ADVANCES IN Cancer IMMUNOTHERAPY™

# Immunotherapy of Hematologic Malignancies

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# Disclosures

- Consulting: Bristol-Myers Squibb, Celgene, Janssen, Karyopharm, Millennium, Onyx, Sanofi, The Binding Site
- Honoraria: Bristol-Myers Squibb, Celgene, Janssen, Karyopharm, Millennium, Onyx, Sanofi, The Binding Site
- Research Support: Celgene
- I will be discussing non-FDA approved indications during my presentation.

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# Acute lymphocytic leukemia (ALL): Case Report

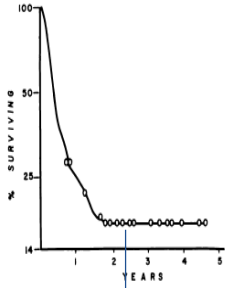
- 01/14: 28 yo male: precursor B cell ALL, 6 cycles of Hyper-CVAD ,plan for allogeneic peripheral blood stem cell transplant (alloPBSCT) but delayed
- 10/14: Bone Marrow (BM) test: 78% blasts, CD 10+, CD20+, CD22+, Trisomy 9 by FISH. Re-induced as per CALGB 10403 (dose intensive regimen for AYA patients)
- 11/14: BM test: 30% blasts, Salvaged with liposomal vincristine, complicated by myopathy, started on prednisone
- 12/14: Goes to MSKCC for CD19 CAR-T-cell x 2 infusions beginning 01/15
- 04/15: BM test: 78% blasts, Blinatumomab (bi-specific T-cell engager, CD3 & CD19) for 1 cycle
- 05/15: Hypercalcemia, acute kidney injury, BM test: 100% blasts, FLAG-IDA re-induction & liposomal vincristine, BM test: ~50% blasts
- 06/15: Severe abdominal pain/ileus, inotuzumab ozogamicin (anti-CD22 & calicheamicin) for 3 doses over 2 weeks, bone marrow test <1% blasts but +MRD by flow (0.02%) Cytogenetics: Absent trisomy 9
- 07/15: Sibling (female) allo PBSCT after fludarabine and melphalan, Day +38 BM Test: Remission, 500/500 female cells & clonal B cell gene re-arrangement
- 10/15: Dies of bacterial meningitis, in remission

# Timeline of Advances in Immunotherapy

**Allogeneic BMT**

One Hundred Patients With Acute Leukemia Treated by Chemotherapy, Total Body Irradiation, and Allogeneic Marrow Transplantation

By E. Donnall Thomas, C. Dean Buckner, Meera Banaji, Reginald A. Clift, Alexander Fefer, Nancy Flournoy, Brian W. Goodell, Robert O. Hickman, Kenneth G. Lerner, Paul E. Neiman, George E. Sale, Jean E. Sanders, Jack Singer, Mary Stevens, Rainer Storb, and Paul L. Weiden




**Donor Lymphocyte Infusions**

Donor Leukocyte Infusions in 140 Patients With Relapsed Malignancy After Allogeneic Bone Marrow Transplantation

By Robert H. Collins, Jr, Ofer Shpilberg, William R. Drobyski, David L. Porter, Sergio Giralt, Richard Champlin, Stacey A. Goodman, Steven N. Wolff, Wendy Hu, Catherine Verfaillie, Alan List, William Dalton, Nadine Ognoskie, Angela Chetrit, Joseph H. Antin, and John Nemunaitis

RAPID COMMUNICATION

Donor Leukocyte Transfusions for Treatment of Recurrent Chronic Myelogenous Leukemia in Marrow Transplant Patients

By H.J. Kolb, J. Mittermüller, Ch. Clemm, E. Holler, G. Ledderose, G. Brehm, M. Heim, and W. Wilmanns

**Autologous BMT**

**INF-α**

**Tumor Infiltrating Lymphocytes**

**IL-2**

**Rituximab (Anti-CD20)**

**Sipuleucel-T**

**Brentuximab Vedotin (Anti-CD30)**

**Blinatumomab (Bi-specific T cell Engager)**

**CAR T Therapies**

**Checkpoint Inhibitors**

1950 1960 1970 1980 1990 2000 2010 2015

***Tumor Specificity Increases Over Time***

CAR T Slide Library, Courtesy D Porter

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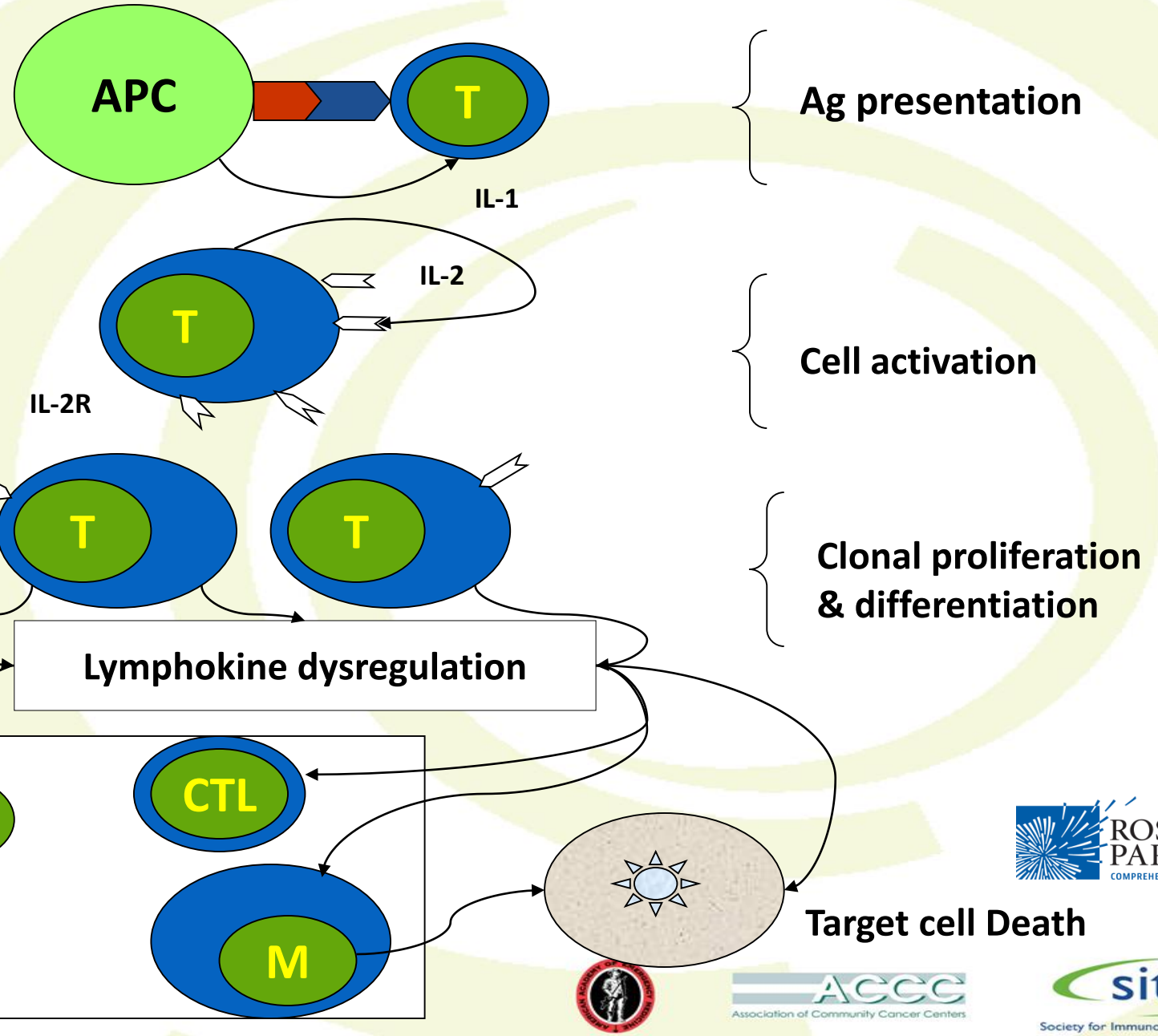
# Graft-versus Host Disease Mechanism




