Society for Immunotherapy of Cancer (SITC)

Immunotherapy for Hematological Malignancies

Abhinav Deol, MD
Assistant Professor of Oncology
Wayne State University/ Karmanos Cancer Institute
Detroit, MI

Advances in Cancer Immunotherapy™ - Michigan
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Outline

1. Background/ Introduction
2. Immunotherapeutic Strategies to Target Hematological Malignancies
3. Clinical Experience
4. Conclusions

Background/ Introduction

Background/ Introduction

1. Malignant cells are easily differentiated from normal cells by unique cell surface markers

2. Tumor cells and immune cells are easily accessible to study effects of immune targeting strategies

3. Graft versus Leukemia (GvL) effect after Allogeneic stem cell transplant used to treat hematological malignancies has helped identify important principles in immunology

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Background/ Introduction

Table 1: Antigens frequently analyzed in the immunophenotyping of hematopoietic malignancies

Antigens with broad expression	
Panmyeloid antigens	CD13, CD33, CDw65, MPO
Pan-B-cell antigens	cyCD22, CD19, cyCD79a
Pan-T-cell antigens	cyCD3, CD2, CD7, CD5
Antigens associated with immaturity or activation	
Immaturity	TdT, CD34, HLA-DR[a]
Antigens with lineage specific and maturation dependent expression	
Myeloid cells	CD14, CD15, glycophorin A, CD41, CD61
B-cells	CD20, CD23, FMC7, cyIgμ, sIg
T-cells	CD1a, CD4, CD8
NK cells[b]	CD16, CD56, CD57

[a]constitutive expression on monocytes and B-cells, [b]in absence of CD3
cy cytoplasmic, sIg surface membrane immunglobulins

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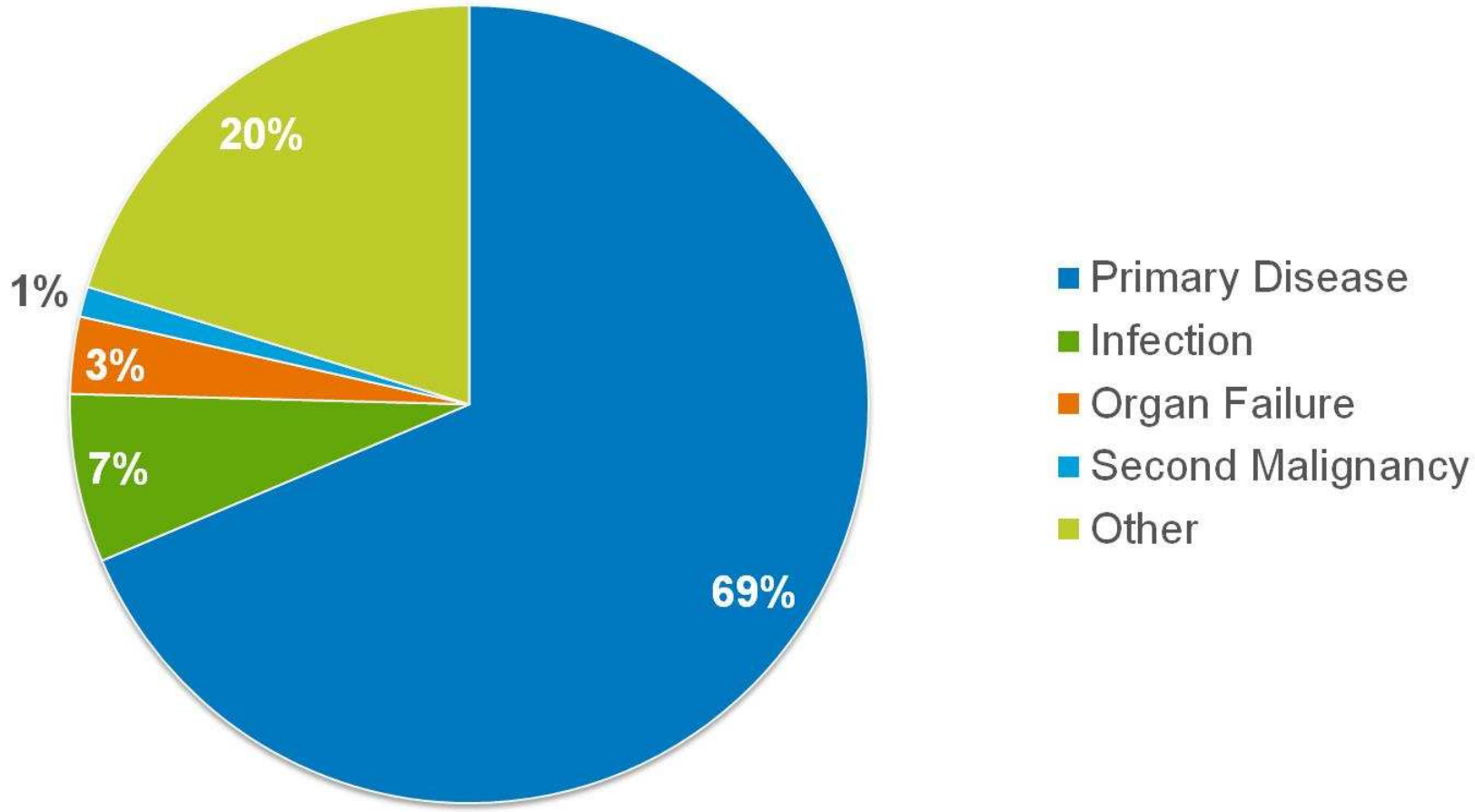
European Society of Hematology Consesus statement on Immunenotyping of Hematological Malignancies, 2001

Causes of Death after Autologous Transplants done in 2011-2012



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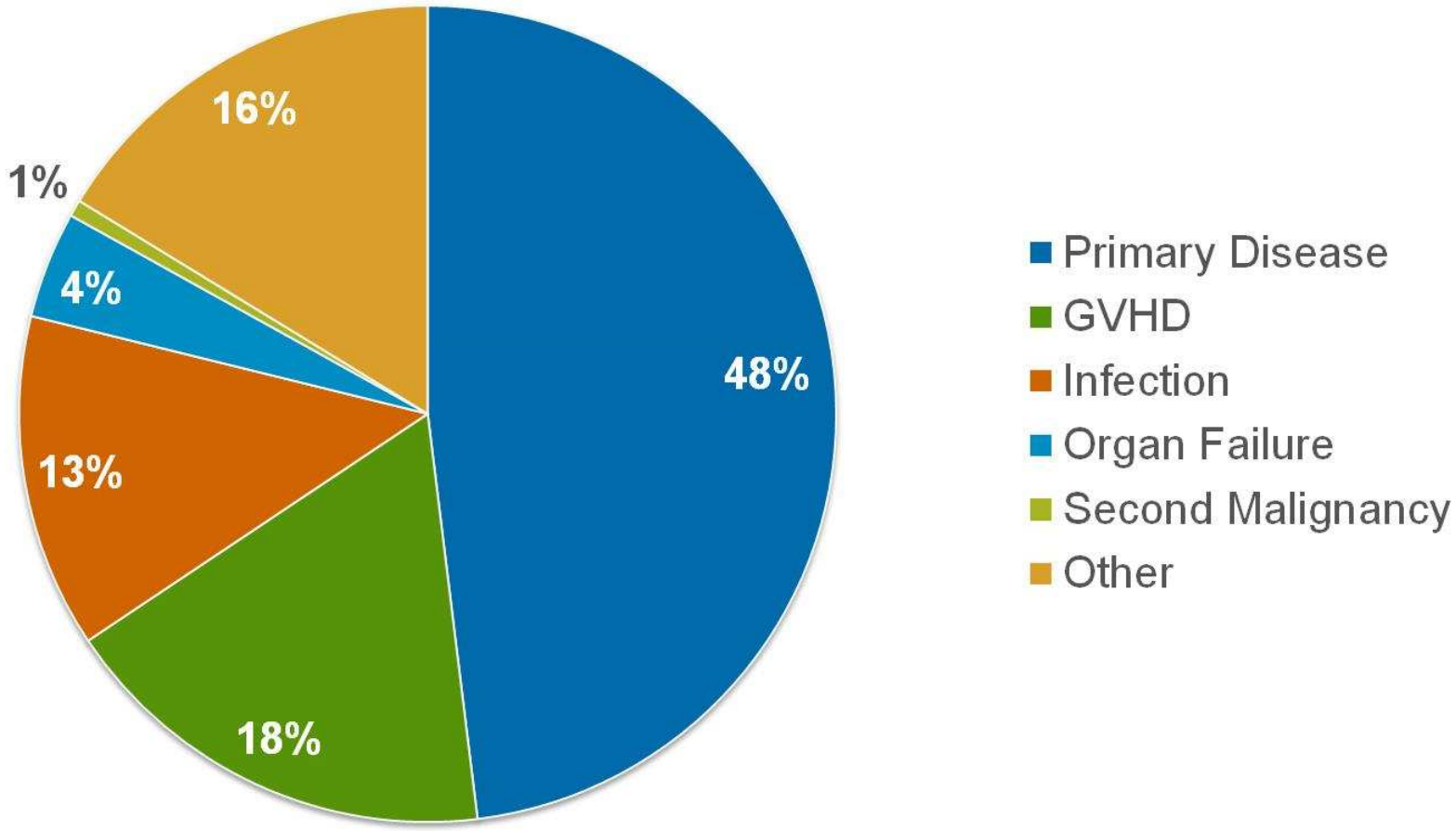
Causes of Death after HLA Match Sibling Transplants done in 2011-2012



