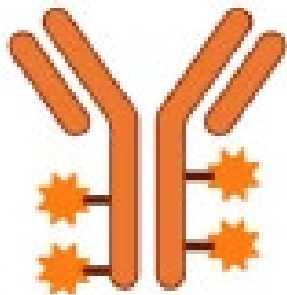
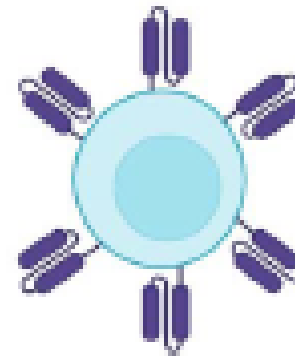


Immunotherapy options for patients with acute leukemia



Gregory Behbehani, MD, PhD
Assistant Professor
The Ohio State University



THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Immunotherapy options for patients with acute leukemia

- What is immunotherapy for treatment of cancer and how does it differ from traditional chemotherapy?
 - Antibodies, Antibody-Drug Conjugates, Bi-specific antibodies, and CAR-T cells
 - Bone marrow transplant – the original immunotherapy – remains highly effective, but will not be discussed today
- How do acute leukemias form and how does this determine which types of acute leukemia can be treated with immunotherapy?
- How is immunotherapy currently used in AML
 - Gemtuzumab Ozogamicin
- How is immunotherapy currently used in B-cell ALL
 - Inotuzumab Ozogamicin
 - Blinatumomab
 - CAR-T
- Future treatments

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- Future treatments

What is immunotherapy?

- Immunotherapy refers to treatments that utilize the body's immune system to treat cancer by stimulating cells of the immune system to attack cancer cells.
 - Immune cell stimulating cytokines (e.g. IL-2)
 - Antibodies
 - Antibody-Drug Conjugates
 - Bi-specific antibodies (BiTEs)
 - Chimeric antigen receptor T (CAR-T) cells
 - Tumor infiltrating lymphocytes (TILs)
- More specific than traditional cytotoxic chemotherapy (which generally targets cancer cells based on growth rate and DNA damage sensitivity) and kills by other mechanisms
- One of the first, and still most effective, immunotherapies is allogeneic stem cell transplant, which completely replaces the patient's immune system with that of an allogeneic donor.
 - Logistically complex
 - Relatively high risk of serious complications
 - Risk of graft vs. host disease (GVHD)

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Available for Leukemia

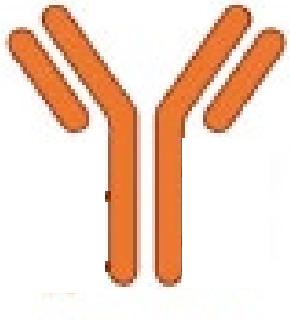
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What is immunotherapy?



Antibody

- Mark cancer cells for immune attack
- Block immune inhibitory signals



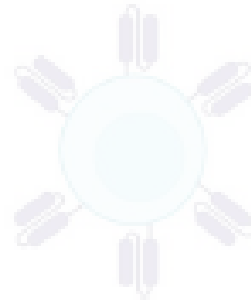
Antibody Drug Conjugate

- Use an antibody to carry a drug specifically to cancer cells
- Drug can be a toxin, a chemotherapy, or an immune stimulant



Bi-specific Antibody

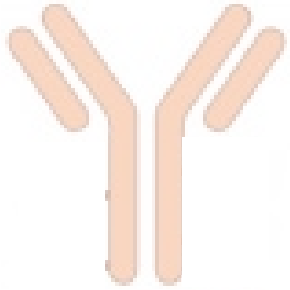
- "Handcuffs" that attach cancer cells to immune cells
- Stimulates bound immune cells to kill cancer cells



CAR-T Cell

- Patient's T cells modified to produce a receptor that binds a protein on target cancer cells
- Stimulates modified T cell to kill cancer cells

