Bispecific Antibody Therapy in Cancer Care: What Acute Care Physicians Need to Know for Safe Administration

September 12, 2024 | 1730–1900 PT

THE UNIVERSITY OF BRITISH COLUMBIA
Continuing Professional Development
Faculty of Medicine

LAND ACKNOWLEDGMENT

We acknowledge that we work on the traditional, ancestral and unceded territory of the Skwxwú7mesh (Squamish), xʷməθkwəy̓əm (Musqueam), and Səl̓ílwətaʔ/Selilwitulh (Tsleil-Waututh) Nations.

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DISCLOSURES

Panelists

- **Dr. Azadeh Arjmandi:** Nothing to disclose
- **Dr. Catherine Clelland:** received compensation from BC Cancer, Doctors of BC, BC Family Doctors, Fraser North West Division of Family Practice, UBC CPD, UBC Post-graduate Education. I am contracted with BC Cancer in my role as Medical Director, Primary Care. for positions on committees with Doctors of BC and BC Family Doctors, as a board member for the FNW Division of Family practice. Holds contracts as a Practice Management Consultant with BC Family Doctors, UBC CPD & UBC Post-Graduate Studies. Financial relationships are **unrelated** to this webinar.
- **Dr. Alina Gerrie:** received compensation from Astrazeneca, AbbVie, Beigene, CARE (Community, Academic, Research and Education), CADTH (Canadian Agency for Drugs and Technology in Health). Content is not influenced by payments. Advisory Board member for Astrazeneca, AbbVie, Beigene, Loxo Lilly, Celgene.
- **Dr. Sian Shuel:** Nothing to disclose

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Planning Team

- **Dr. Bob Bluman (UBC CPD):** Nothing to disclose
- **Allison Macbeth (UBC CPD):** Nothing to disclose
- **Caldon Saunders (UBC CPD):** Nothing to disclose

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BC CANCER
Provincial Health Services Authority

LEARNING OBJECTIVES

- Identify bispecific antibodies, a new class of immunotherapy, and their role in cancer management
- Describe inpatient (and subsequent outpatient) administration of bispecific antibodies
- Recognize bispecific antibody-related toxicities including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome
- Demonstrate an approach to the management of bispecific antibody-related toxicities

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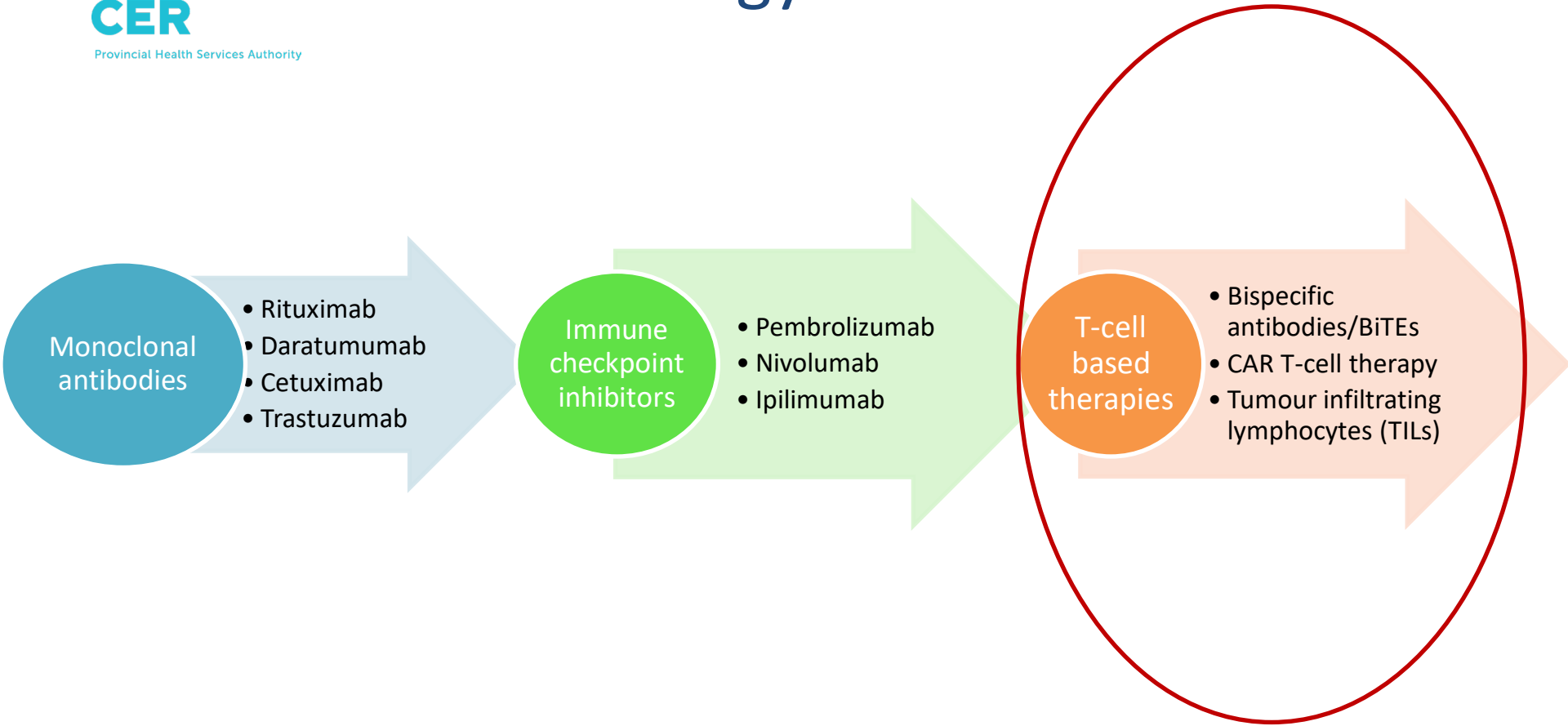
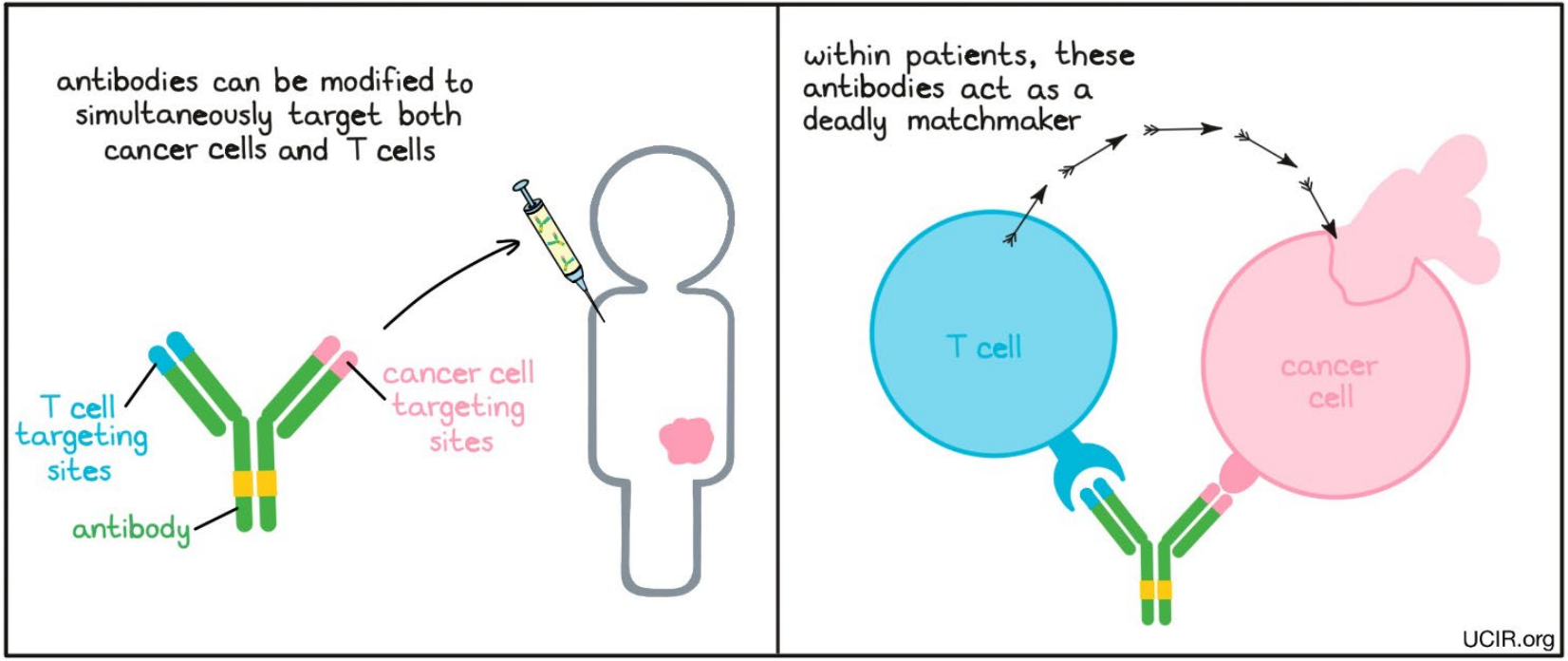
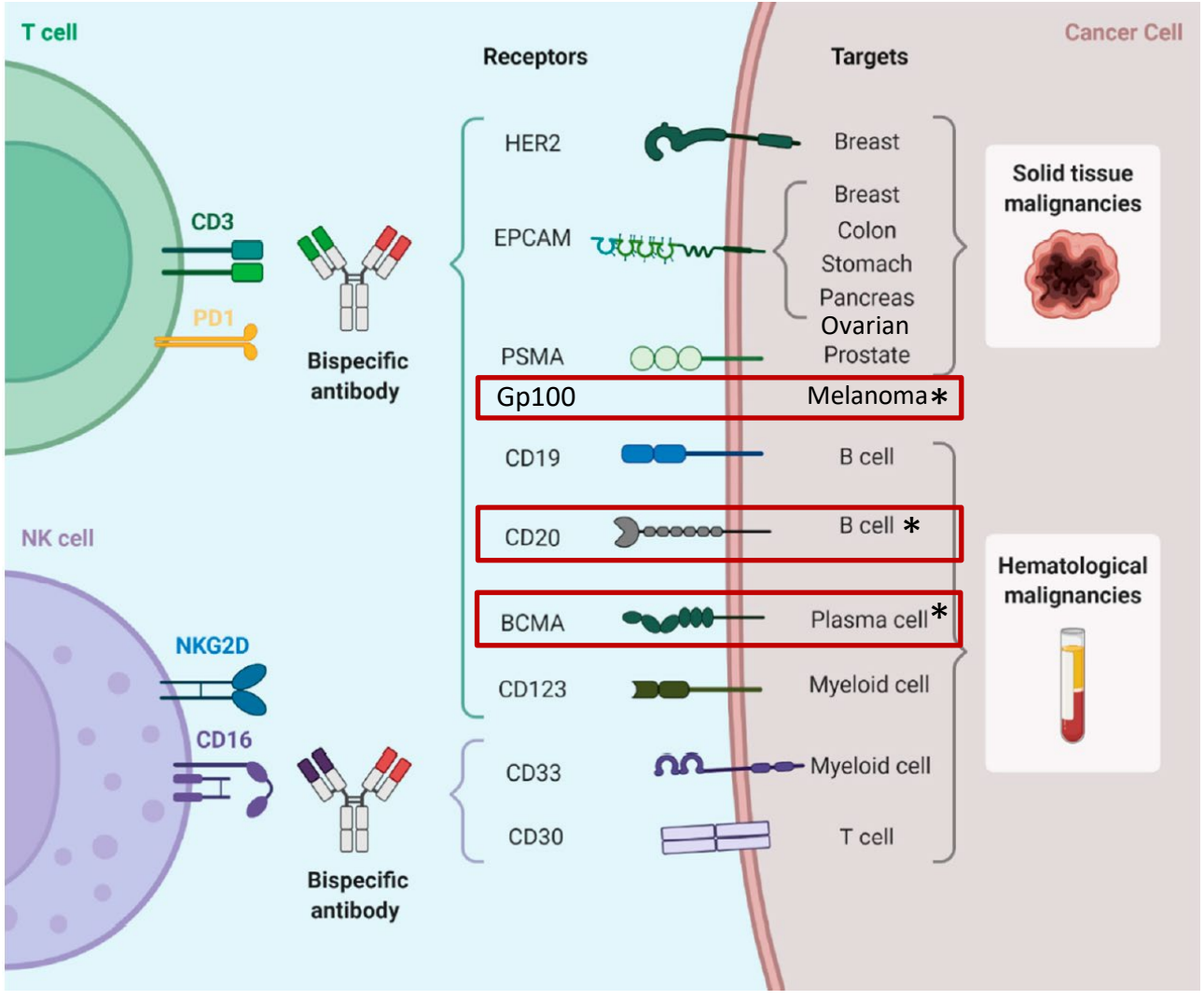
Immuno-oncology trends over time



