Clinical Pharmacology & Toxicology Pearl of the Week

~ Bispecific T cell Engagers (BiTEs) ~

Background

- ✓ Bispecific T-cell engagers (BiTEs) are monoclonal antibodies that target both a tumour-specific antigen and CD3 on T-cells to bring together a tumour cell and a cytotoxic T cell

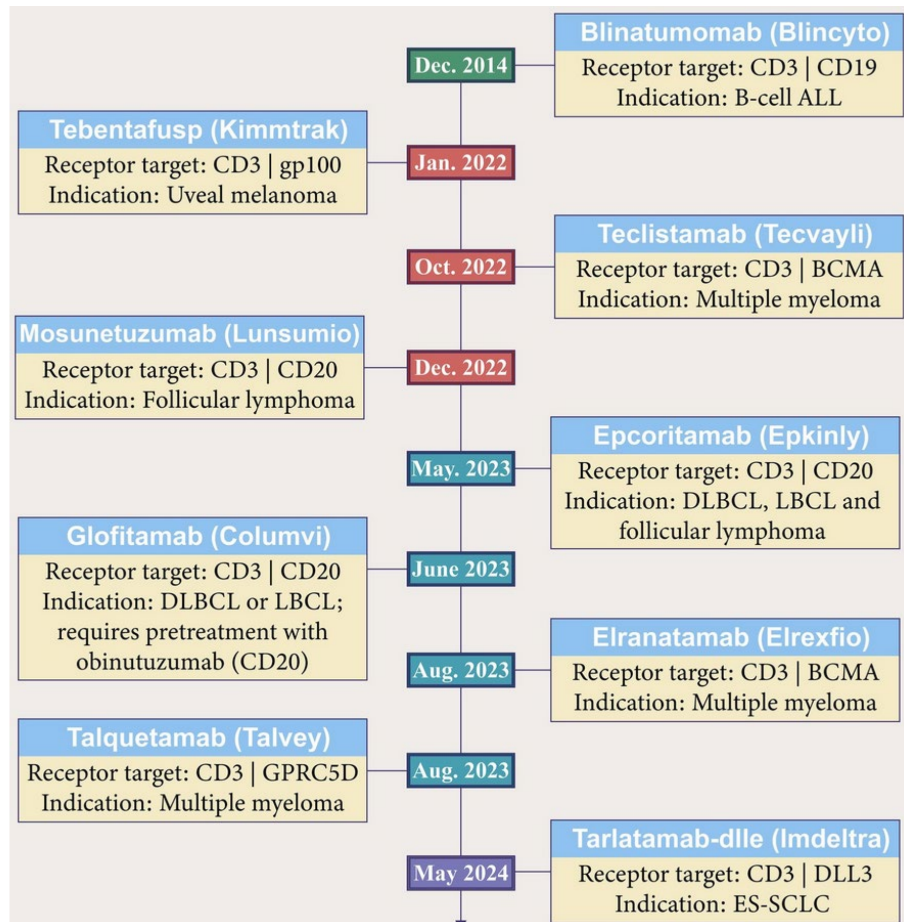

Figure 1. BiTE FDA approvals. Source: Wattana et al. Cancer Treat. Rev. 2025: 102889

Mechanism of Action

- ✓ CD3 activation by the BiTE leads to cytotoxic T cell activation, leading to further proliferation of T cells and secretion of granzymes such as perforins to cause tumour cell lysis and apoptosis
- ✓ This activation is principally similar to chimeric antigen receptor T-cell therapy, and these two classes of treatment share similar side effect profiles, but is often less severe in BiTEs

