BLOOD CANCER
Connect & Learn

Innovations in Treatment: Immunotherapy & Targeted Therapy

Dr Perusini

Our expert

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Dr. Maria Agustina Perusini earned her medical degree from Hospital Italiano de Buenos Aires, Argentina, in 2010, where she also completed a residency in Internal Medicine and a fellowship in Hematology. In 2022, she joined the Princess Margaret Cancer Centre in Toronto, Canada, where she completed a fellowship in Leukemia and Myeloproliferative Neoplasms (MPN).

She is currently a Clinical Investigator in the Leukemia Program within the Division of Medical Oncology at the University of Toronto. Dr. Perusini’s academic interests center on translating laboratory research into clinical practice to improve patient outcomes, with a particular focus on Acute Leukemia and Chronic Myeloid Leukemia.

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Disclosures

- No financial disclosures related to this presentation
- A perspective for non-hematology experts

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Outline

Immunotherapy & Targeted Therapy

- Definitions
- Common adverse events
- Advances and what's coming

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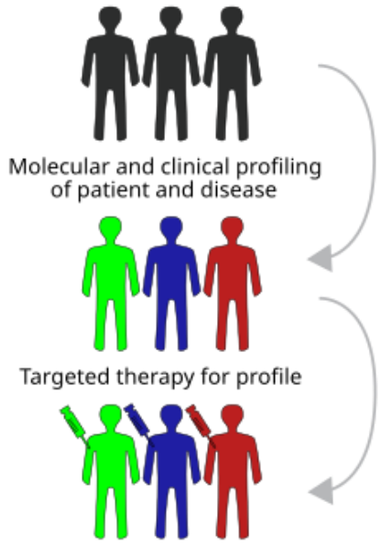
Paradigm Change in Cancer Therapy

Non-specific
“Broad spectrum”
Targeting cells with
high turn-over

More specific
Narrow spectrum
Targeting unique
markers present in
cancer cells



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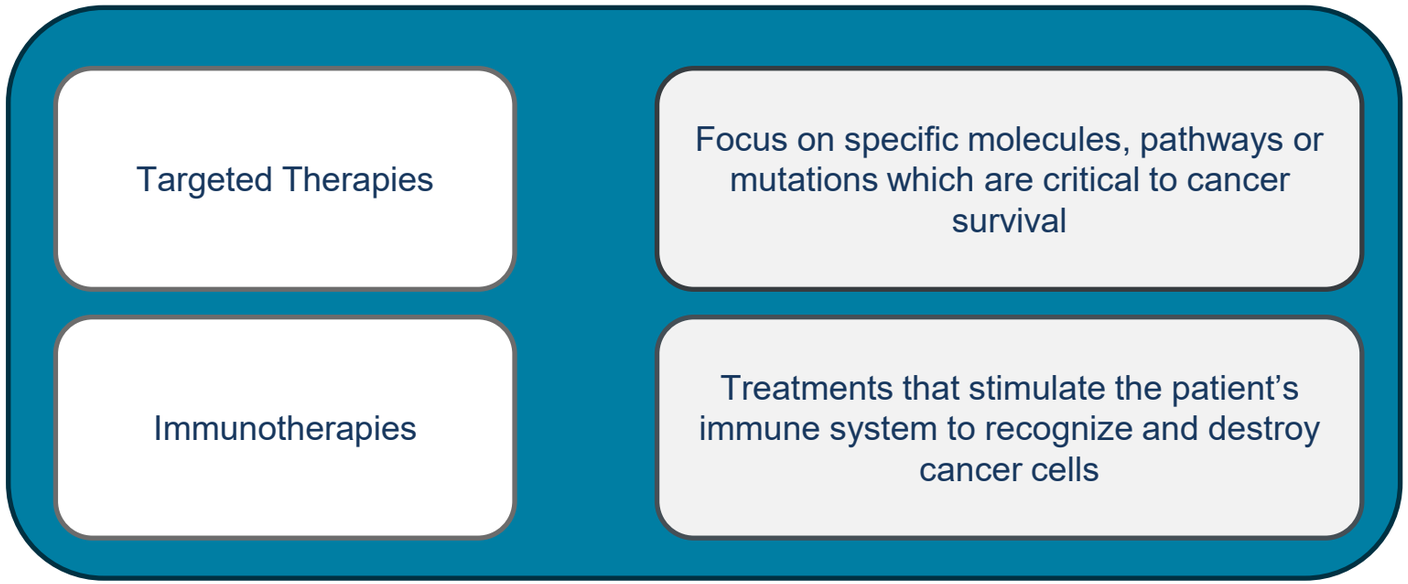
Novel Therapies for Cancer