Bispecific antibodies



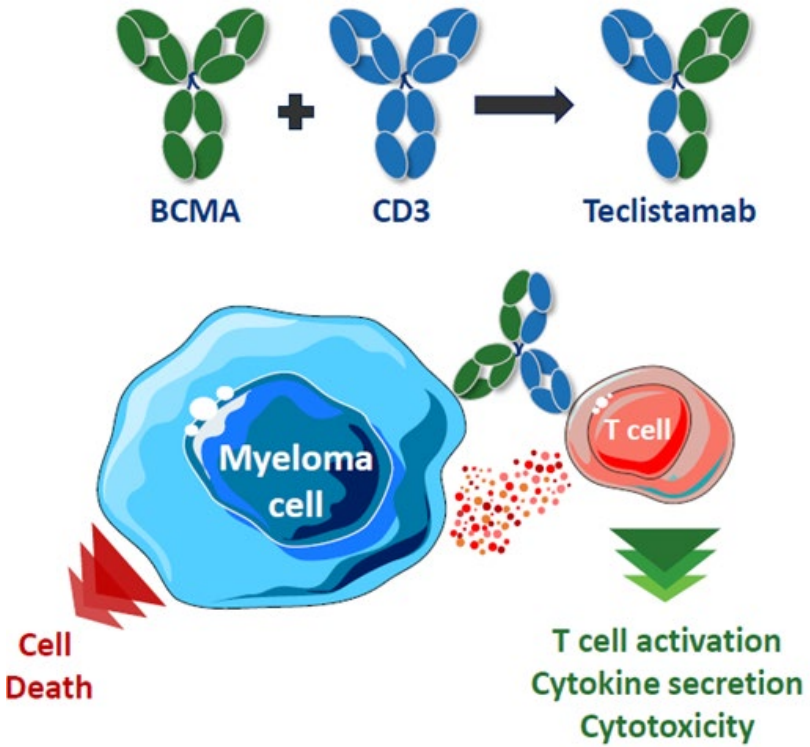
Targets



DLL3 – lung*
CEA – GI, lung
EGFR –GI, glioblastoma
SSTR2 – NET, GIST
4-1BB – Solid tumours
MUC16 - Ovarian