Afferent phase

Ag presentation

Cell activation

Clonal proliferation & differentiation

Efferent phase

Courtesy of
Mohamed Soliman
RPCCC Flow Cytometry

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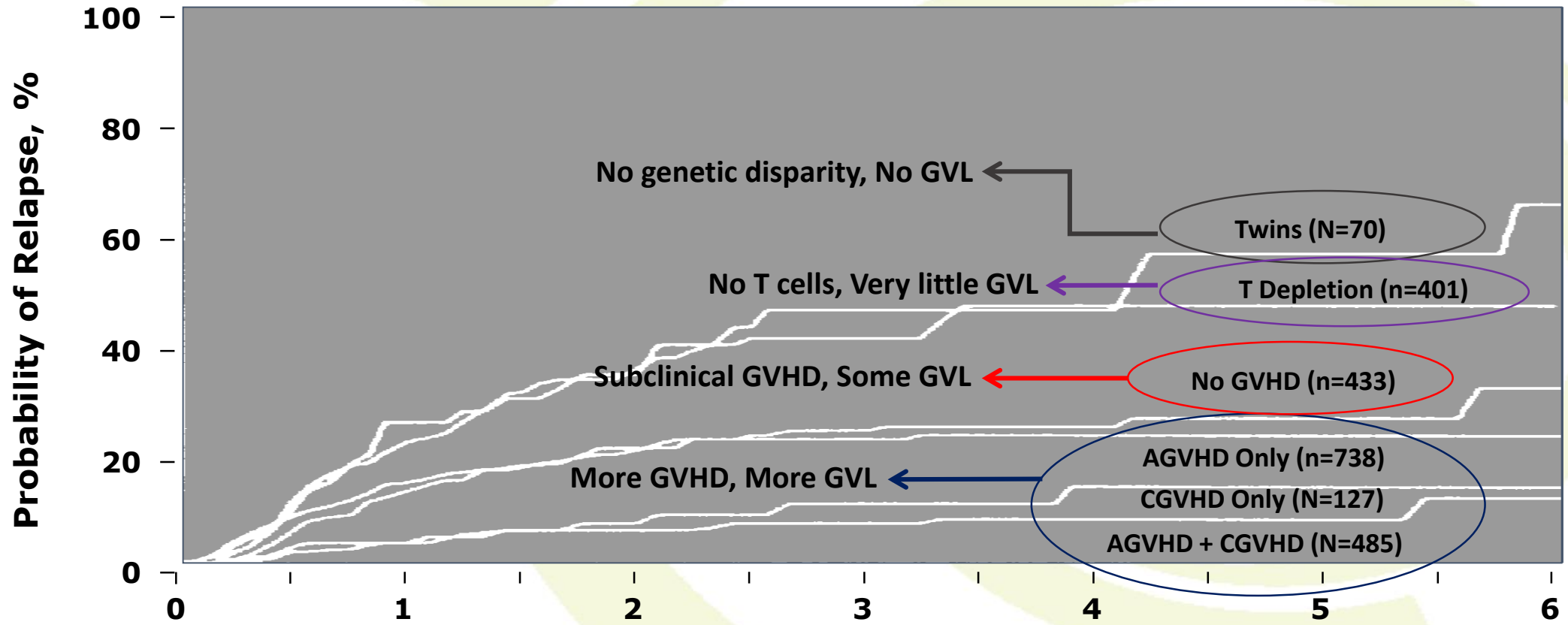
# Graft-versus-Host Disease (GVHD) and Graft-versus-Leukemia (GvL) response

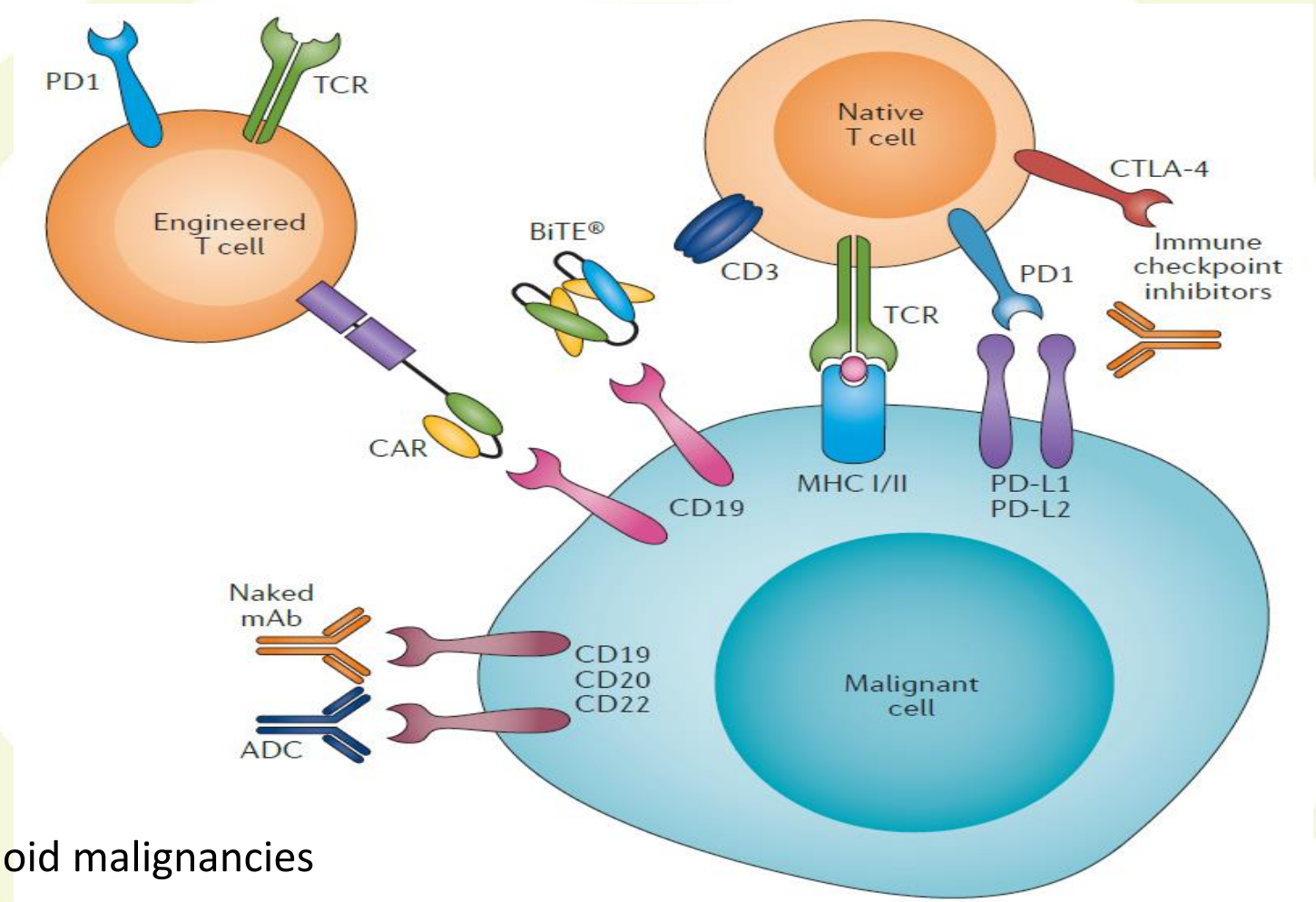



**Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia, Slide Courtesy Wei Du**

Horowitz MM et al Blood 1990

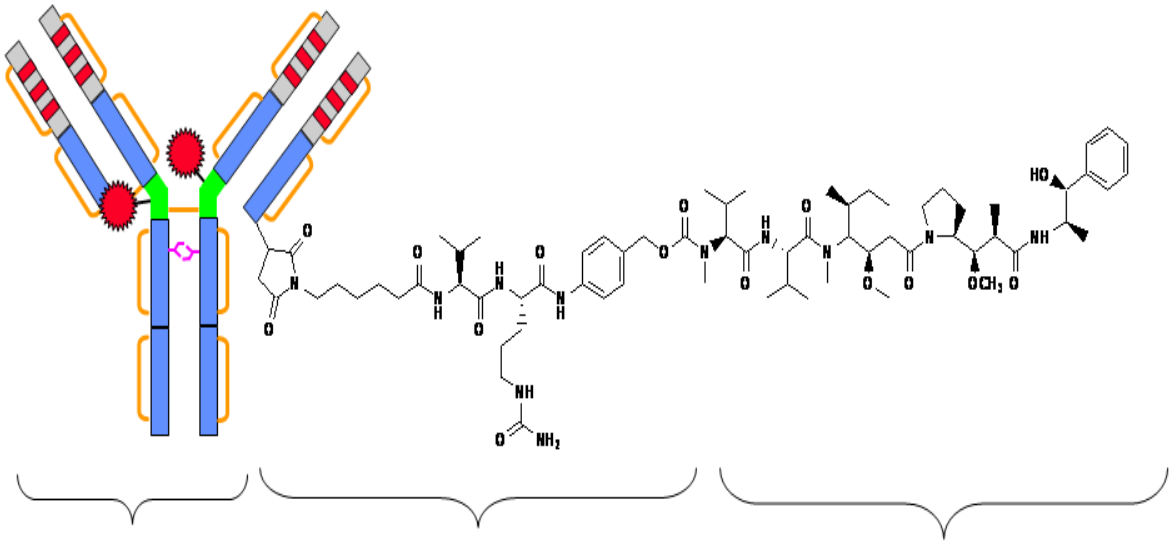
# Mechanisms of Selected Immunotherapies

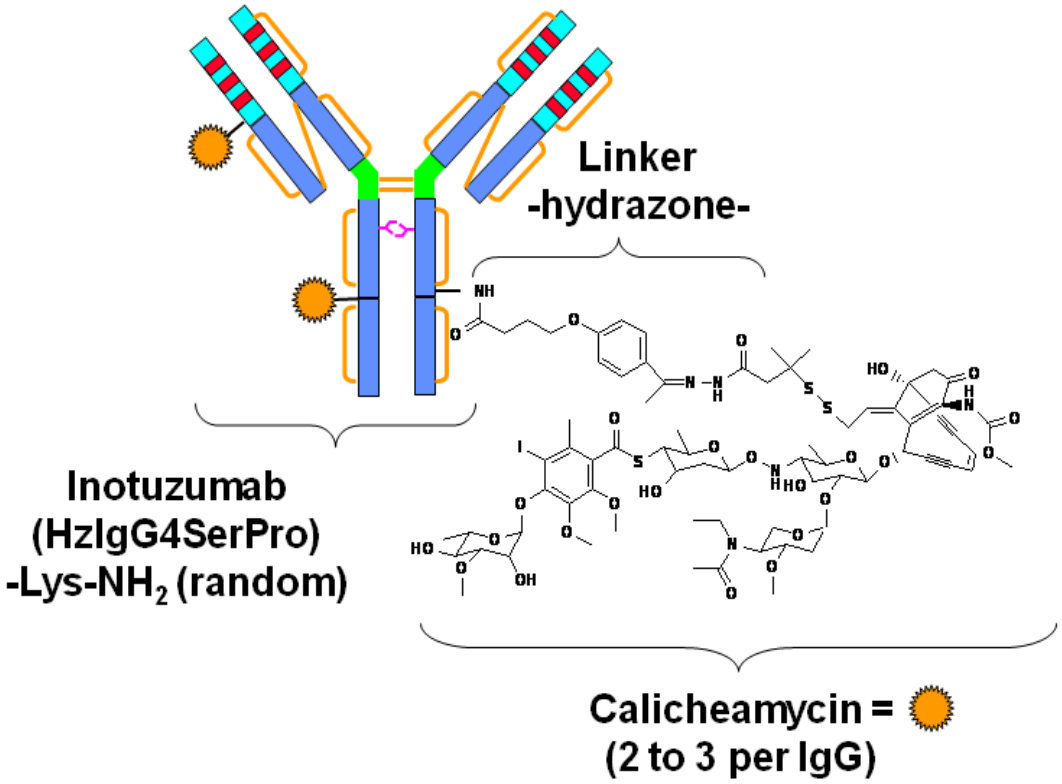
- Checkpoint Inhibitors (PD-1/PD-L1,PD-L2; CTLA-4;Lab-3
- Antibody agonists (CD137;GITR; CD40)
- Bi-specific T cell engagers (BITE) (blinatumumab) or other targets
- Naked antibodies (Rituximab, Herceptin)
- Chimeric Antigen Receptor T cells (Engineered)
- NK cells




