Bispecific T-Cell Engagers (e.g., *BiTEs*™) : An Emerging Strategy for Immunotherapy

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Background

Since Rituximab's approval in the late 1990s for B-cell Non-Hodgkin lymphoma (NHL), immunotherapy has advanced, leading to innovations like bispecific T-cell engagers (*BiTEs*). *BiTEs* use an innovative approach by simultaneously engaging both cytotoxic T-cells and tumor cells, enhancing the T-cell attack and increasing its potency.

Clinical Significance

- Selective targeting tumor-associated antigens (TAA) by Major Histocompatibility Complex (MHC) independent mechanism
- T-cell activation produced by binding to the constant part of the T-cell receptor (TCR) complex
- Off-shelf rapid therapy

Mechanism of Action

BiTE consists of two-single chain variable fragments (scFv) from monoclonal antibodies. One scFv binds to the TAA on the cancer cell, while the other binds to a CD3, a TCR on the surface of the T-cell. The T-cell becomes activated once it engages with the tumor cell triggering malignant cell lysis. Additionally, co-stimulatory agents are not required therefore, the *BiTE* molecules can engage any T-cell.

Clinical Applications

- Hematologic Malignancies:
  - Blinatumomab (Blincyto) was the first approved *BiTE* by the FDA.
  - Glofitaman (Columvi)
  - Epcoritamab (Epkinly)
  - Mosunetuzumab (Lunsumio)
  - Teclistamab (Tecvayli)
  - Talquetamab (Talvey)
  - Elranatamab (Elrexfio)
- Solid Tumors:
  - Tarlatamab (Imdelltra)
  - Tebentafusp (Kimmtrak)- considered a bispecific molecule, not a bispecific antibody.
- Combination Therapies in development:
  - *BiTEs* + Checkpoint inhibitors (PD-1/PD-L1)
  - *BiTEs* + Other Cancer Therapies

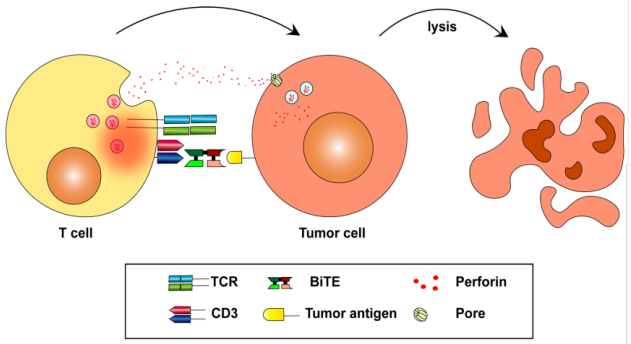

Fig 1. *BiTEs* mechanism of action leading to cell lysis.

Challenges

- Cytokine release syndrome (CRS): results from T-cell activation and cytokine release, causing fever, hypotension, and organ dysfunction.
- Immune effector-associated neurotoxicity syndrome (ICANS): is thought to occur when activated T-cells interact with the blood-brain barrier, causing inflammation and resulting in neurological symptoms, ranging from mild confusion to severe encephalopathy.
- Immune escape: can occur through an immunosuppressive tumor microenvironment (TME) that inhibits TAA-specific T-cells or by losing target antigen expression.
- Short half-life: 2-4 hours requires continuous dosing or modifications to maintain effectiveness.

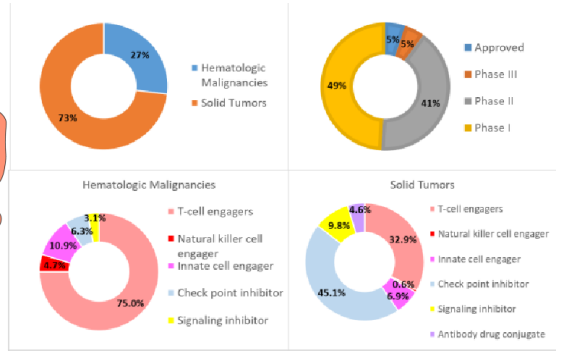

Fig 2. Bispecific antibodies on clinical development.

Summary

BiTEs engage both T-cells and tumor cells, offering off-the-shelf availability and broader therapeutic applications. They have shown potency in hematologic cancers, and ongoing efforts aim to optimize them for solid tumors, with potential for combination therapies to prevent T-cell exhaustion and reduce toxicities.

Reference(s)

1. Navab R, Futela P, Kumari V, Valecha J, Gupta RB, Jain R. Advancing Multiple Myeloma Immunotherapy: A Review of Chimeric Antigen Receptor T-Cell and Bispecific T-Cell Engagers Cell Therapies in Revolutionizing Treatment. *Iran J Med Sci*. 2025;50(1):1-10. Published 2025 Jan 1. doi:10.30476/ijms.2024.101739.3446
2. Shanshal M, Caimi PF, Adjei AA, Ma WW. T-Cell Engagers in Solid Cancers-Current Landscape and Future Directions. *Cancers (Basel)*. 2023;15(10):2824. Published 2023 May 18. doi:10.3390/cancers15102824
3. Tian, Z., Liu, M., Zhang, Y. *et al.* Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. *J Hematol Oncol* 14, 75 (2021). doi.org/10.1186/s13045-021-01084-4
4. Goebeler ME, Bargou RC. T cell-engaging therapies - BiTEs and beyond. *Nat Rev Clin Oncol*. 2020;17(7):418-434. doi:10.1038/s41571-020-0347-5
5. Litzow MR, Sun Z, Mattison RJ, et al. Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults. *N Engl J Med*. 2024;391(4):320-333. doi:10.1056/NEJMoa2312948
6. Paz-Ares L, Champiat S, Lai WV, et al. Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study. *J Clin Oncol*. 2023;41(16):2893-2903. doi:10.1200/JCO.22.02823
7. Klein C, Brinkmann U, Reichert JM, Kontermann RE. The present and future of bispecific antibodies for cancer therapy. *Nat Rev Drug Discov*. 2024;23(4):301-319. doi:10.1038/s41573-024-00896-6

Disclosure

The author has no financial interests or relationships to disclose. *BiTEs* ™ is trademarked by Amgen.

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