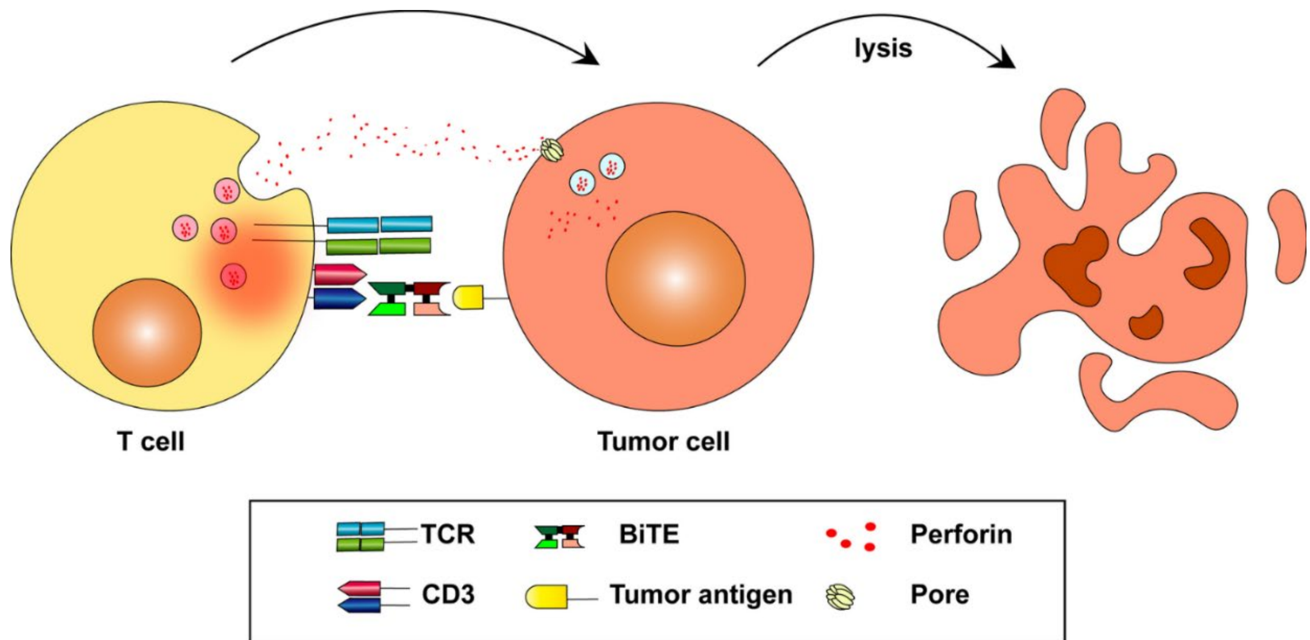

Figure 2. BiTE activation of T cells. Source: Tian et al, J. Hem. Onc. 2021, 14(75).

<u>Toxicity</u>

- ✓ Wide range of toxicities, from mild to fatal, typically driven by widespread inflammation and is typically more severe in patients with greater burden of disease
  - General treatment is supportive – holding treatment, use of immunosuppressive agents such as steroids and tocilizumab
- ✓ Suggest early involvement of patient's hematologist and ruling out other potential causes

- ✓ **<u>Cytokine release syndrome (CRS; 20-63%)</u>**
  - Diagnosis of exclusion with fever (T>38C or anti-pyretic use) ± hypotension, hypoxemia
  - Timing – Typically 1st cycle, 2 days after most recent dose
  - Management (see grading table below)
    - Usual septic work-up, attention to line infections
      - Of note – lines for blinatumomab infusions should not be flushed or used for other medications or blood draws as this medication is given as a continuous 24h infusion owing to its short half-life
    - Supportive care – Anti-pyretics, IV fluids, supplemental oxygen
    - Dexamethasone 10mg IV q6-12h
    - Tocilizumab 8mg/kg (max 800mg) IV q8h x 2-3x per CRS event
    - Other cytokine dampening agents – anakinra, siltuximab

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever T>38C	+	+	+	+
Hypotension	-	+	**Vasopressors**	Multiple pressors
Hypoxemia	-	Nasal prongs	6+L O2 requirements	Positive pressure ventilation required
Management	Supportive	IV fluids Steroids +- Tocilizumab	Steroids Tocilizumab	Solumedrol pulse Tocilizumab Other cytokine agents

- ✓ **Immune effector cell-associated neurotoxicity syndrome (ICANS; 6-8%)**
  - Extensive spectrum of neurologic dysfunction with headaches, dizziness, and tremors being the most common
    - Can also lead to encephalopathy, discoordination, gait imbalance, speech disorders, seizures, and cognitive impairment
  - Timing – Typically 1st cycle, 7-16 days after most recent dose
  - Management
    - Consider work-up for alternative etiologies with head imaging, lumbar puncture
    - Assessment of fine motor coordination with handwriting, speech via ICE tool
    - Supportive care – Abortive seizure medications PRN, anti-epileptics
    - Dexamethasone 10-20mg IV q6-12h
    - Tocilizumab should only be added in concurrent CRS

Immune-effector cell-associated encephalopathy (ICE) Category	Points
Orientation – year, month, city, place	1 per item
Naming 3 objects	1 per item
Following commands (ie. “Close your eyes and stick out your tongue)	1
Writing a sentence (ie. “The flag is red and white.”)	1
Attention: Count backwards from 100 by 10	1

ICANS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Level of consciousness	Awakens spontaneously	Awakens to voice	Awakens to touch	Stupor or coma
Encephalopathy Confusion Tremor	Mild	Limiting IADLs	Limiting self-care ADLs	Life-threatening
ICE score	7-9	3-6	0-2	Unable to perform
Seizure	-	-	+	Status epilepticus
Raised ICP	-	-	Focal edema on imaging	Diffuse edema, papilledema, or CN 6 palsy
Management	Steroids	Steroids	Steroids	Solumedrol pulse ±Anakinra

✓ **Immune effector cell Hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS, <1%)**

- Due to abnormal macrophage transactivation leading to fever, organomegaly, cytopenia, liver injury, and elevated inflammatory markers (sIL2R, ferritin, triglycerides), decreased fibrinogen
- Most commonly reported with blinatumomab amongst the BiTEs
- Timing – After resolution/resolving CRS despite initial improvement