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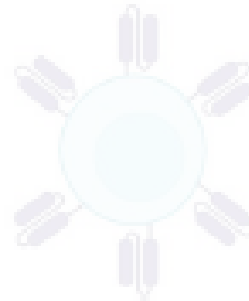
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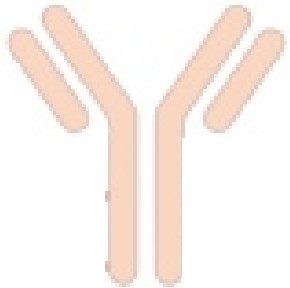
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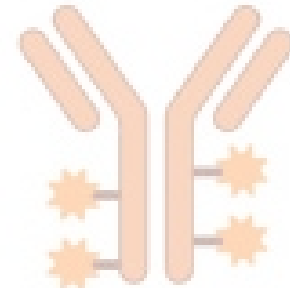
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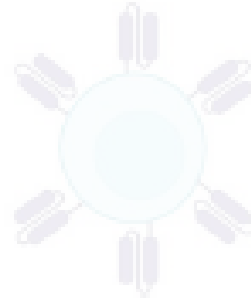
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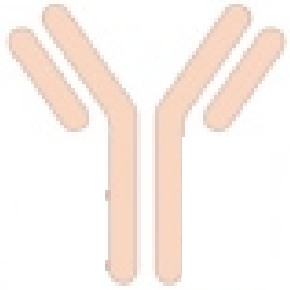
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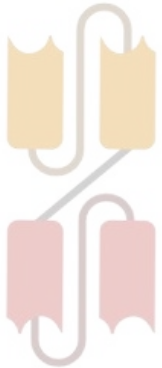
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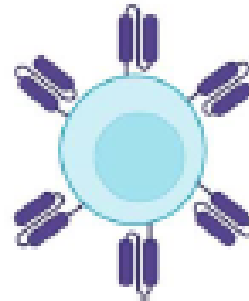
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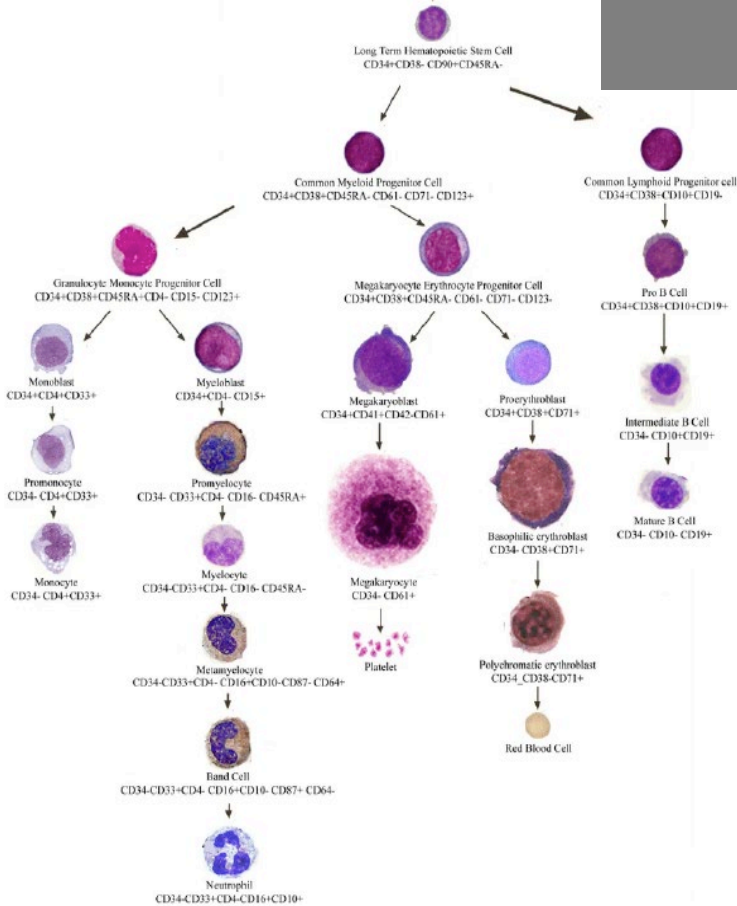
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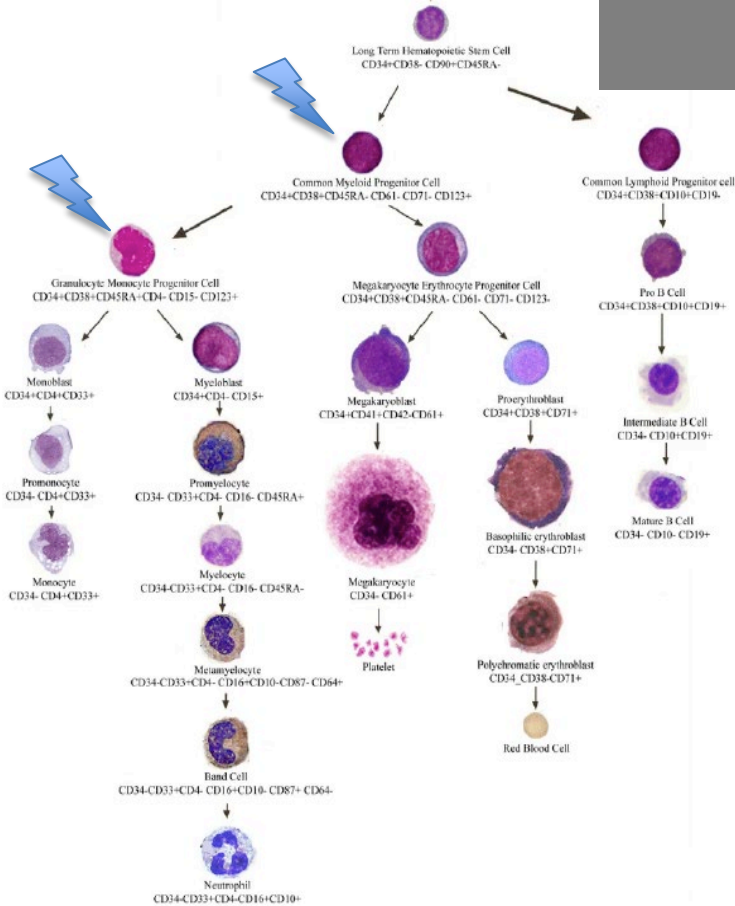
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What normal cells transform into acute leukemia?



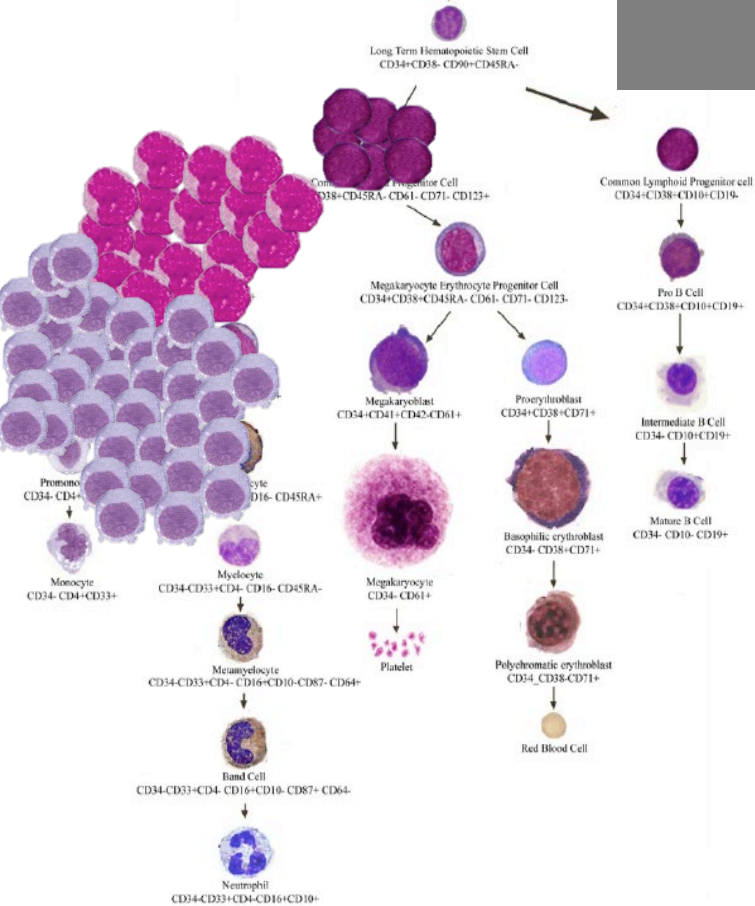
- Acute leukemia tend to develop when mutations occur in an early hematologic progenitor cell
 - AML
 - Common Myeloid Progenitor (CMP)
 - Granulocyte Monocyte Progenitor (GMP)
 - ALL
 - Pro-B cell
 - Pre-T cell