Batlevi CL et al Novel immunotherapies in lymphoid malignancies
Nature Rev Clin Oncol January 2016

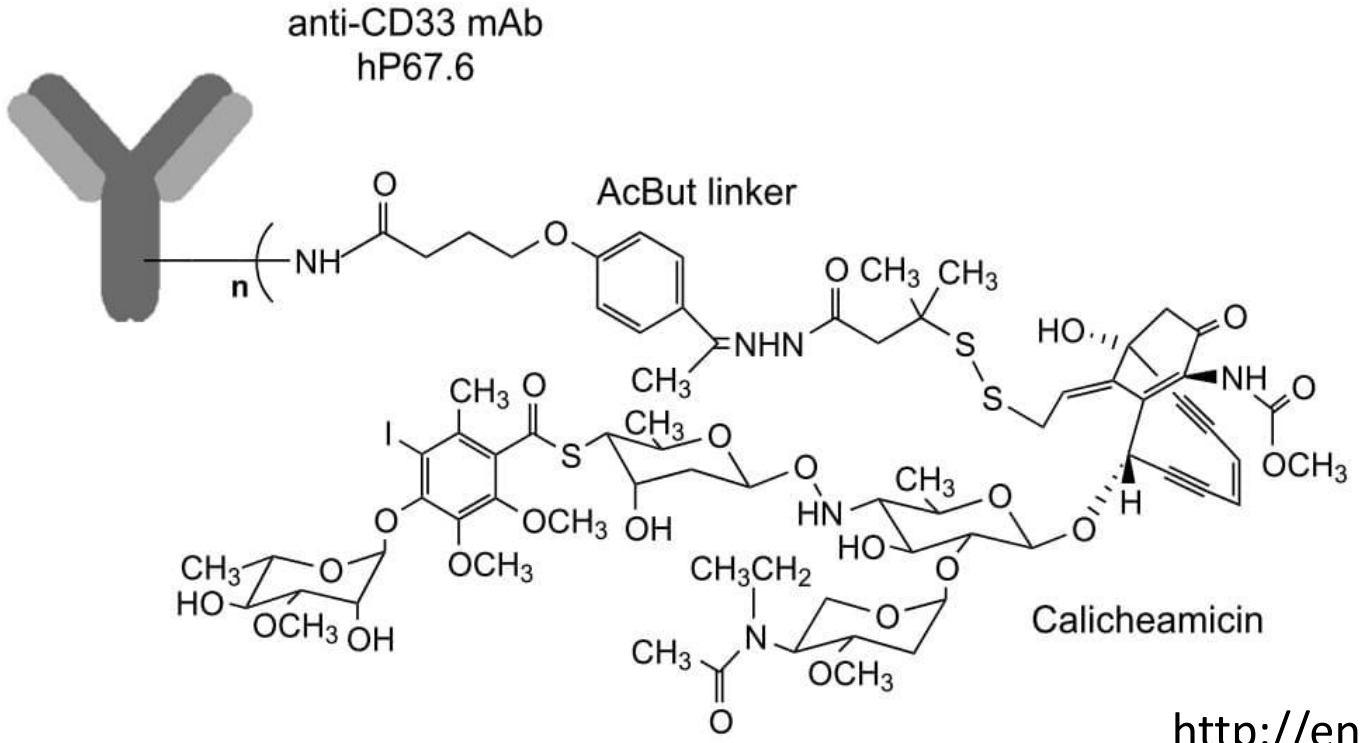
# Monoclonal Antibody Drug Conjugates
# Brentuximab Vedotin and Inotuzumab Ozogamicin

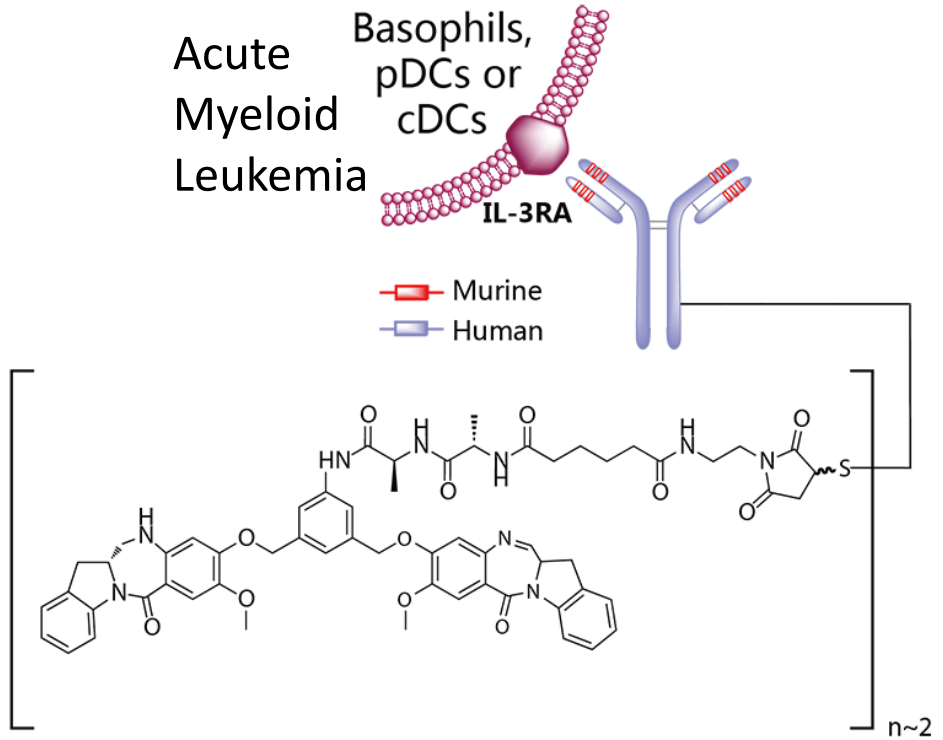



http://www.discoverymedicine.com/Alain-Beck/2010/10/16/the-next-generation-of-antibody-drug-conjugates-comes-of-age/

# Monoclonal Antibody Drug Conjugates Gemtuzomab Ozogamicin and IMGN632




https://www.pfizermedicalinformation.com/en-us/mylotarg/description

http://en.pharmacodia.com/web/basic/query?page=1&text.field=text&text.fieldShowName=KeyWord&text.val=imgn-632&text.valShowName=imgn-632

CD123: The interleukin (IL)-3 receptor α-chain

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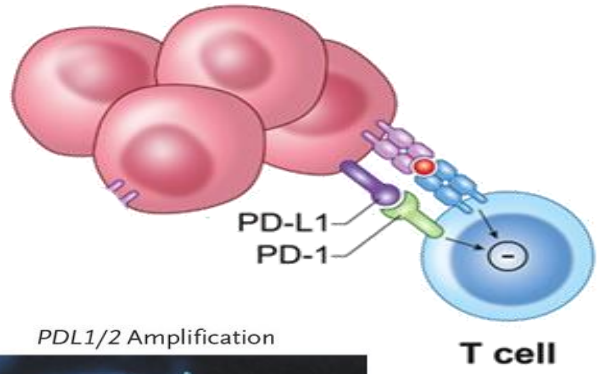
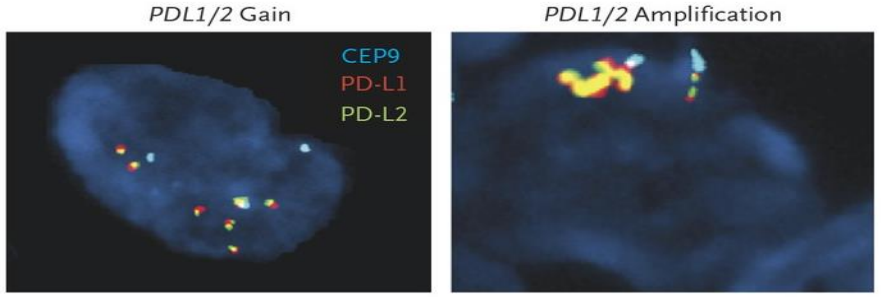
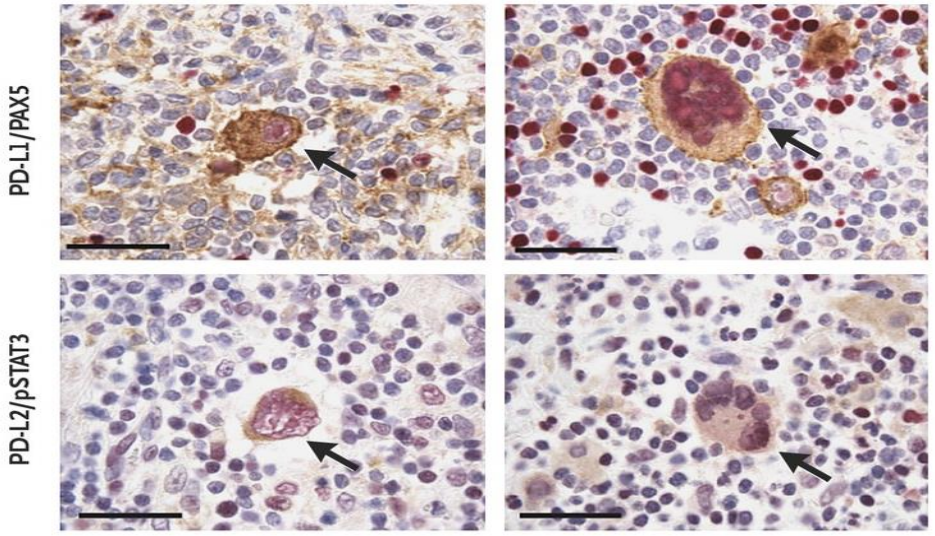
# Checkpoint inhibitors