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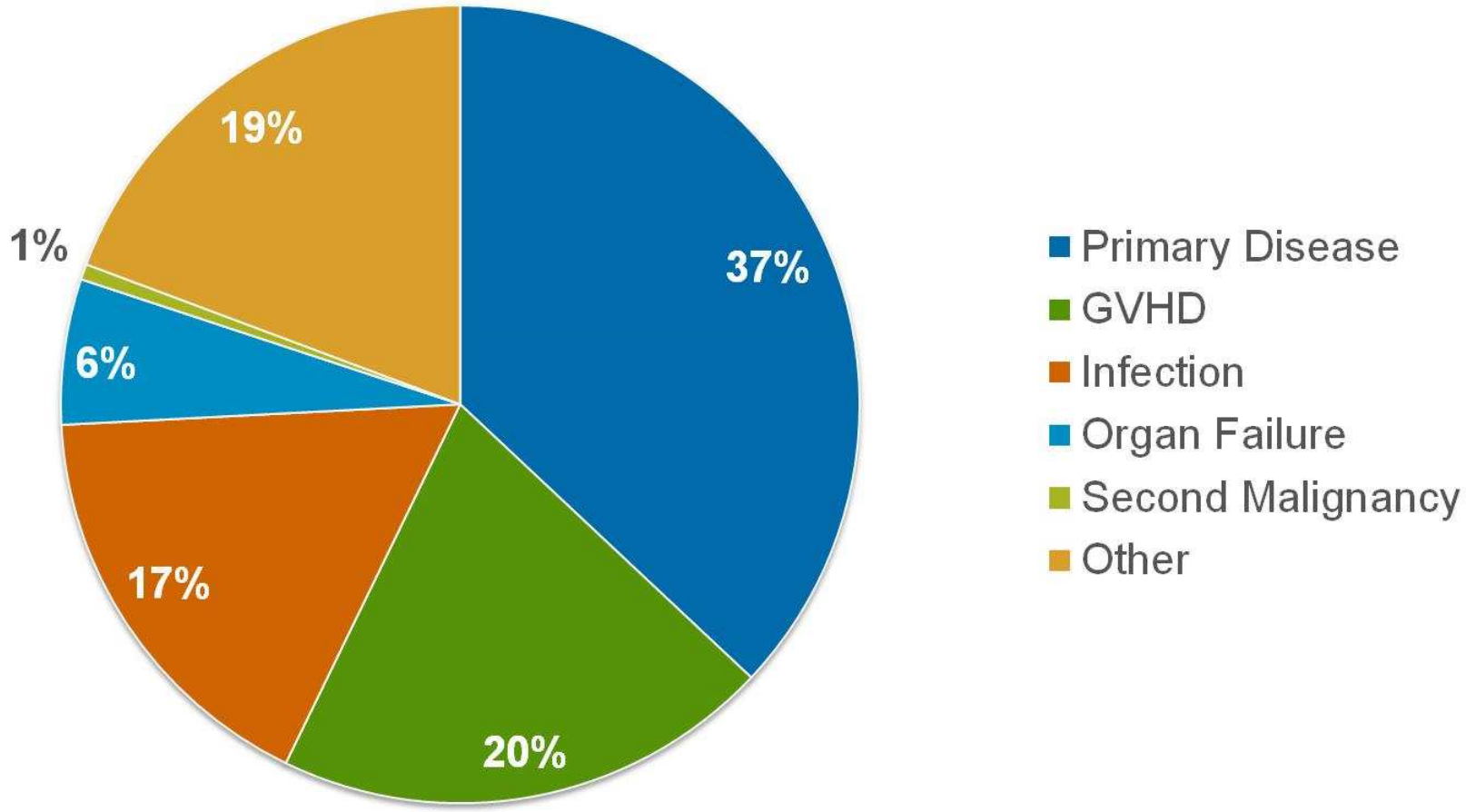
Causes of Death after Unrelated Donor Transplants done in 2011-2012



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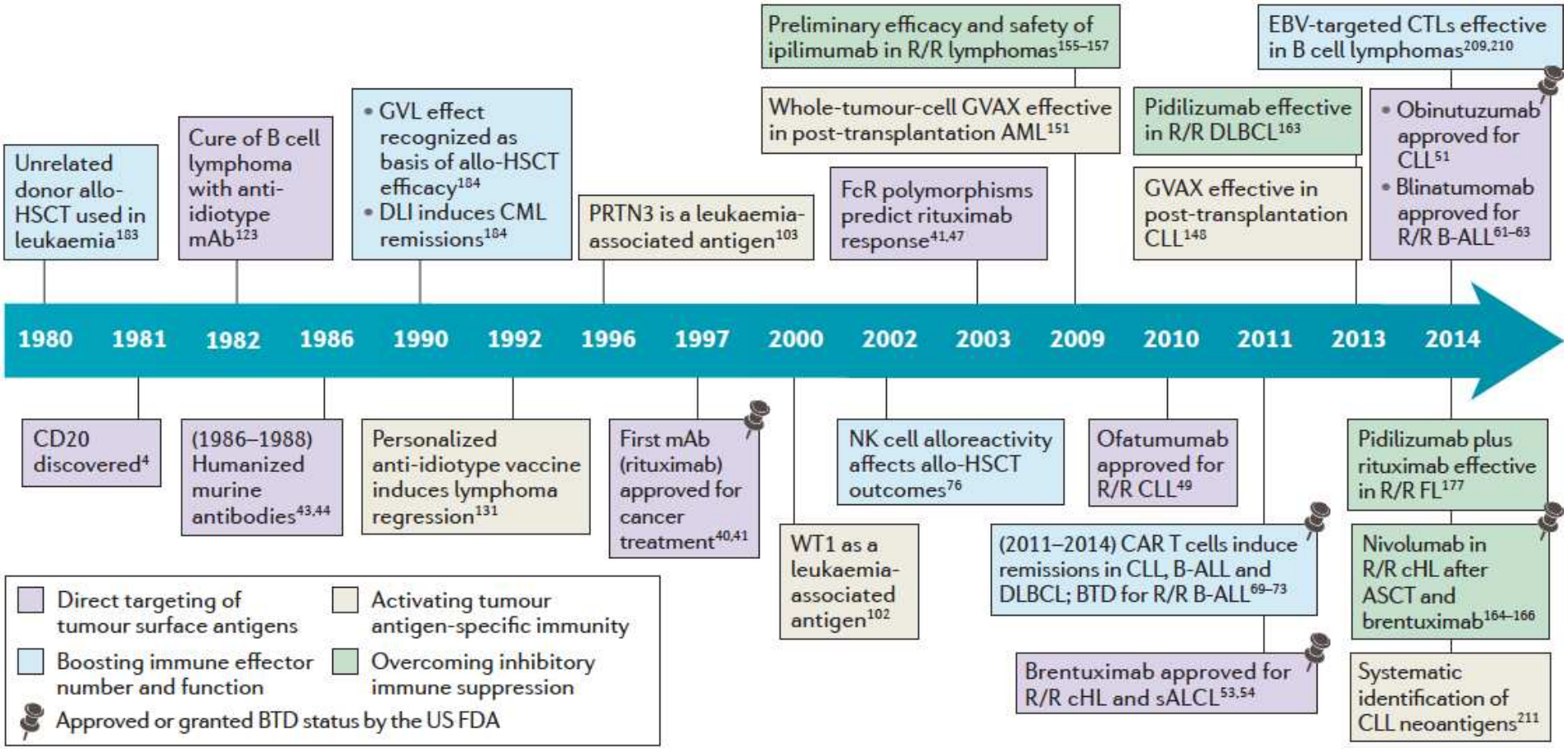
Immunotherapy for Hematological Malignancies