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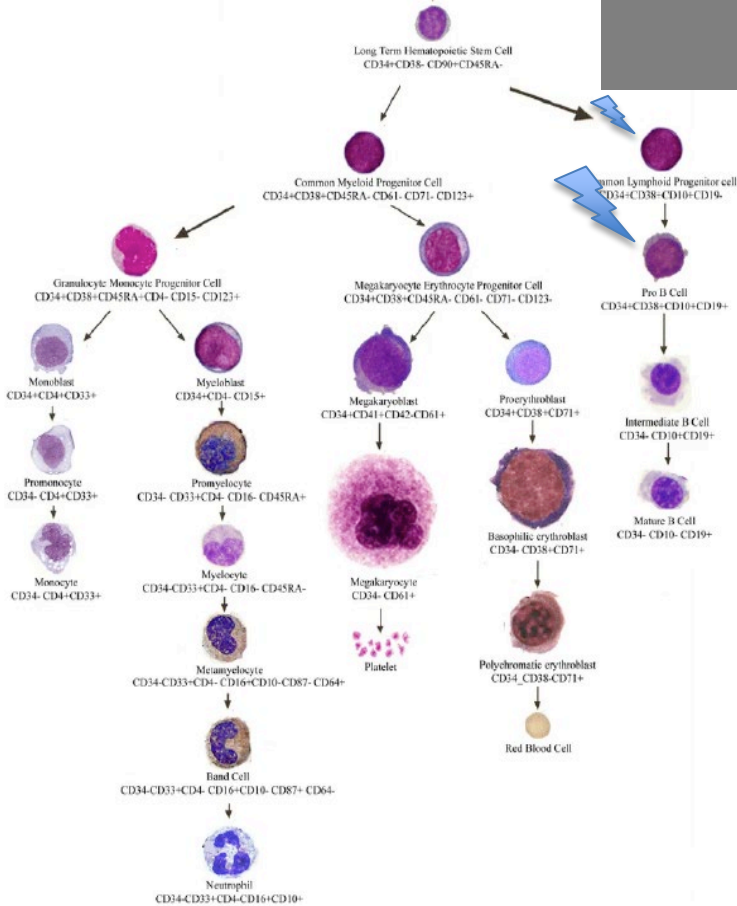
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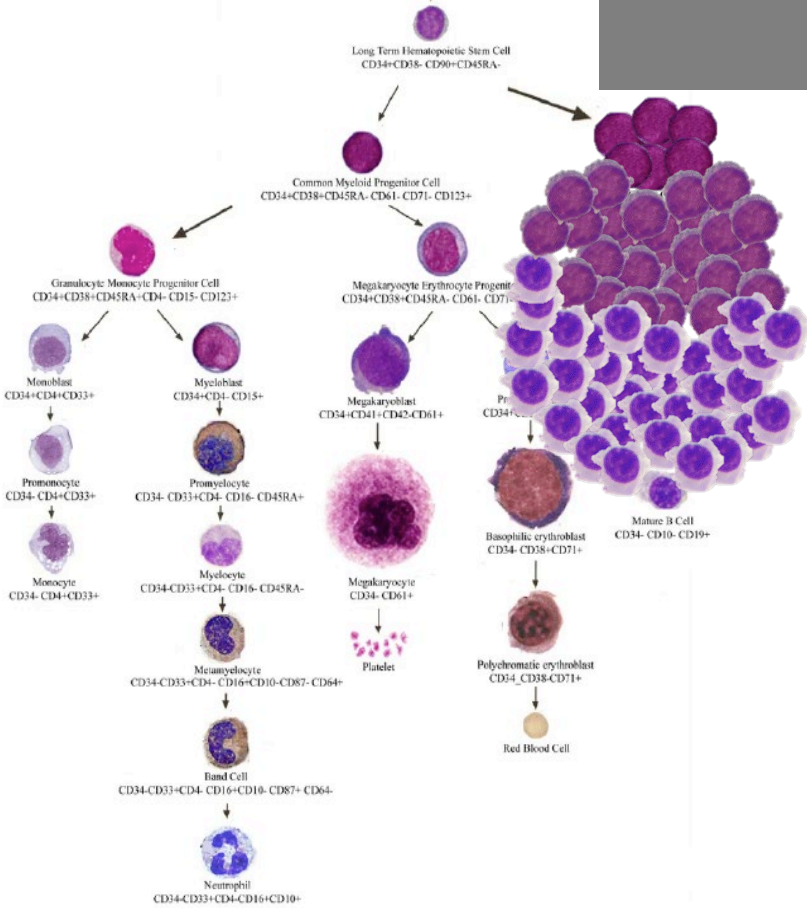
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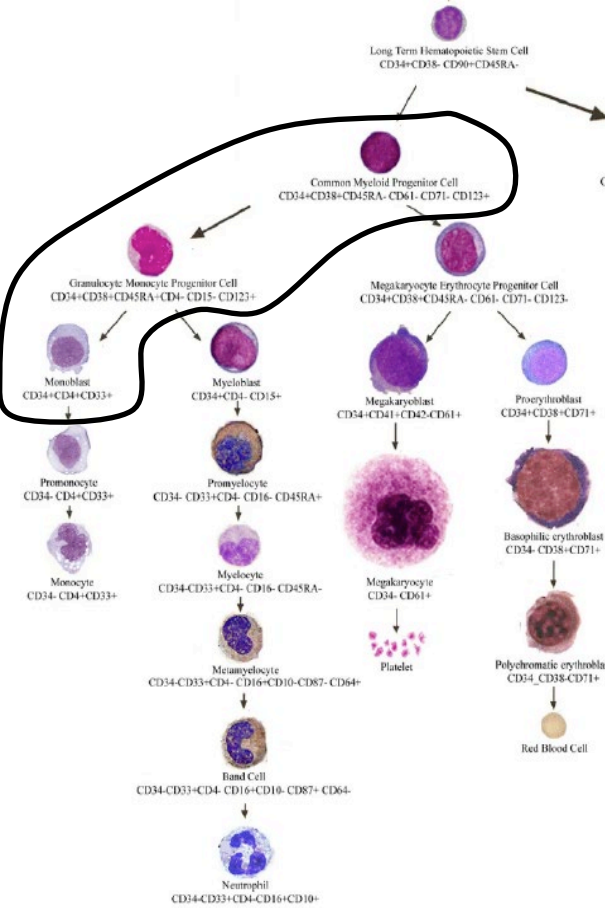
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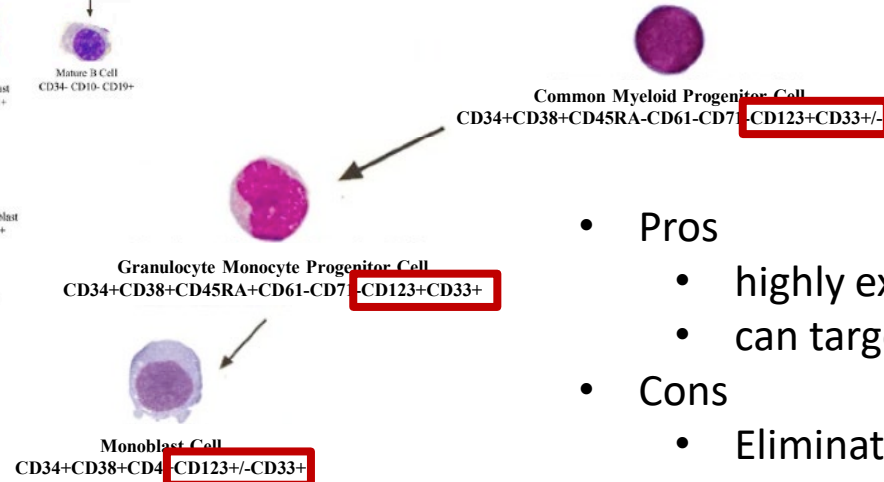
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What acute leukemias can be treated with immunotherapy?