Ordonez-Reyes, Pharmaceutics 2022;14:1243

Teclistamab – BCMA x CD3 Bispecific Ab for Multiple Myeloma

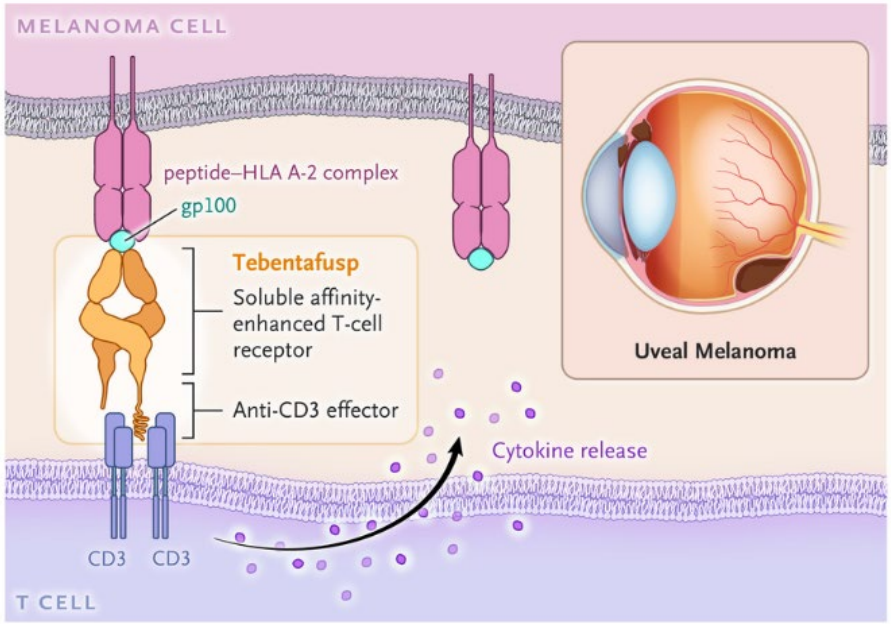


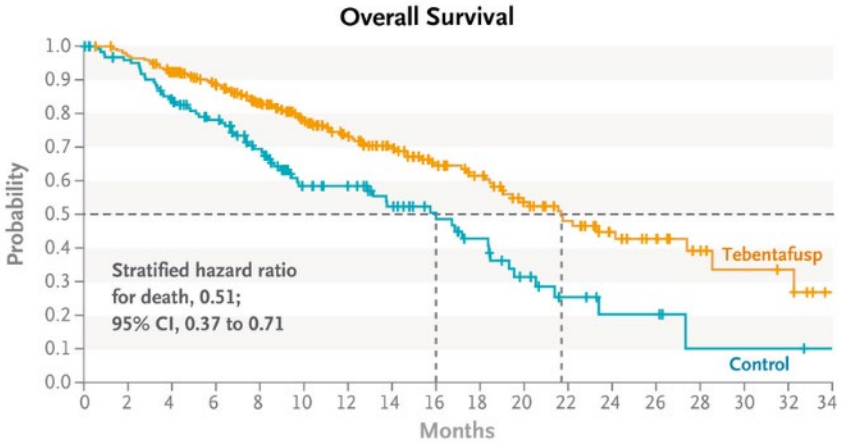
- BCMA expression is restricted to B-cell lineage, minimal expression within other tissues
- Teclistamab is a humanized BCMA X CD3 bispecific IgG-4 antibody that redirects $CD3^+$ T cells to BCMA-expressing myeloma cells
- **High response rates and prolonged remissions in heavily pre-treated patients[1]**

→ Clinical trials and compassionate access programs available, soon to be funded as standard of care

[1]Moreau et al, NEJM 2022;387:495-505

Tebentafusp for metastatic uveal melanoma



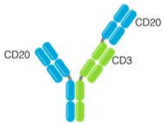
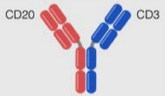
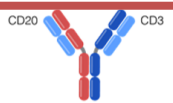
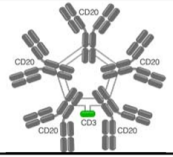


1-Year Survival		
Tebentafusp Group	73%	95% CI, 66 to 79
Control Group	59%	95% CI, 48 to 67

→ **First Health Canada approved bispecific for solid tumours**

Nathan et al, NEJM 2021;385:1196-1206

Lymphoma CD20 x CD3 bispecifics in development

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab[18]		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (No FcγR binding)
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1(type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (No FcγR binding)
Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (No FcγR,C1q binding)
Odronexamab[17]		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (No FcγRIII binding)
Plamotamab[90]		IgG1	Fab-Fc x scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.)(CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (No FcγR binding)
IgM 2323[19]		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

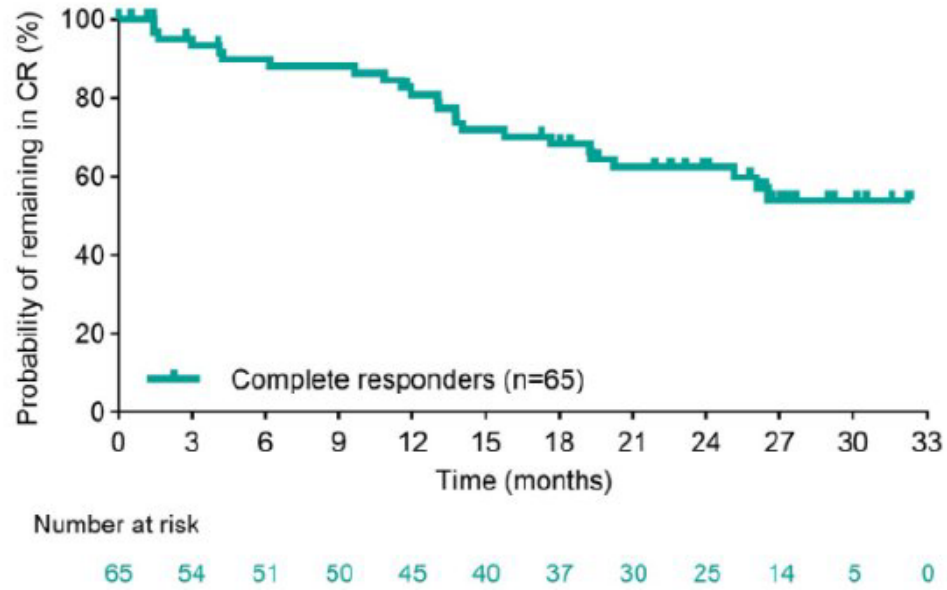
* These Fc silencing mutations do not abolish the binding of BsAb to FcRn

Falchi et al, Blood 2022 Epub

ENCORE NHL-1: **Epcoritamab** for relapsed diffuse large B-cell lymphoma, 3rd line

Figure. Duration of complete response (**A**) and efficacy outcomes (**B**) among complete responders with LBCL (n=65)

A



Best Overall Response, n (%)	LBCL N=157[a]	DLBCL n=139[a]
Overall response	99 (63)	86 (62)
Complete response	62 (39)	55 (40)

B

Timepoint estimate, % (95% CI)	Pts in CR	Progression-free survival	Overall survival	Pts who have not initiated next line of therapy
24 mo	62 (48–74)	65 (52–76)	76 (64–85)	82 (69–90)
30 mo	54 (39–67)	55 (39–68)	71 (58–81)	78 (64–87)
33 mo	NA	55 (39–68)	71 (58–81)	78 (64–87)

Data cutoff: October 16, 2023. Kaplan–Meier estimates. NA, not assessed.

