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Treatments and Current Research in Leukemia

Richard A. Larson, MD

University of Chicago

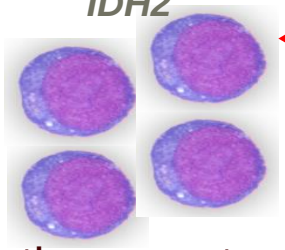
	Myeloid	Lymphoid
Acute (rapid progression)	Acute myeloid leukemia (AML) Acute promyelocytic leukemia (APL)	Acute lymphoblastic leukemia ALL, B-cell ALL, T-cell ALL, Ph+ Burkitt-type leukemia
Chronic (slower progression; indolent)	Chronic myeloid leukemia (CML; Ph+) Myelodysplastic syndrome (MDS)	Chronic lymphocytic leukemia CLL, B-cell Prolymphocytic leukemia PLL, B-cell PLL, T-cell Hairy cell leukemia (HCL)

Formation of mature blood cells from stem cells: hematopoiesis

P53	*CBF*
NF-1	*RUNX1*
WT-1	*CEBPA*
WNT	*MLL*
RAS	*NPM1*
HOX	*FLT3*
NUP98	*MYB*
IDH1	*TET*
IDH2	

Stem cells

Progenitor cells



Maturation arrest

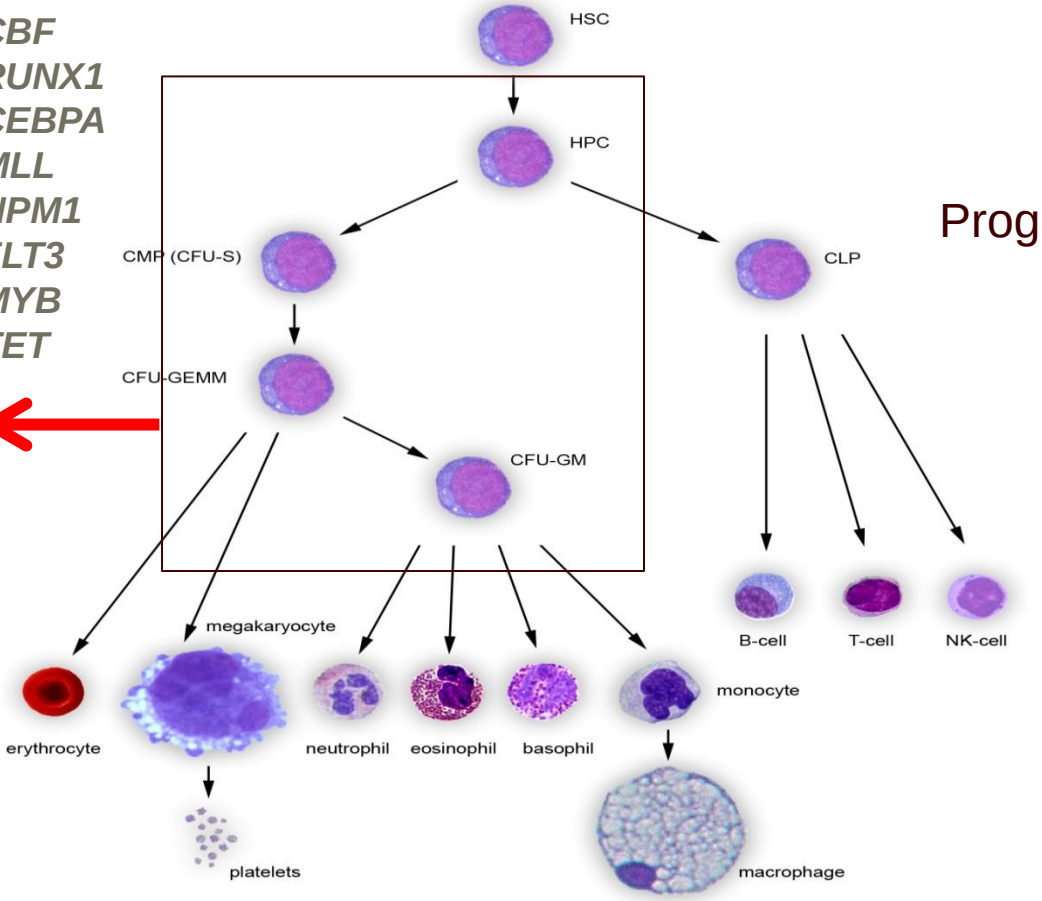


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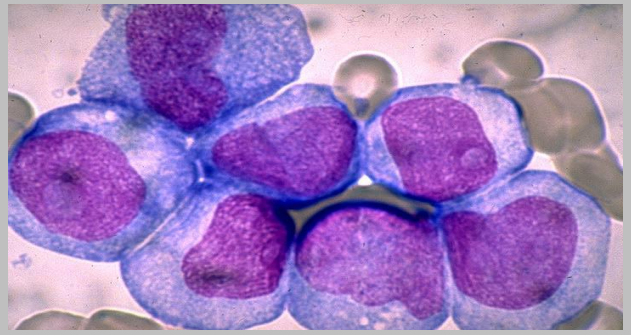
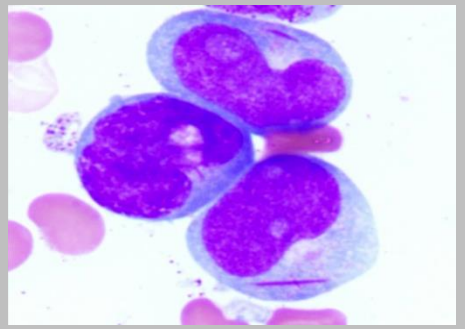
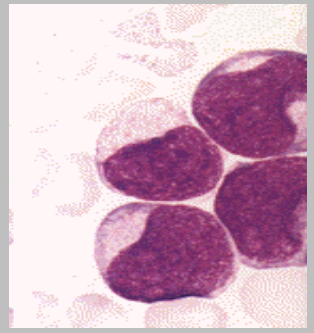
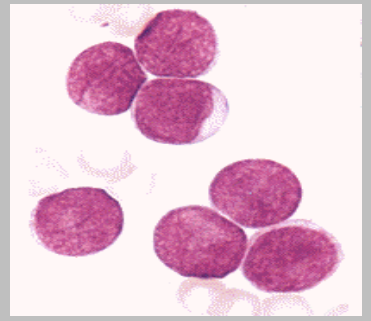
Figure courtesy of Clayton Smith

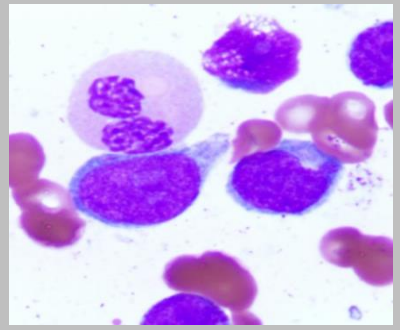


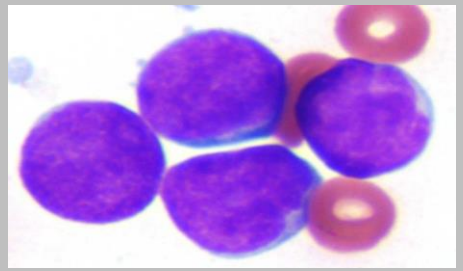


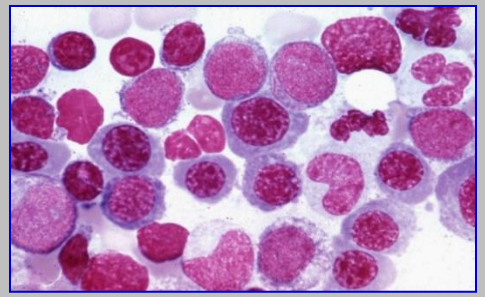


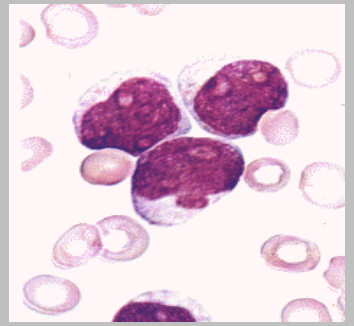
How do these cases of leukemia differ?