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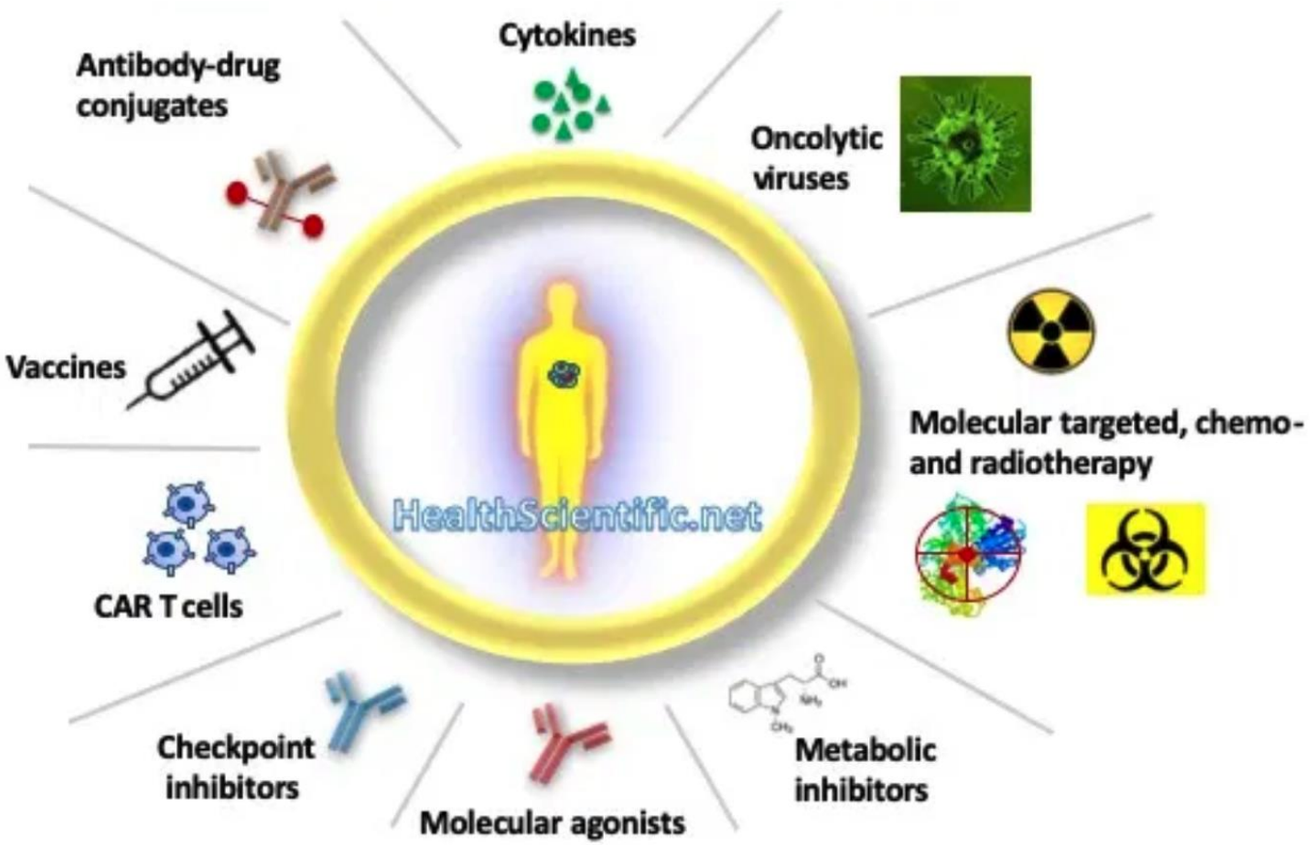
Novel Therapies for Cancer

Feature	Immunotherapies	Targeted Therapies
Definition	Treatments that harness or enhance the patient's immune system to recognize and kill cancer cells.	Drugs designed to block specific molecular pathways, mutations or antigen markers critical for cancer cell growth and survival.
Mechanism	Activate or redirect immune cells (T-cells, NK cells, antibodies).	Inhibit mutated or overactive signaling pathways (e.g., kinases, receptors).
Examples	- Monoclonal antibodies - Checkpoint inhibitors - Bispecific antibodies - CAR-T cell therapy	- Tyrosine kinase inhibitors (imatinib, dasatinib, ibrutinib, gilteritinib) - FLT3, IDH1/2 inhibitors (midostaurin, enasidenib, ivosidenib) - BCL2 inhibitors (venetoclax) - JAK inhibitors (ruxolitinib)
Toxicities	Immune-mediated: CRS, ICANS Cytopenia – infections	"On-target" toxicities: cytopenia, cardiac, vascular, GI, hepatic (depending on pathway).
Administration	IV infusions (mAbs, bispecifics), cellular infusion (CAR-T)	Pills or IV. Monotherapy or complementary
Cost/Logistics	Often complex (CAR-T requires specialized centers, bispecifics need close monitoring).	More accessible; oral outpatient treatment common.