Median follow-up 25.1 mos

Thieblemont, EHA, June 2024

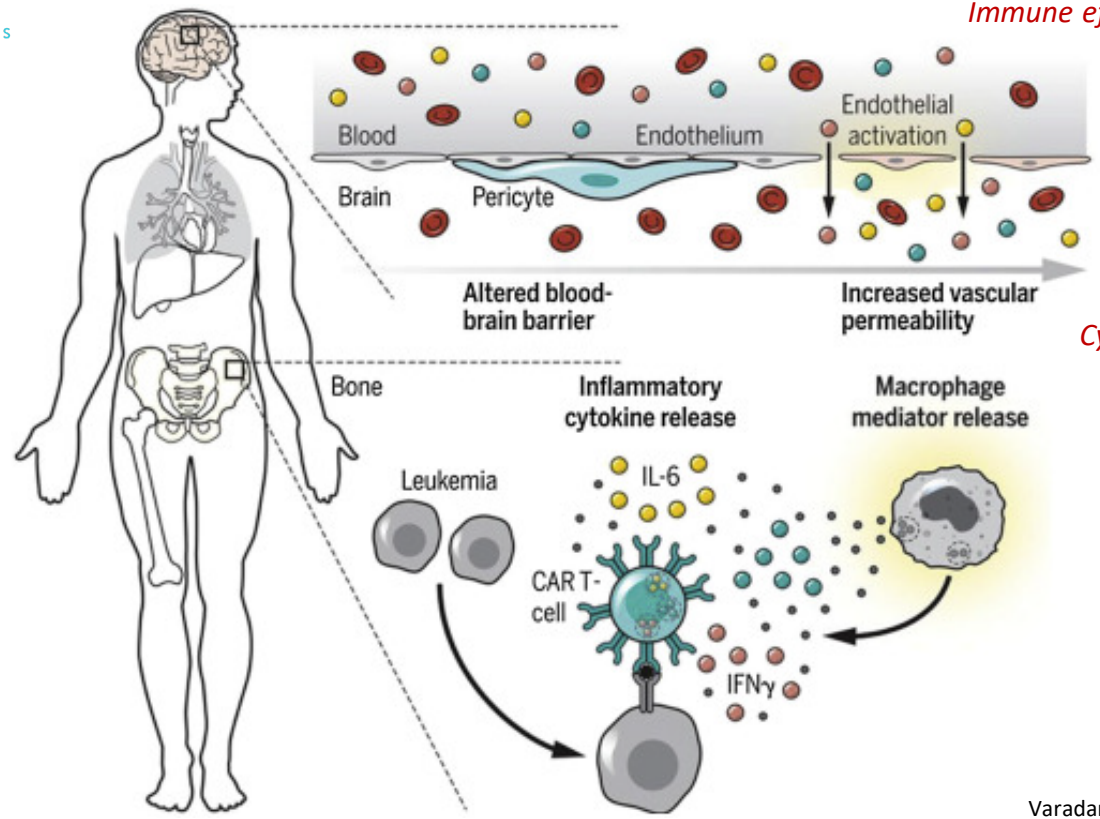
CRS Was Predictable and Primarily Low Grade

	LBCL N=157
CRS, n (%)[a]	80 (51)
Grade 1	50 (32)
Grade 2	25 (16)
Grade 3	5 (3)
Median time to onset after first full dose, h	20
Treated with anticytokine therapy, n (%)	23 (15)
Leading to treatment discontinuation, n (%)	1 (1)
CRS resolution, n/n (%)	79/80 (99)
Median time to resolution, d (range)[b]	2 (1–27)

- CRS occurred primarily following the first full dose (C1D15)
- Tocilizumab was used predominantly to treat CRS events following the first full dose (C1D15) in patients who experienced grade 2 or grade 3 CRS events

[a]Graded by Lee et al 2019[1] criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS. **1.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

Bispecific complications



Immune effector-cell associated neurotoxicity

Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

ICANS

Cytokine release syndrome

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

CRS

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

Varadarajan et al. Management of Cytokine Release Syndrome – Chapter 5; CAR T-cell therapies for cancer, Elsevier 2020: 45-64.

Bispecific complications

- **Cytokine release syndrome (CRS)**
  - Caused by large, rapid release of cytokines (IL6) into the blood by immune cells
  - Generally within 24-48 hours after first full-dose infusion
  - Fever, nausea, headache, bone pains, rash, hypotension, hypoxia
  - Grade 1 (mild) to Grade 4-5 (life-threatening)
  - **Treatment: Tocilizumab (IL6 antibody) +/- steroids**

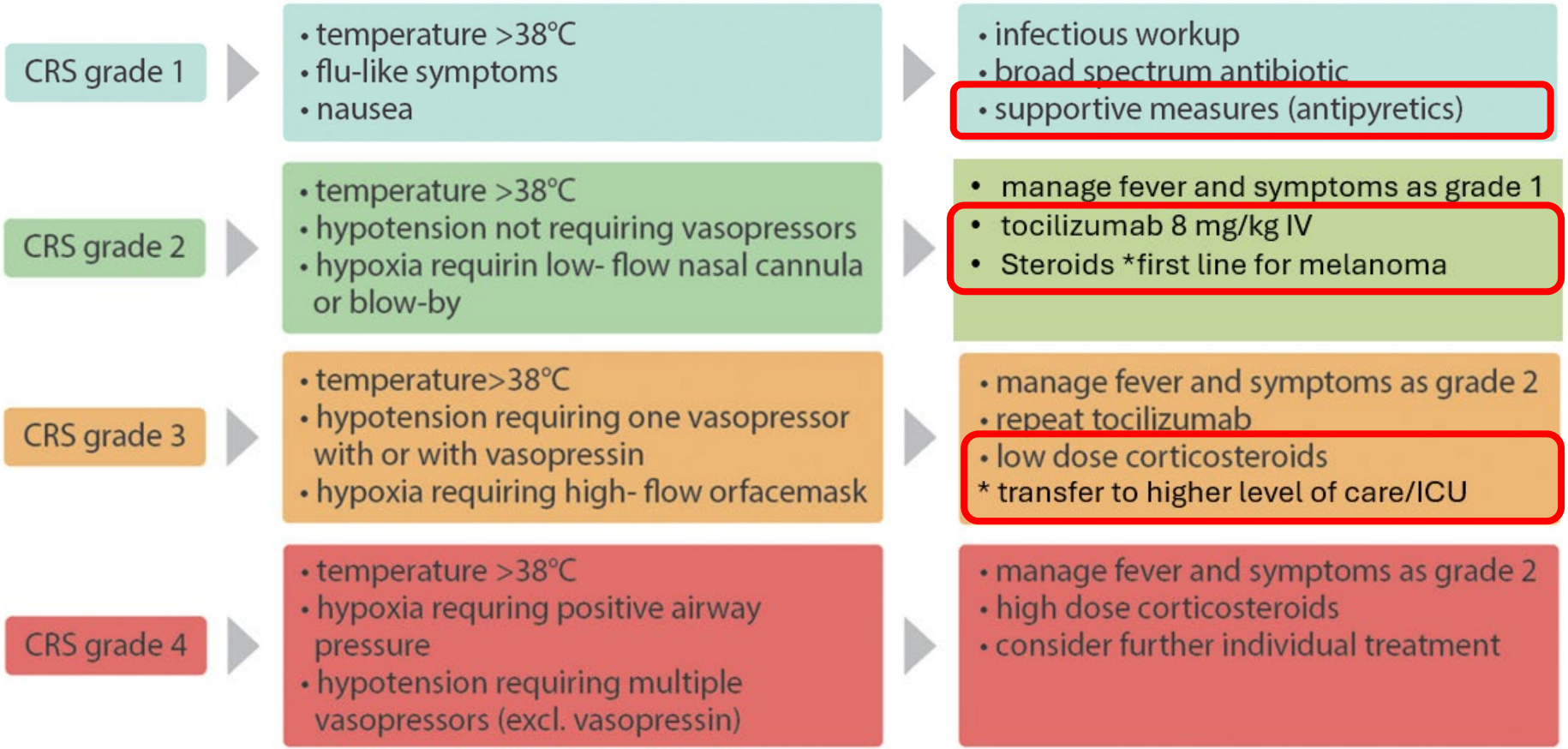
- **Immune effector-cell associated neurotoxicity (ICANS)**
  - Clinical and neuropsychiatric syndrome
  - Confusion, disorientation, speech disturbances, change in LOC, seizures, motor weakness
  - Usually occurs later (4-5 days) and in combination with CRS but can occur alone
  - **Treatment: Steroids**