• AML surface targets

- CD33 on CMP, GMP, and Monoblasts (approved)
- CD123 on CMP, GMP, and most Monoblasts (in development for AML; approved for BPDCN)



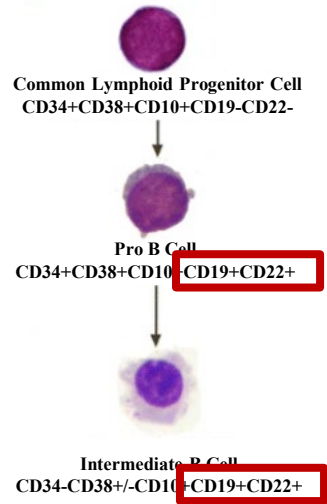
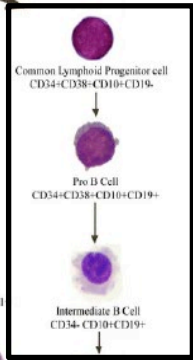
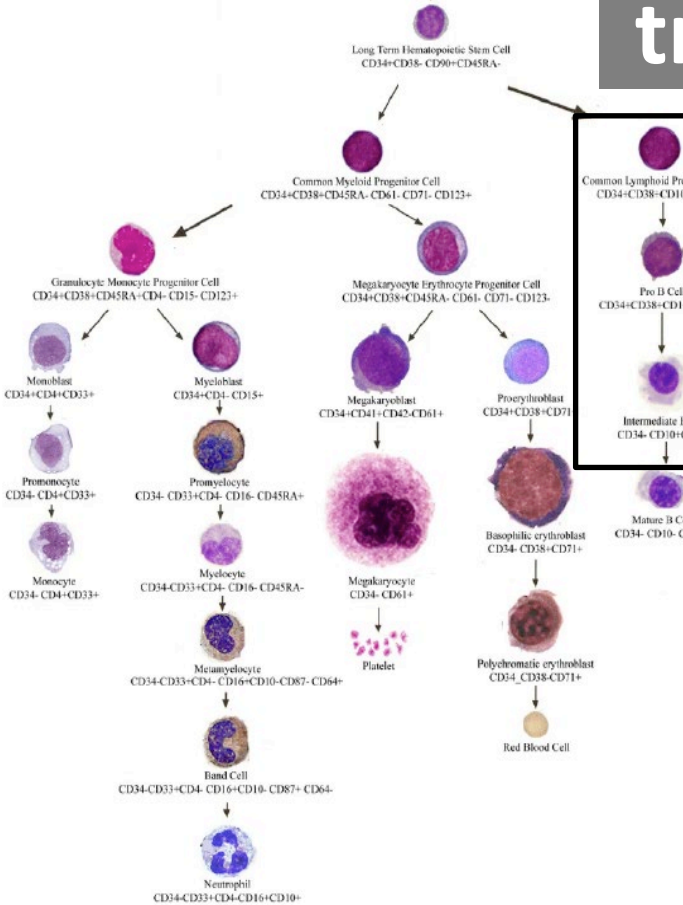
• Pros

- highly expressed on AML
- can target early leukemia cells

• Cons

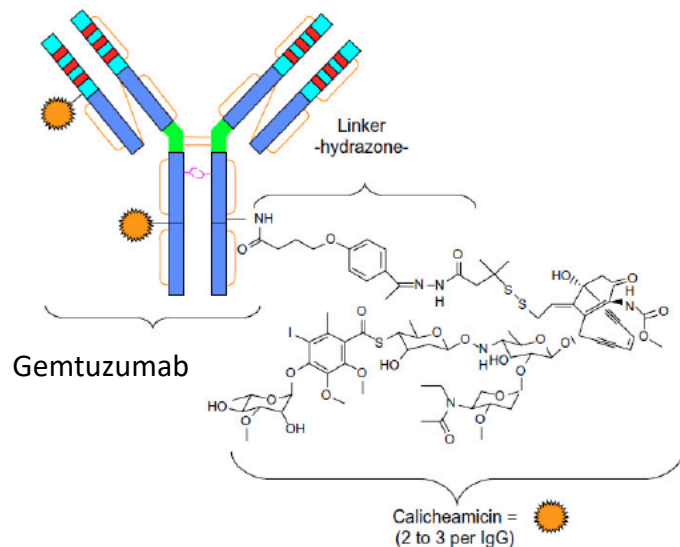
- Eliminates most myeloid cells

What acute leukemias can be treated with immunotherapy?



- B - ALL surface targets
 - CD19 on Pro-B, Pre-B, Intermediate B cells (approved)
 - CD22 on Pro-B, Pre-B, Intermediate B cells (approved)
- Pros
 - highly expressed on most ALL cells
 - can target chemo-resistant leukemia cells
 - people can live without B cells
- Cons
 - Some early ALL progenitors lack both CD19 and CD22

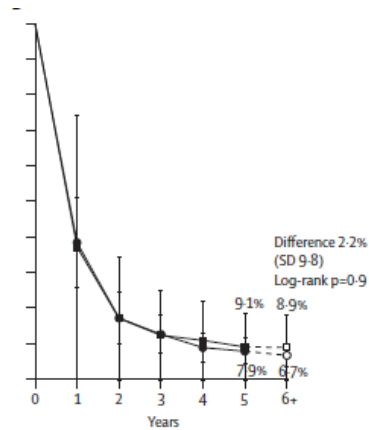
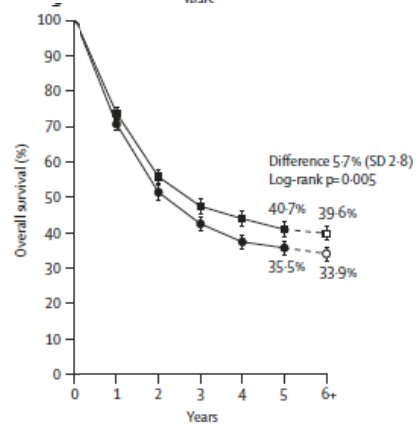
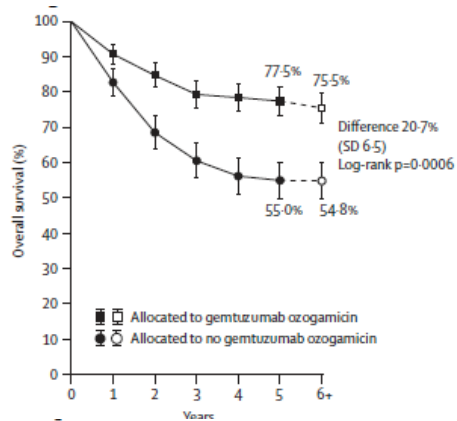
Gemtuzumab Ozogamicin