Immunotherapies

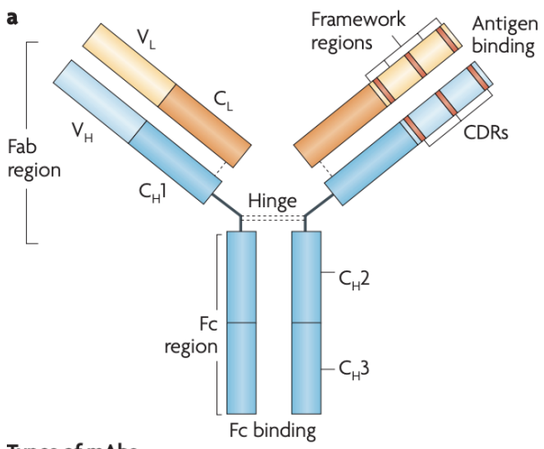


Source: *www.healthscientific.net*

Monoclonal antibodies

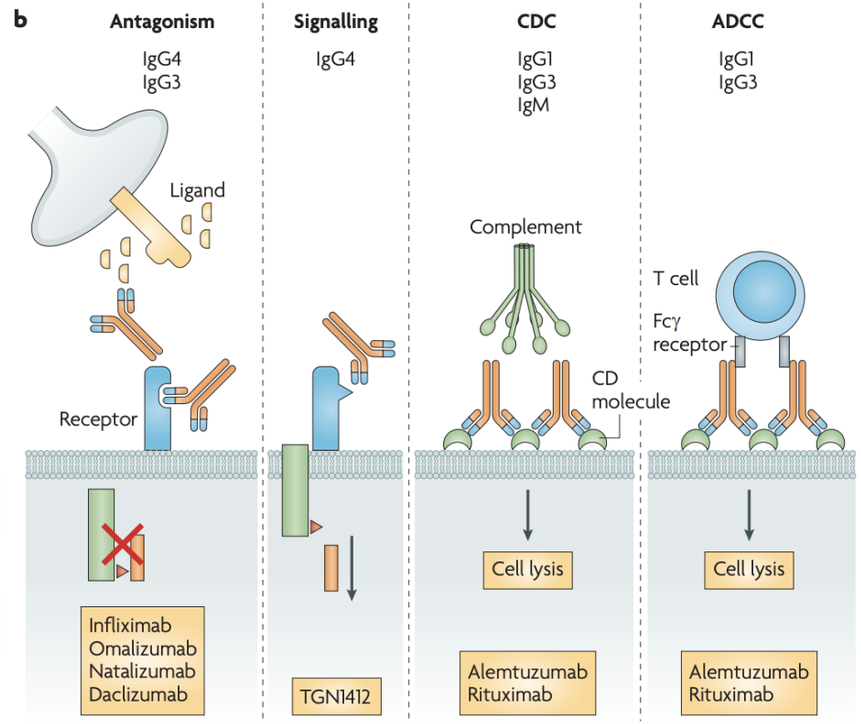
- Antibodies are proteins made by the body's immune system
- They recognize and defend against foreign substances like bacteria and viruses
- Monoclonal antibodies are molecules produced in a laboratory to mimic the antibodies produced naturally by the immune system
- FDA first approved monoclonal antibody therapy in 1986. Monoclonal antibodies have been used to treat many diseases
- Monoclonal antibodies are a type of passive immunity, in which antibodies are delivered as a medication

Monoclonal antibodies



Types of mAbs

Murine	Entirely murine amino acids	'o' = mouse e.g. muromonab
Chimeric	Human constant (C) + murine variable (V) regions	'xi' = chimeric e.g. rituximab
Humanized	Murine complementarity determining regions (CDRs)	'zu' = humanized e.g. alemtuzumab
Human	Entirely human amino acids	'u' = human e.g. adalimumab



The safety and side effects of monoclonal antibodies Trevor T. Hansel*‡, Harald Kropshofer §, Thomas Singer §, Jane A. Mitchell‡ and Andrew J. T. George||

Monoclonal antibodies – adverse events

1. Infusion-Related Reactions

Common with CD20 (rituximab, obinutuzumab, ofatumumab) and others.

Symptoms: fever, chills, hypotension, bronchospasm, rash.

Usually occur during the first infusion.

Management: premedication (antihistamines, acetaminophen, steroids), slow infusion, supportive care.

2. Cytopenia

Neutropenia, thrombocytopenia, anemia (can be delayed).

Seen with anti-CD20, anti-CD38 (daratumumab, isatuximab), anti-CD22 (inotuzumab ozogamicin).

Monitor blood counts, adjust doses, supportive transfusions or G-CSF as needed.

3. Infections

Due to B-cell or plasma cell depletion and hypogammaglobulinemia.

Opportunistic infections (e.g., PJP, CMV reactivation, HBV reactivation).

Prevention: antimicrobial prophylaxis, vaccination, IVIG replacement in selected cases.

4. Organ Toxicities

Hepatotoxicity: HBV reactivation (especially with rituximab).

Cardiotoxicity: rare, but possible

Pulmonary toxicity: interstitial pneumonitis (rare with rituximab).

5. Specific Antibody-Drug Conjugate Toxicities

Inotuzumab ozogamicin (anti-CD22): veno-occlusive disease (VOD/SOS).