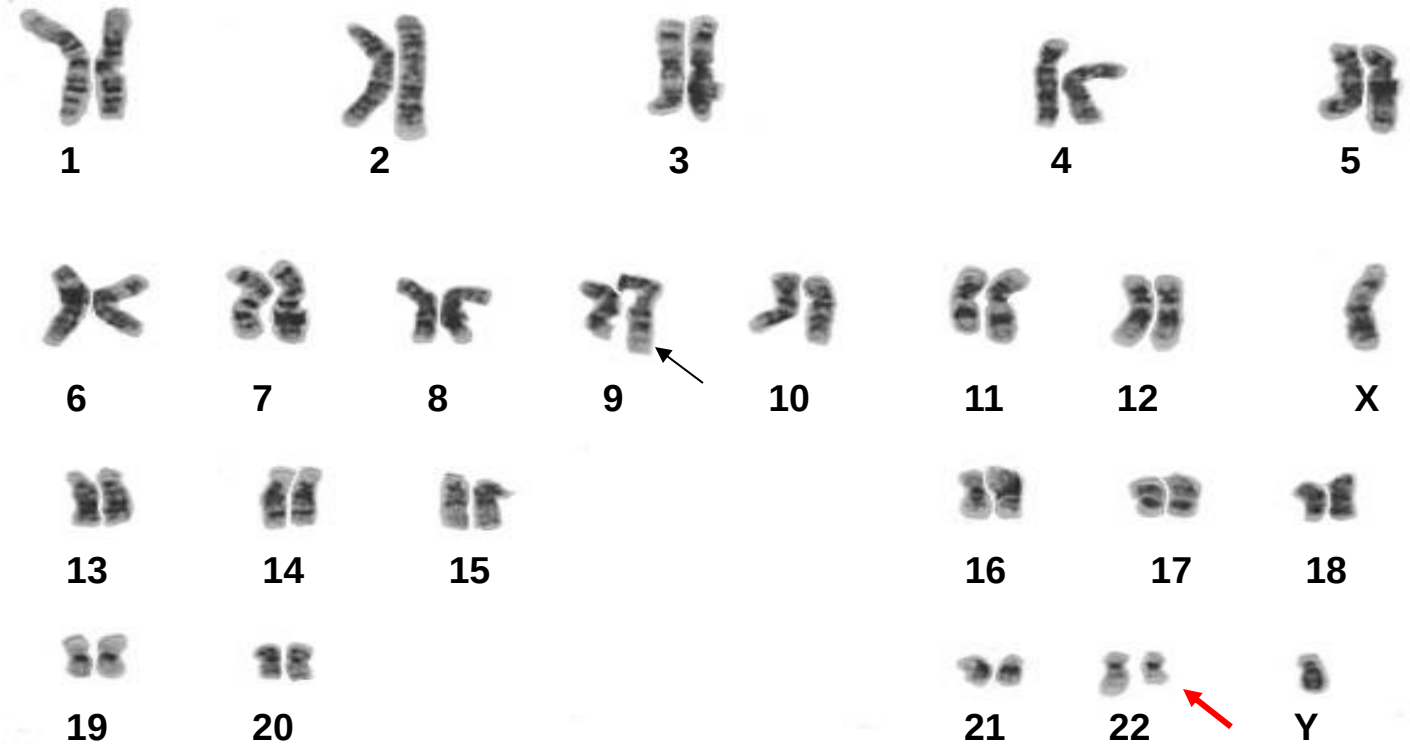






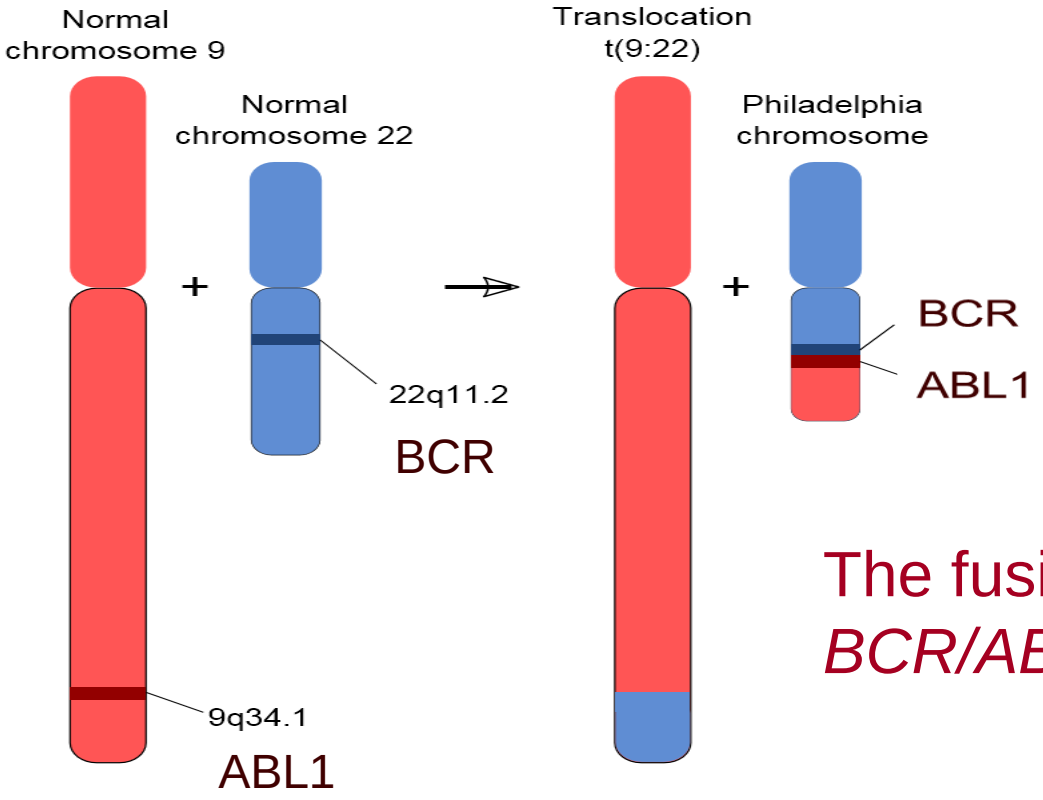


Philadelphia chromosome in a CML cell with t(9;22)