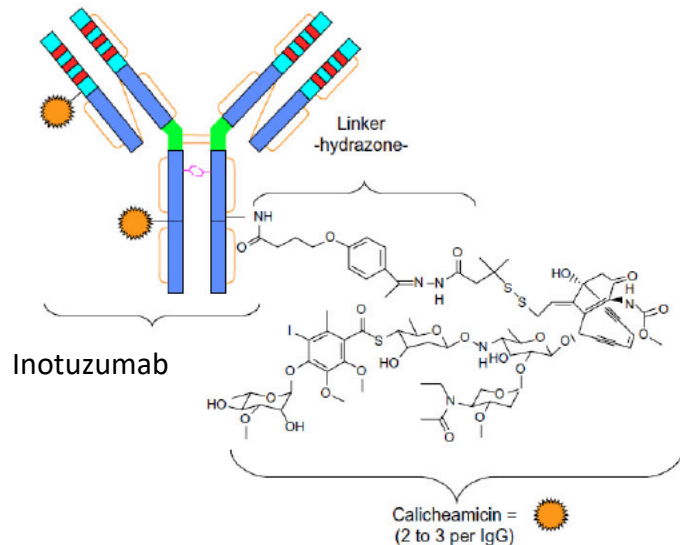
- Gemtuzumab ozogamicin binds to CD33 on AML cells, is transported into the cell where the attached calicheamicin toxin is released
- Calicheamicin is a very potent chemotherapy agent which binds DNA and induces DNA-double-strand breaks leading to cell death
- Toxicity is due to “on-target” killing of CD33+ normal cells and toxicity from free calicheamicin released from the antibody
- Approved for relapsed disease, but now primarily used in addition to chemotherapy for patients with good risk disease to increase cure rates

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Inotuzumab Ozogamicin

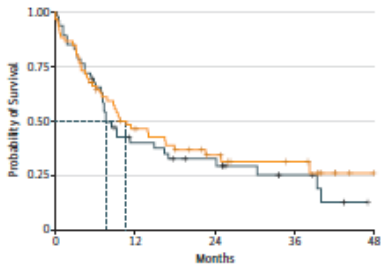


- Inotuzumab ozogamicin binds to CD22 on ALL cells, is transported into the cell where the attached calicheamicin toxin is released
- Calicheamicin is a chemotherapy agent which binds DNA and induces DNA-double-strand breaks leading to cell death
- Toxicity is primarily due to toxicity from free calicheamicin released from the antibody
- Effective and well-tolerated salvage treatment option for relapsed B-ALL
- Now being added to a variety of initial treatment regimens to enhance efficacy or reduce toxicity (A041703 study)

Inotuzumab Ozogamicin

A General OS and responder RFS

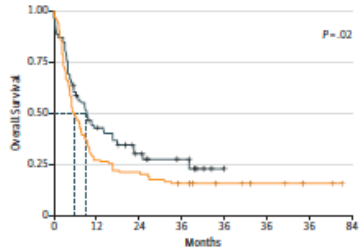
Strata	Total	Fail	1 y (95% CI), %	2 y (95% CI), %	Median
OS	59	39	46 (33-58)	34 (22-47)	11 mo
RFS	46	31	40 (26-54)	32 (19-46)	8 mo



No. at risk	0	12	24	36	48
OS	59	25	12	7	1
RFS	46	16	10	5	0

B OS by therapy

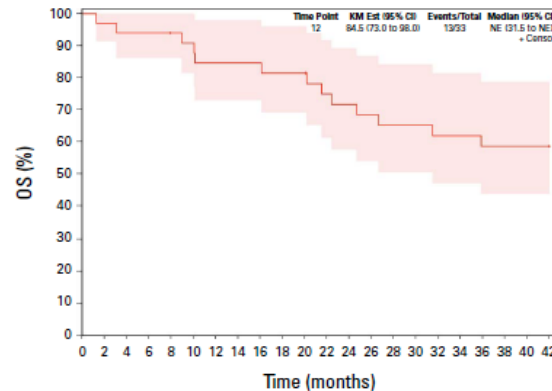
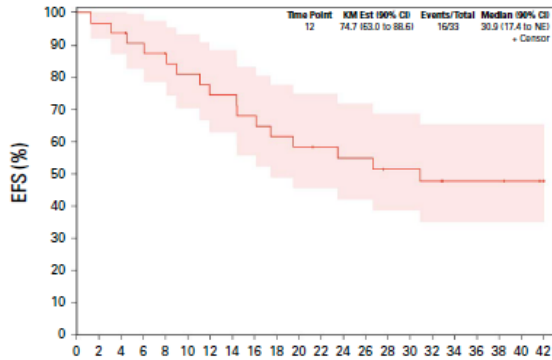
Strata
IND + MINI-HCVD
IND alone



No. at risk	0	12	24	36	48	60	72	84
IND + MINI-HCVD	59	25	12	7	1	0	0	0
IND alone	84	20	15	9	6	4	2	0