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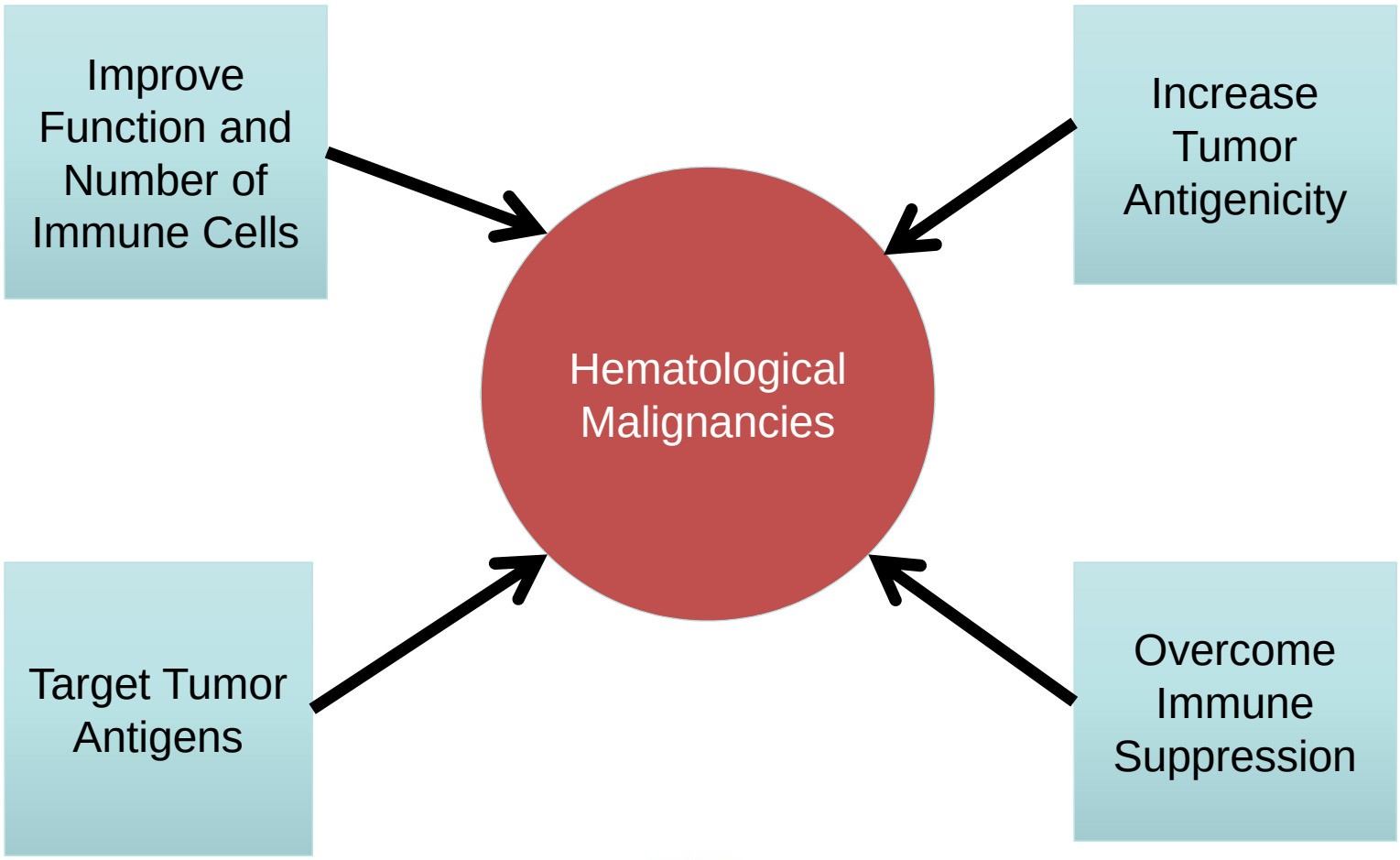
Bachireddy P, Burkhardt UE, Rajasagi M, Wu CJ.
Haematological malignancies: at the forefront of immunotherapeutic innovation.
Nat Rev Cancer. 2015 Apr;15(4):201-15

Immunotherapeutic Strategies to Target Hematological Malignancies

Immunotherapeutic Strategies to Targe Hematological Malignancies



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Ideal Tumor Antigen

1. Expressed on tumor cells
2. Not expressed or minimally expressed on normal cells
3. Targetable

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Target Tumor Antigen

Targeting Tumor Antigen has led to development of :

1. Antibodies

1. Immune Conjugates

2. Bispecific Antibody Armed Activated T cells

3. Bispecific T cell Engaging Antibodies

4. Chimeric Antigen Receptor T cells

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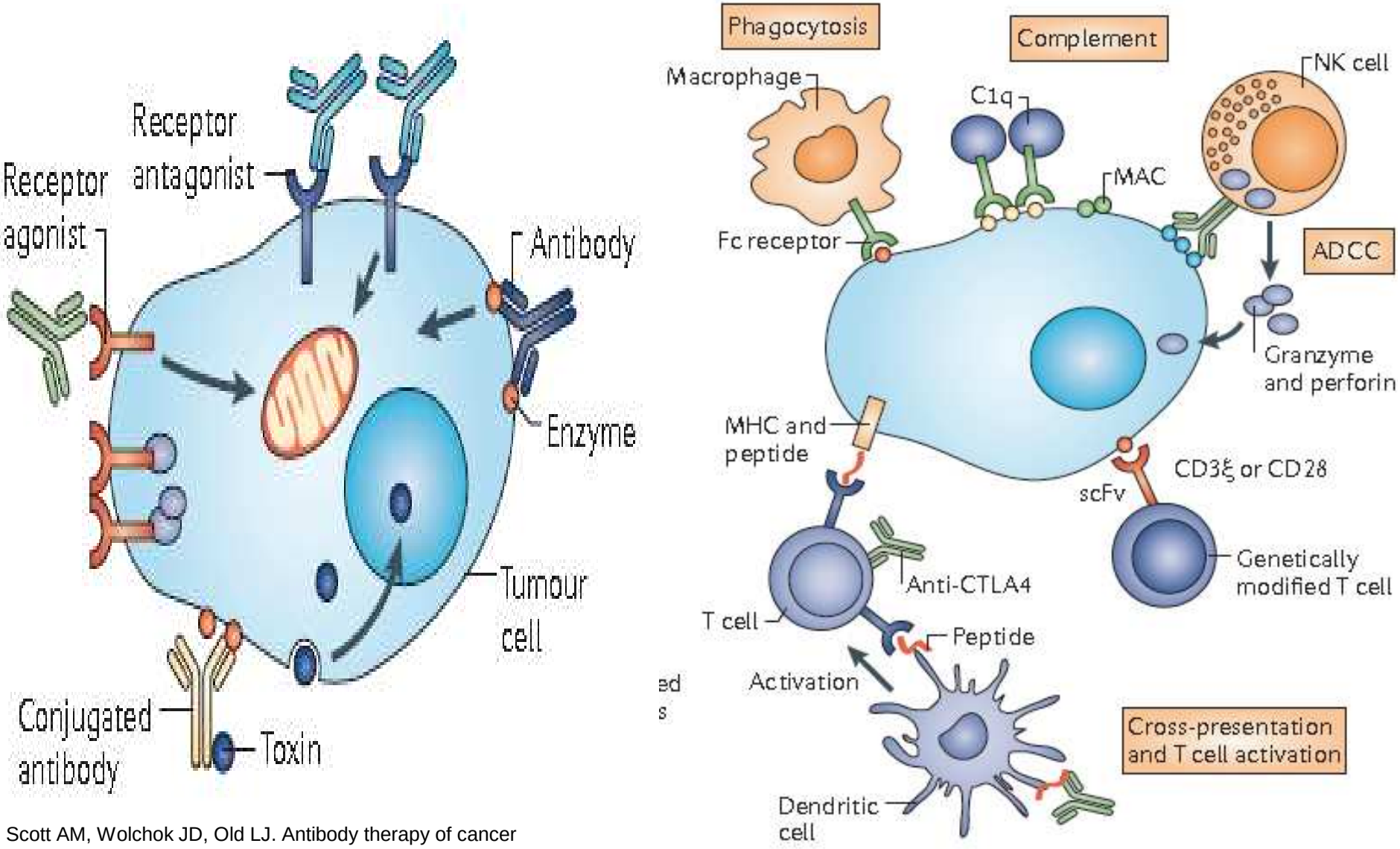
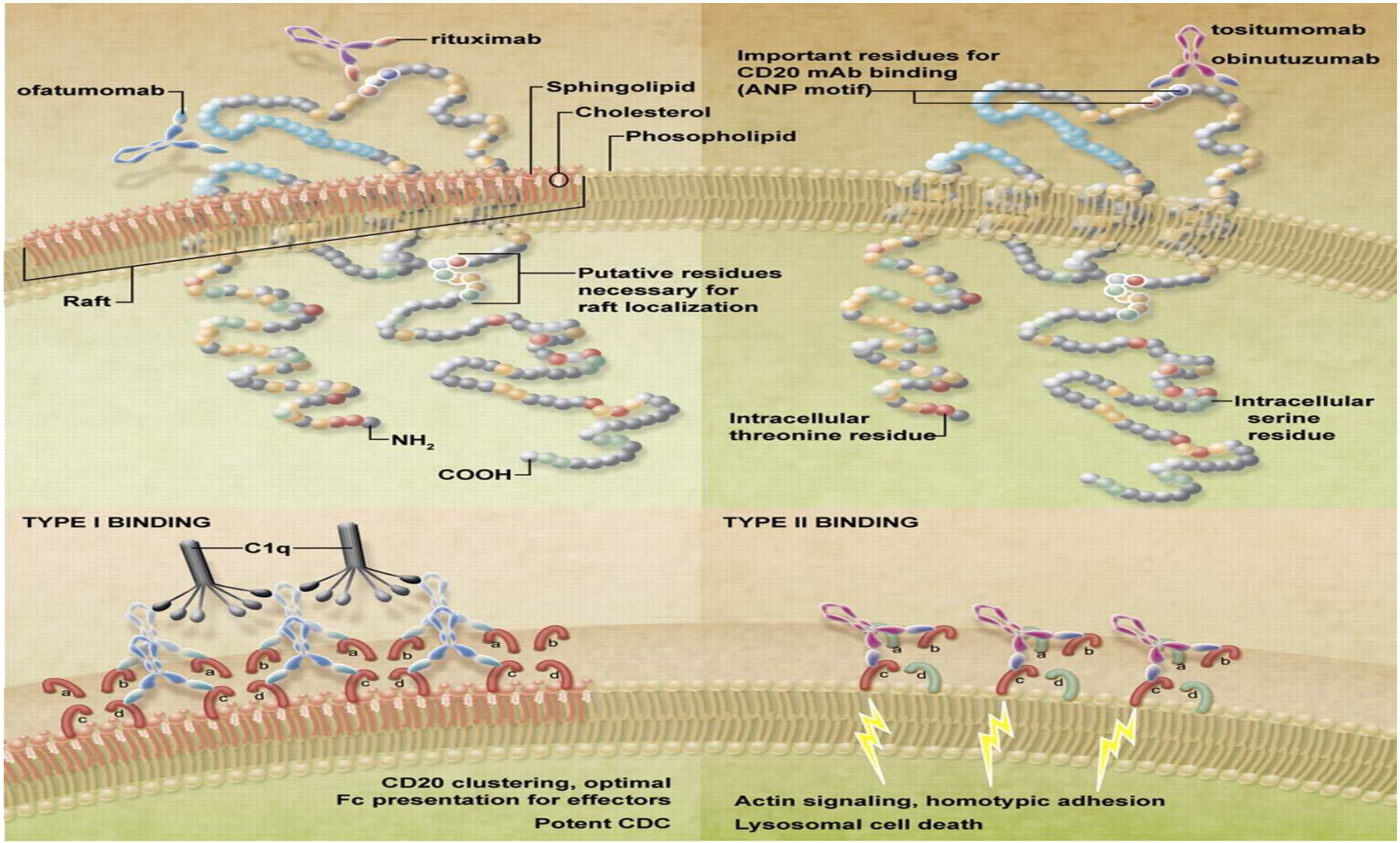
Antibodies – Mechanism of Action