Janet Rowley, MD. University of Chicago. 1973

Philadelphia Chromosome Translocation t(9;22) in Chronic Myeloid Leukemia



The fusion gene:
BCR/ABL1

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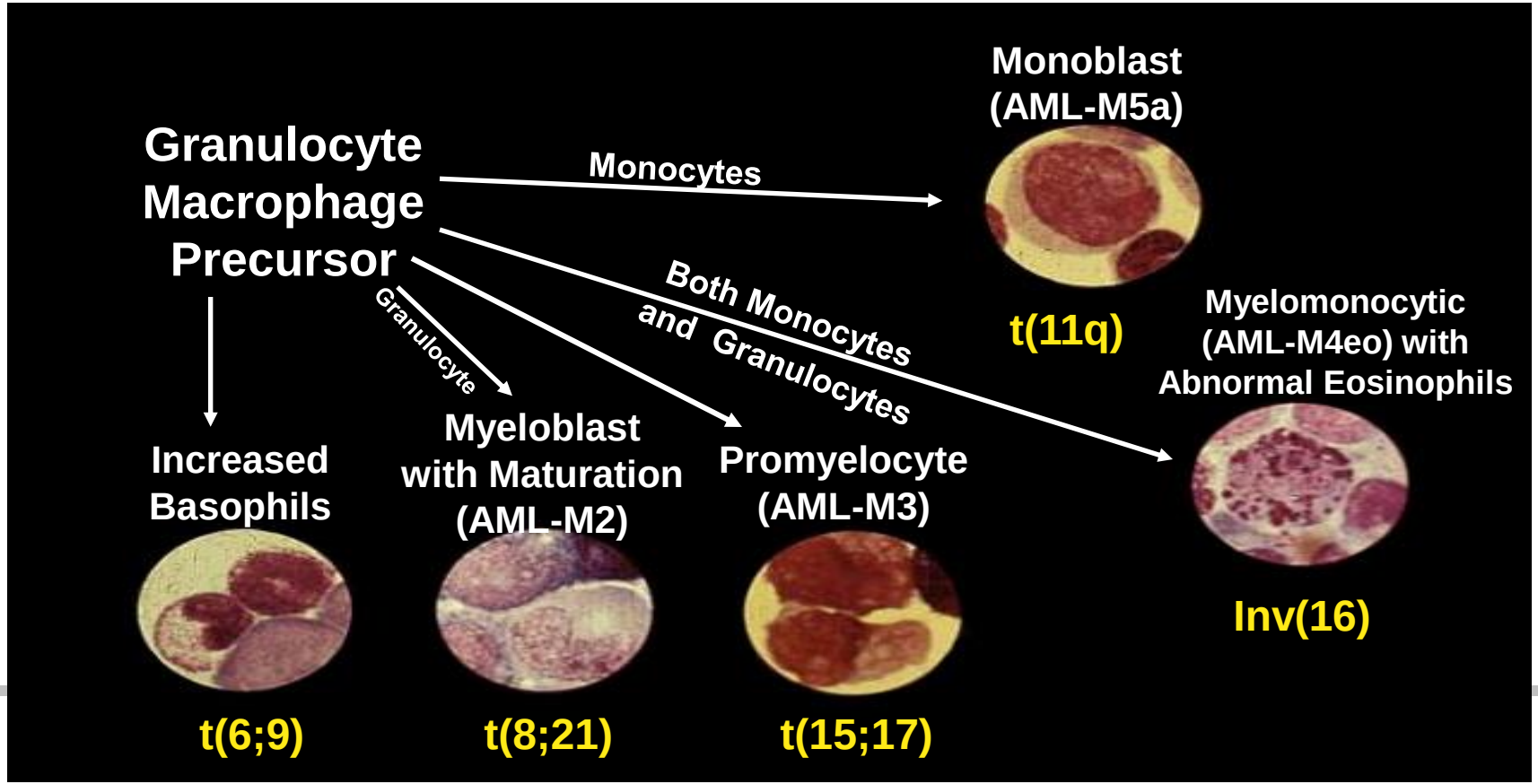
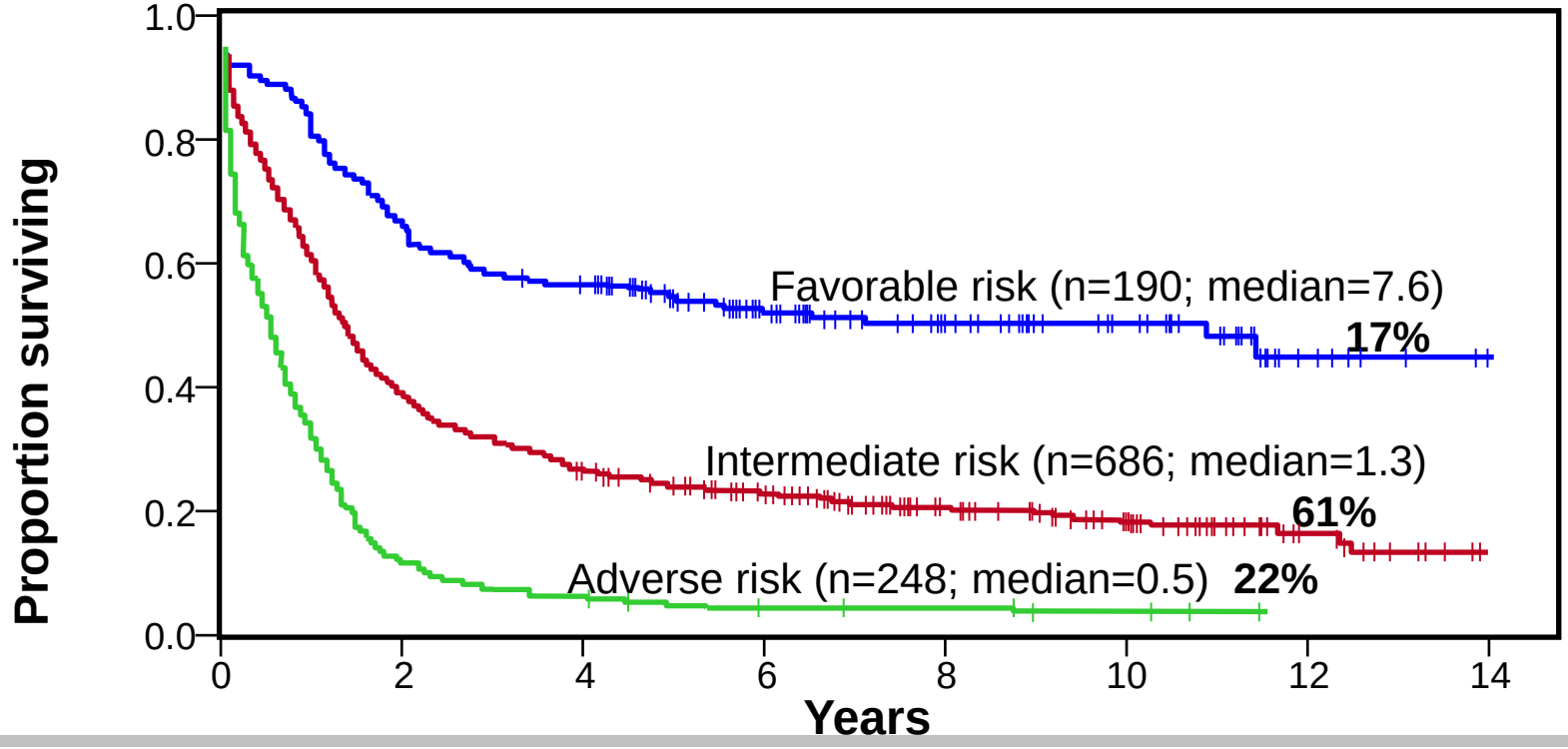
Specific Chromosome Abnormalities in Human Acute Myeloid Leukemia: translocations & inversions



Survival of 1120 adults (>16 years old) with newly diagnosed AML according to cytogenetic risk group (1984-2000)



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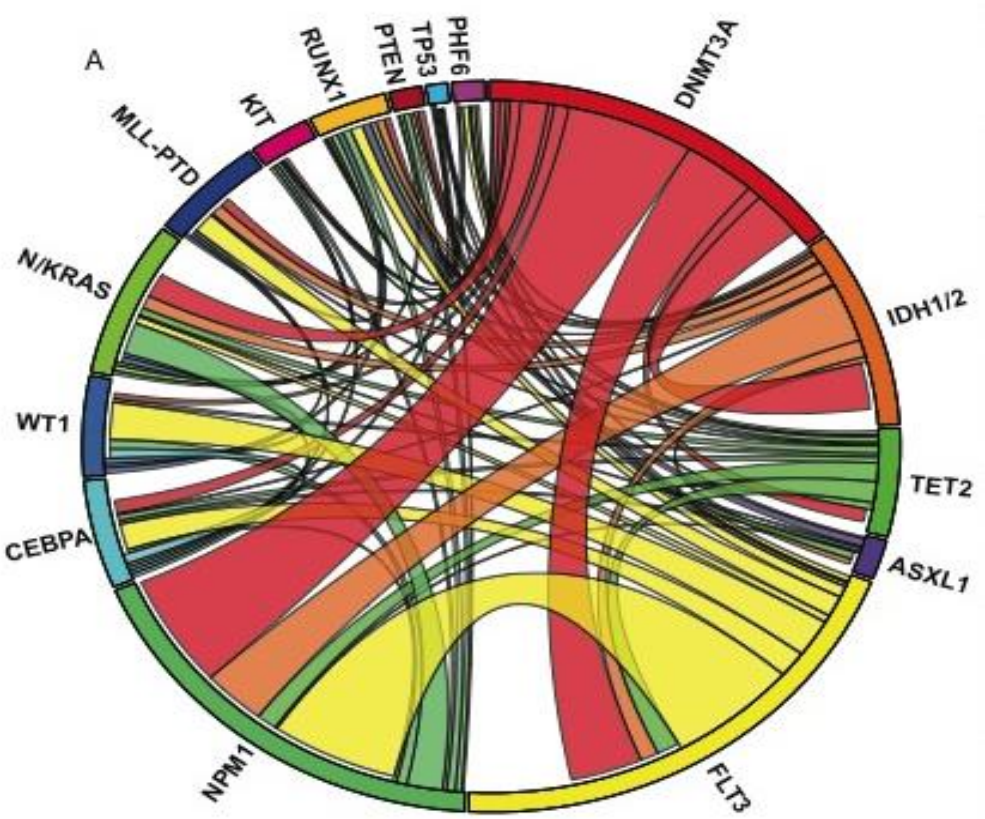
Byrd et al. (CALGB 8461) Blood 2002: 100: 4325