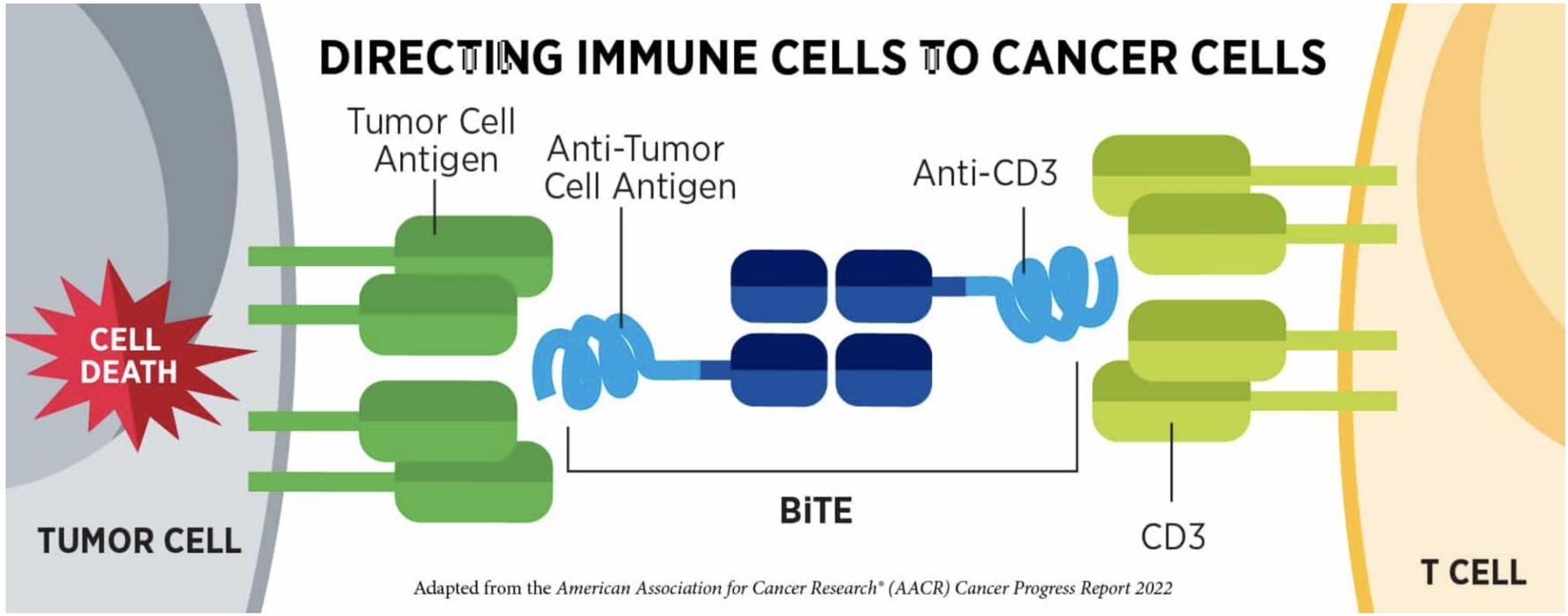
Brentuximab vedotin (anti-CD30): peripheral neuropathy, myelosuppression.

6. Immune-Mediated Toxicities

Autoimmune cytopenias

Infusion-related cytokine release (less severe than CAR-T or BiTEs).

Bi-Specific Cancer Therapies (BITE)



AACR website

CAR-T cells

- Genetically engineered T-cells
- Evidence for efficacy in:
  - Acute lymphoblastic leukemia
  - Lymphoma
  - Multiple Myeloma
- Ongoing research for many others (including non-malignant diseases)

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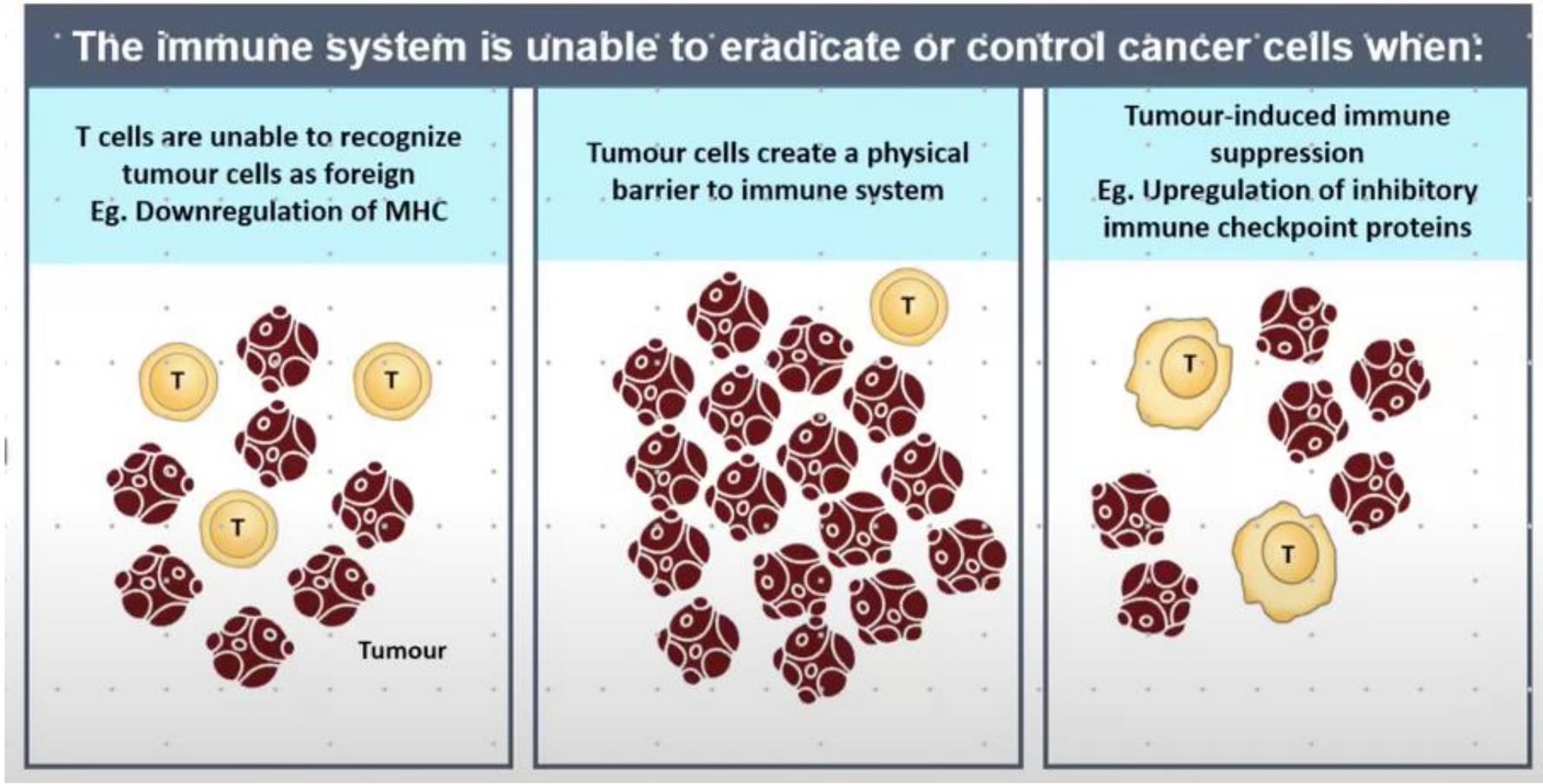
CAR-T cells