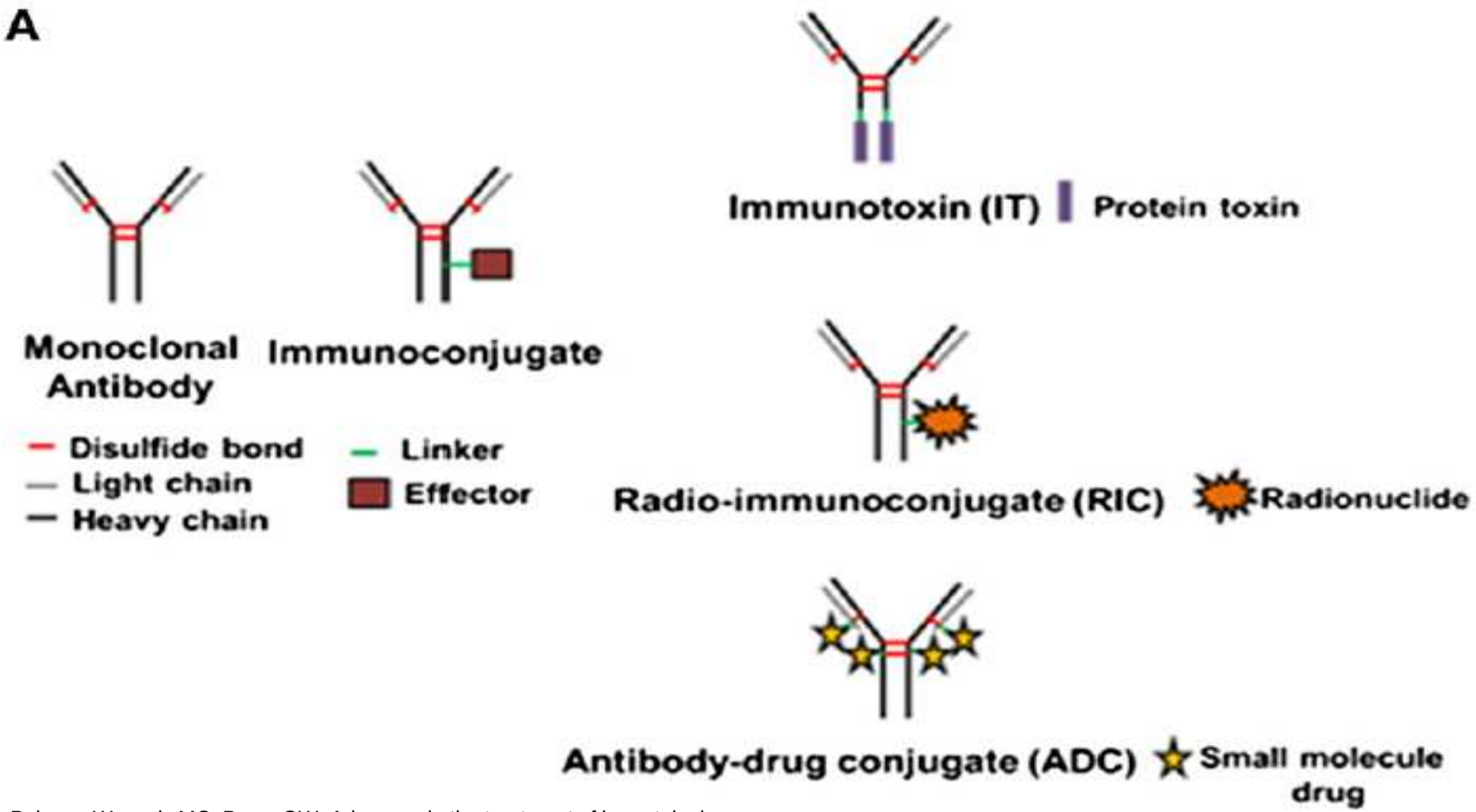
Scott AM, Wolchok JD, Old LJ. Antibody therapy of cancer
Nature Reviews Cancer 12, 278-287 (April 2012) | doi:10.1038/nrc3236

Binding of type I and II anti-CD20 mAbs.



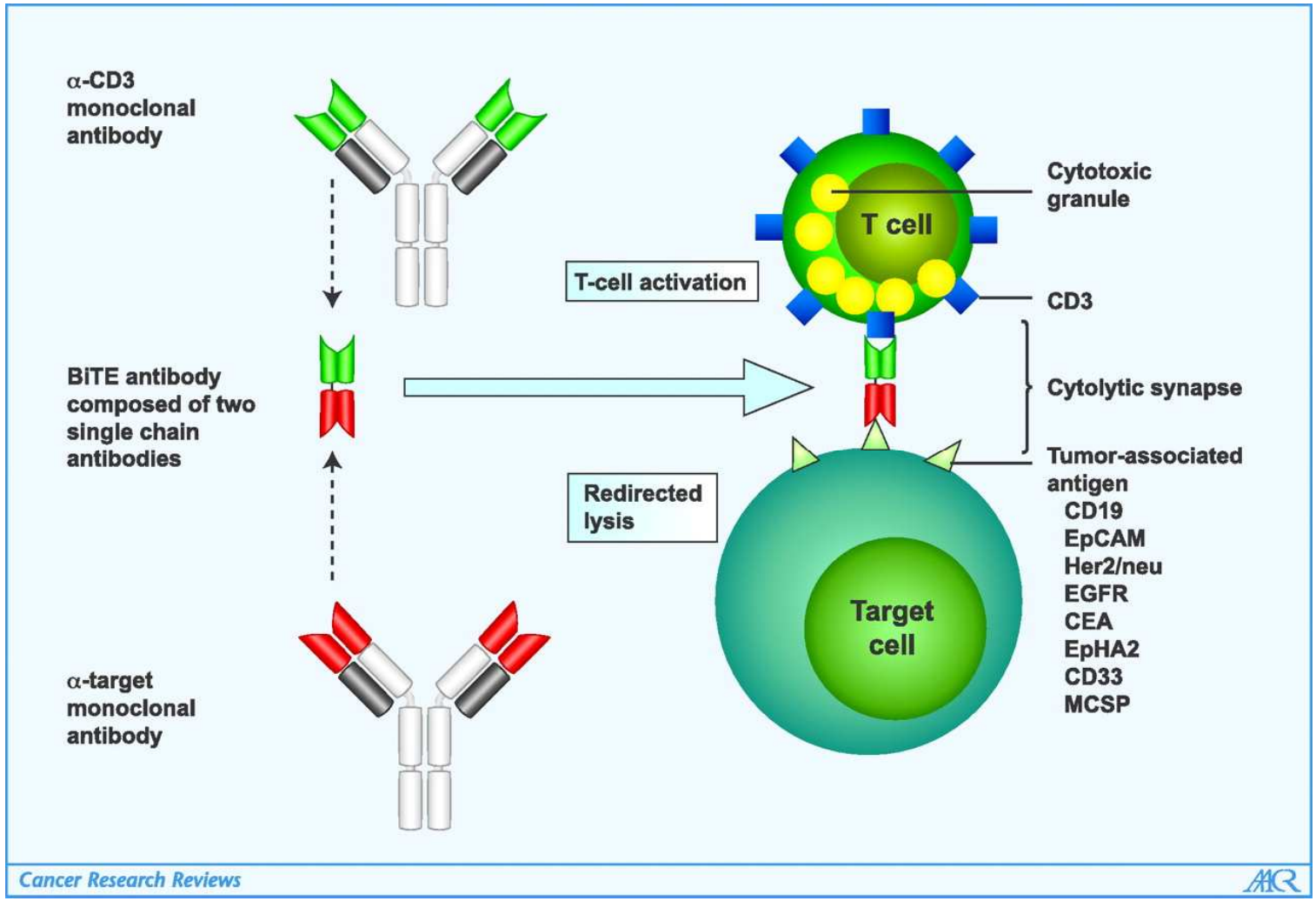
Mark S. Cragg Blood 2011;118:219-220

Immune Conjugates



Palanca-Wessels MC, Press OW. Advances in the treatment of hematologic malignancies using immunoconjugates. Blood. 2014 Apr 10;123(15):2293-301