- Reed-Sternberg cells express both PD-L1 and PD-L2
- Expression of ligands increases with advanced disease
- Unclear whether PD-L1/L2 expression correlates with response to treatment




Ansell SM et al. N Engl J Med 2015;372:311-319



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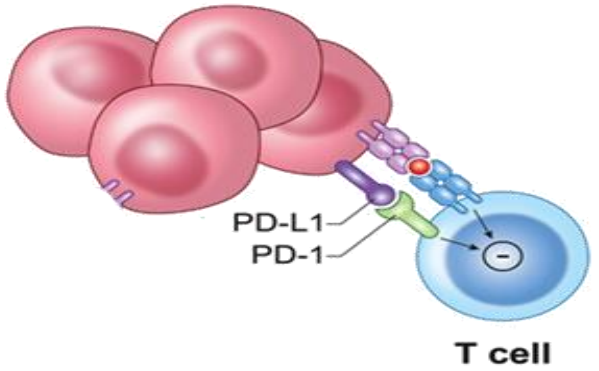


# FDA-approved checkpoint inhibitors for hematologic malignancies

- Nivolumab (anti-PD-1)
  - CheckMate – 205/039: Patients with cHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation and posttransplantation brentuximab vedotin
  - Accelerated approval – May 17th, 2016

- Pembrolizumab (anti-PD-1)
  - KEYNOTE – 087: Adult and pediatric patients with refractory cHL, or patients whose disease has relapsed after three or more lines of therapy
  - Accelerated approval – March 14th, 2017



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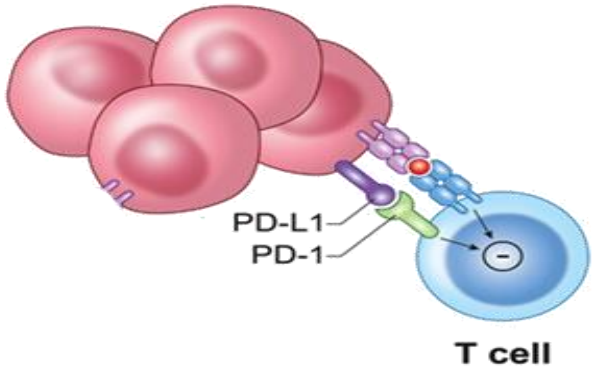
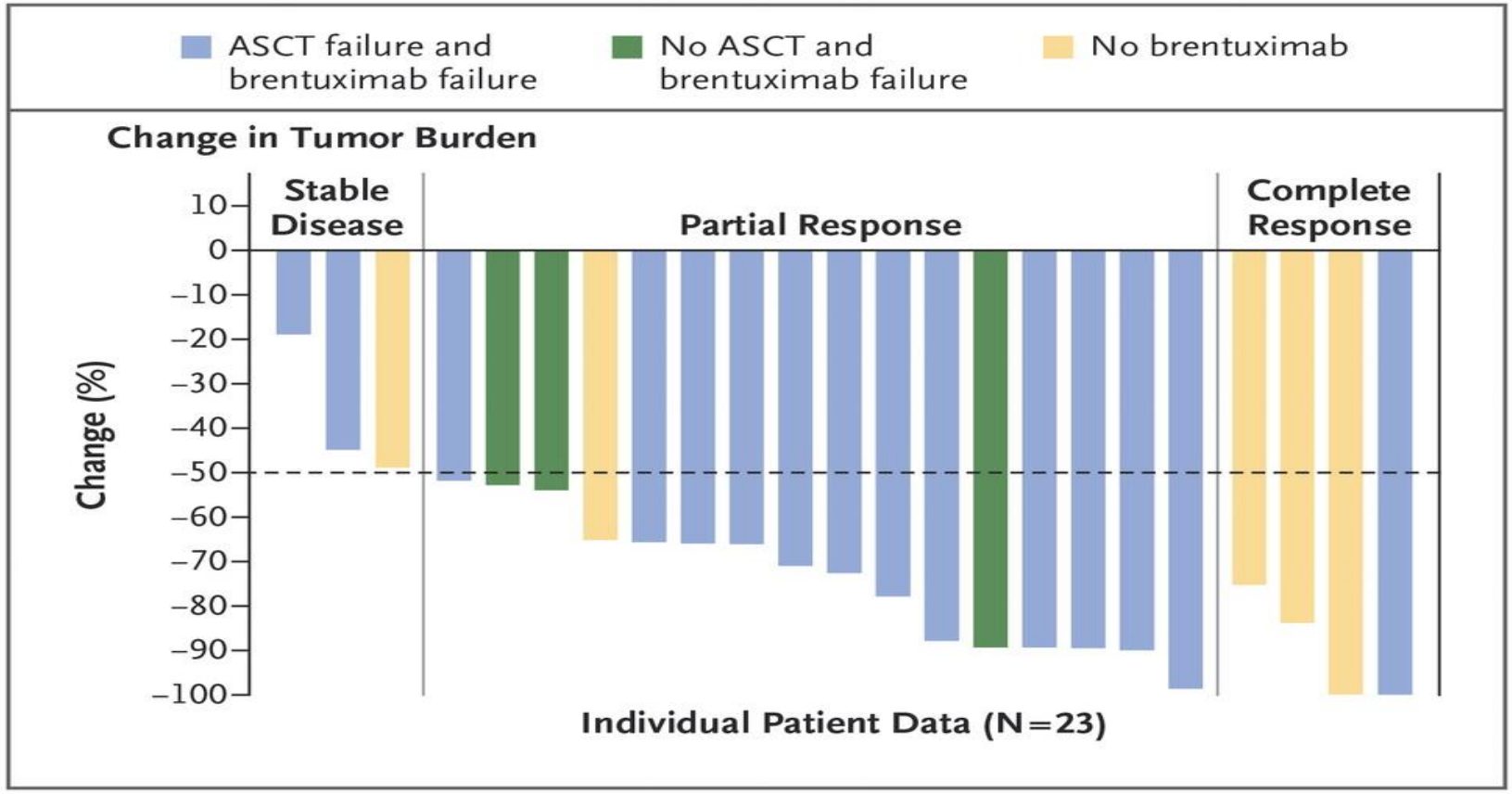



# Nivolumab in Hodgkin lymphoma




Ansell SM et al. N Engl J Med 2015;372:311-319



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# Patient selection criteria for checkpoint inhibitor therapies

- Expression of the ligand for checkpoint inhibition
  - e.g. PD-L1 expression for anti-PD-1 therapy
- Relapse or progression after previous therapies
  - Nivolumab: After prior HSCT and brentuximab therapy
  - Pembrolizumab: Relapse after three prior treatments
- Presence of co-morbidities:
  - e.g. Presence of active autoimmune diseases which could be worsened



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CLINICAL TRIALS AND OBSERVATIONS

# Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma

Alex F. Herrera,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Stephen M. Ansell,[8] Craig H. Moskowitz,[2] Keenan Fenton,[9] Carol Anne Ogden,[9] David Taft,[9] Qu Zhang,[9] Kazunobu Kato,[10] Mary Campbell,[9] and Ranjana H. Advani[11]

[1]City of Hope National Medical Center, Duarte, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Division of Hematology and Oncology, Washington University School of Medicine, St. Louis, MO; [4]University of Nebraska Medical Center, Omaha, NE; [5]Karmanos Cancer Institute, Detroit, MI; [6]Hackensack University Medical Center, Hackensack, NJ; [7]Dana-Farber Cancer Institute, Boston, MA; [8]Mayo Clinic, Rochester, MN; [9]Seattle Genetics, Inc, Bothell, WA; [10]Bristol-Myers Squibb, Princeton, NJ; and [11]Stanford University Medical Center, Palo Alto, CA

**In this phase 1/2 study, brentuximab vedotin (BV) and nivolumab (Nivo) administered in combination were evaluated as initial salvage therapy in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (HL). Patients received up to 4 cycles of combination treatment, with BV administered on day 1 and Nivo on day 8 of the first cycle. For cycles 2 to 4, BV and Nivo were both administered on day 1. After study treatment, responses were evaluated by investigators per the 2014 Lugano classification, and patients could proceed to autologous stem cell transplantation (ASCT). Sixty-two patients were enrolled; the complete response rate among all treated patients (n = 61) was 61%, with an objective response rate of 82%. Before ASCT, adverse events (AEs) occurred in 98% of patients, mostly grades 1 and 2.**