Mutational Profiling in AML

Gene	Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
DNMT3A	24
NPM1	24
KIT	14
TET2	10
WT1	10
CEBPA	10
NRAS	10
IDH2	8
IDH1	6
ASXL1	4
KRAS	2.5
PHF6	2.5
RUNX1	5
PTEN	1.5
TP53	2
MLL	10



Patel et al. NEJM 2012

2017 ELN Risk Stratification by Genetics

Risk Category	Genetic Abnormality (Acute Myeloid Leukemia)
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{Low}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{High}
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{Low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favorable or adverse

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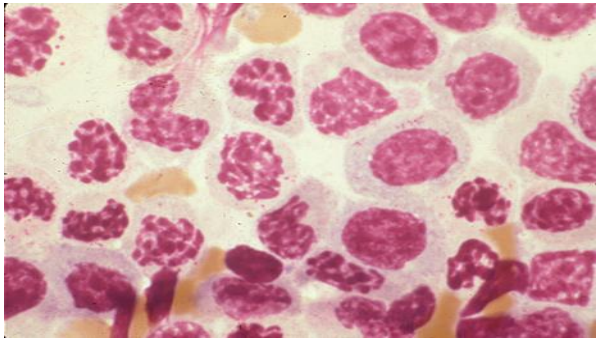
Döhner et at. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017.

2017 ELN Risk Stratification by Genetics

Risk Category	Genetic Abnormality
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM (EVI1)*
	-5 or del(5q); -7; -17/ abnormal (17p)
	Complex karyotype; monosomal karyotype
	Wild type *NPM1* and *FLT3*-ITD^{High}
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*

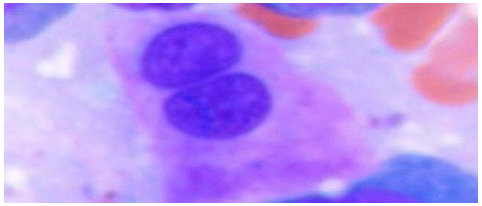
Döhner et at. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017.



Myelodysplastic syndrome (a chronic leukemia)

MDS → Bone Marrow Failure →

- Transfusions
- Infections
- Bleeding
- Leukemia



New agents in AML

- Azacitidine or decitabine (post-remission maintenance)
- **Liposomal cytarabine + daunorubicin** (CPX-351)
- **Gemtuzumab ozogamicin** (antiCD33 immunoconjugate)
- **Midostaurin** (multi-kinase FLT3 and mutKIT inhibitor)
- **Enasidenib** (IDH2 inhibitor)
- *Gilteritinib; quizartinib (FLT3 inhibitors)*
- *Ivosidenib (IDH1 inhibitor)*
- *Venetoclax (anti-apoptotic agent; BCL2 inhibitor)*
- *Nivolumab (PD-1 checkpoint inhibitor)*

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Bold, approved in 2017
Italics, investigational

	Myeloid	Lymphoid
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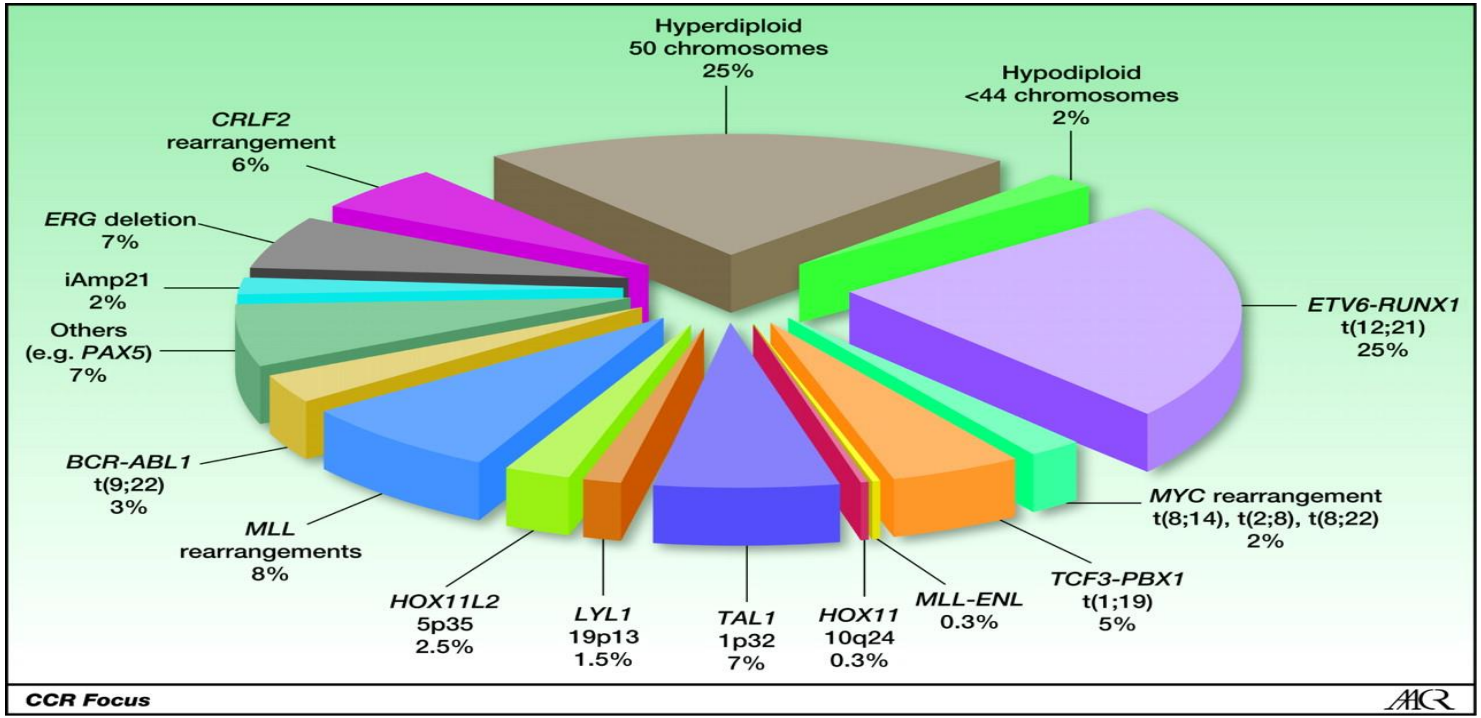
Recurring chromosomal rearrangements in Childhood Acute Lymphoblastic Leukemia