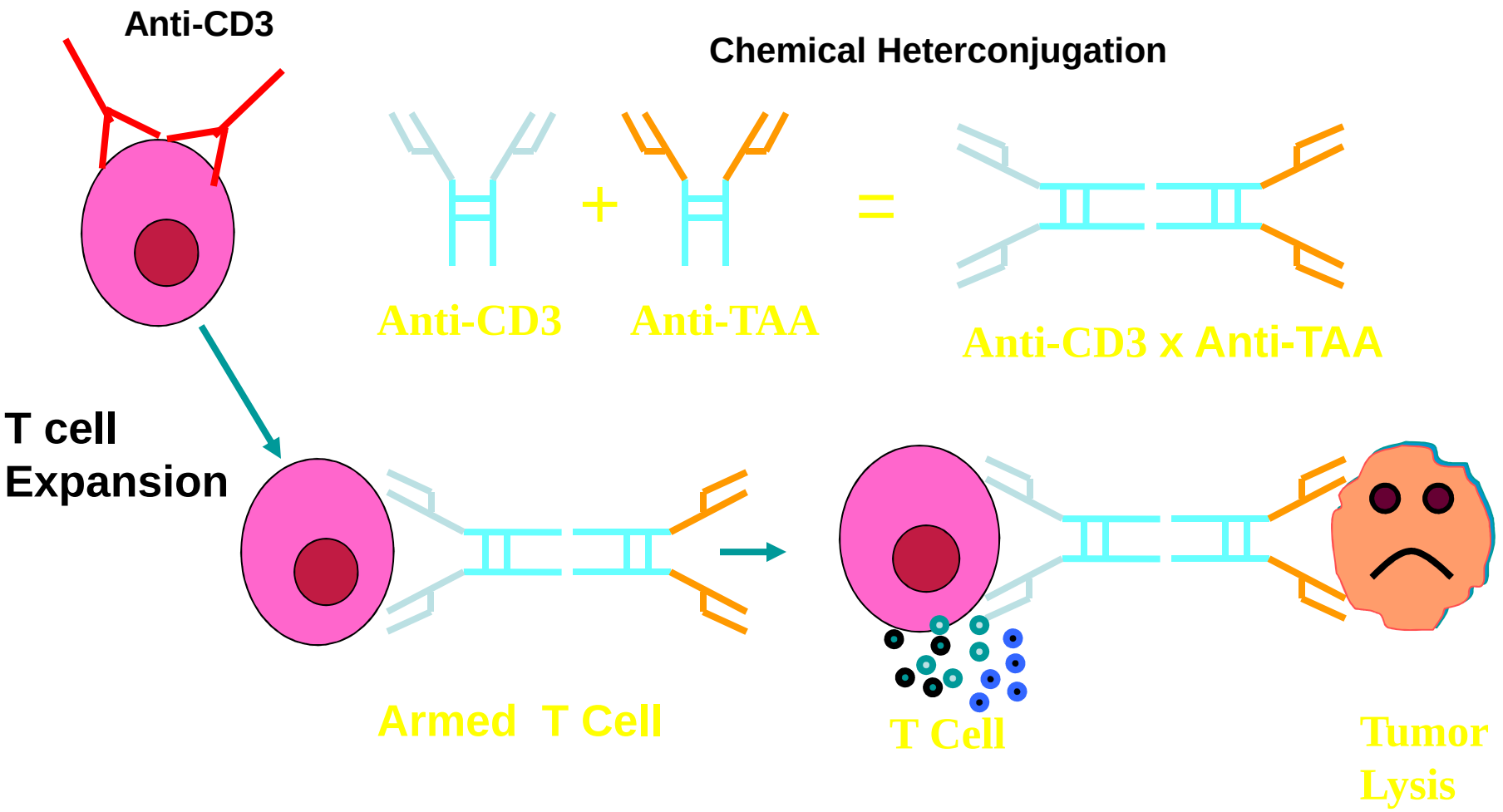
The BiTE antibody principle.



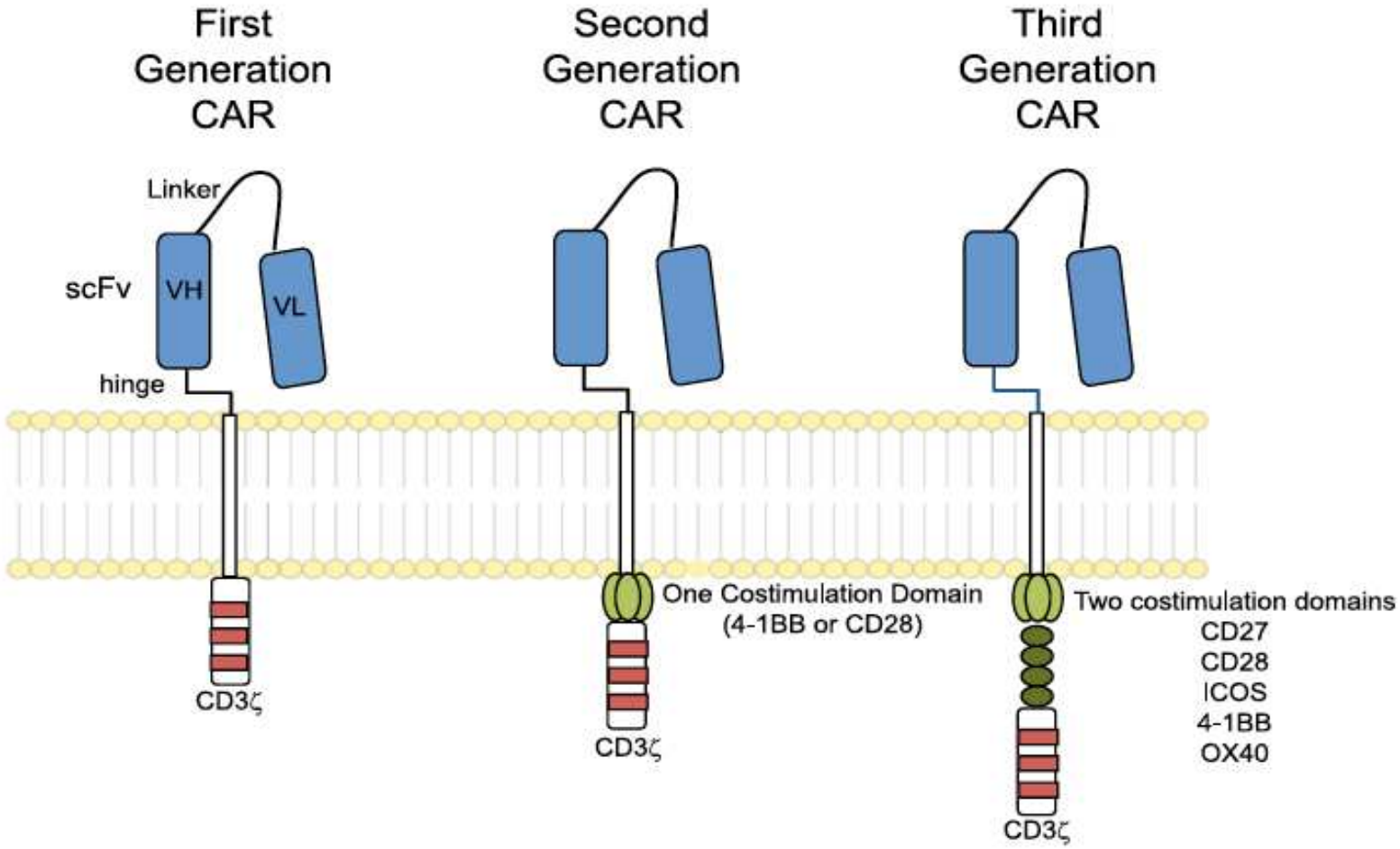
Patrick A. Baeuerle, and Carsten Reinhardt Cancer Res 2009;69:4941-4944

