agent

ICE questionnaire		
Ask the patient the following questions (1 point per question):		
What year is it?	1 point	
What month is it?	1 point	
What city are you in?	1 point	
What street do you live on?	1 point	
Naming 3 objects (1 point per object) Hold up 3 separate available objects and see if the patient can easily identify what the objects are		
Object 1	1 point	
Object 2	1 point	
Object 3	1 point	
Following simple commands (1 point total):		
*Raise your left hand *Raise your right hand *Touch your fingertip to your nose	1 point	
Writing standard sentence		
“The sky is blue, and the grass is green”	1 point	
Attention to count backwards from 100 by 10	1 point	
Total point score:		

ICANS Management

Definition: neurological AEs after BsAb therapy most frequently consist of headache and dizziness; occasionally, ICANS-like symptoms occur; these may or may not accompany CRS

Symptoms: delirium, dysgraphia, tremor, lethargy, difficulty concentrating, agitation, confusion, expressive aphasia, apraxia, depressed level of consciousness, encephalopathy, and seizures

Recommendations: patients and caregivers need to be educated on symptoms and patients cannot drive or operate heavy machinery if symptomatic

Workup and evaluation:

- Pertinent history and PE
- Review medications including last dose of antipyretic therapy, steroids, or anticytokine therapy
- Perform ICE score on all patients with neurologic symptoms
- Assess for alternate cause of symptoms; consider performing CT head, EEG, MRI, or LP, as appropriate
- Assess for concurrent symptoms of CRS (fever, hypoxia, and hypotension); treatment of CRS can occur concurrently if appropriate
- If any concern for neurological AEs exists, patient should be evaluated in outpatient center or ED. If any worsening symptoms (eg, somnolence, worsening confusion, weakness, etc), patients should be promptly referred to the ED

ICE scoring system	
Orientation to year, month, city, hospital	4 points
Naming 3 objects	3 points
Following simple commands	1 point
Writing standard sentence	1 point
Attention to count backward from 100 by 10	1 point

ICANS grading	**Management**
Grade 1: ICE 7-9 or depressed level of consciousness but awakens spontaneously	• Pending clinical scenario and social situation, can consider observation or close monitoring in outpatient setting. Can consider dexamethasone 10 mg × 1
Grade 2: ICE 3-6 or depressed level of consciousness but awakens to voice	• Admit patient to hospital for monitoring • Dexamethasone 10 mg IV every 12 h, followed by taper once grade ≥1
Grade 3: ICE 0-2 or depressed level of consciousness but awakens to tactile stimulus or any clinical seizure that resolves rapidly or focal/local edema on neuroimaging	• Monitor in ICU setting • Neurology consult • Dexamethasone 10 mg IV every 6 h, followed by taper once grade ≥1 • Use antiepileptics for seizure management as needed • Consider adding anakinra 100 mg every 12 h if symptoms persist beyond 24 h, continue until resolution
Grade 4: ICE is 0 or patient is unarousable or requires vigorous or repetitive tactile stimuli, or life-threatening prolonged seizure (>5 min) or repetitive seizures without return to baseline or deep focal motor weakness or diffuse cerebral edema on neuroimaging	• Monitor in ICU setting • Neurology consult • Dexamethasone 10 mg IV every 6 h, followed by taper once grade ≥1 • Use antiepileptics for seizure management as needed • Consider adding anakinra 100 mg every 12 h if symptoms persist beyond 24 h, continue until resolution

It’s Normal to Feel Nervous

- New treatment
  - Additional education
  - Safety Plans
  - Close monitoring
  - You are not alone

Caregivers: Your Role Matters

- Watch for fever
- Notice changes in behavior
- ICE questions
- Help communicate concerns
- You are part of the care team

What to Expect in the First Month

- Frequent visits initially
- Longer clinic days at first
- Monitoring calls
- Need for additional medications (Tylenol, steroids)
- CRS and ICANs usually happen early

Common Questions

- How long will I stay on treatment?
- How often will I have to be in the office?
- Do I have to stay in the hospital?
- Will I lose my hair?
- Can I travel?
- What if it stops working?

What Kind of Results Do We See?

- Increased response rates vs chemo-immunotherapy
- Increased complete response or remissions
- Increased disease-free intervals
- Potential cure?

Infection Risk

- Immune system is redirected
  - Preventive medications may be needed
  - Vaccinations
  - IVIG

Practical Guidance for Late Toxicity

- **Patients should be monitored for:**
  - B-cell aplasia (IgG levels): replete with IVIG for levels <400 mg/dL, generally needed every 1-3 mo
  - Infection
  - Cytopenias: transfuse as indicated; G-CSF as needed

- **Antimicrobial (herpes and PJP) prophylaxis**
  - Variable practices: can be tailored to CD4 counts (<200)

- **Vaccination**
  - Influenza: yearly
  - COVID vaccination (unknown)

You Are Not Doing This Alone

- Education matters
  - Communication keeps you safe
  - We walk this journey together

Resources & Support

- Blood Cancer United (LLS) www.bloodcancerunited.org
- Lymphoma Research Foundation www.lymphoma.org
- International Myeloma Foundation www.myeloma.org
- CancerCare – www.cancercare.org
- National Cancer Institute www.cancer.gov
- Pharma sponsored patient and caregiver support
- Ask your care team about local support groups