Loh ML , Mullighan CG. Clin Cancer Res 2012; 18: 2754

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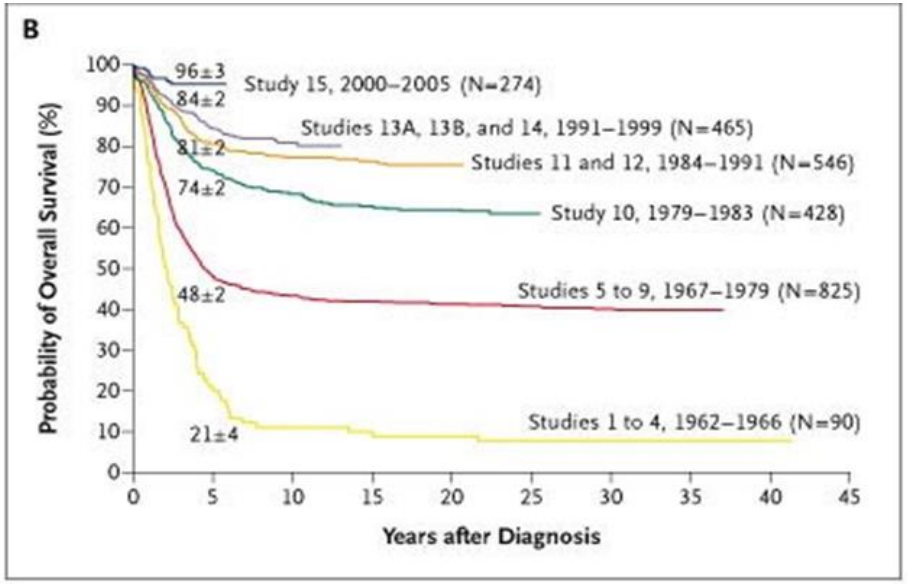
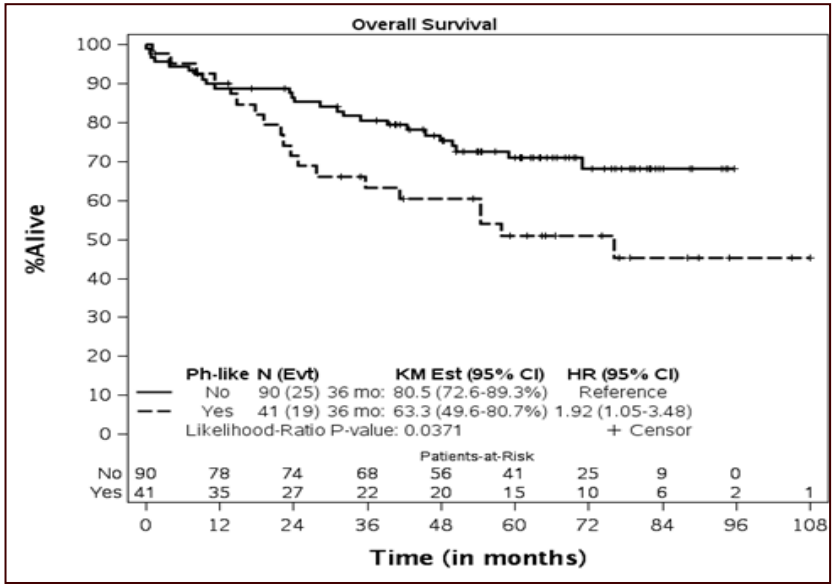
Outcomes in ALL (Pediatrics vs Young adults)





Pui C, Evans WE.
N Engl J Med 2006;354:166-178.

Survival of 16-39 year old ALL patients treated on the CALGB 10403 trial.
Stock et al. ASH 2015

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New agents in ALL

- **Blinatumomab (bispecific anti-CD19/anti-CD3 MoAb)**
- **Inotuzumab ozogamicin (antiCD22 MoAb)**
- Liposomal vincristine
- Dasatinib, ponatinib (BCR/ABL1 inhibitors)
- **Chimeric antigen receptor T-cells**
- *Entospletinib (MLL rearranged ALL)*
- *Navitoclax + venetoclax (BCL2 inhibitors)*

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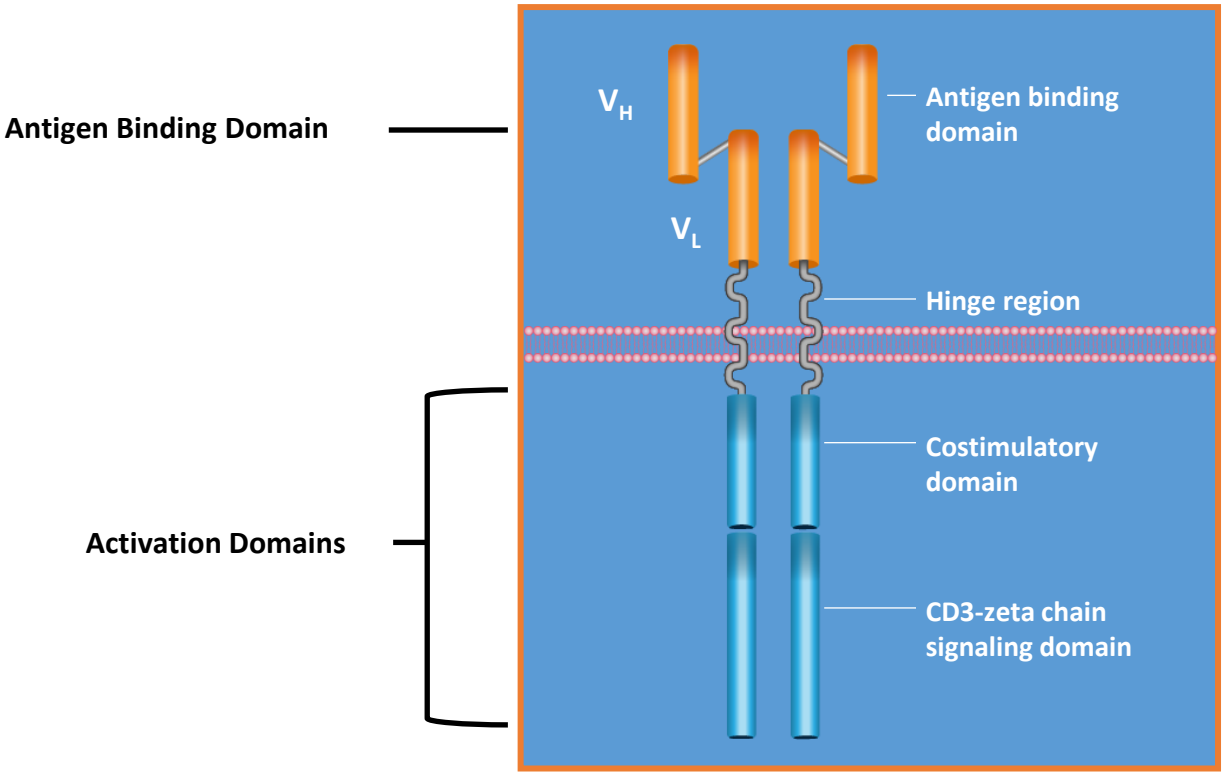
Bold, approved in 2017
Italics, investigational

Chimeric Antigen Receptor (CAR) T-Cells

Chimeric Antigen Receptors



scFv
Single-chain variable fragment (scFv) allows direct activation of T cell by cancer cell antigens.

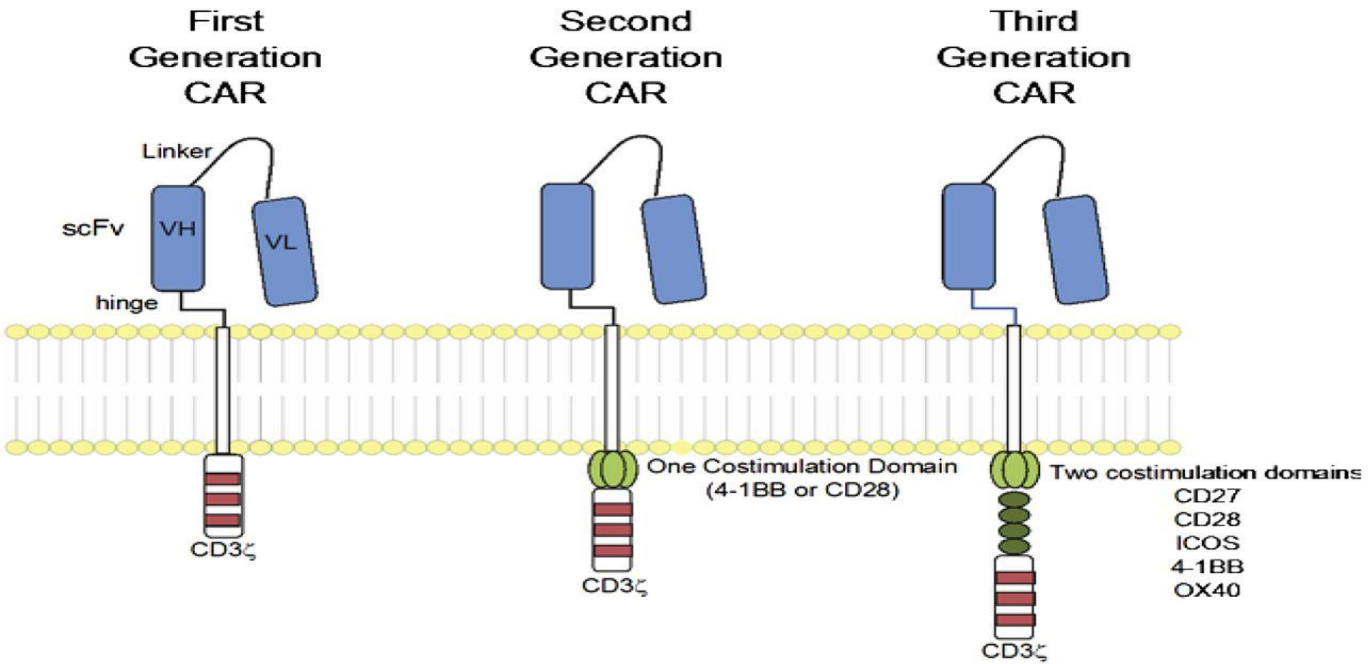
Hinge region
Allows optimal antigen binding.