AACR American Association for Cancer Research
Cancer Research

Targeted Killing by T cells with BiAbs



Chimeric Antigen Receptor T Cells



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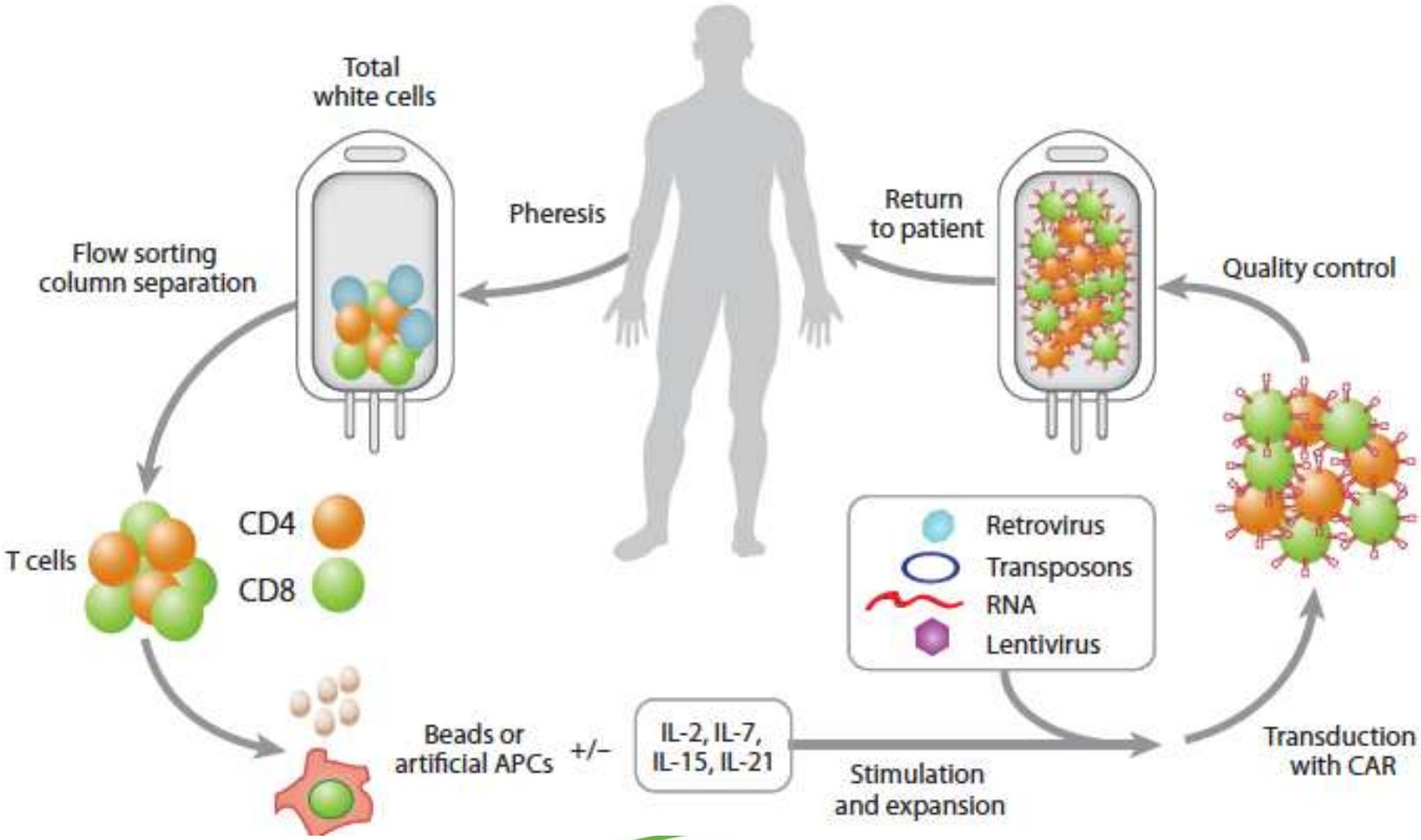
Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take he front seat for hematologic malignancies Blood. 2014 Apr 24;123(17):2625-35..

Chimeric Antigen Receptor T Cells



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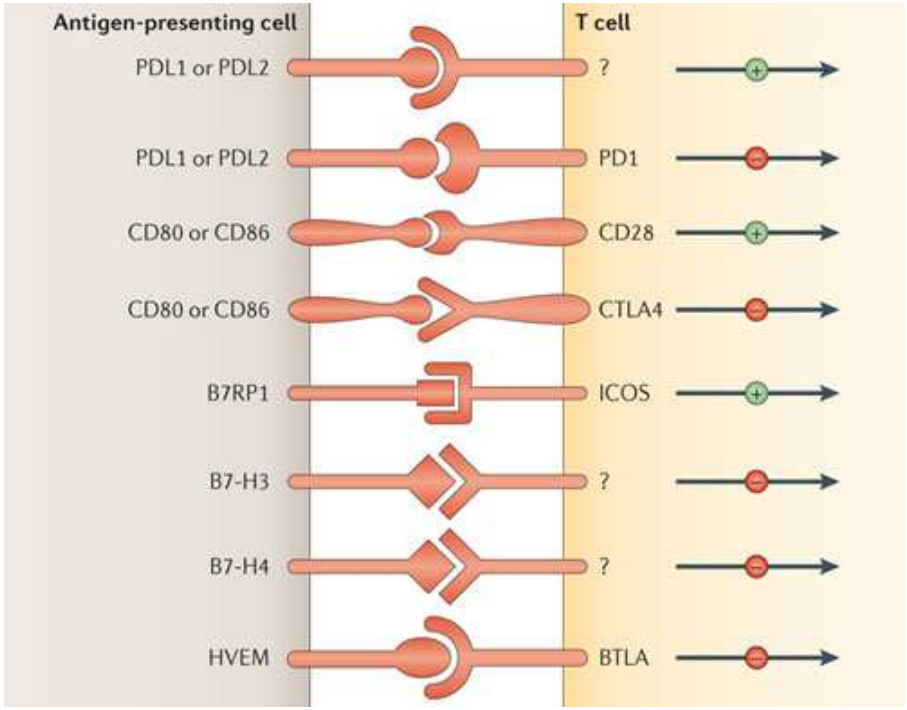
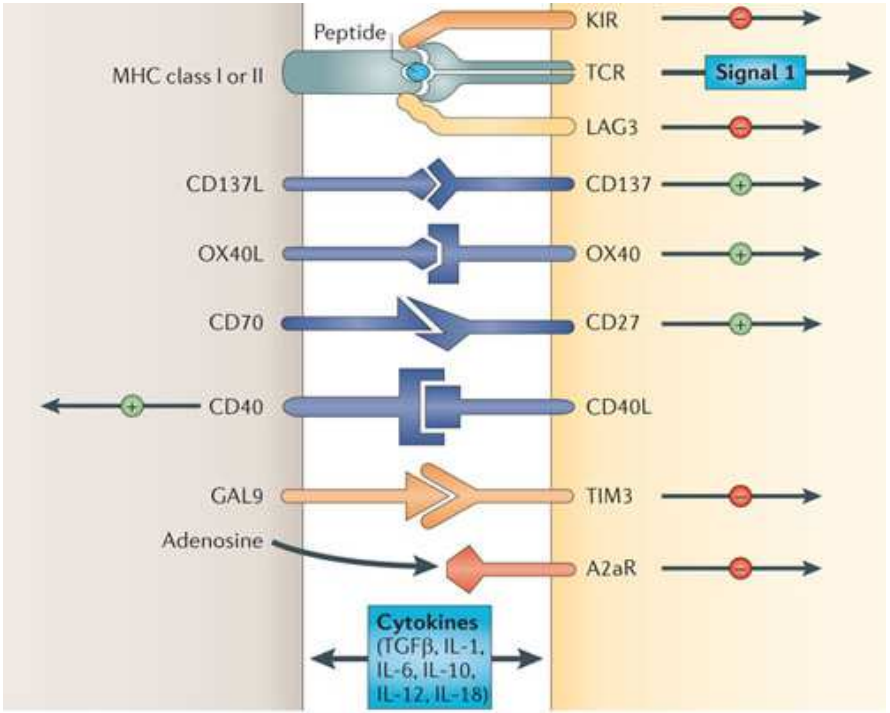
Checkpoint Inhibitors





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Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer* 12, 252-264

Clinical Experience

FDA Approved Antibodies

1. Rituximab (Anti CD 20)
2. Ofatumumab (Anti CD 20)
1. Alemtuzumab (Anti CD 52)

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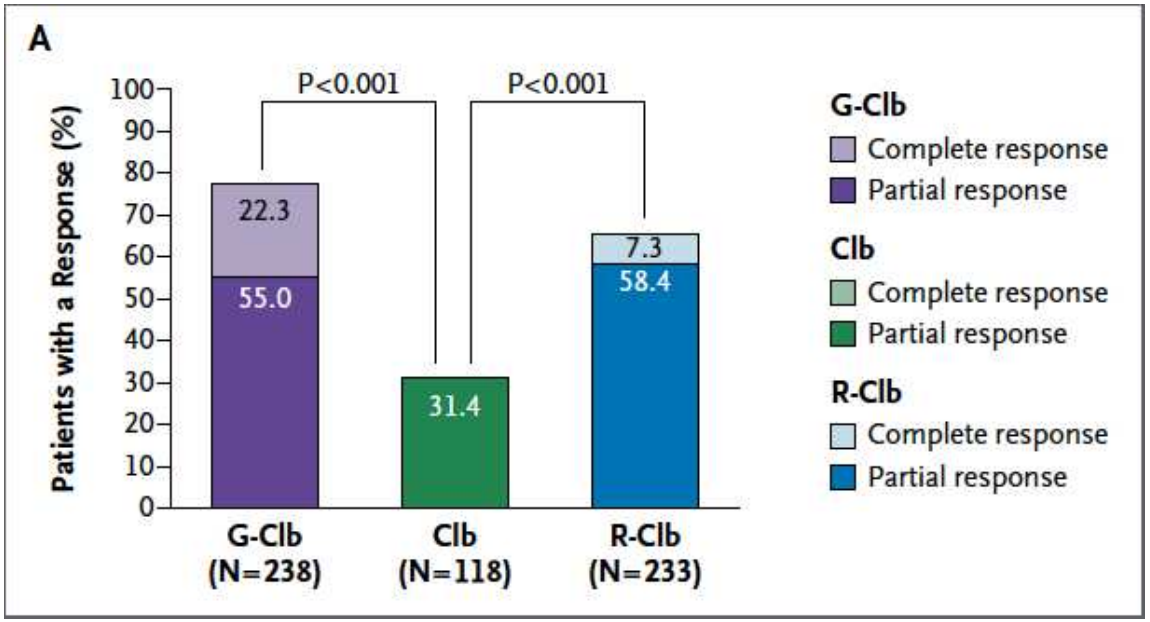
FDA Approved Antibodies

