



# Updates on Bispecifics

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# Bispecific Antibodies (BsAbs)

- More than 100 formats for BsAbs
- Concept first appeared in early 1960s
- First example constructed in 1985
- BsAbs are divided into 3 categories:
  - Antibodies targeting 2 different tumor antigens
  - Antibodies targeting one tumor antigen and one immune-related molecule
  - Antibodies targeting 2 immune-related molecules

Perez P, Hoffman RW, Shaw S, Bluestone JA, Segal DM. Specific targeting of cytotoxic T cells by anti-T3 linked to anti-target cell antibody. *Nature*. 1985;316(6026):354-6.

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). <https://doi.org/10.1186/s13045-021-01084-4> Segal DM. Specific targeting of cytotoxic T cells by anti-T3 linked to anti-target cell antibody. *Nature*. 1985;316(6026):354-6.



## Bispecific T-Cell Engagers (BiTEs)

- Bispecific T cell engagers (BiTEs) are well designed formats of BsAbs
- BiTE is the BsAb designed to target CD3 and tumor-specific antigens simultaneously to promote the cytotoxicity of T-cells
- 2014- Blinatumomab CD3/CD19

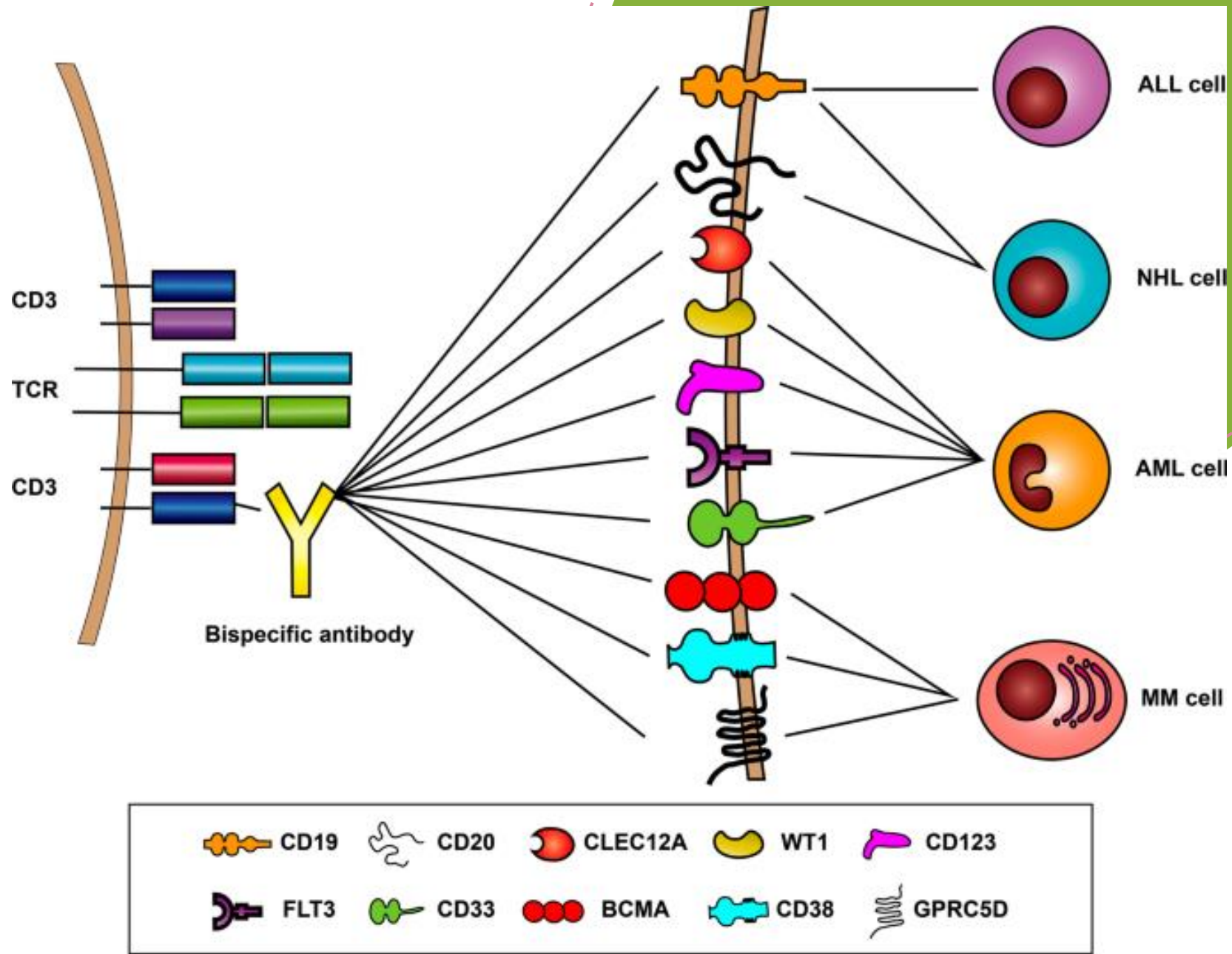
Disease	Target	Name	Antibody format
<b>AML</b>	CD123-CD3	MGD006	DART
		XmAb14045	XmAb
	CD33-CD3	AMG 330	BiTE
		AMV 564	TandAb
	FLT3-CD3	7370	BiTE
	CLEC12A-CD3	MCLA-117	Biclonics
	WT1-CD3	ESK1-BiTE	BiTE
<b>ALL</b>	CD19-CD3	Blinatumomab	BiTE
		AFM11	TandAb
<b>MM</b>	BCMA-CD3	AMG420	BiTE
		AMG701	BiTE-Fc
	GPRC5D-CD3	Talquetamab	DuoBody
	CD38-CD3	AMG424	XmAb
	Bi38-3	BiTE	
	FCRL5-CD3	anti-FcRH5/CD3 TDB	Knobs-into-holes
<b>NHL</b>	CD19-CD3	Blinatumomab	BiTE
	CD20-CD3	REGN1979	Veloci-Bi platform
		Mosunetuzumab	Knobs-into-holes
		RG6026	2:1 CrossMab
<b>MDS</b>	CD33-CD3	AMV564	TandAb
	CD123-CD3	MGD006	DART