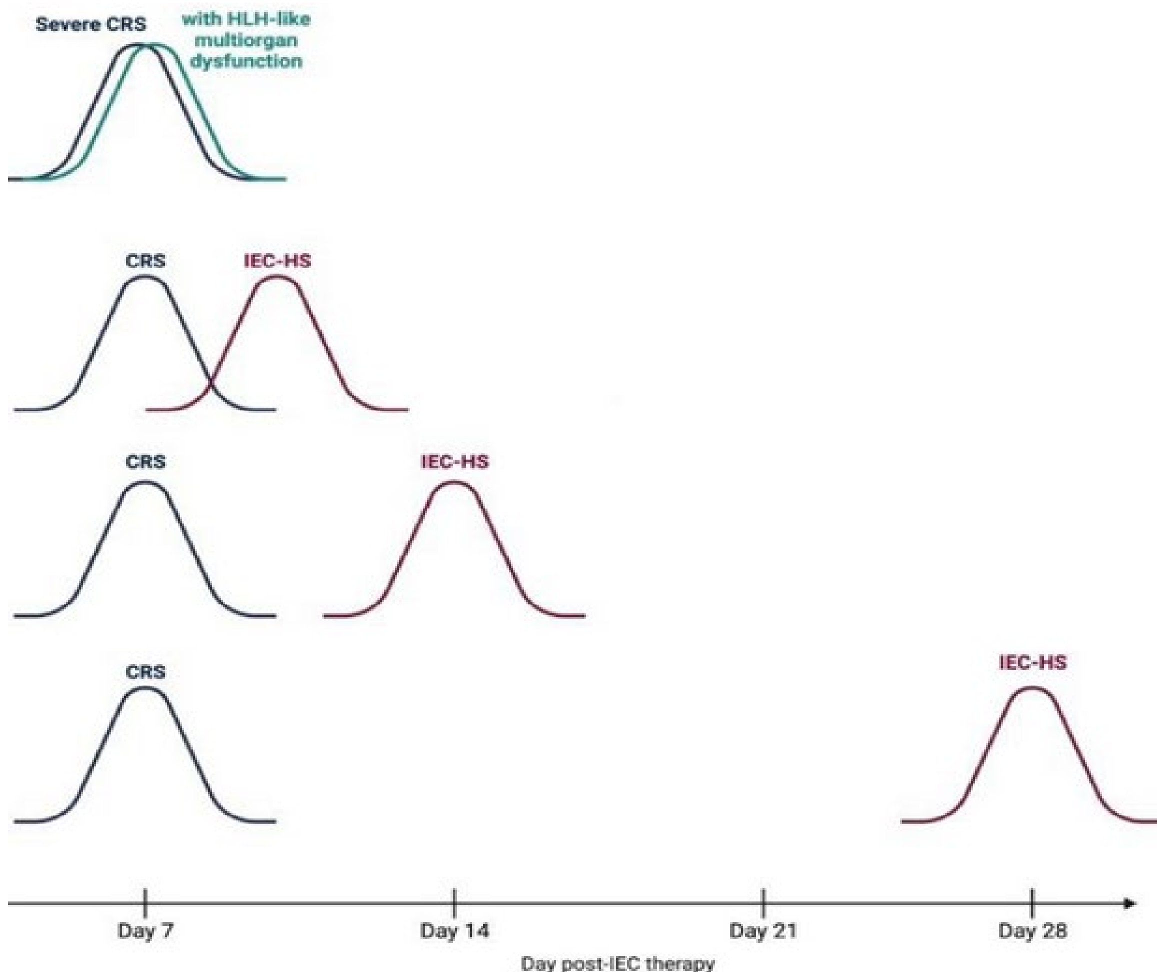

Figure 3. Timing of IEC-HS. Source: Hines et al, Transplatn Cell Ther. 2023 Mar 9;29(7)438.

- Management
  - HScore calculation, ordering a CBC, inflammatory markers, liver, renal panel.
  - Supportive management of cytopenias and coagulopathy
  - Anakinra 100-200ug SC/IV q6-12h is preferred
  - ± Dexamethasone 10mg q6h
  - ± Ruxolitinib 10mg BID

✓ Other toxicities including direct marrow toxicity leading to pancytopenia, hypogammaglobulinemia, DIC, tumour lysis syndrome can also be seen in BiTE use.

References

1. Wattana, Monica K., et al. "Diagnosis and management of bispecific T cell–engaging antibody toxicity: A primer for emergency physicians." *Cancer Treatment Reviews* (2025): 102889.
2. Tian, Zheng, et al. "Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies." *Journal of Hematology & Oncology* 14.1 (2021): 1-18.
3. Cancer Care Alberta, Alberta Health Services (2024). Clinical Practice Guideline on Lymphoma, Version 20. Available from: www.ahs.ca/guru.
4. Lee, Daniel W., et al. "ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells." *Biology of blood and marrow transplantation* 25.4 (2019): 625-638.
5. Hines, Melissa R., et al. "Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome." *Transplantation and cellular therapy* 29.7 (2023): 438-e1.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm, excluding stat holidays. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link, and RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

Created and Reviewed March 21, 2025