CRS Grading

Grade	Fever	with Hypotension	and/or Hypoxia
1	≥ 38.0 ºC	None	None
2	≥ 38.0 ºC	Not requiring vasopressors (ie. responsive to IV fluids)	Requiring oxygen delivered by low-flow nasal cannula (≤ 6 L/min) or blow-by
3	≥ 38.0 ºC	Requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula (>6 L/min), facemask, nonrebreather mask, or Venturi mask
4	≥ 38.0 ºC	Requiring multiple vasopressors (excluding vasopressin)	Requiring oxygen delivered by positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT consensus grading, Lee et al. Biol Blood Marrow Transplant 2019

CRS grading and management approaches



Adapted from Garcia Borrega, HemaSphere 2019

Cytokine release syndrome - Pearls

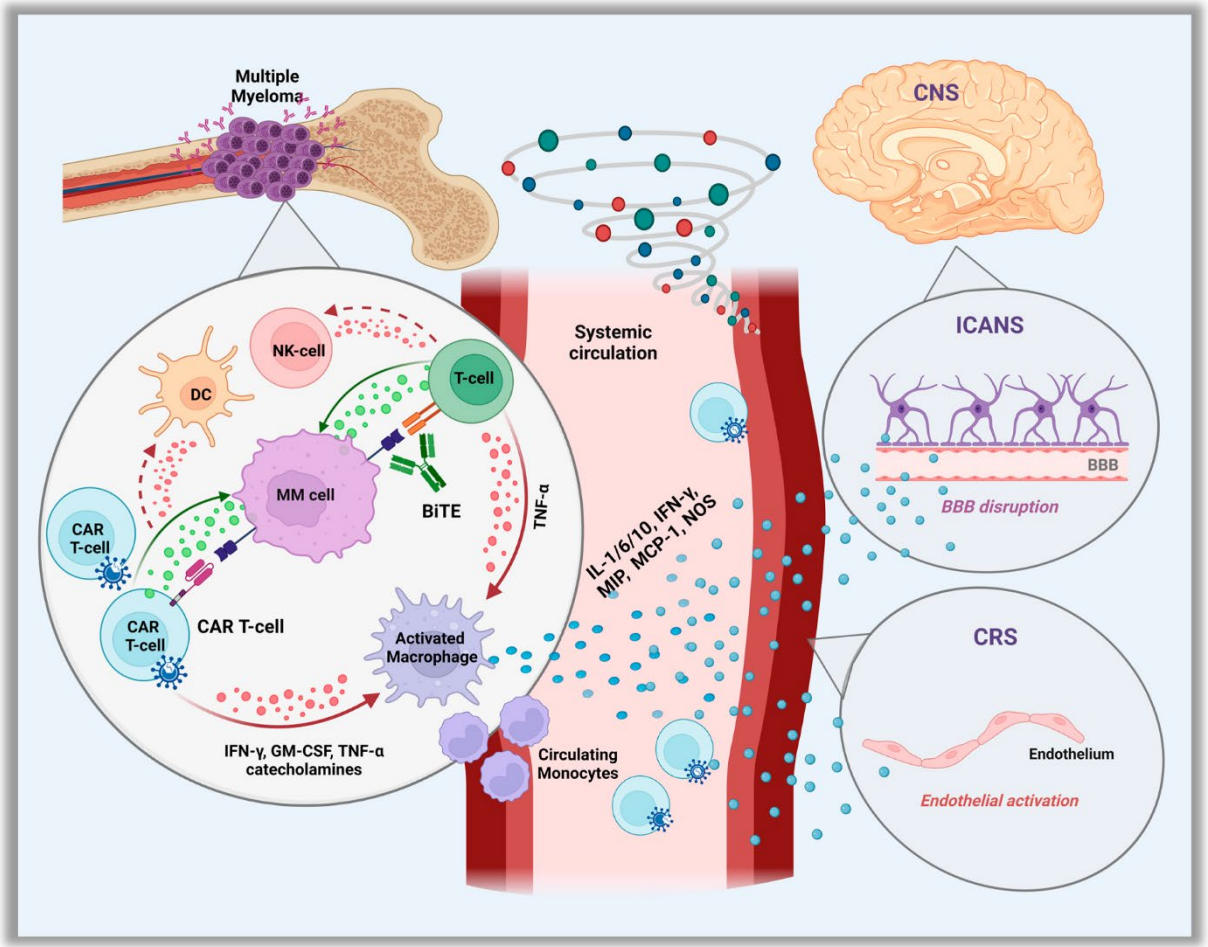
- Like sepsis but without a bug! → Give tocilizumab (or steroids) instead of antibiotics
- MD should be called at first sign of CRS (fever)
- Start supportive care right away (acetaminophen, diphenhydramine, etc)
- Frequent vitals (q1h), updates to MD often

- If hypotension, give immediate fluid bolus and re-check
- If no improvement or if recurs, LOW THRESHOLD TO ORER TOCILIZUMAB (or STEROIDS if tebentafusp)

CRS starts Grade 1 and slowly progresses to higher grades

Therefore early intervention with toci/steroids can usually avoid progression

Immune effector
Cell
Associated
Neuro-
Toxicity
Syndrome



Markoulli, M *et al* Current Onc, 2023

ICANS

Table 1. Immune effector cell-associated encephalopathy score: ICE tool

Category	Points
1. Orientation: orientation to year, month, city, place*	4 points
2. Naming: ability to name 3 objects (ie. pen, cup, glasses) *	3 points
3. Following commands: ability to follow simple command (ie. “Close your eyes and stick out your tongue”)	1 point
4. Writing: ability to write a standard sentence (ie. “The flag is red and white”)	1 point
5. Attention: ability to count backwards from 100 by 10	1 point