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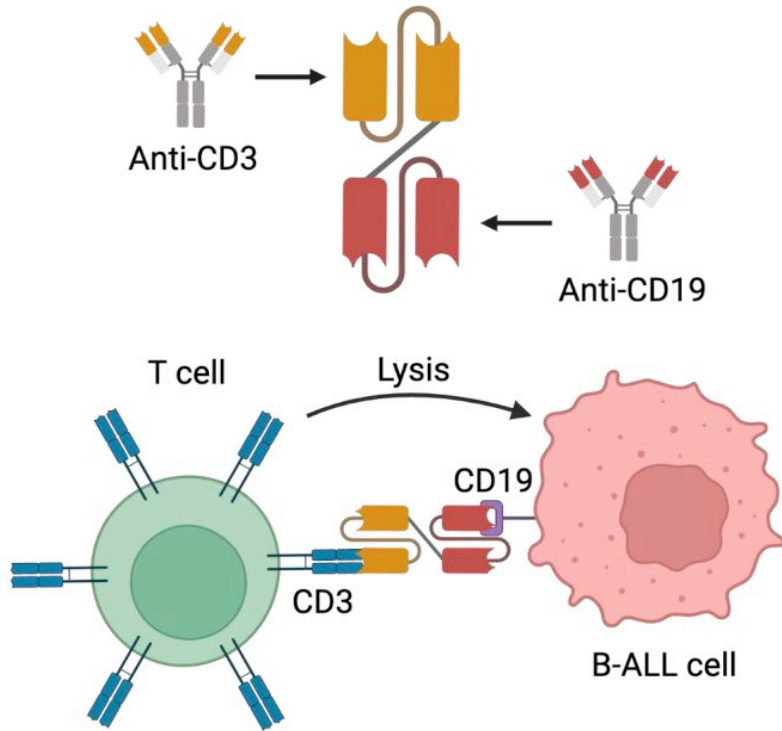
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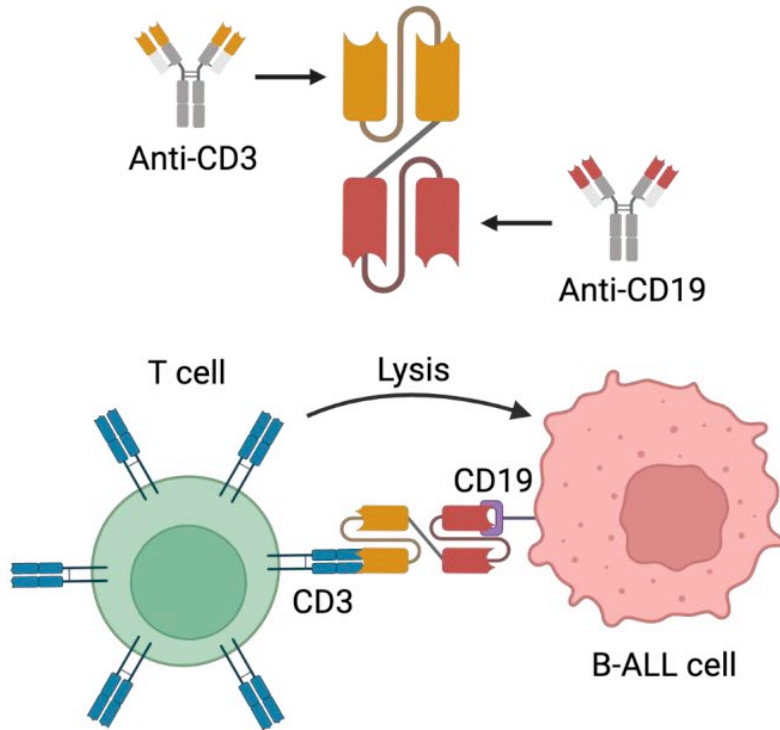


Bi-specific T cell Engaging (BiTE) Antibody

- "Handcuffs" that attach cancer cells to immune cells
- Stimulates bound immune cells to kill cancer cells
- Mechanism of cell killing largely independent of mechanisms involved in chemotherapy-mediated cell killing. Thus, can target cells resistant to traditional chemotherapy.
- Resistance can be due loss/mutation of target antigen, or to "exhaustion" or suppression of the T cells
- Toxicity mainly due to over-activation of the immune system (cytokine release syndrome, neurotoxicity).

Blinatumomab

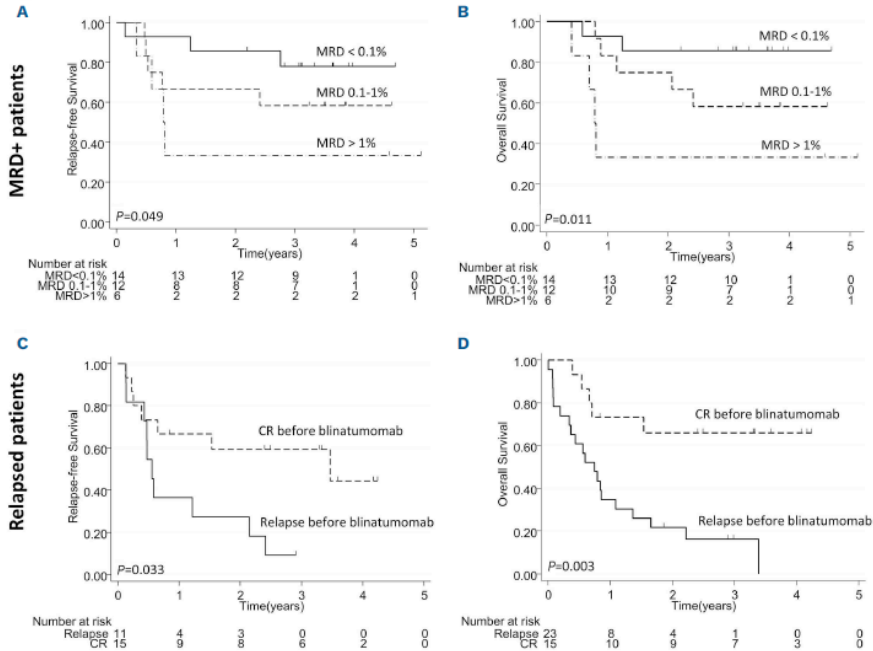
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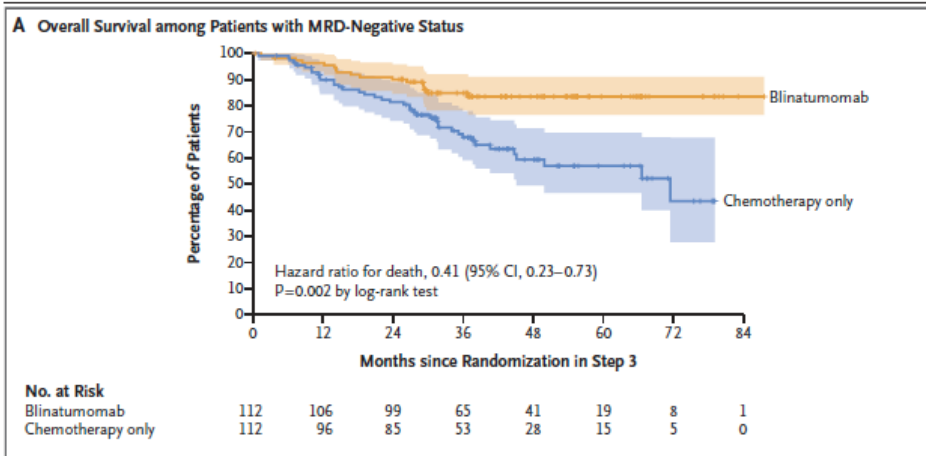
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- Initially approved for patients with relapsed disease but has had greatest impact when used as part of initial therapy to prevent relapse.
- Blinatumomab is more effective in patients with low-levels of disease at the time of treatment
- Patients with almost no disease at all (MRD-negative) seem to have the greatest benefit (E1910 study).