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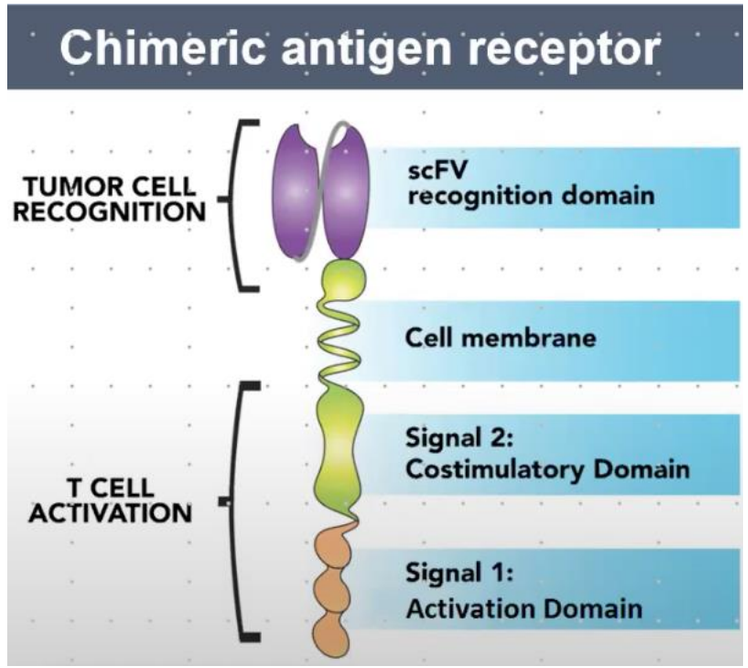
Murphy KM, *et al*. Janeway Immunobiology book; 2017

CAR-T cells

GOAL:

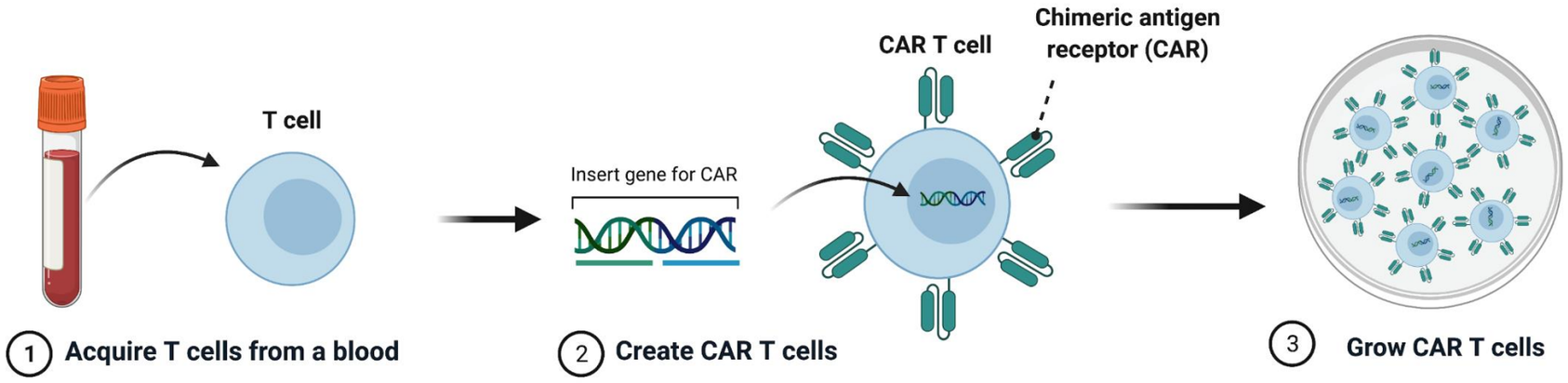
1- Target cancer cells by engineering a recognition domain (commonly a single fragment on the T cell surface)