*1 point for each item

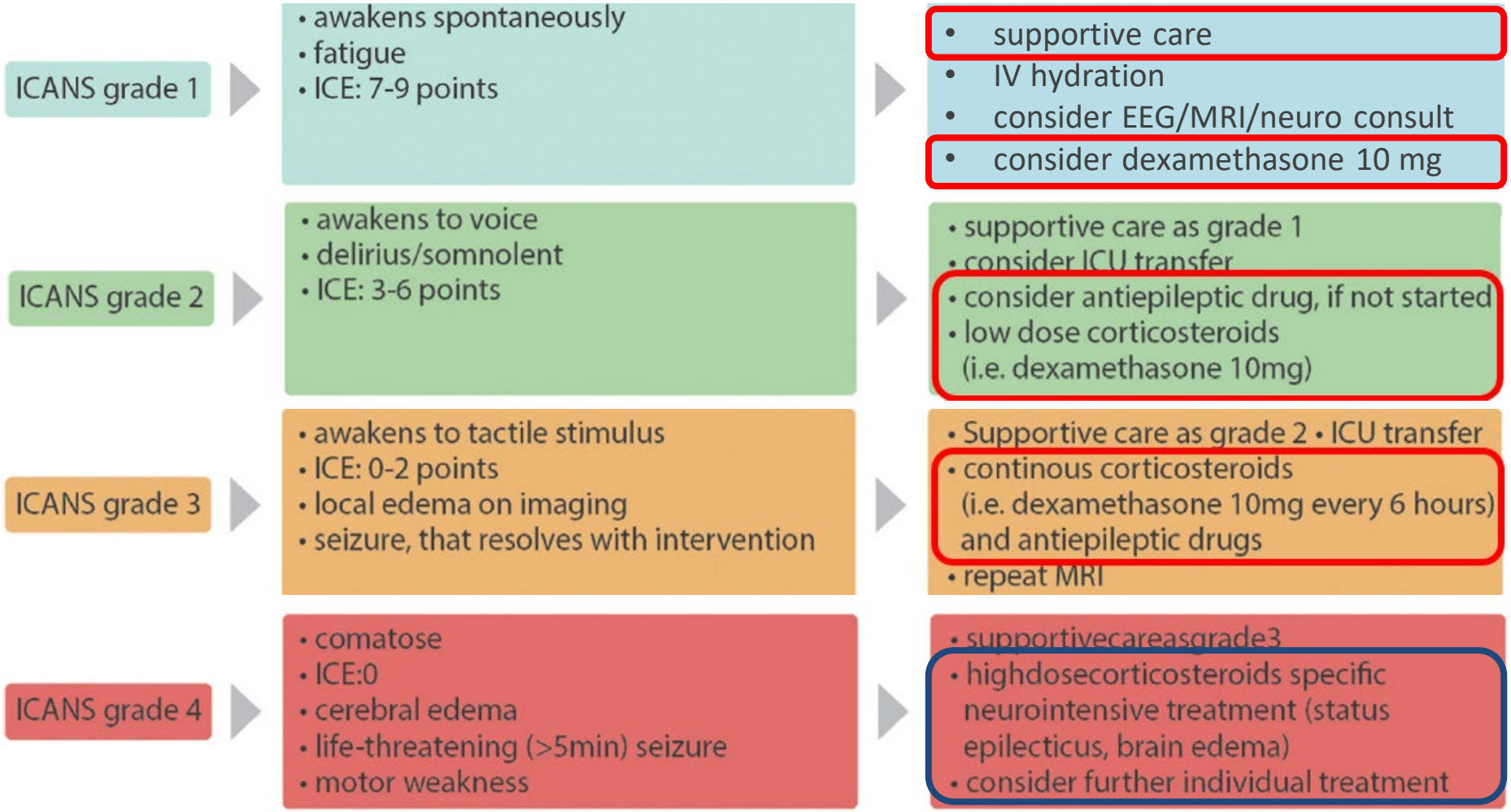
10 points

ICANS Grading

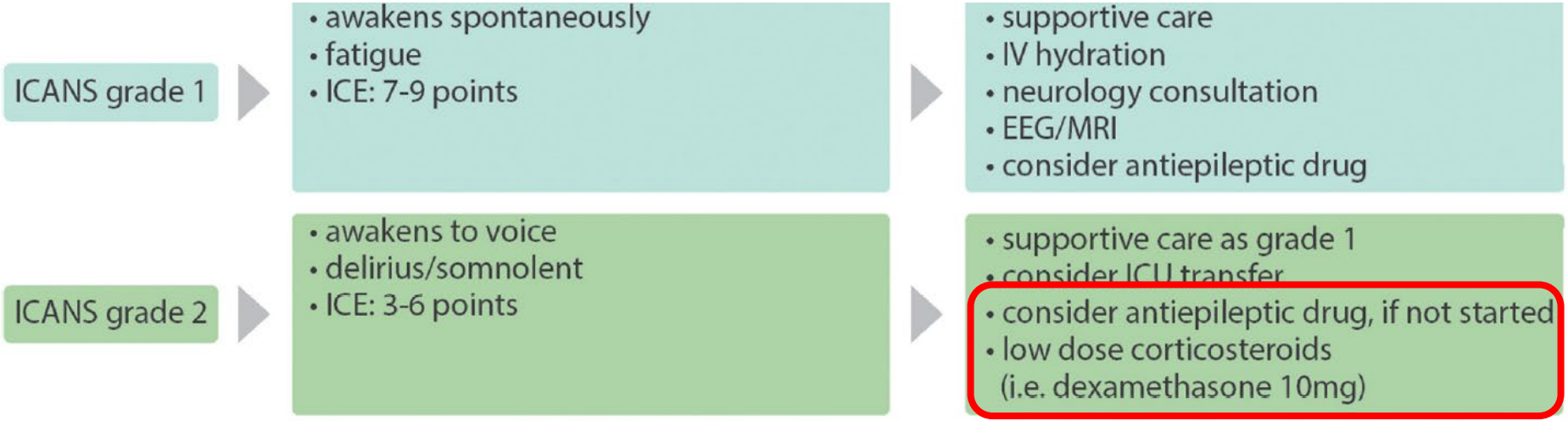
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unrousable and unable to do ICE testing)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unrousable or requires significant tactile stimulus to awaken
Seizures	N/A	N/A	Any seizure (focal, general) that resolves rapidly. Non-convulsive seizure on EEG that resolve with intervention.	Life-threatening prolonged seizures (>5min). 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
Raised ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging (excluding intracranial hemorrhage)	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; papilledema; cranial nerve VI palsy; Cushing's triad

*ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

BC Cancer SCICANS Protocol



Garcia Borrega, HemaSphere 2019



ICANS Supportive Care:

- Seizure and fall precautions
- Elevate head of bed 30 degrees
- Aspiration precautions – if swallowing concerns, meds to be converted to IV
- Avoid medications that cause CNS depression
- Monitor for ICANS symptoms with ICE score every 8-12 hours
- Vitals q4h to monitor for concurrent CRS

BC Cancer SCICANS Protocol

ICANS - Pearls

- Very uncommon with bispecifics, seen more with CAR T-cell therapy
- Generally occurs later, around 4-6 days after infusion
- May be subtle speech changes, slight confusion → use ICE tool to document
- Monitor for concurrent CRS (often occur together)

Mainstay of treatment is

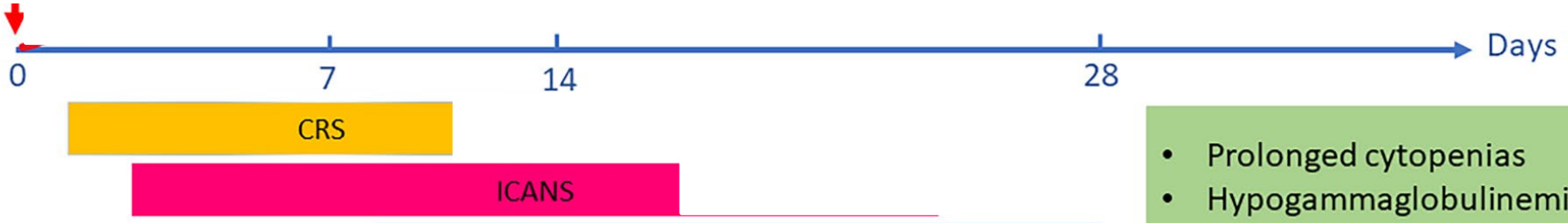
supportive care, anti-epileptics and dexamethasone

Bispecific complications

- To prevent CRS/ICANS, bispecifics given in **step-up dosing**
  (e.g. day 1, 8, 15 with increasing doses to full-dose)
- May require **in-patient administration** for first doses (highest CRS risk)
- Risk of CRS/ICANS exists **only during step up dosing**
- **Once full-dose administered without complications, there is no further risk of CRS/ICANS**
- Patients may return to their home communities for ongoing treatment as outpatients (usually every 3 to 4 weeks)

Bispecific complications – longer term

- Risks of immunosuppression (esp. lymphoma/myeloma pts):
  - Low immunoglobulins and overall immune suppression
  - May not be neutropenic!
- Fevers/infections must be taken seriously, similar to febrile neutropenia – treat with antibiotics, consider atypical infections (CMV, fungal)



Bispecific Antibodies

Bispecific antibodies engaging T-cells have emerged as an innovative form of immunotherapy, seamlessly combining two antigen-recognizing elements into a single structure. This unique design enables the antibody to engage with two distinct targets simultaneously and to bring them into close proximity. By binding to both a T-cell and a cancer cell concurrently, it triggers a potent antitumor immune response, ultimately leading to the destruction of cancer cells. Notably, the specificity of bispecific antibodies reduces collateral damage to healthy cells in the vicinity, introducing a more targeted and potentially more effective treatment approach for patients.