Costimulatory Domain: CD28 or 4-1BB
Enhances CAR T cell proliferation, cytotoxicity and persistence.

Signaling Domain: CD3-zeta chain
Proliferation & activation of CAR T cells.
CAR T cell-mediated killing of tumor cells.

Adapted from Park JH., et al. *Discov Med*. 2010;9:277-288.

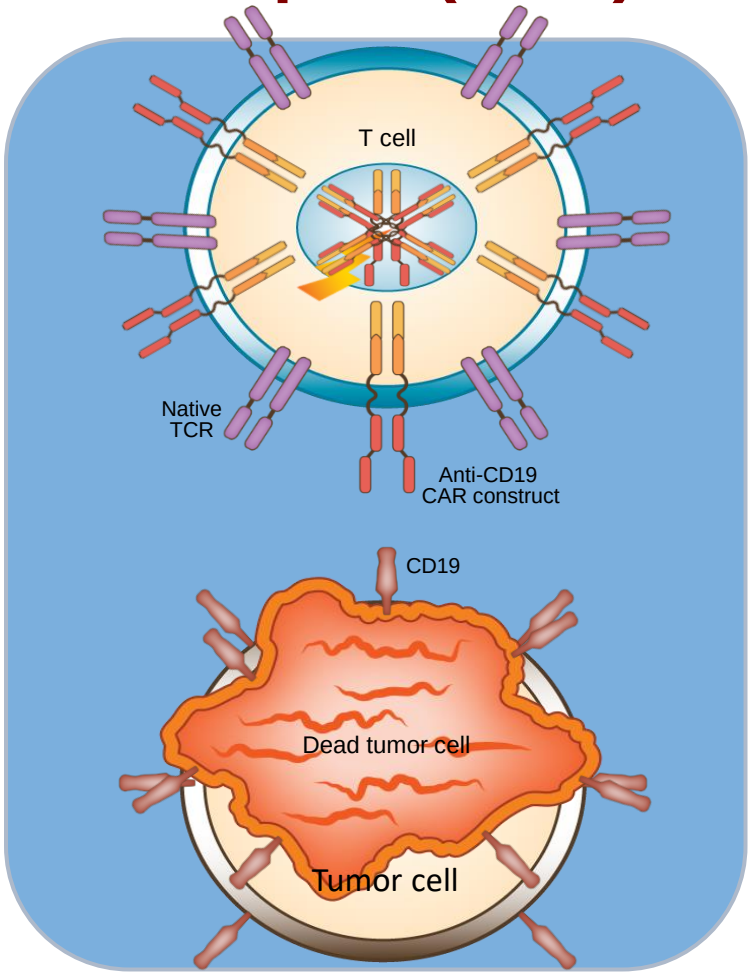
CD19-targeted chimeric antigen receptor T-cell therapy for ALL



Maude SL, et al. *Blood* 2015; 125: 4017-4023

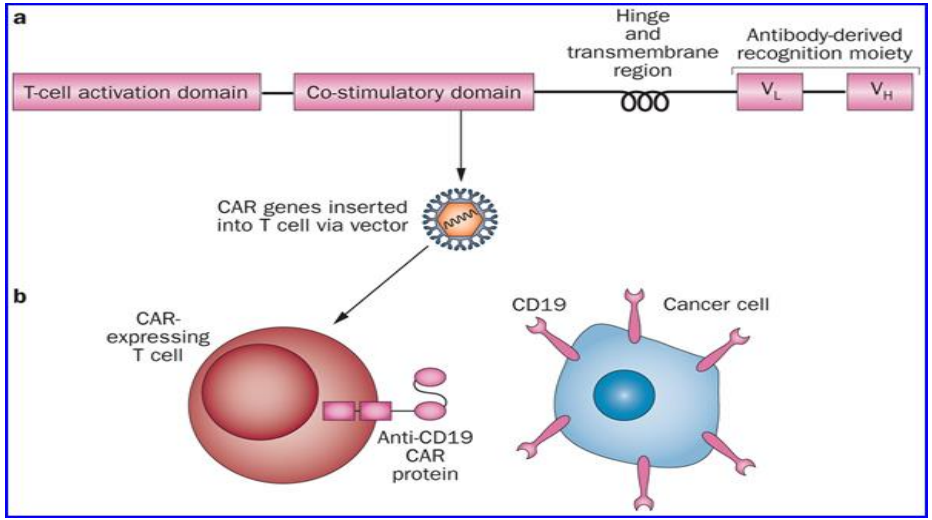
Chimeric Antigen Receptor (CAR) T-cells

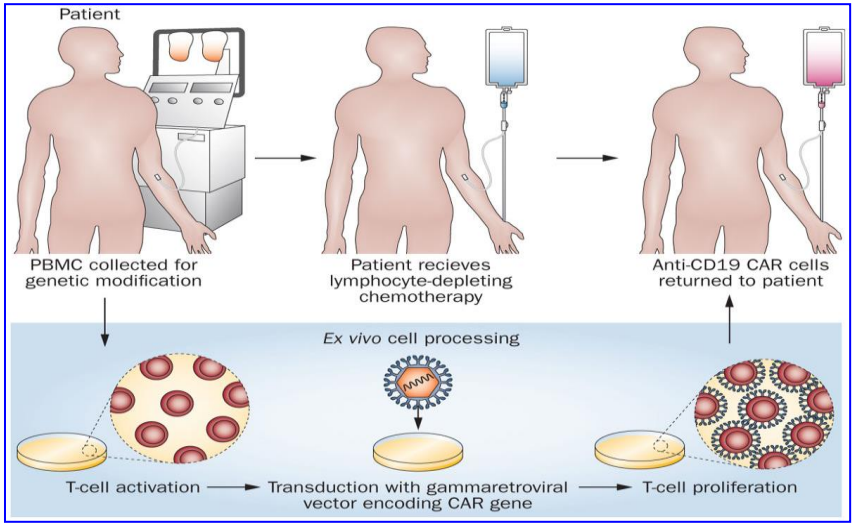
- **Uses patients own cells**
- **Tumor specific**
- **Can be applied to multiple malignancies**