Obinutuzumab

- Anti CD 20, Type 2 Antibody
- Approved for use in CLL for pts with Co morbidities



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Valentin Goede, M.D., Kirsten Fischer, M.D., Raymonde Busch et al. Obinutuzumab plus Chlorambucil in Patients with CLL and Coexistin ConditionsN Engl J Med 2014; 370:1101-1110

Promising Antibodies

Daratumumab

- Anti CD 38, Type 2 Antibody
- Phase 2 study reported at ASCO 2015
- 106 Pts with MM, refractory to ≥ 3 lines of therapy
- ORR was 29.2%, with 3 sCR, 10 VGPR, and 18 PR
- Median duration of response was 7.4 months

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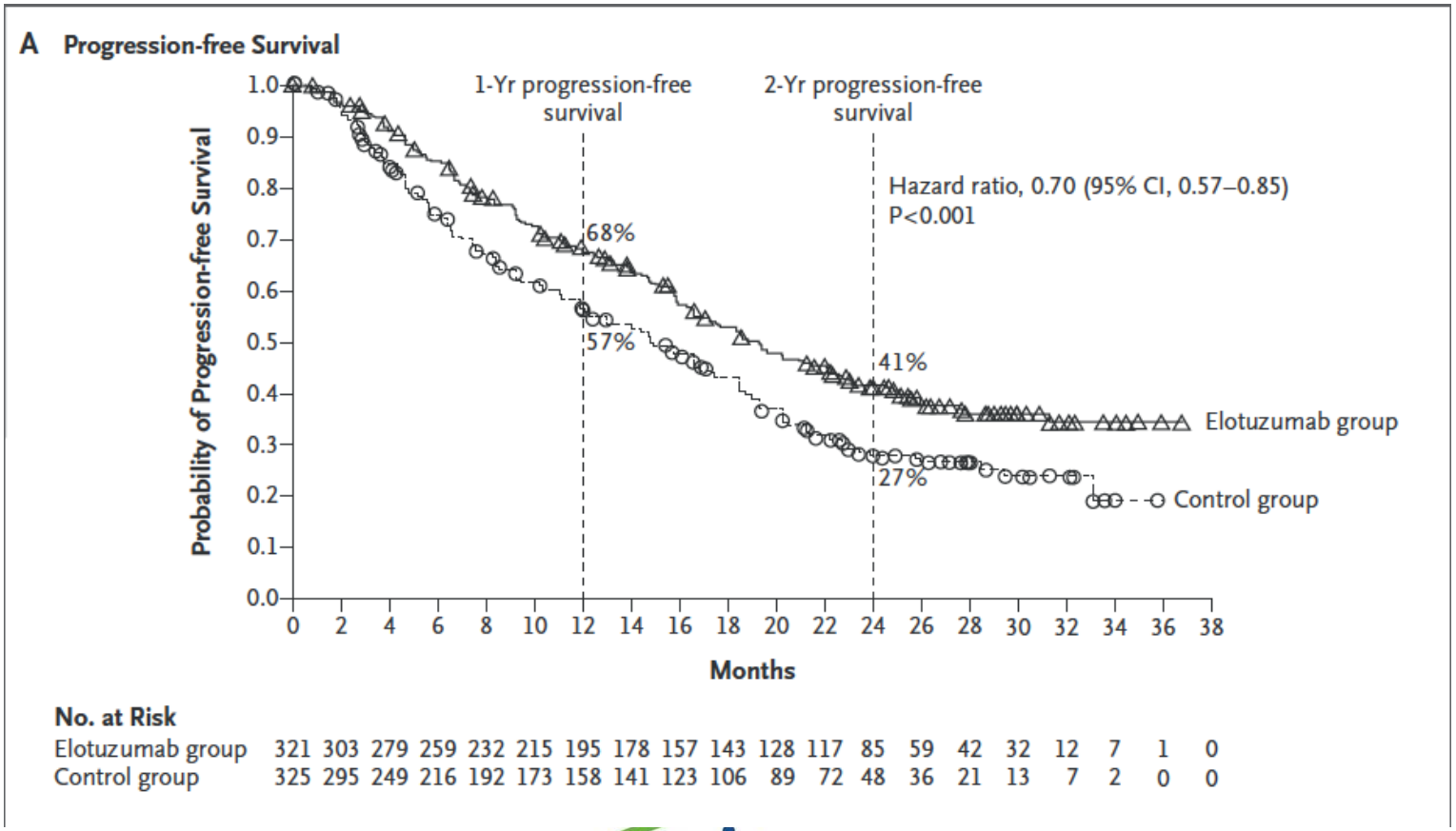
Promising Antibodies

Elotuzumab (Anti SLAM F-7 Antibody), Phase 3 Study RD vs RD+ Elotuzumab



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Sagar Lonial, Meletios Dimopoulos., Antonio Palumbo et al.
Elotuzumab Therapy for Relapsed or Refractory MM
NEJM, June 2, 2015

Radioactive Immune Conjugates

Antibody	Target	Isotope	Indication	Stage of development
Anti-Tac antibody (^{90}Y-HAT)	CD25	^{90}Y	T-cell NHL, HL	Phase 1 NCT00001575
BB4 antibody	CD138	^{131}I	MM	Phase 1 NCT01296204
BC8 antibody-streptavidin conjugate	CD45	^{131}I, ^{90}Y	AML, ALL, MDS	Phase 1 NCT00988715
Daclizumab (CHX-A daclizumab)	CD25	^{90}Y	HL	Phase 1/2 NCT01468311
Epratuzumab	CD22	^{90}Y	B-cell NHL, WM	Phase 1/2 NCT01101581, NCT00004107
Ibritumomab tiuxetan	CD20	^{90}Y	B-cell NHL	Approved 2002
Lintuzumab	CD33	^{225}Ac	AML	Phase 1/2 NCT01756677
Tositumomab	CD20	^{131}I	B-cell NHL	Approved 2003; to be discontinued February 2014

Antibody Drug Conjugates

Antibody	Target	Drug	Indication	Stage of development
BV	CD30	Monomethyl auristatin E	HL, ALCL	Approved 2011
BT062	CD138	DM4 (Maytansinoid)	MM	Phase 2 NCT01001442, NCT01638936
Polatuzumab vedotin (DCDS4501A)	CD79b	Monomethyl auristatin E	DLBCL, FL	Phase 2 NCT01691898
GO	CD33	Calicheamicin	AML	Approved 2000; withdrawn June 2010
INO (CMC-544)	CD22	Calicheamicin	B-cell NHL, B-cell ALL	Phase 3 NCT01564784, NCT01232556
IMGN529	CD37	DM1 (Maytansinoid)	B-cell NHL, B-cell CLL	Phase 1 NCT01534715
Milatuzumab-doxorubicin (hLL1-Dox; IMMU-110)	CD74	Doxorubicin	MM, CLL, NHL	Phase 1/2 NCT01101594
PV (DCDT2980S)	CD22	Monomethyl auristatin E	DLBCL, FL	Phase 2 NCT01691898
SAR-3419	CD19	DM4 (Maytansinoid)	DLBCL, B-cell ALL	Phase 2 NCT01472887, NCT01440179
SGN-CD19A	CD19	Monomethyl auristatin F	B-cell NHL, B-cell ALL	Phase 1 NCT01786135, NCT01786096
SGN-CD33A	CD33	Pyrrolobenzodiazepine dimer	AML	Phase 1 NCT01902329

Blinatumomab

- Approved in Dec 2014 for use in Ph negative B cell ALL
- Given as a continuous infusion for 4 weeks
- Response rates of around 30% were observed in relapsed/ refractory setting
- Side effects include **cytokine release syndrome**

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CAR T Cells

- Most clinical data is available for CAR T cells directed at CD19
- Used for CLL, ALL, DLBCL, PMBCL
- Very effective but can cause **cytokine release syndrome**
- Pts treated with CD19 CAR T cells need lifelong IVIg replacement as they have no B cells