Bispecific antibodies have shown great promise in cancer treatment. However, they have the potential for unique toxicities and safe administration requires collaboration between a multidisciplinary team to closely monitor patients and proactively manage potential side effects such as cytokine release syndrome (**CRS**) and neurotoxicity, specifically, immune effector cell-associated neurotoxicity (**ICANs**).

Adverse Events

Bispecific antibodies can cause over activation and dysregulation of the immune system, with a large number of activated white blood cells releasing inflammatory cytokines. **Cytokine release syndrome (CRS)** and **neurotoxicity**

In this section

- Chemotherapy Protocols
  - Breast
  - Gastrointestinal
  - Genitourinary
  - Gynecology
  - Head & Neck
  - Immunotherapy —
    - Bispecific Antibodies
    - Immune Checkpoint Blockade

BC CANCER
Provincial Health Services Authority

Google BC Cancer -
“Immunotherapy”
“Bispecific antibodies”
“CRS”
“ICANS”

For more details and management recommendations, see the **BC Cancer Supportive Care CRS and ICANS** management guidelines (links below).

Resources

SCCRS

- Cytokine release syndrome management
  - SCCRS Protocol
  - SCCRS Preprinted Order
  - SCCRS Patient Handout

SCICANS

- Management of Immune Effector Cell-Associated Neurotoxicity Syndrome
  - SCICANS Protocol
  - SCICANS Preprinted Order
  - SCICANS Patient Handout

Nursing

- Please visit the following page for Nursing resources related to Bispecific Antibodies

Additional Patient Resources

- Bispecific Antibodies Alert Card
- Bispecific Antibodies Patient Letter

Call Heme/Med Onc on-call at patient’s cancer centre**

CASE 1

The following patient has presented to the Emergency Department:

65M with metastatic uveal melanoma who is on treatment with the bispecific Ab **tebentafusp**.
Received cycle 2, day 1 dose earlier today.
He has developed a fever, chills, dizziness, back pain, a pruritic rash, and nausea and vomiting.

Vital signs: T: 38.6 C, HR: 112 bpm, BP: 94/54 mmHg (baseline 140/70 mmHg)
RR: 20 bpm, SpO2: 96% on room air

Physical exam:

General: A+O, rigors present, no increased WOB, R eye prosthesis, dry oral mucosa
Resp: GAEB, no adventitia; CVS: tachycardia, otherwise normal HS, JVP flat
Neuro exam grossly normal
Skin: diffuse erythematous patches over chest, back and all extremities

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CASE 1:

What is the most likely diagnosis?

1. Febrile neutropenia
2. Cytokine release syndrome secondary to recent bispecific Ab therapy
3. Systemic infection
4. Allergic reaction to recent bispecific Ab therapy

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CASE 1:

What is the most likely diagnosis?

1. Febrile neutropenia
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3. Systemic infection
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CASE 1 – CONTINUED:

What is the severity/grade of CRS initially?

1. Grade 1
2. Grade 2
3. Grade 3
4. Grade 4

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CASE 1 – CONTINUED:

What is the severity/grade of CRS initially?

1. Grade 1 (fever alone)
2. Grade 2 (fever and hypotension, not requiring vasopressors)
3. Grade 3 (fever and hypotension, requiring a vasopressor)
4. Grade 4 (fever and hypotension, requiring multiple vasopressors)

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CRS Grading

Grade	Fever	with Hypotension	and/or Hypoxia
1	≥ 38.0 ºC	None	None
2	≥ 38.0 ºC	Not requiring vasopressors (ie. responsive to IV fluids)	Requiring oxygen delivered by low-flow nasal cannula (≤ 6 L/min) or blow-by
3	≥ 38.0 ºC	Requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula (>6 L/min), facemask, nonrebreather mask, or Venturi mask
4	≥ 38.0 ºC	Requiring multiple vasopressors (excluding vasopressin)	Requiring oxygen delivered by positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT consensus grading, Lee et al. Biol Blood Marrow Transplant 2019

CASE 1 – CONTINUED:

What will you do next?

1. Administer acetaminophen and observe closely.
2. Administer acetaminophen plus IV fluids.
3. Administer IV fluids plus a dose of tocilizumab +/- methylprednisolone.
4. Draw blood and urine cultures and administer empiric antibiotics.

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CASE 1 – CONTINUED:

What will you do next?

1. Administer acetaminophen and observe closely.
2. Administer acetaminophen plus IV fluids.
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4. Draw blood and urine cultures and administer empiric antibiotics.*

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CASE 1 – CONTINUED – 2 HOURS LATER

So far, you have:

- administered acetaminophen 975 mg, 1L of IV normal saline, cetirizine 10 mg and ondansetron 8 mg
- done blood work (including cultures), urine studies and a CXR
- given a dose of IV antibiotics

Current symptoms: rigors and back pain milder, rash unchanged, nausea resolved
Vital signs: T: 38.4 C, HR: 98 bpm, BP: 92/52 mmHg, RR: 18, SpO2: 96% RA

What will you do next?

1. Give another dose of acetaminophen
2. Meperidine 25 mg for rigors, another liter of IV fluids with close observation
3. More IV fluids plus a dose of tocilizumab at 8 mg/kg
4. More IV fluids plus a dose of IV methylprednisolone at 1 mg/kg

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3. More IV fluids plus a dose of tocilizumab at 8 mg/kg
4. More IV fluids plus a dose of IV methylprednisolone at 1 mg/kg

Side note: rash is very common in patients treated with tebentafusp (unrelated to CRS) as tebentafusp targets both T-cells and melanocytes. Rash also responds well to steroid therapy.

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CASE 1 – CONTINUED – 1 HOUR LATER

So far you have:
- given acetaminophen 975 mg, cetirizine 10 mg, and ondansetron 8 mg (all 3 hours ago)
- given a total of 1.5 L of IV fluids over 3 hours
- done blood work (including cultures), urine studies and a CXR
- given a dose of IV antibiotics to cover for possible infection
- given a dose of methylprednisolone (1 hour ago)

Symptoms: rigors now resolved, mild back pain ongoing, rash improving, no nausea
Vital signs: T: 39.0 C, HR: 95 bpm, BP: 90/50 mmHg, RR: 18 bpm, SpO2: 95% on RA
Labs: CBC shows mild anemia, no neutropenia or thrombocytopenia, urine dip and CXR clear

UBC CPD Medicine
CONTINUING PROFESSIONAL DEVELOPMENT

What will you do next?