Courtesy of N. Frey

Chimeric antigen receptor (CAR) T-cells directed against CD19+ malignant B-cells





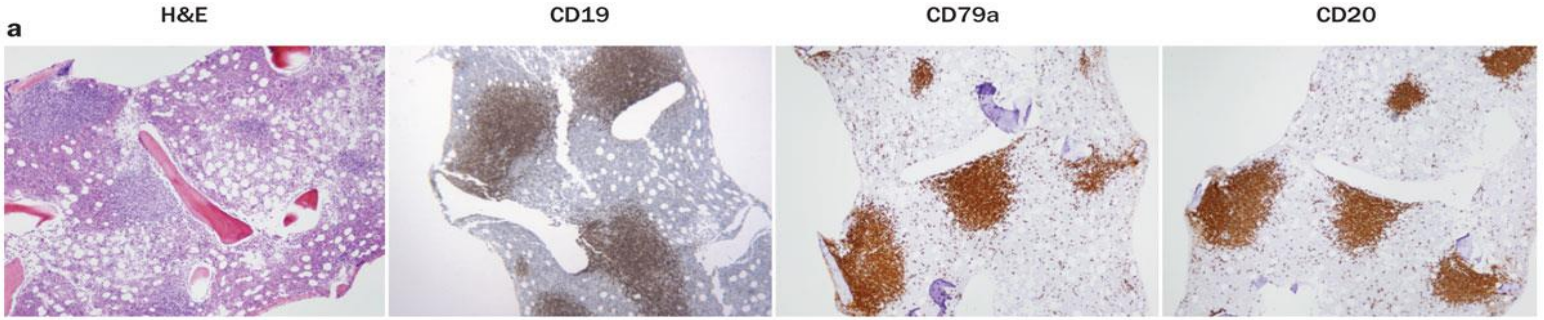
Kochenderfer & Rosenberg. Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat Rev Clin Oncol* 2013

CAR T Cell Products in Clinical Trials

	Axicabtagene Ciloleucel (KTE-C19)	Tisagenlecleucel (CTL-019)	Lisocabtagene Maraleucel (JCAR017)
Company	KITE	Novartis	Juno
Binding Domain (All Murine ScFv)	FMC63	FMC63	FMC63
Indications	DLBCL, TFL, PMBCL, MCL, ALL, CLL	NHL, ALL, CLL	Adult NHL, Pediatric ALL, CLL
Spacer Domain	CD28	CD8α	IgG4 hinge
Transmembrane Domain	CD28	CD8α	CD28
Stimulatory Domain	CD28-CD3ζ	4-1BB-CD3ζ	4-1BB-CD3ζ
Starting Cell Population Selection	None	None	CD4+ and CD8+
Final CD4/CD8 ratio	Variable	Variable	1:1
Ablation Technology	None	None	EGFRt

Eradication of marrow B-cells

Before

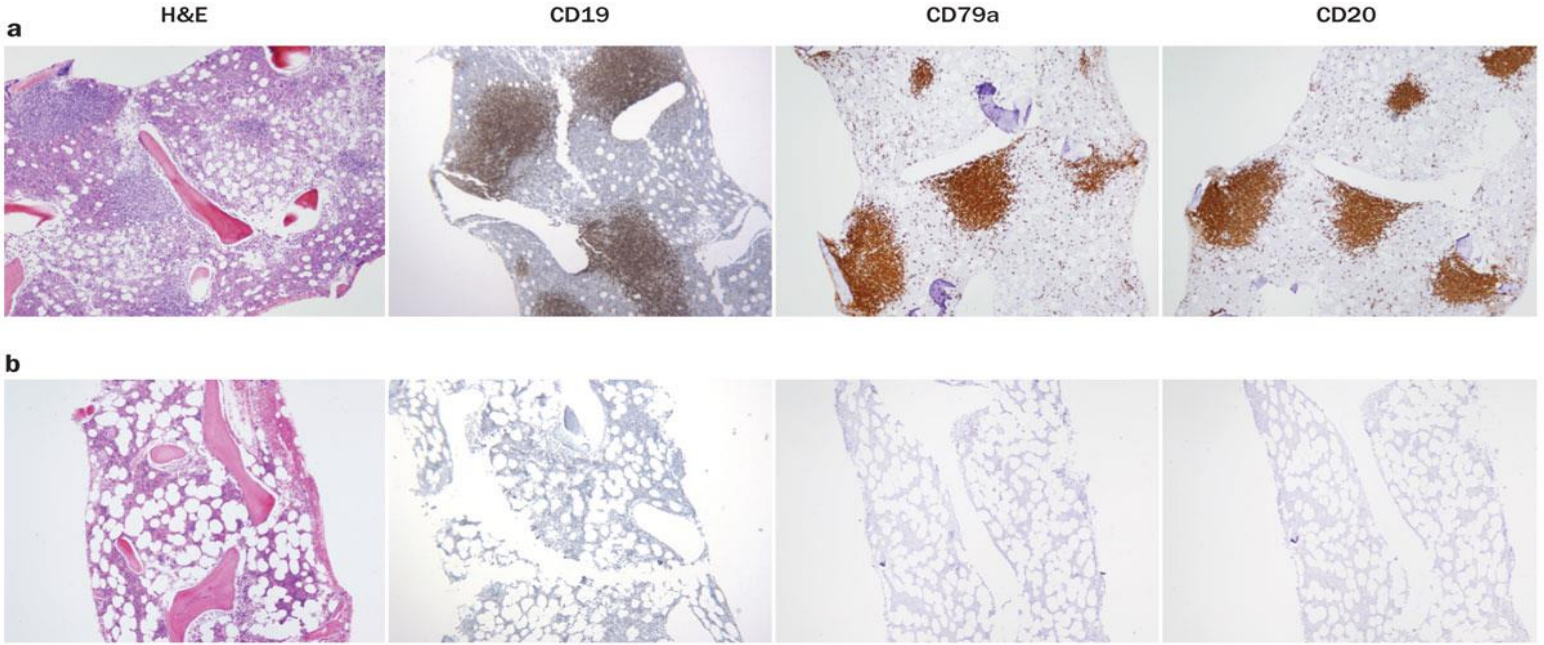


Kochenderfer & Rosenberg (2013) Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat. Rev. Clin. Oncol. 2*013

Eradication of marrow B-cells

Before

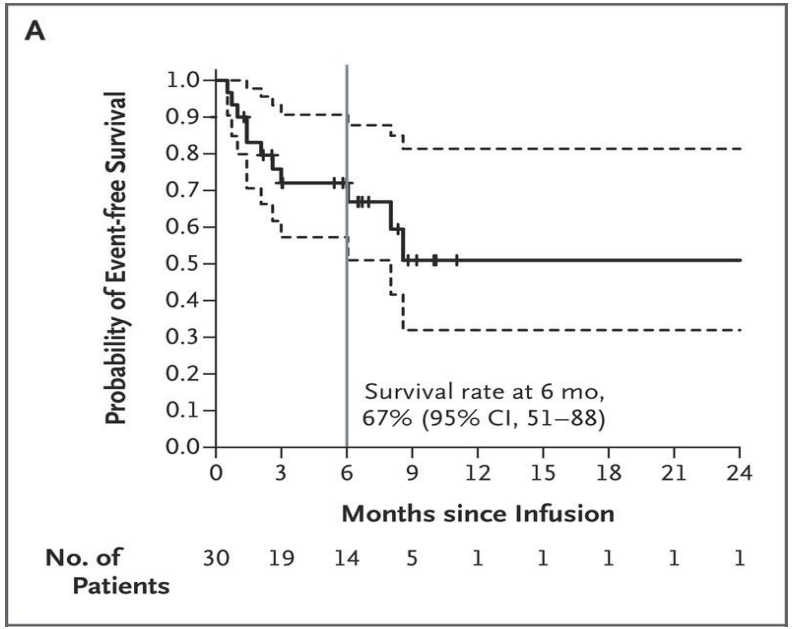
After anti-CD19 CAR T-cell infusion



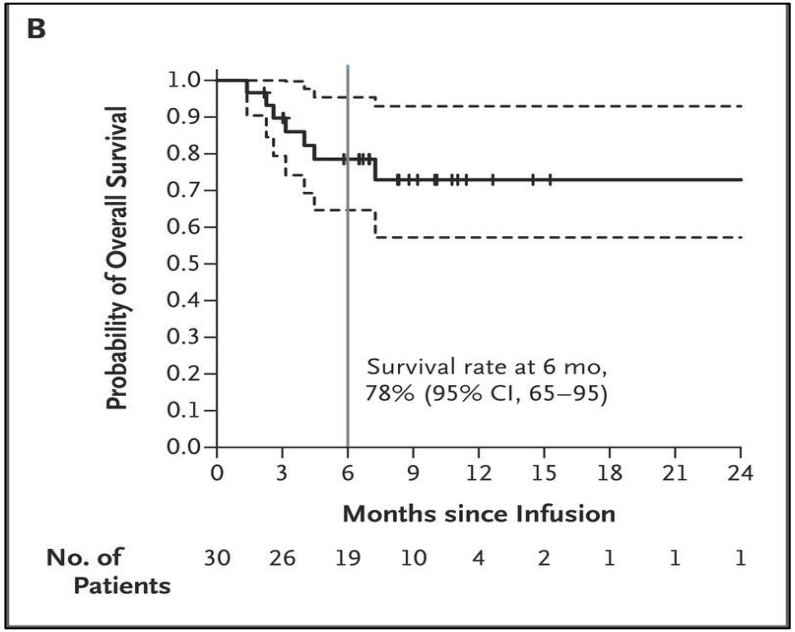
Kochenderfer & Rosenberg (2013) Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat. Rev. Clin. Oncol. 2*013