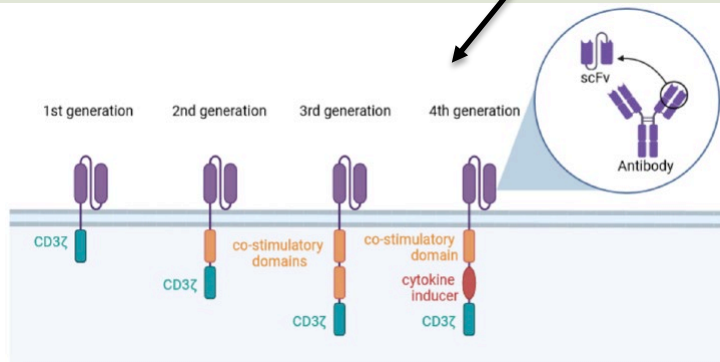
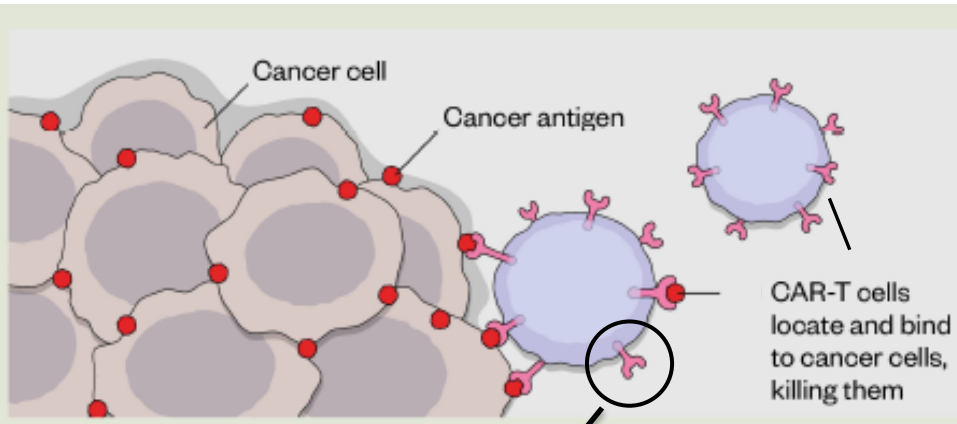
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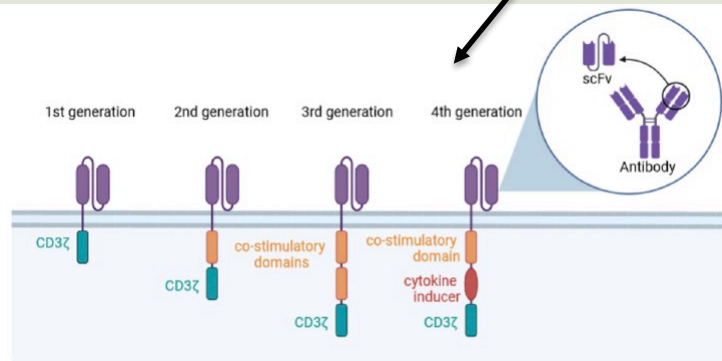
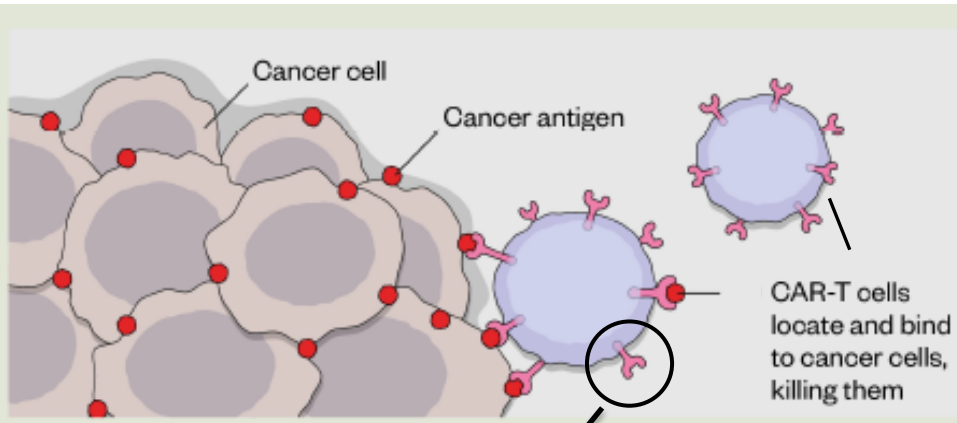


Chimeric Antigen Receptor T cells (CAR-T)



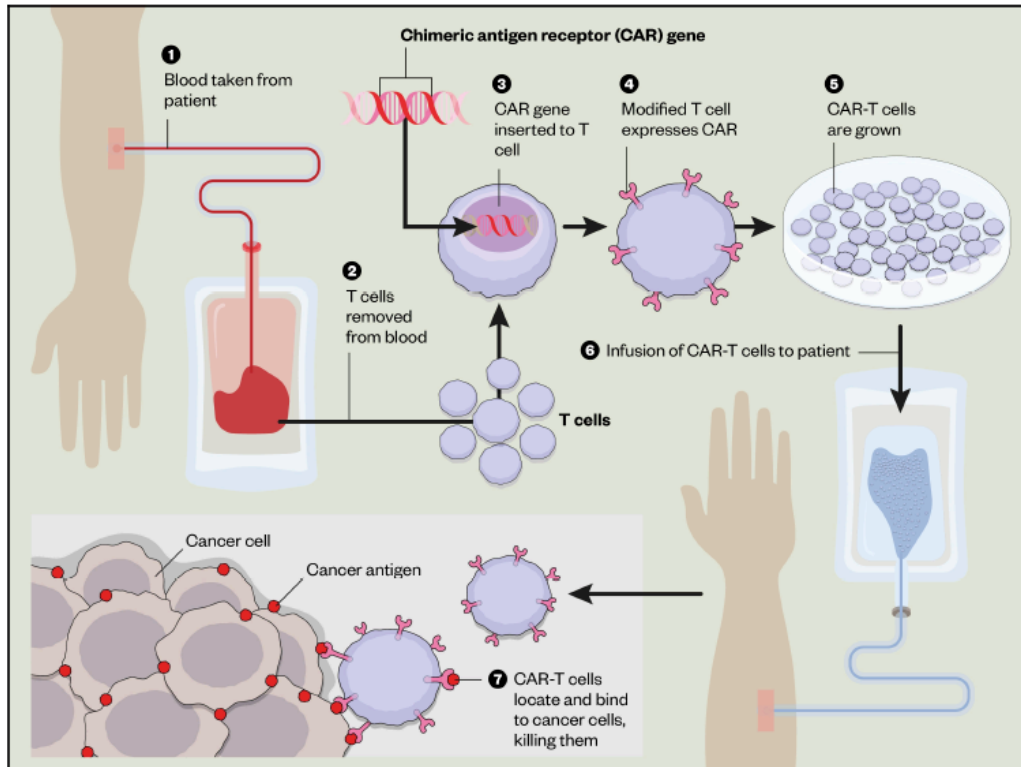
- CAR-T cells are the most sophisticated form of immunotherapy currently in use
- A patient's T cells are removed and modified to express a chimeric T cell receptor that binds to the target antigen on the cancer cells
- The CAR-T cells are then infused into the patient after a dose of chemotherapy
- The cells attack and kill the cancer cells, while also reproducing themselves, potentially persisting for many years.
- Toxicity comes primarily from immune-over activation (cytokine release, neurotoxicity).
- Resistance from cell "exhaustion" and antigen loss.