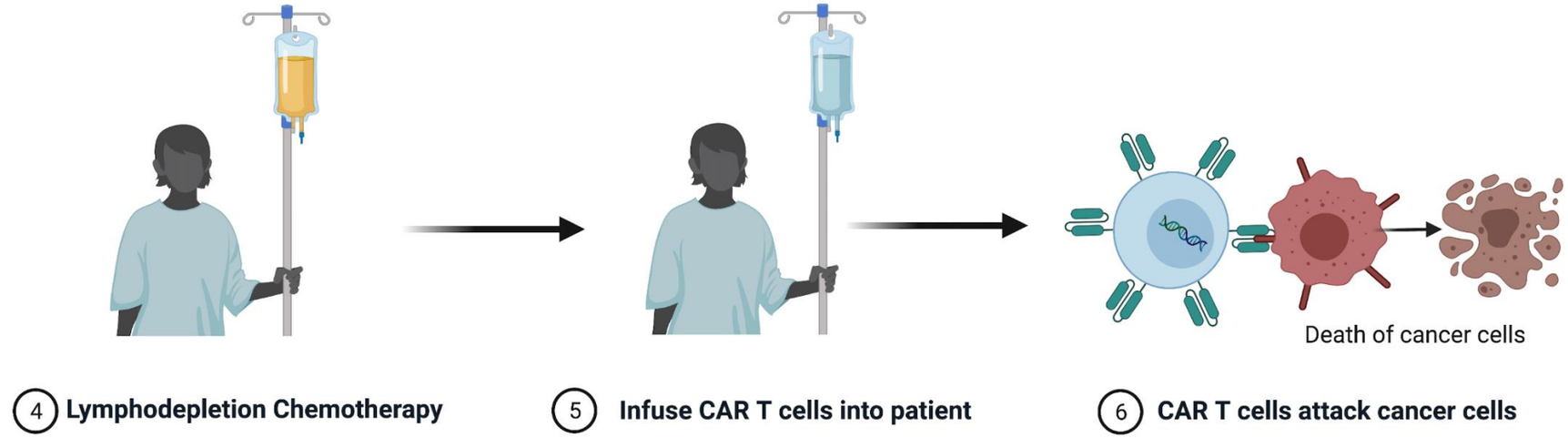
2 - Activate the T cell by signaling through the CAR's transmembrane and intracellular signaling domain with the goal of
•Activation & expansion of the T cell
•CAR T cell-mediated killing of tumour cells



Mol Cancer. 2015 Dec 11;14:207
N Engl J Med 2018; 379:64-73.

CAR-T Cells - Overview





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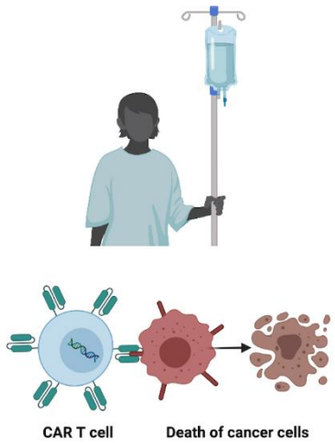
CAR-T Cells and BiTE– Overview of Toxicity



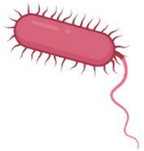
Immune Activation

Cytokine Release Syndrome

HLH

Immunosupression

Sepsis



Death of Cancer Cells

Tumour Lysis Syndrome

CNS Involvement

Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

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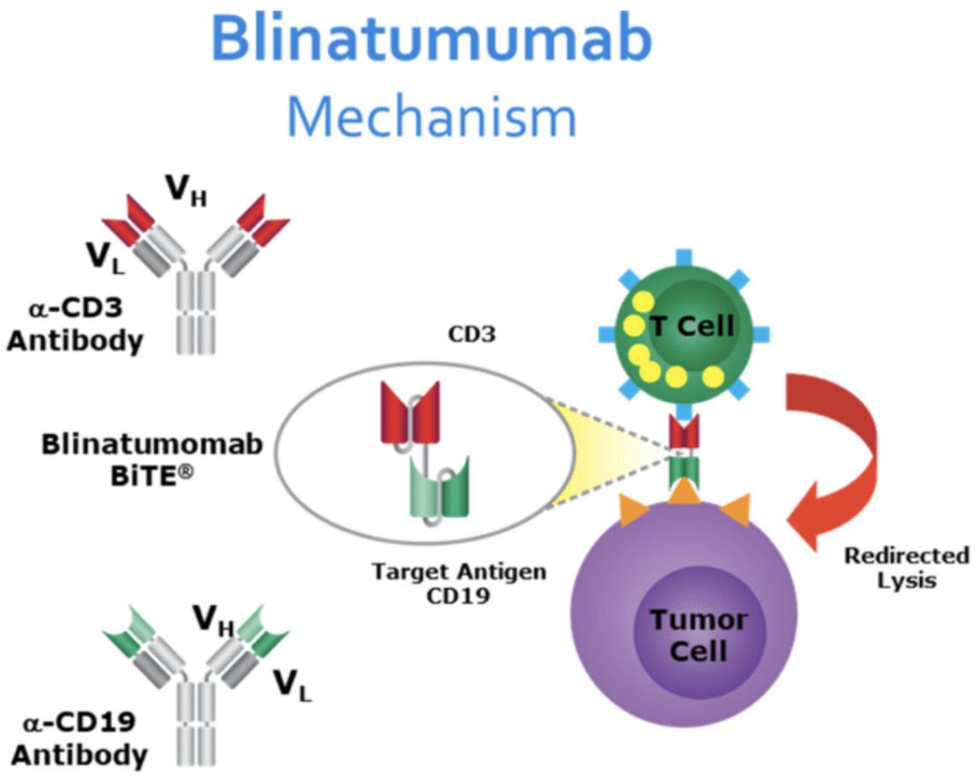
BiTEs vs CART