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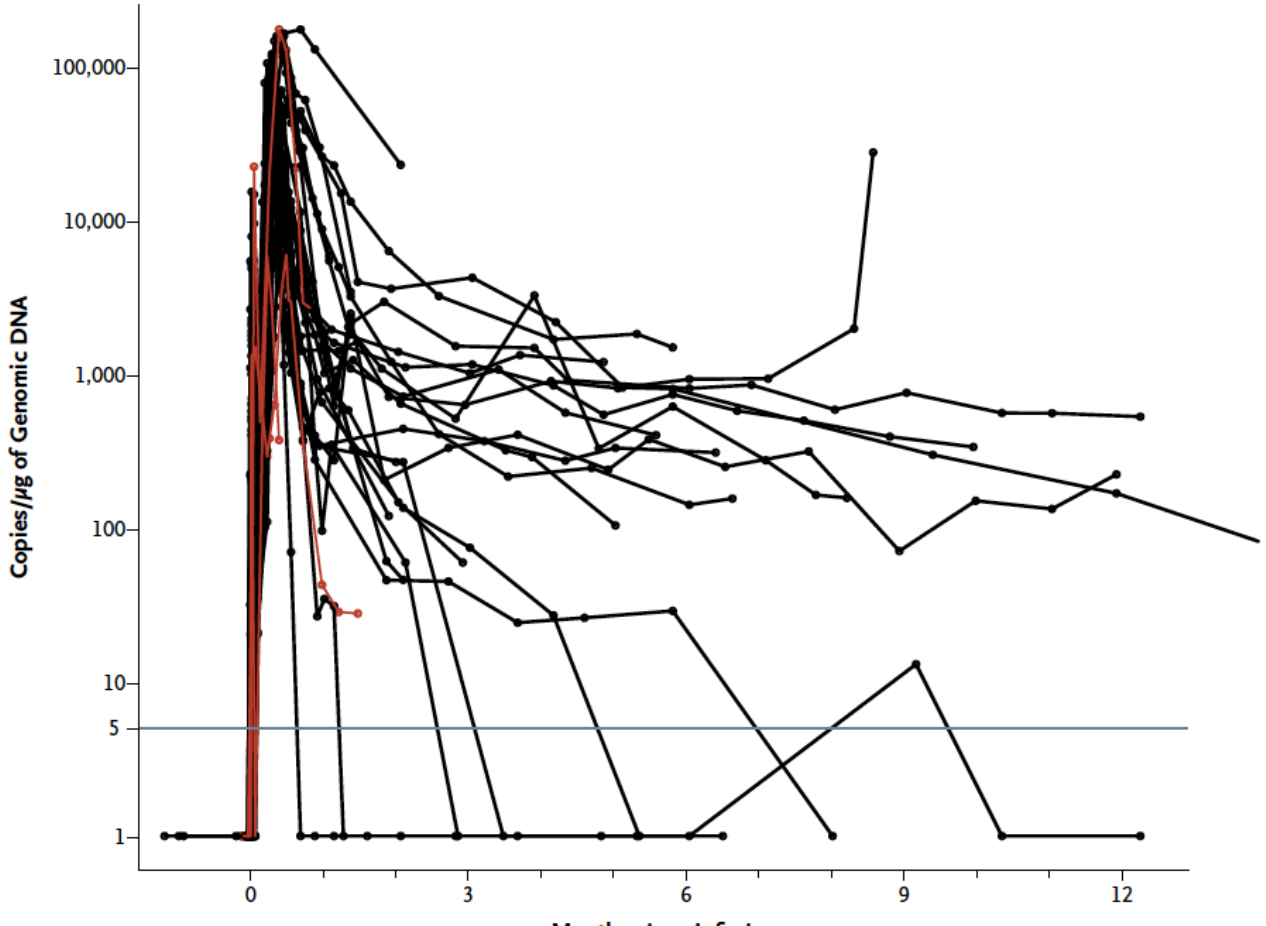
CTL019 - Expansion after Infusion



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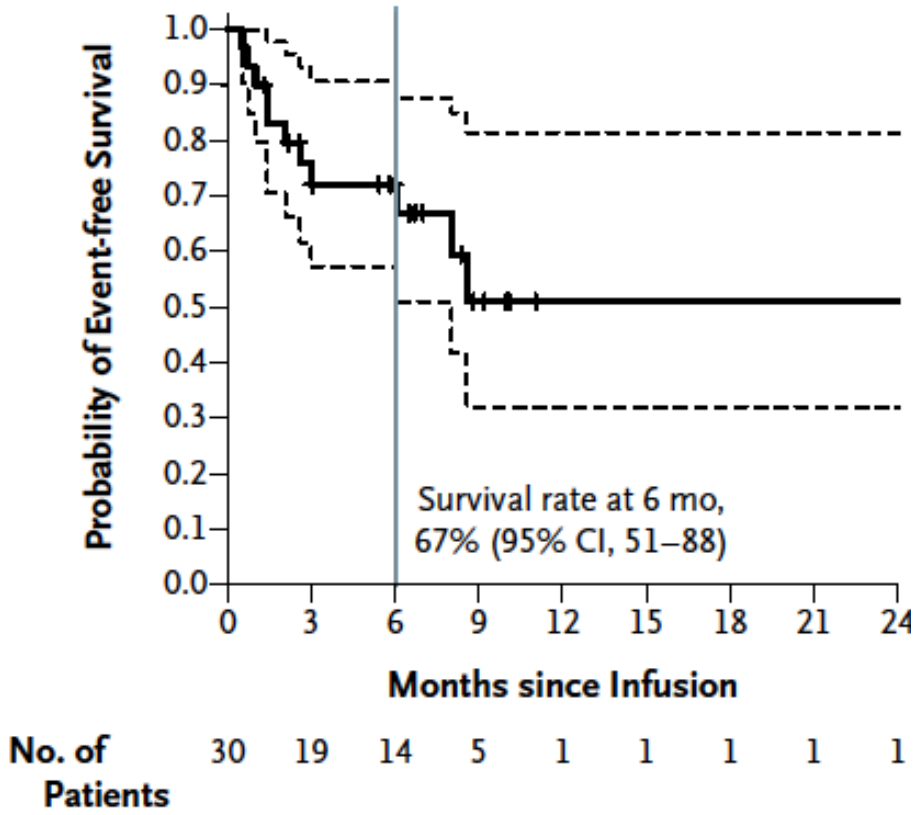
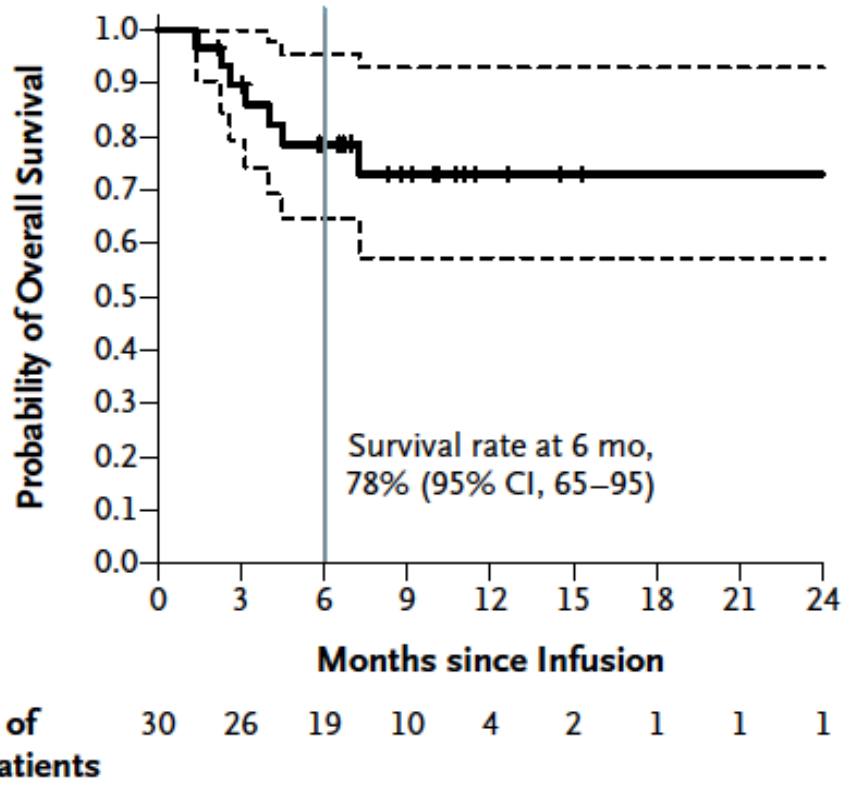
Shannon L. Maude, Noelle Frey, Pamela A. Shaw et al. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia N Engl J Med 2014; 371:1507-1517

CTL019





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Checkpoint Inhibitors

- Promising results in some hematological malignancies
- In Hodgkin Lymphoma these agents have been tested in pts who relapsed post Auto transplant and most pts were previously treated with Brentuximab Vedotin
- ORR for Nivolimumab was 87%
- ORR for Pembrolizumab was 65%
- Potential to cause auto immune phenomenon

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CYTOKINE RELEASE SYNDROME

- Seen with CAR T cells and BITEs
- Characterized with high fevers, altered mentation and high levels of pro inflammatory cytokines
- Can be fatal if not recognized and treated emergently
- Treatment consists of steroids, IL-6 antibody and supportive care

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Points to Ponder

1. Durability of responses
2. Rationale Combinations and Toxicities
3. Personalized Strategies

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Conclusions

Immunotherapy for Hematological Malignancies

1. Immunotherapeutic strategies may provide response in setting where conventional chemotherapy has failed

2. Rationale combinations of immune therapeutic strategies with chemotherapy may improve outcomes in the future

3. Effective strategies to deal with side effects of immune therapeutic strategies will lead to more patients being treated with these modalities

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FUTURE……

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