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# Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma

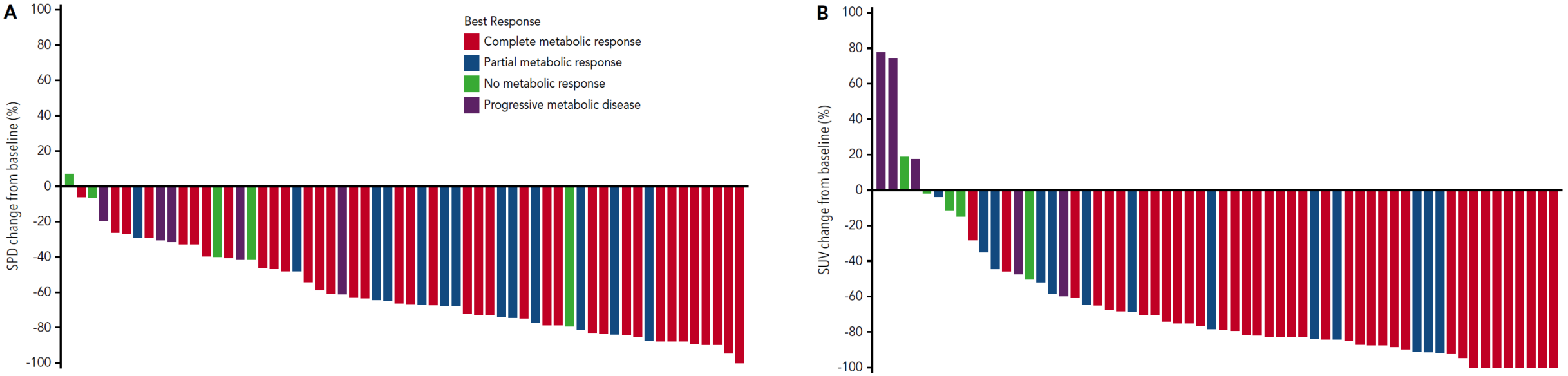


**Figure 1. Percent change in the sum of the product of diameters and maximum percent change in the standard uptake value in efficacy-evaluable patients (n = 60).** (A) Sum of the product of diameters (SPD) percent change and (B) maximum standard uptake value (SUV) percent change are calculated as the percent change from the baseline SPD/SUV to the minimum post-baseline SPD/SUV measured before initiation of subsequent anticancer treatment (chemotherapy or radiotherapy, including conditioning regimen for ASCT).

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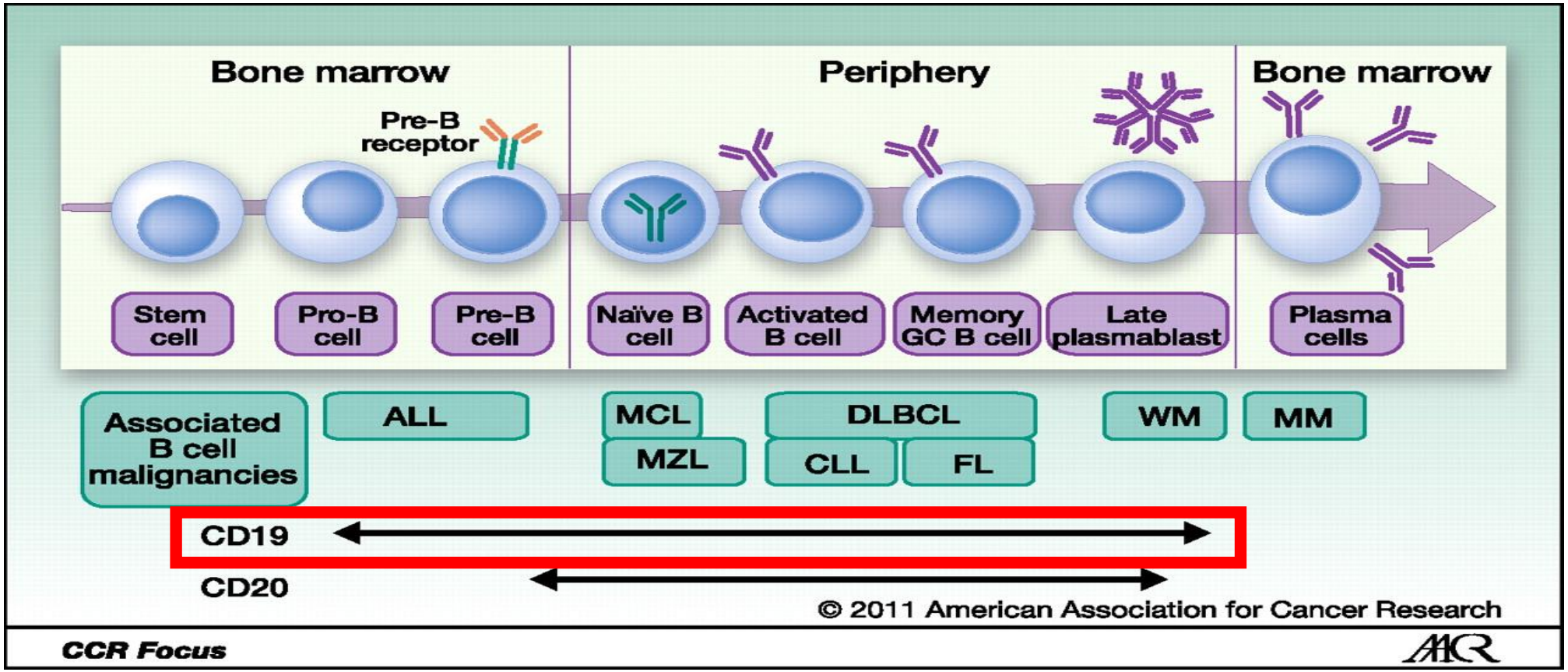
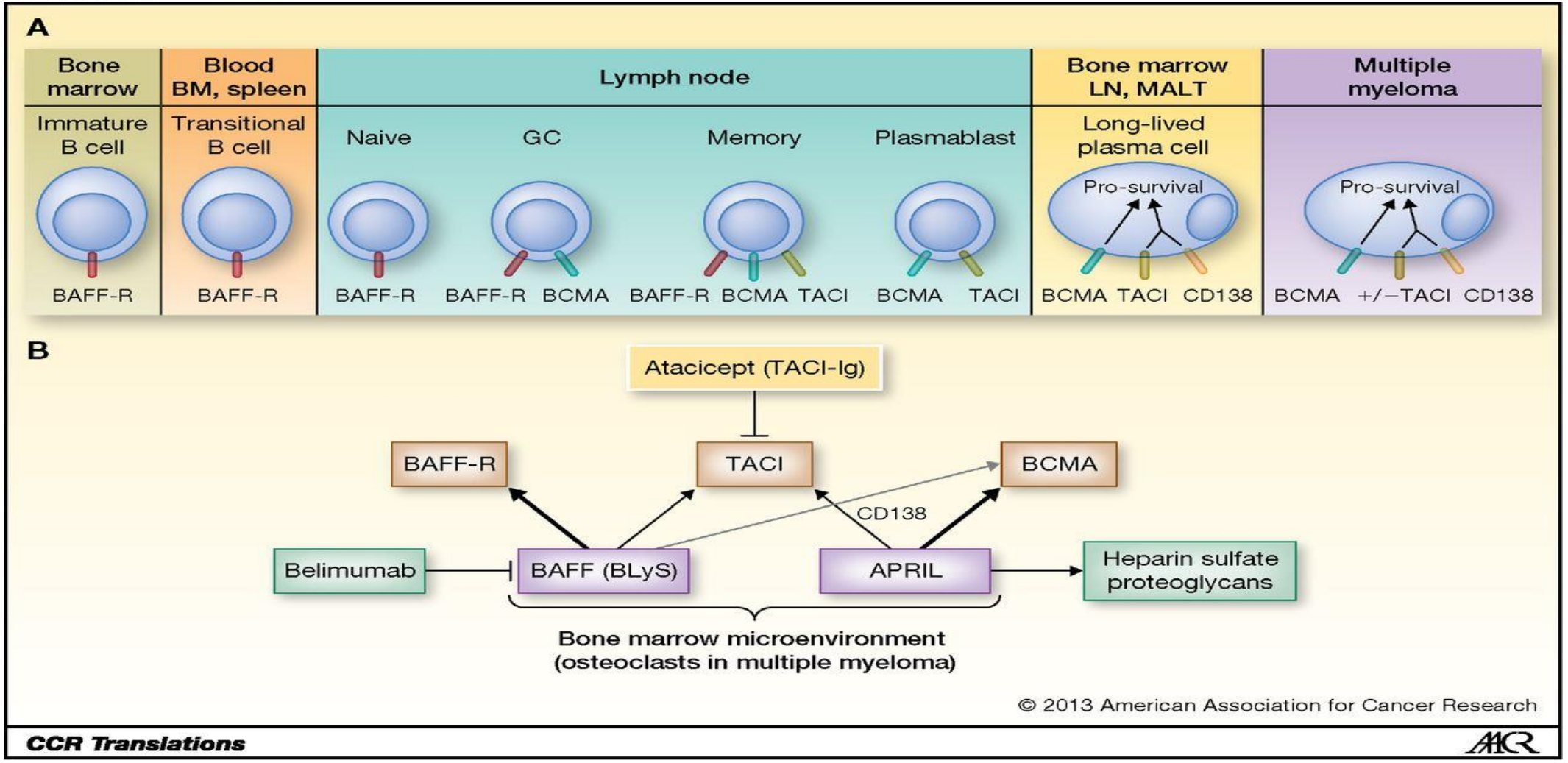
# B cell malignancies are CD19+