Feature	**BiTE (Bispecific T-cell Engager)**	**CAR-T (Chimeric Antigen Receptor T-cell)**
Mechanism	Small antibody construct that links CD3 on T-cells to a tumor antigen (e.g., CD19), redirecting T-cells to kill cancer cells.	Patient's T-cells are genetically engineered to express CARs that recognize tumor antigens (e.g., CD19), then reinfused to attack cancer.
Administration	Continuous or frequent IV infusion (short half-life, requires ongoing dosing).	One-time infusion after leukapheresis, genetic modification, expansion, and lymphodepletion.
Onset of Action	Rapid, reversible (effect depends on ongoing infusion).	Delayed onset (manufacturing time 2–6 weeks), but durable once infused.
Duration of Effect	Requires continuous treatment; effect stops once drug is cleared.	Potentially long-lasting, with persistent CAR-T cells providing ongoing surveillance.
Efficacy	High initial response in B-ALL, but often less durable; relapse is common.	High response rates and more durable remissions in some patients.
Toxicities	Cytokine Release Syndrome (CRS), neurotoxicity (often lower grade, manageable).	CRS, ICANS (can be severe), prolonged cytopenias, infections, hypogammaglobulinemia.
Logistics	"Off-the-shelf," immediately available; no manufacturing delay.	Personalized, complex manufacturing; requires specialized centers.
Cost	Lower upfront cost, but long-term costs accumulate due to continuous treatment.	Very high upfront cost, but potentially curative with one infusion.
Best Suited For	Patients needing rapid bridging, those unfit for CAR-T, or where CAR-T not available.	Patients eligible for cellular therapy with access to specialized centers.

BITE- LEUKEMIA



Blinatumomab is a **bispecific T-cell engager antibody** designed to direct cytotoxic T-cells to CD19 expressing cancer cells

Approved
1- R/R B-ALL
2- MRD positive B-ALL post induction
3- Upfront in consolidation regardless of MRD

	Ph-Positive	Ph-Negative		Positive MRD
Parameter	Pivotal Phase II (ALCANTARA)	Confirmatory Phase II	Tower Phase III	BLAST Phase II
No. of Patients	45	189	271	116
CR/CRh/ CRi, %	36	43	45	NA
MRD* negativity, %	88	82	76	78
OS, median, mo	7.1	6.1	7.7	36

Kantarjian H, Jabbour E. Am Soc Clin Oncol Educ Book 2018;574–78.

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Next steps – CAR-T - BiTE

Less toxicity

Greater durability

More accessible (off-the-shelf options)

New and multiple targets

Predictors of response

Sequential treatment strategies

Earlier use of better therapies

Targeted therapies

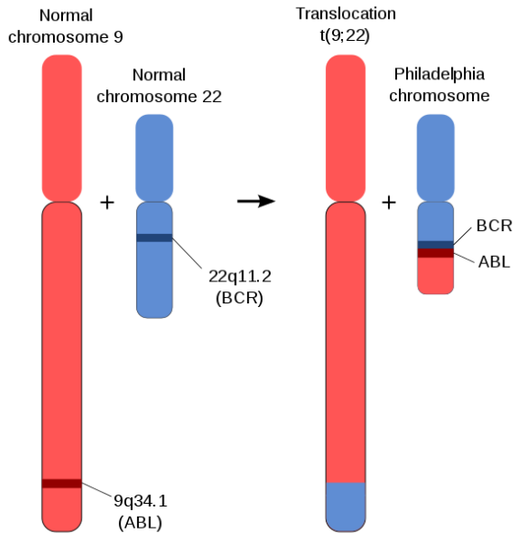
Hematologic malignancies are driven by distinct genetic and molecular abnormalities.

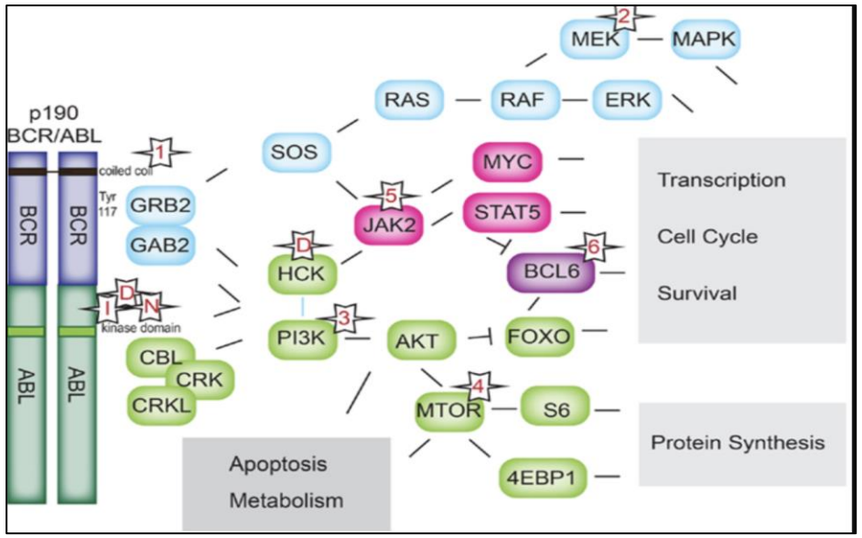
Targeted therapies are designed to inhibit antigens or pathways essential for cancer cell survival and proliferation.