Chimeric Antigen Receptor T Cells for Sustained Remissions in Acute Lymphoblastic Leukemia

Event-free Survival



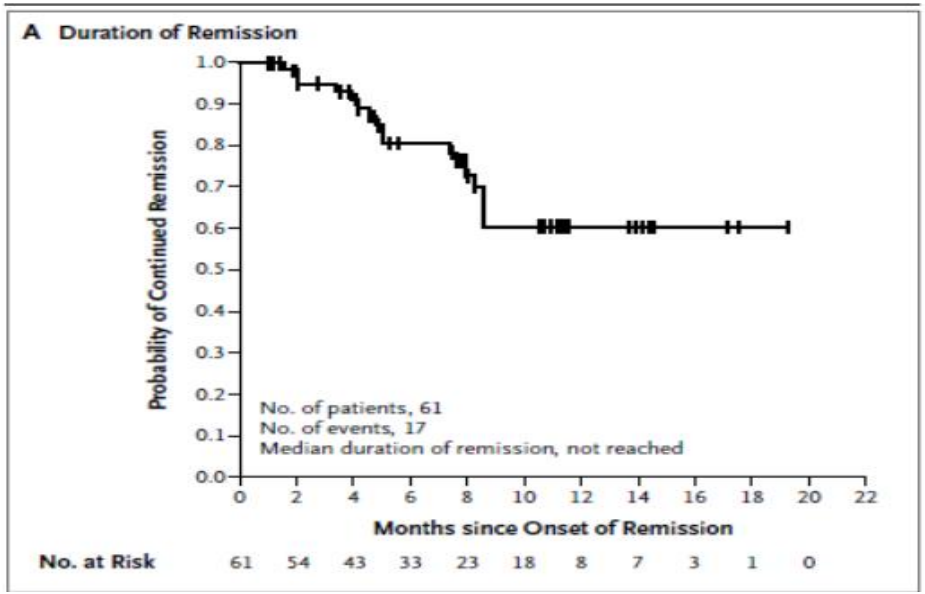
Overall Survival

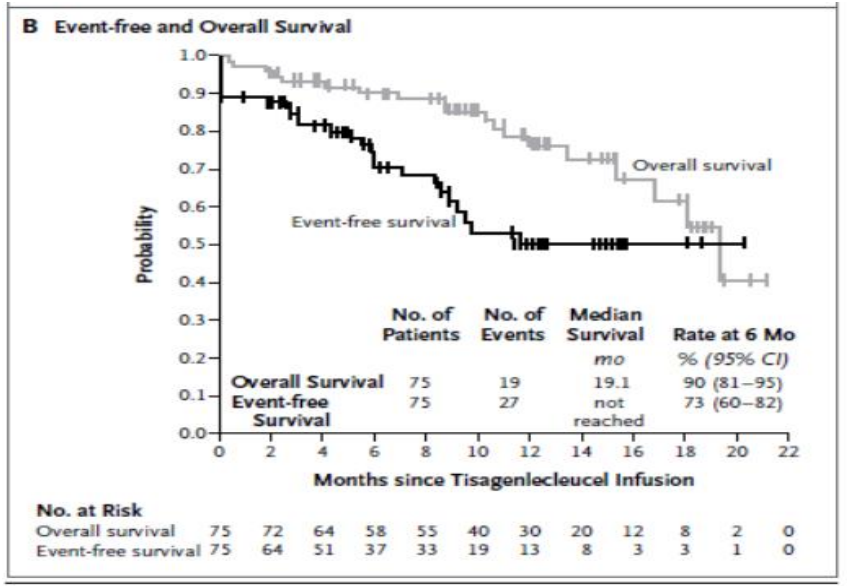


N = 30

Maude et al. N Engl J Med 2014; 371:1507-1517

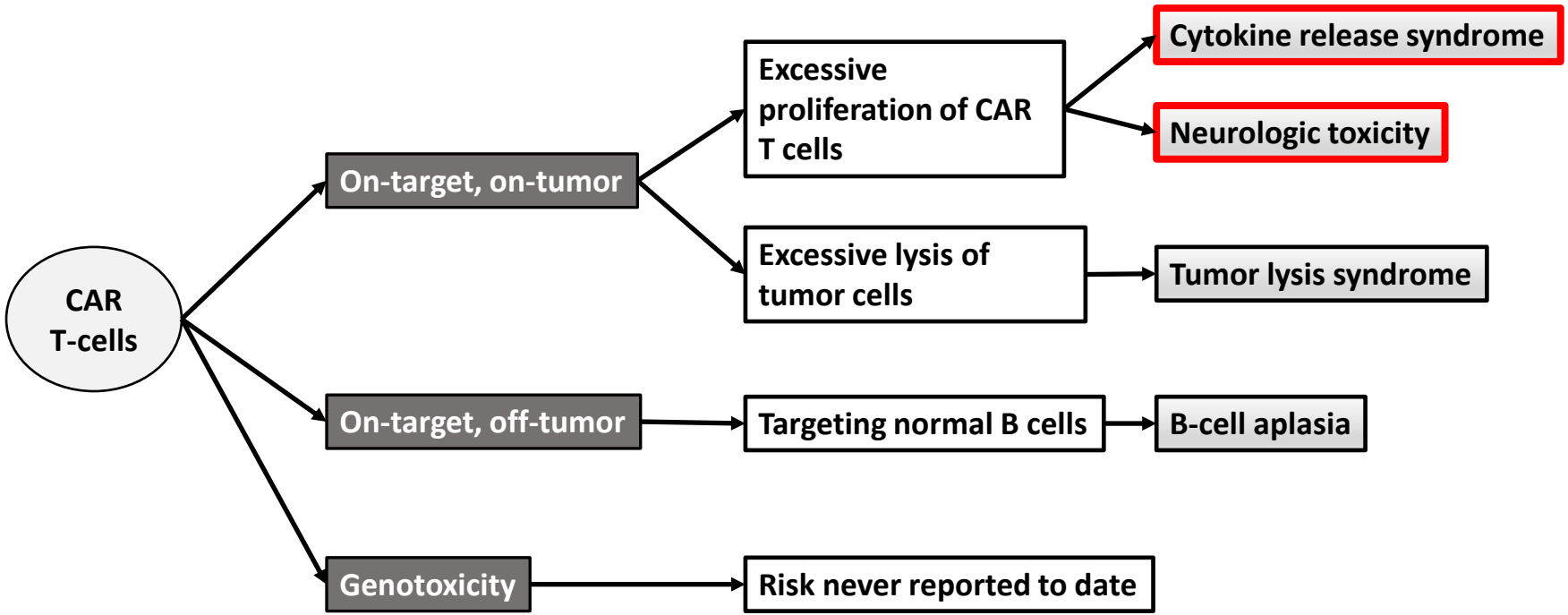
Chimeric Antigen Receptor T Cells for Sustained Remissions in Acute Lymphoblastic Leukemia





Maude et al. Tisagenlecleucel in childhood ALL.
N Engl J Med 2018

CAR T Cell Therapy: Toxicity



Adapted from Kalaitsidou et al. Immunotherapy, 2015

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Thank you.