# Bispecific T Cell-recruiting antibodies for the treatment of hematologic malignancies

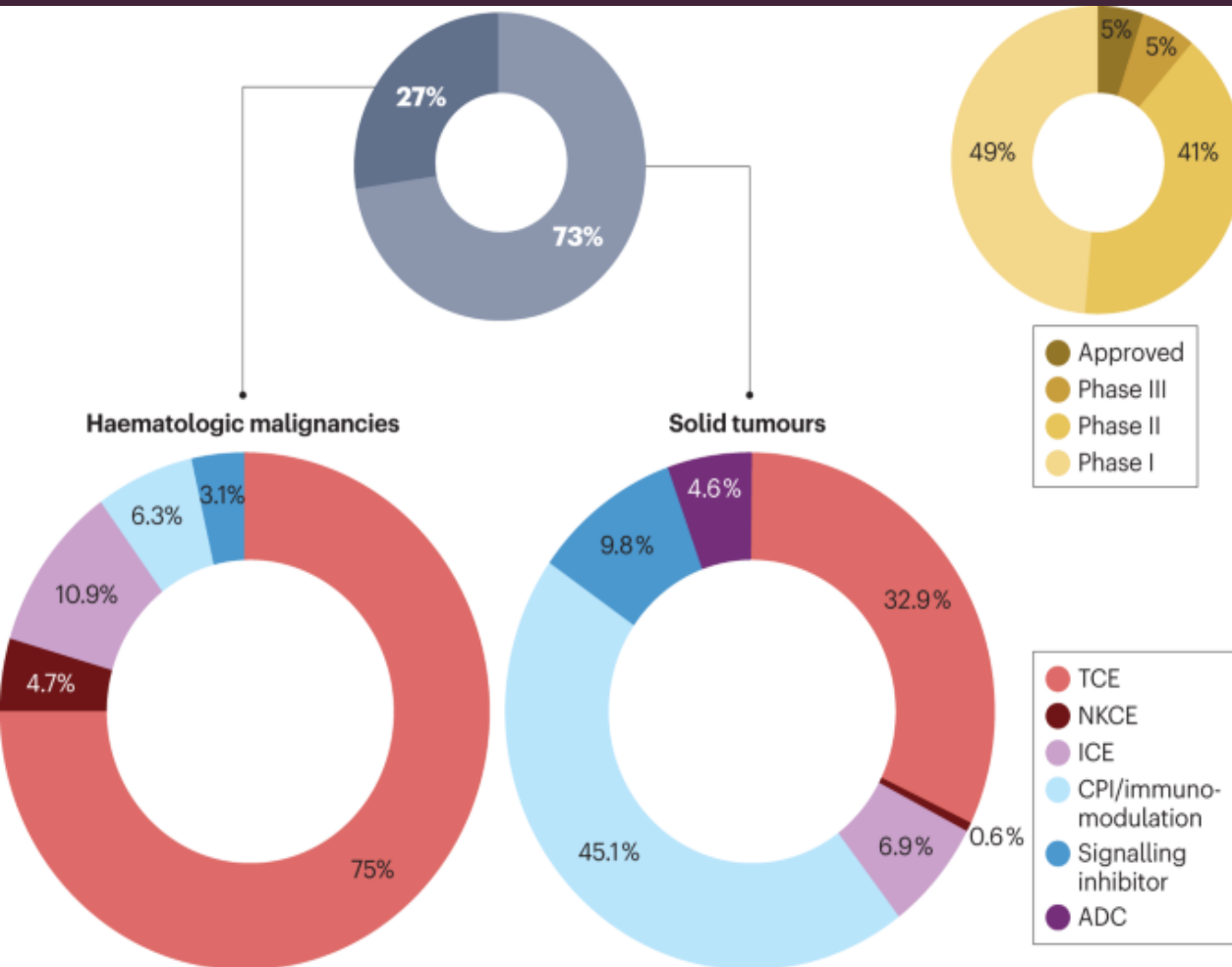
Tian, Z., Liu, M., Zhang, Y. *et al.* Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. *J Hematol Oncol* **14**, 75 (2021). <https://doi.org/10.1186/s13045-021-01084-4> Segal DM. Specific targeting of cytotoxic T cells by anti-T3 linked to anti-target cell antibody. *Nature*. 1985;316(6026):354–6.