1. It is too early to see any effects from steroids. Continue to observe and monitor vital signs hourly.

2. Give another dose of acetaminophen, continue fluids and observe.

3. Continue fluids and administer a dose of tocilizumab at 8 mg/kg over 1 hour.

4. As BP is dropping despite IV fluids, transfer to ICU for vasopressors, if within patient's goals.

CASE 1 – CONTINUED – 1 HOUR LATER

So far you have:
- given acetaminophen 975 mg, cetirizine 10 mg, and ondansetron 8 mg (all 3 hours ago)
- given a total of 1.5 L of IV fluids over 3 hours
- done blood work (including cultures), urine studies and a CXR
- given a dose of IV antibiotics to cover for possible infection
- given a dose of methylprednisolone (1 hour ago)

Symptoms: rigors now resolved, mild back pain ongoing, rash improving, no nausea
Vital signs: T: 39.0 C, HR: 95 bpm, BP: 90/50 mmHg, RR: 18 bpm, SpO2: 95% on RA
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CRS	Management
Grade 2 Symptoms require and respond to moderate intervention. Grade 1 CRS symptoms and: ▪ Hypotension not requiring vasopressors And/or ▪ Hypoxia requiring low-flow oxygen (≤ 6L/min) or blow-by If patients have extensive comorbidities or poor performance status, manage per grade 3 CRS guidance below	**Immediately interrupt/delay infusion until event improves to CRS grade ≤ 1** Page the admitting physician or covering physician if not already done. Administer the following as ordered: ▪ 500 mL to 1 L NaCl 0.9% IV fluid bolus or continuous infusion ▪ acetaminophen 650 mg or 975 mg PO every 4 hours PRN ▪ diphenhydrAMINE 50 mg IV every 4 hours PRN ▪ metoclopramide 10 mg PO/IV every 4 hours PRN ▪ ondansetron 8 mg PO/ IV every 8 hours PRN *Supportive care* If blood pressure does not respond to IV fluids (i.e. after 2 fluid boluses), tocilizumab and/or steroids should be strongly considered. Early administration of tocilizumab decreases rates of progression to grade 3 or 4 CRS. If grade 2 CRS occurs, **administer tocilizumab first*,** reserving steroids if no response to tocilizumab within 1 to 2 hours. ***Note:** Melanoma patients are particularly responsive to steroids, therefore **for melanoma patients only, administer steroids first**, reserving tocilizumab if symptoms do not resolve post steroid administration within 1 to 2 hours. Tocilizumab dosing: ▪ tocilizumab 8 mg/kg (maximum 800 mg) IV in 100 mL NS over 1 hour. Repeat every 8 hours as needed if not responding to IV fluids or supplemental oxygen (limit 3 doses in 24 hours, 4 doses total). Steroid dosing: ▪ methylPREDNISolone 1 mg/kg IV every 12 hours or ▪ dexamethasone 10 mg IV every 6 hours Continue corticosteroids until event is Grade 1 or less, then taper over 3 days. If required: ▪ salbutamol 5 mg nebule for inhalation by nebulizer every 20 minutes (maximum 3 doses) Vital sign monitoring and pulse oximetry frequency should increase to at least every hour, and more frequently if necessary, until resolution of CRS symptoms.

CASE 2

You are working on the inpatient unit and you are about to discharge the following patient:

A 57F with diffuse large B cell lymphoma, admitted 2 days ago for cycle 1 day 15 treatment with **epcoritamab**. This was her first full dose. Her day 8 and day 15 treatments were both complicated by grade 1 CRS. She was observed on the unit for 24 hours post CRS.

RN tells you that she was not able to count backwards from 100 in 10s or write a standard sentence this morning, saying that she was too tired to do those things. She was oriented and able to follow simple commands. She has had no history of cognitive symptoms.

Exam findings: oriented, cranial nerves, extremity strength, reflexes and sensory exam are all WNL. There is a subtle change in her gait. She declines to sign her name and says that she is extremely tired.

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CASE 2

What is the most likely issue?

1. Delirium NYD
2. Fatigue secondary to anemia
3. Secondary CNS lymphoma, until proven otherwise
4. Immune effector cell associated neurotoxicity syndrome (ICANS)

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CASE 2

What is the grade/severity of ICANS in this case:

1. Grade 1
2. Grade 2
3. Grade 3
4. Grade 4

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CONTINUING PROFESSIONAL DEVELOPMENT

CASE 2

What is the grade/severity of ICANS in this case:

1. Grade 1
2. Grade 2
3. Grade 3
4. Grade 4

Remember that ICANS presentation can be subtle

→ The ICE tool can be helpful

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CONTINUING PROFESSIONAL DEVELOPMENT

ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unrousable and unable to do ICE testing)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unrousable or requires significant tactile stimulus to awaken
Seizures	N/A	N/A	Any seizure (focal, general) that resolves rapidly. Non-convulsive seizure on EEG that resolve with intervention.	Life-threatening prolonged seizures (>5min). 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
Raised ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging (excluding intracranial hemorrhage)	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; papilledema; cranial nerve VI palsy; Cushing's triad

*ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

BC Cancer SCICANS Protocol ; 1 Jun 2024

ICANS

Table 1. Immune effector cell-associated encephalopathy score: ICE tool

Category	Points
1. Orientation: orientation to year, month, city, place*	4 points
2. Naming: ability to name 3 objects (ie. pen, cup, glasses) *	3 points
3. Following commands: ability to follow simple command (ie. “Close your eyes and stick out your tongue”)	1 point
4. Writing: ability to write a standard sentence (ie. “The flag is red and white”)	1 point
5. Attention: ability to count backwards from 100 by 10	1 point

*1 point for each item

10 points

BC Cancer SCICANS Protocol ; 1 Jun 2024

CASE 2

What will you do next?

1. Monitor ICE score and neuro vitals q8h, perform bedside fundoscopy, obtain urgent EEG.

2. Monitor ICE score and neuro vitals q8h, perform bedside fundoscopy, consider lab workup and brain imaging, administer dexamethasone 10 mg IV.

3. Obtain urgent EEG, lumbar puncture and Neurology consultation, administer dexamethasone 10 mg IV.

4. Obtain urgent EEG, lumbar puncture and Neurology consultation, consider lab workup and brain imaging, administer tocilizumab .

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CONTINUING PROFESSIONAL DEVELOPMENT

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CONTINUING PROFESSIONAL DEVELOPMENT

CASE 2 – CONTINUED – THE NEXT DAY…

ICANS symptoms fully resolved after 2 doses of dexamethasone. MRI was unremarkable. EEG ordered but not yet done.

What does this mean for patient management?

1. Due to the history of ICANS, further epcoritamab therapy should be discontinued.
2. Observe patient for 24 hours post ICANS resolution, may then discharge and readmit for the next dose of epcoritamab.
3. Patient should remain admitted for observation until after her next dose of epcoritamab.
4. Will need to taper steroids over 3 days first, then consider discharge.

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CONTINUING PROFESSIONAL DEVELOPMENT

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SUMMARY

Bispecific Abs are a new class of immunotherapy that bind receptors on both cancer cells and immune cells (usually T cells), thus facilitating the targeting and destruction of cancer cells by circulating immune cells.

CRS and ICANS are important side effects associated with bispecific Ab therapy.

Other treatment side effects (e.g. nausea, fatigue, cytopenia, rash) can still occur in patients treated with bispecific Abs. CRS is more common than febrile neutropenia in patients treated with bispecific Abs. History/exam to guide workup and treatment for other diagnoses.

A step-wise increase in the dose of bispecific Abs improves tolerability. The first few doses usually require inpatient administration and monitoring.

Grading criteria direct both CRS and ICANS management. Please refer to BC Cancer's website for detailed CRS and ICANS protocols.

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Conclusions: Promise of bispecific antibodies

- Immunotherapy has dramatically changed the landscape of cancer treatment
- Bispecific antibodies are in numerous phase 1-3 clinical trials and rapidly gaining regulatory approvals
- Toxicities including CRS and ICANS are unique however predictable and manageable
- Safe administration and management of complications requires education, multidisciplinary teams, and strong infrastructure across BC

BC CANCER

Provincial Health Services Authority

FAMILY PRACTICE ONCOLOGY NETWORK

BC Cancer Primary Care Program's FPON Educational Communications

Sign up through the QR code!