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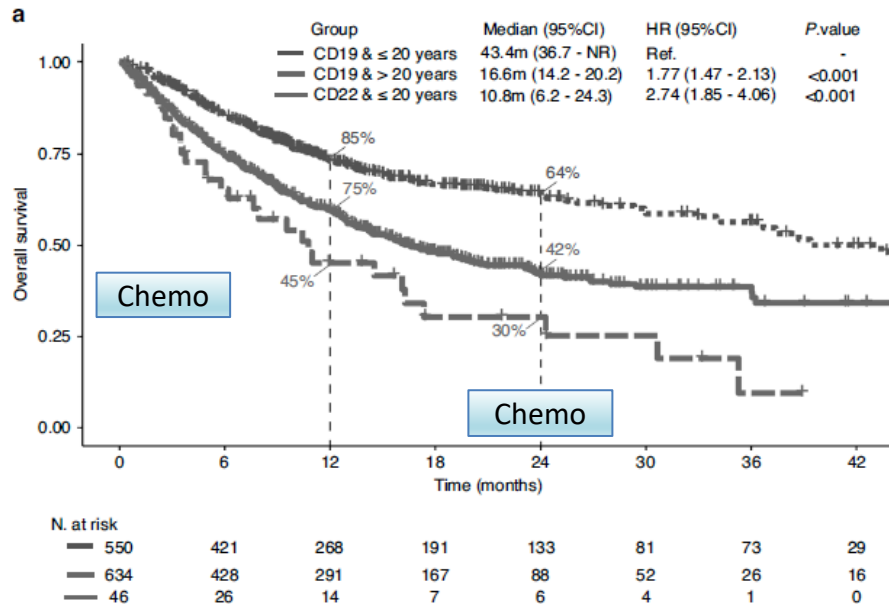
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- The cells attack and kill the cancer cells, while also reproducing themselves, potentially persisting for many years.
- Primarily used for relapsed patients, where it has dramatically improved response and cure rates relative to chemotherapy and even blinatumomab and inotuzumab.

Future Therapies

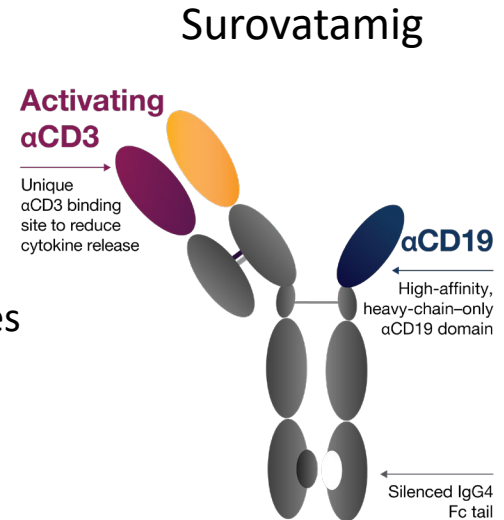
The field of immunotherapy continues to develop rapidly.

- Several new types of immunotherapies are in development that could eventually be utilized in leukemia
 - Gamma-delta T (gdT) cell and CAR-gdT cells
 - Expanded NK and CAR NK cells
 - “Armored” CAR-T cells
 - “Universal” CAR-T cells
 - Trispecific antibodies
- There are also several new improvements to existing treatment classes that may soon be relevant to leukemia treatment
 - Bi-specific CAR-T cells
 - More effective, and/or better tolerated BiTE molecules (e.g. Surovatamig)
 - VNX-101 – viral gene therapy that enables patients to produce blinatumomab

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 - “Universal” CAR-T cells
 - Trispecific antibodies
- There are also several new improvements to existing treatment classes that may soon be relevant to leukemia treatment
 - Bi-specific CAR-T cells
 - More effective, and/or better tolerated BiTE molecules (e.g. Surovatamig)
 - VNX-101 – viral gene therapy that enables patients to produce blinatumomab

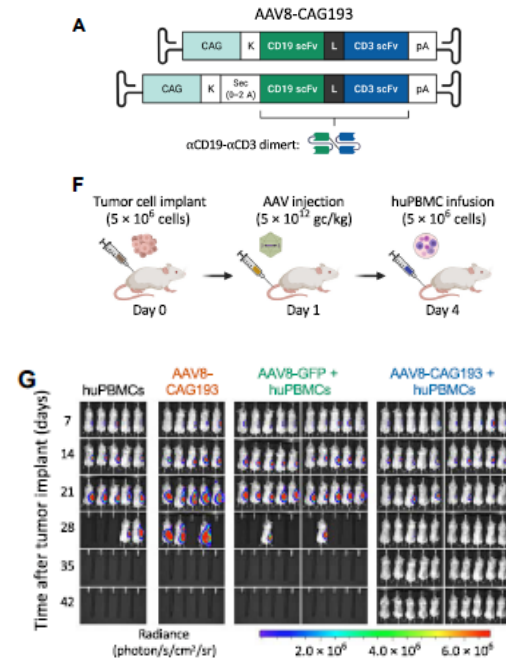


Future Therapies

The field of immunotherapy continues to develop rapidly.

- Several new types of immunotherapies are in development that could eventually be utilized in leukemia
 - Gamma-delta T (gdT) cell and CAR-gdT cells
 - Expanded NK and CAR NK cells
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VNX-101



Conclusions

- Immunotherapy has revolutionized cancer treatment with many new treatments across numerous malignancies
- Immunotherapy has been particularly beneficial to patients with ALL where it has greatly improved outcomes
 - Enabled by the highly conserved expression of CD19 and CD22 on malignant B cells
 - Surprisingly, humans can survive long-term without B cells
- Immunotherapy approaches (particularly when combined) have enabled patients with B-cell ALL to receive curative treatments with little or no traditional cytotoxic chemotherapy.
- Blinatumomab is now a standard part of B-ALL therapy for almost all patients.
- CAR-T is now a standard salvage treatment for patients with CD19+ ALL and has greatly improved cure rates.
- Bone marrow transplant is now less frequently needed, and immunotherapies can be a successful bridge to a transplant.

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