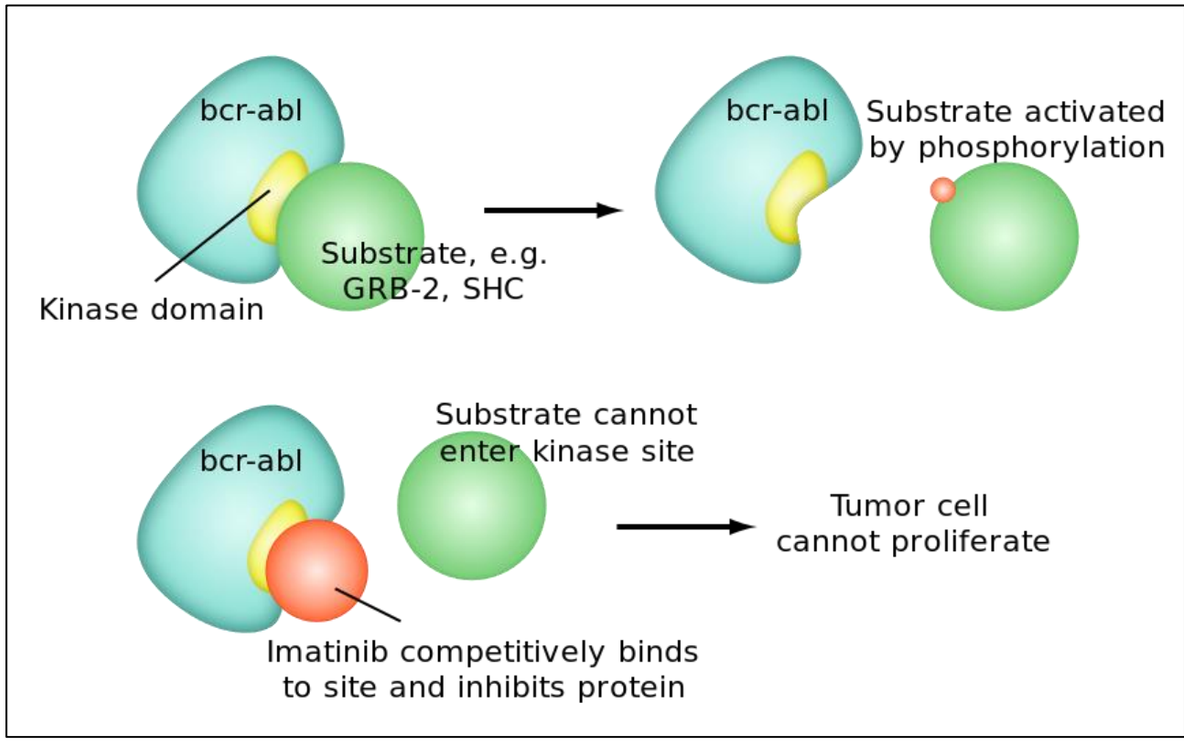
Emerging therapeutic strategies focus on overcoming resistance and reducing relapse, including mutation-specific targeting

Key classes of targeted therapies include: Tyrosine Kinase Inhibitors (TKIs), BCL2 inhibitors, IDH inhibitors, FLT3 inhibitors, JAK inhibitors, and proteasome inhibitors.

Tyrosine Kinase Inhibitors (TKIs)







The Philadelphia (Ph) chromosome, t(9;22), is associated with expression of the *BCR-ABL1* oncogene. Although Ph+ ALL was historically considered an adverse feature, its prognostic importance is uncertain in the era of tyrosine kinase inhibitors

*Bernt KM and Hunger SP (2014) Current concepts in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. Front. Oncol. **4**:54. doi: 10.3389/fonc.2014.00054*

Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014; 28:1467.

Targeted therapies – toxicities

Chemotherapy	Targeted Therapy
Non-specific cytotoxicity (affects all rapidly dividing cells)	Mechanism-specific toxicities
Myelosuppression (neutropenia, anemia, thrombocytopenia)	**Cytopenias** (common across TKIs, FLT3i, BCL2i)
GI toxicity (nausea, vomiting, mucositis, diarrhea)	**GI effects** (mild, drug-specific)
Alopecia	Rare alopecia
Infections due to profound immunosuppression	Infections possible, but usually less severe
Organ toxicity (cardiac, renal, hepatic)	**Target-specific AEs**: TKIs → vascular, QT prolongation IDH inhibitors → differentiation syndrome FLT3 inhibitors → liver enzyme ↑, QT prolongation Venetoclax → tumor lysis syndrome

Future direction

- **Less toxicity**
- **More durable responses** – combinations
- **More accessible therapies**
- **New and multiple targets**
- **Predictors of response**
- **Sequential treatment**

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