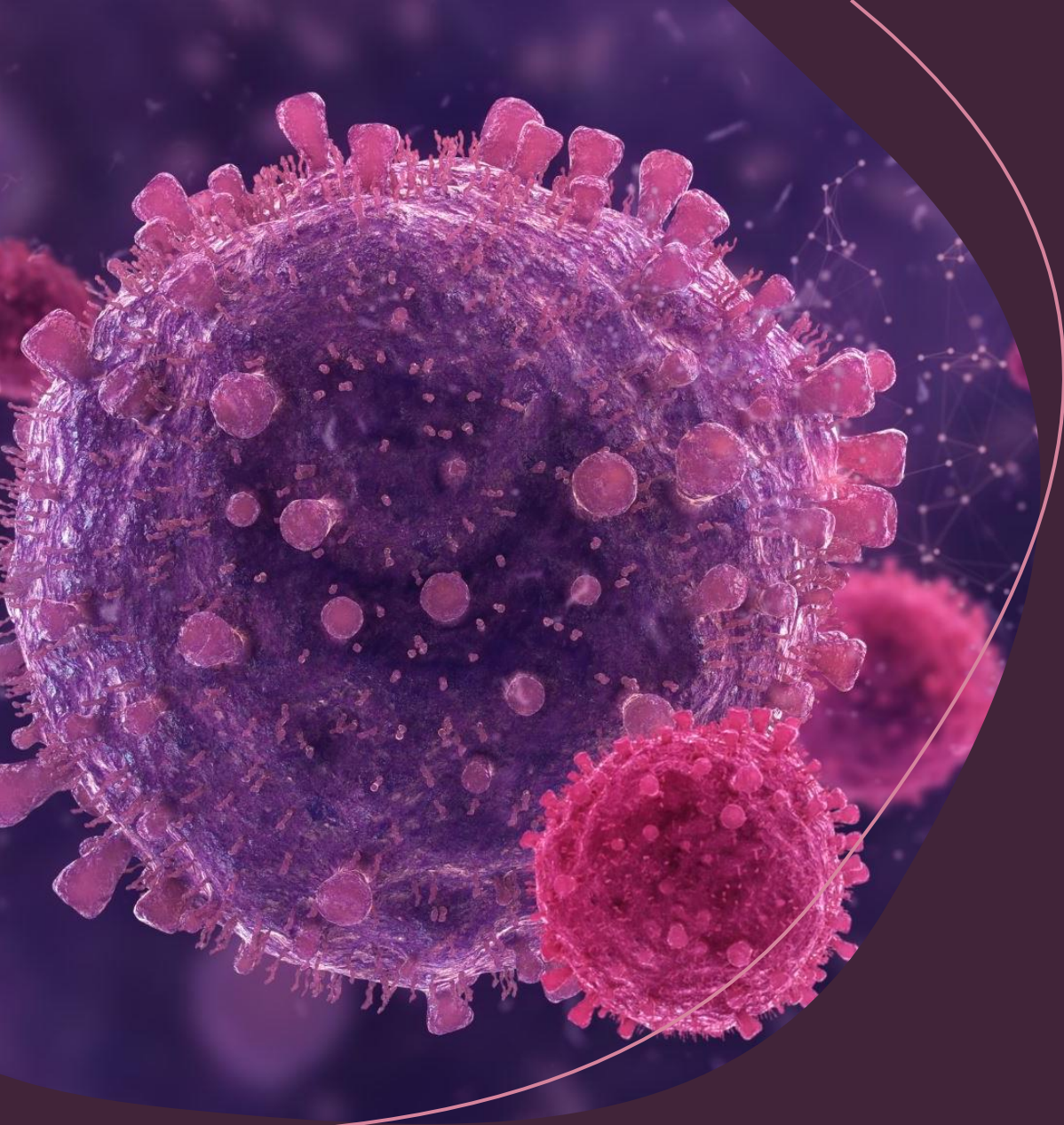
# Mechanisms of Action



# Bispecific antibodies in clinical development for cancer therapy



- >200 BsAbs in development
- 50% are in PII, PII and/or approved
- 75% of BsAbs in development for hematologic malignancies are T-cell Engagers



## Common Adverse Events

- Neutropenia
- Hypogammaglobulinemia
- Fatigue
- Nausea
- Fever
- Myalgias
- Cytokine Release Syndrome (CRS)
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)





# Managing Adverse Events

- Use of prophylactic antibiotics/antivirals/antifungals
- MIG replacement as needed
- Dose step-up or ramp-up
- Subcutaneous injections
- Pre-medications including antipyretics and steroids
- Close and frequent monitoring
- Use of anti-IL-6 medications



# Cytokine Release Syndrome (CRS)

- Overreaction of the immune system to the therapy given
- Diagnosed via labs, CXR, CTs, MRI
- Classified by grading 1-4, using key symptoms of fever and blood pressure
- Grades 1-2 can be managed via close observation, IV-hydration, tocilizumab or steroids
- Grades 3-4 CRS require hospitalization to ICU for close monitoring and management



# Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

- May occur during or after CRS symptoms
- Vary among patients
- Variety of assessment tools (thanks to CAR-T) CARTOX-10, ICE, CTCAE and others
- Treatment is largely supportive and dependent upon severity
- $\geq$  Grade 2 treatment includes steroids in high doses with a rapid taper