Blanc, V et al., Clinical Cancer Research, Volume 17 , Issue 20

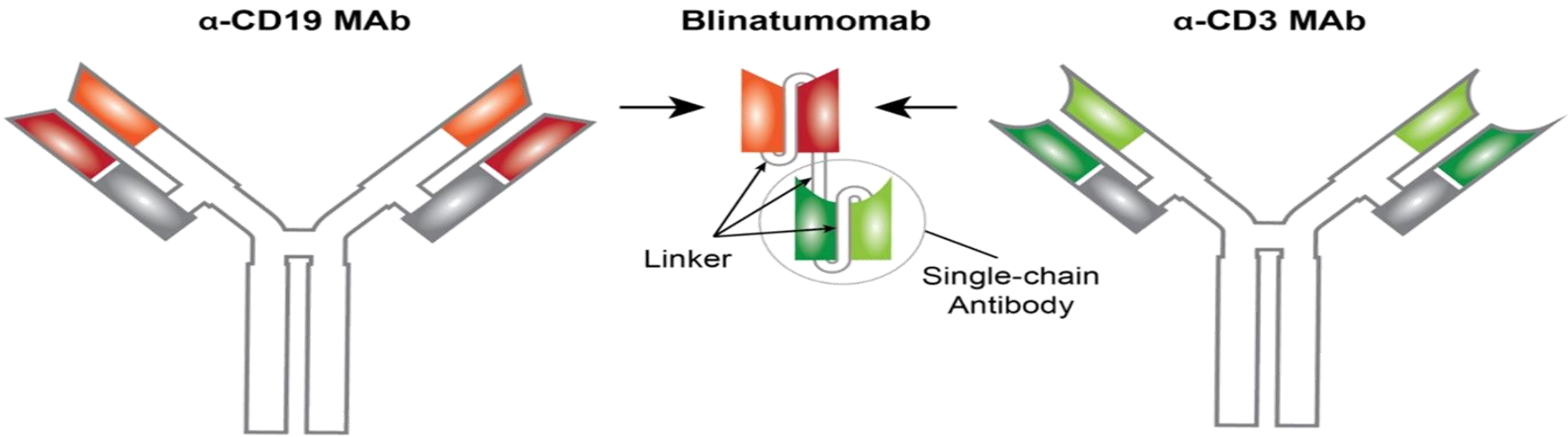
**A: TNF-R family members BAFF-R, TACI, and BCMA during B-cell development**
**B: Ligands and inhibitors of B cell signalling**




Maus MV, June CH. Clin Cancer Res 2013;19:1917. APRIL: proliferation-inducing ligand; BAFF: B-cell activating factor; BCMA: B-cell Maturation Antigen; TACI: transmembrane activator and calcium modulator and cyclophilin ligand interactor

# BiTE (blinatumumab) therapy

- Combines anti-CD19 F(ab) with anti-CD3 F(ab)
- Lacks the Fc region
- TOWER: Patients with relapsed/refractory B-cell precursor ALL
  - FDA Approval: July 11th, 2017



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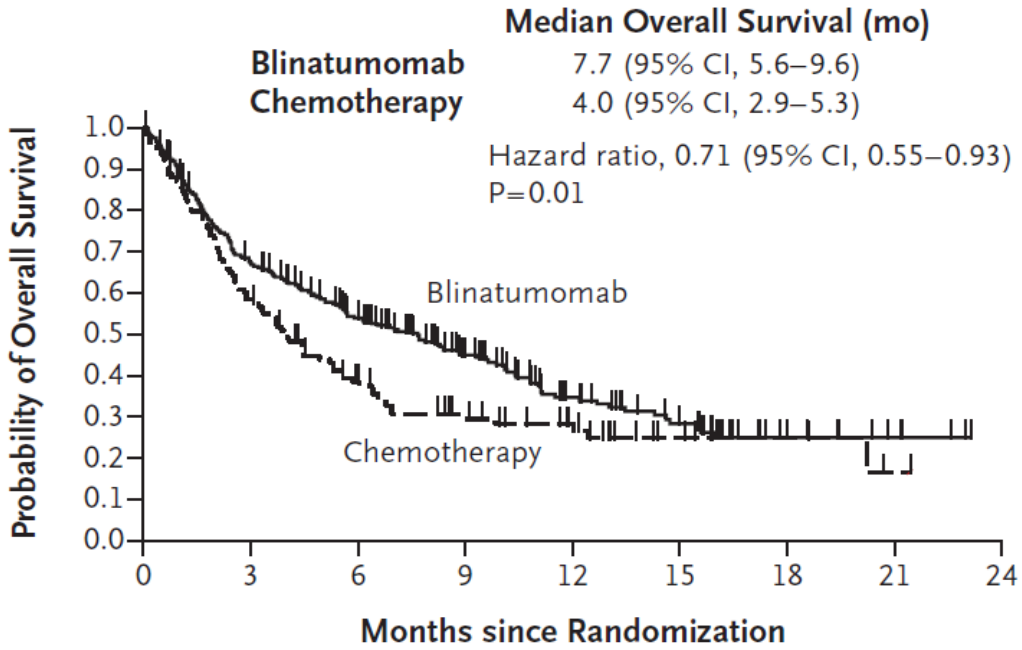
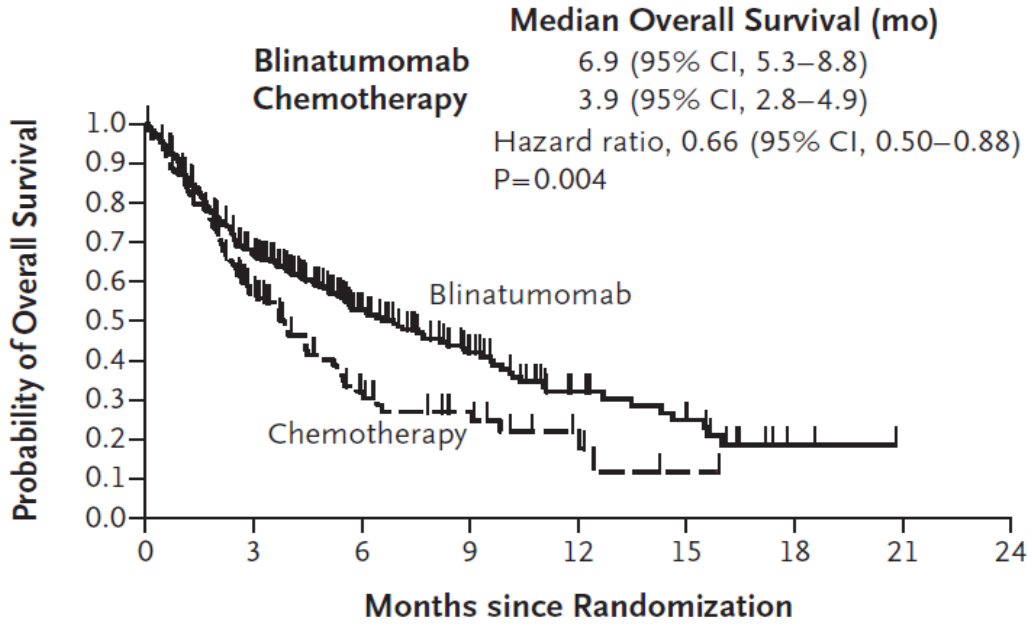
# Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

**A** Overall Survival




| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Blinatumomab | 271 | 176 | 124 | 79 | 45 | 27 | 9 | 4 | 0 |
| Chemotherapy | 134 | 71 | 41 | 27 | 17 | 7 | 4 | 1 | 0 |

**B** Overall Survival Censored at Time of Stem-Cell Transplantation




| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Blinatumomab | 271 | 163 | 80 | 44 | 21 | 13 | 2 | 0 | 0 |
| Chemotherapy | 134 | 56 | 21 | 12 | 5 | 1 | 0 | 0 | 0 |

Kantarjian et al N ENGL J MED 376;9 NEJM.ORG MARCH 2, 2017

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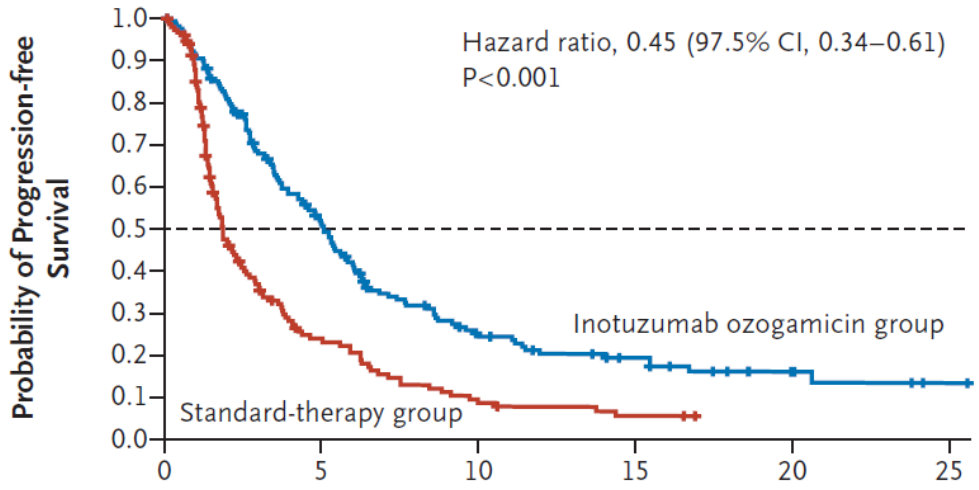
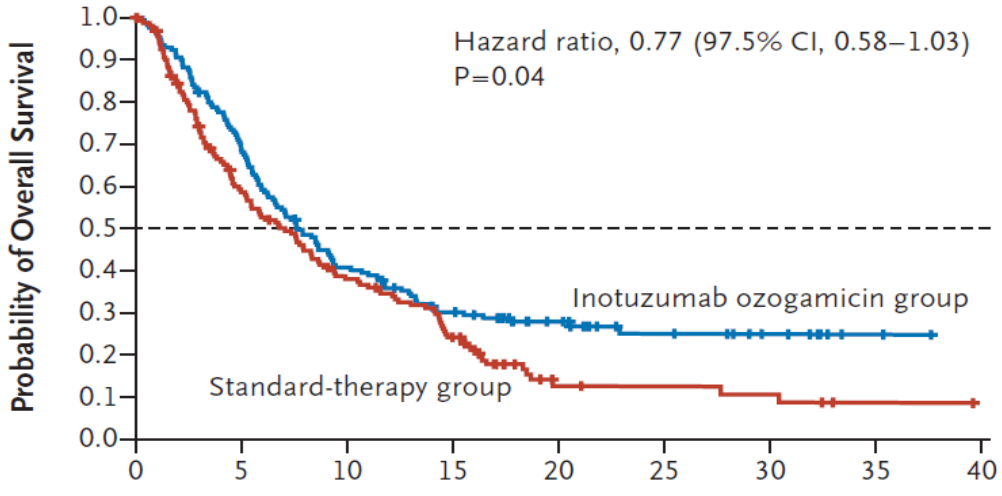
# Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

**B** Progression-free Survival




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Inotuzumab ozogamicin group | 164 | 72 | 28 | 16 | 6 | 1 |
| Standard-therapy group | 162 | 24 | 6 | 2 | 0 | 0 |

**C** Overall Survival




| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Inotuzumab ozogamicin group | 164 | 112 | 62 | 41 | 24 | 13 | 8 | 2 | 0 |
| Standard-therapy group | 162 | 85 | 51 | 30 | 6 | 5 | 4 | 1 | 0 |

Kantarjian et al N ENGL J MED 375;8 NEJM.ORG AUGUST 25, 2016

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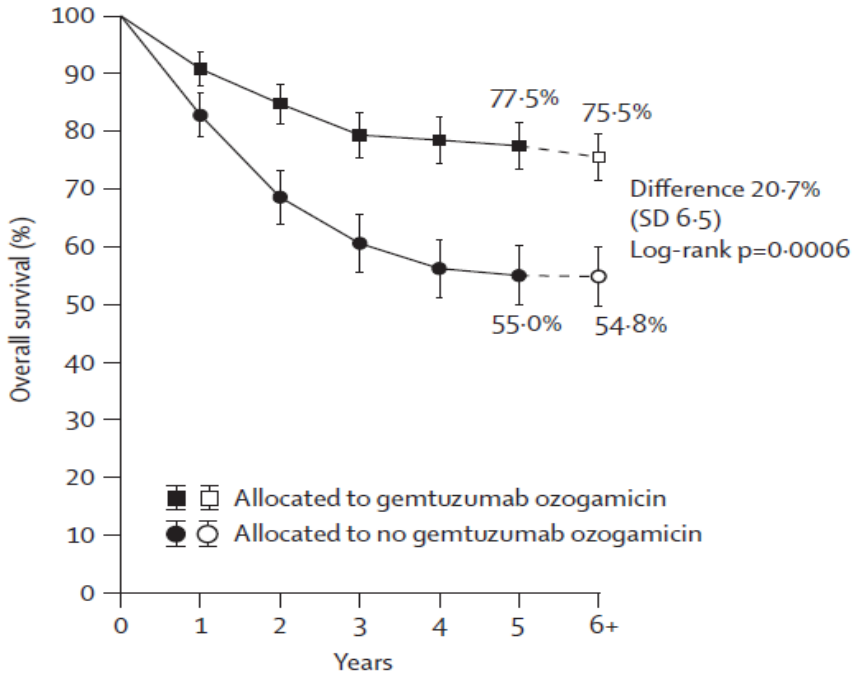
# Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials

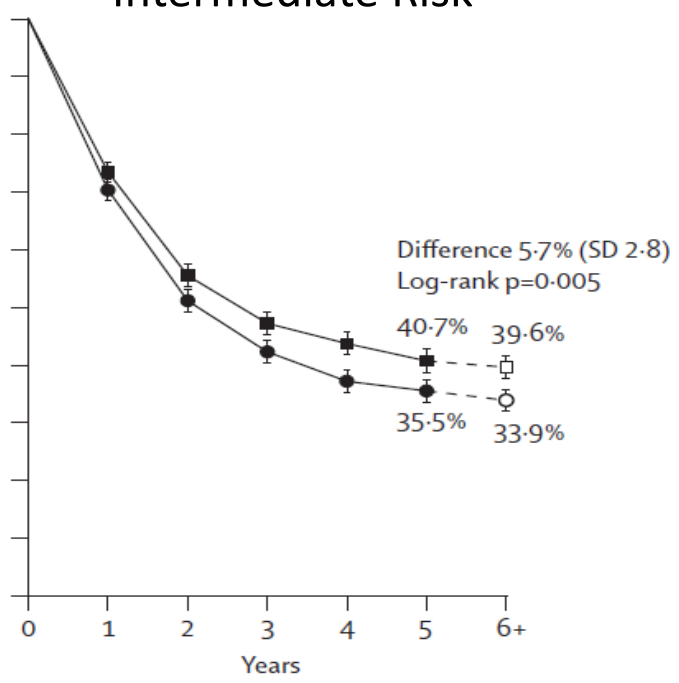
**FDA Re-approved in 2017**

## B Std Risk



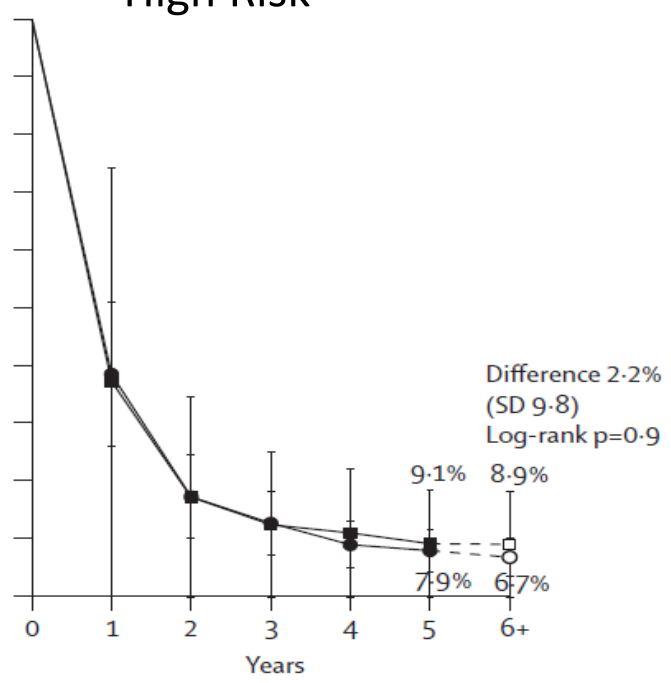

| Annual event rates | Years 1–5 | Years 6+ |
|---|---|---|
| Gemtuzumab ozogamicin | 5·8% SD 1·1 | 2·3% SD 1·3 |
| No gemtuzumab ozogamicin | 14·1% SD 1·9 | 0·0% SD 0·0 |

## C Intermediate Risk




| Annual event rates | Years 1–5 | Years 6+ |
|---|---|---|
| Gemtuzumab ozogamicin | 22·4% SD 1·0 | 2·7% SD 0·9 |
| No gemtuzumab ozogamicin | 26·2% SD 1·1 | 4·9% SD 1·3 |

## D High Risk




| Annual event rates | Years 1–5 | Years 6+ |
|---|---|---|
| Gemtuzumab ozogamicin | 73·8% SD 4·6 | 2·4% SD 2·4 |
| No gemtuzumab ozogamicin | 76·7% SD 4·8 | 21·1% SD 10·5 |

Hills et al www.thelancet.com/oncology Vol 15 August 2014

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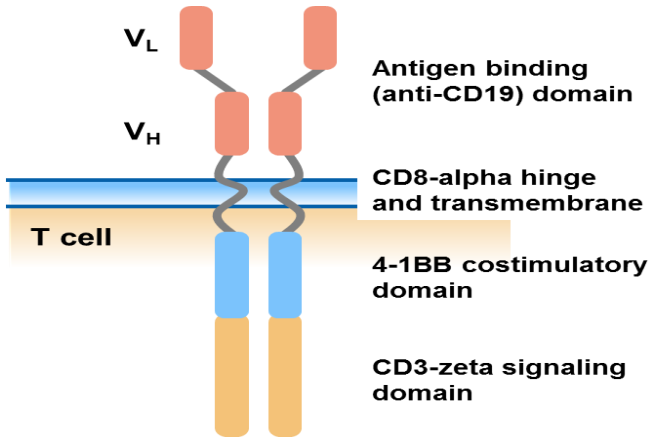
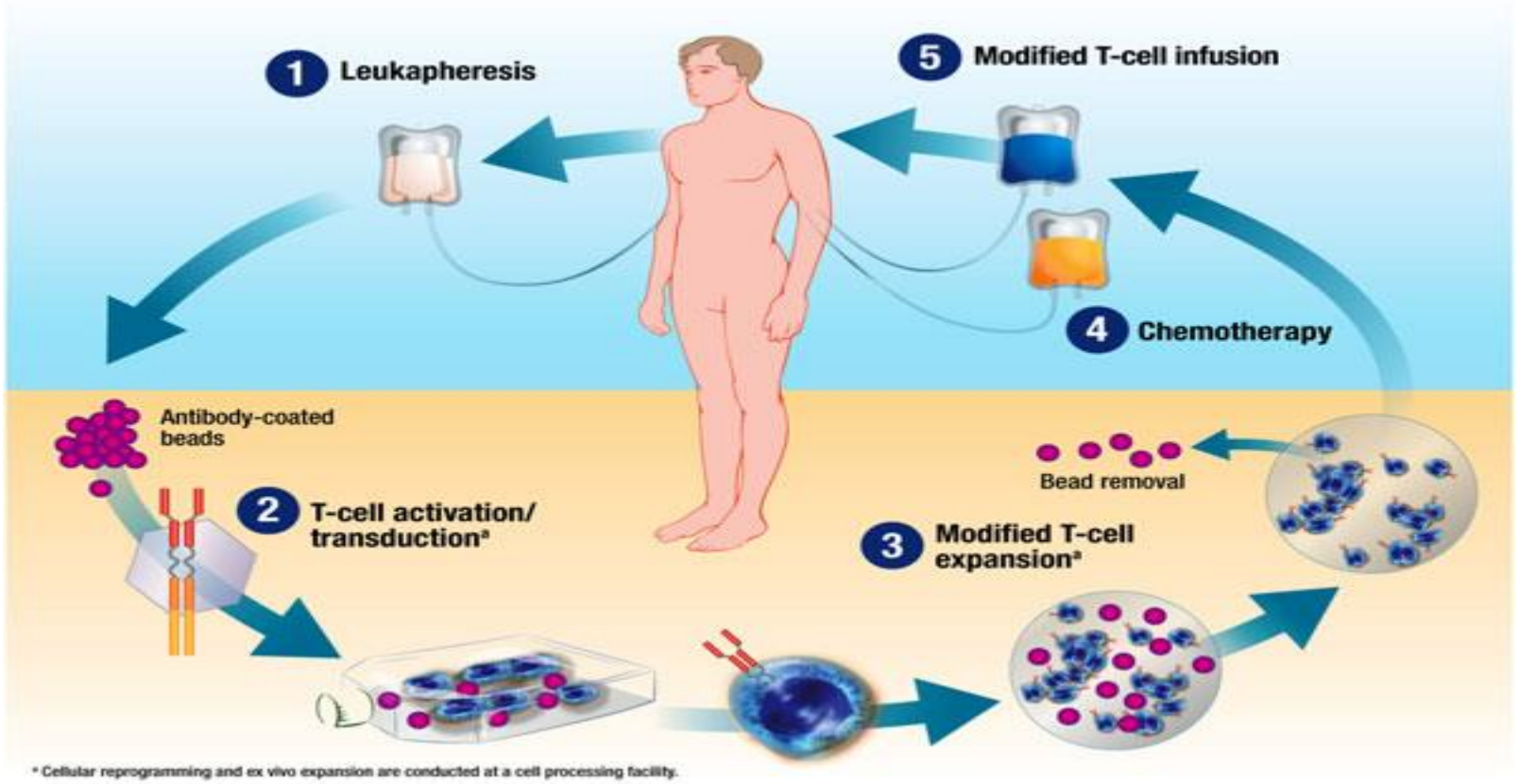
# CAR T cell therapy



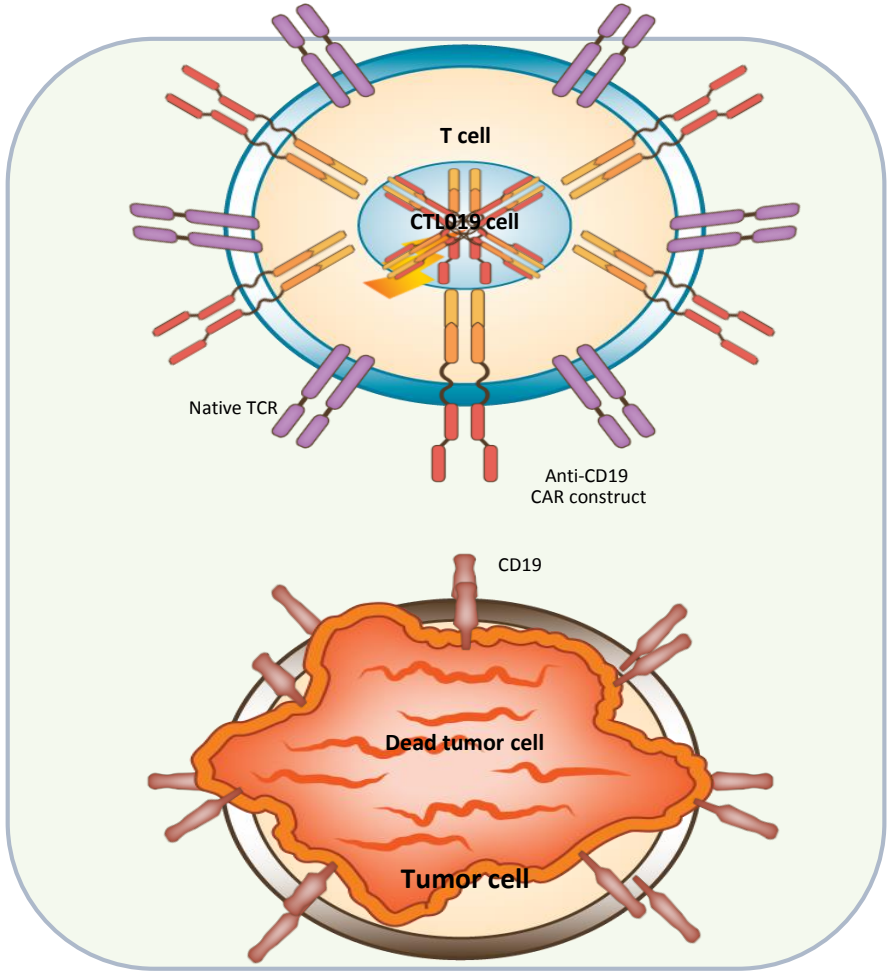

Original Slide Courtesy of D Porter

# Chimeric Antigen Receptor (CAR) T cell therapy

- Gene transfer technology stably expresses CARs on T cells[1,2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3,4]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3,4]
- First human trial in resistant CLL patients[4]
- **T cells are *non-cross resistant* to chemotherapy**


1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.
4. Porter DL et al. *NEJM.* 365:725-33


Original Slide Courtesy of D Porter

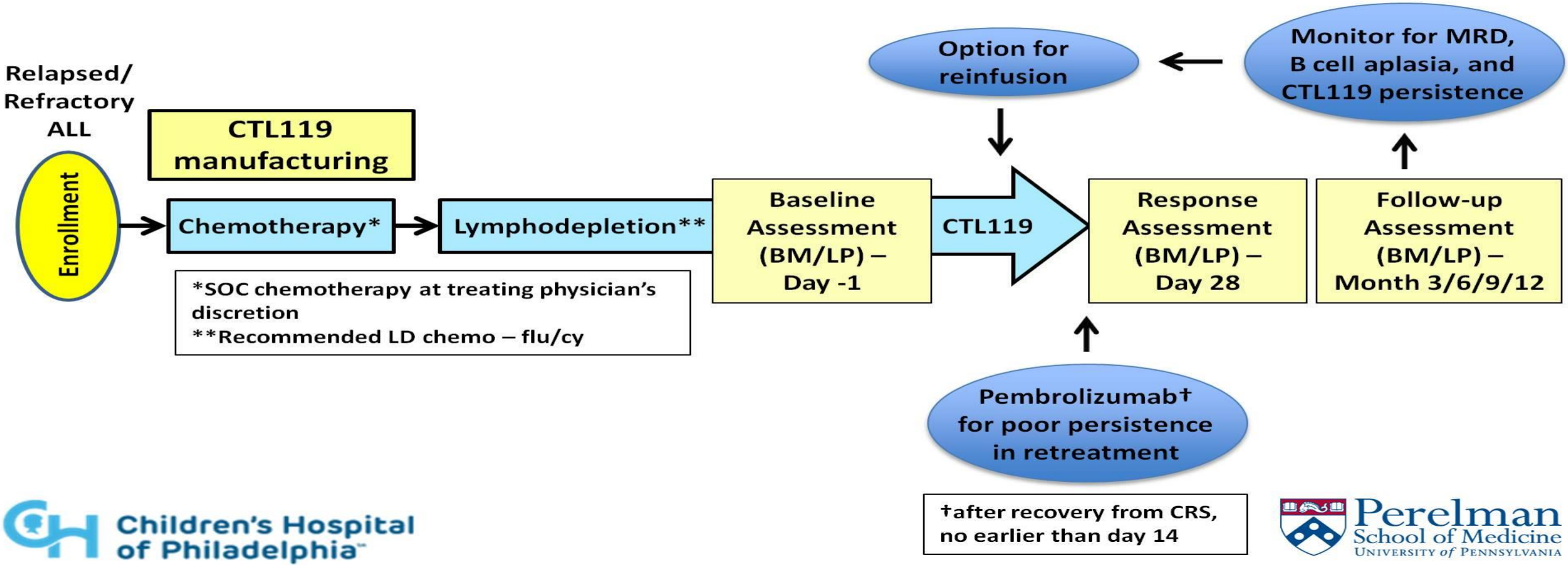


# FDA-approved CAR T cell therapies for hematologic malignancies

- Kymriah (tisagenlecleucel)
  - Patients who are 25 years of age and younger with B-cell precursor ALL that is refractory or in second or later relapse
  - Accelerated approval – August 30th, 2017

- Yescarta (axicabtagene ciloleucel)
  - ZUMA-1: Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
  - Accelerated approval – October 18th, 2017

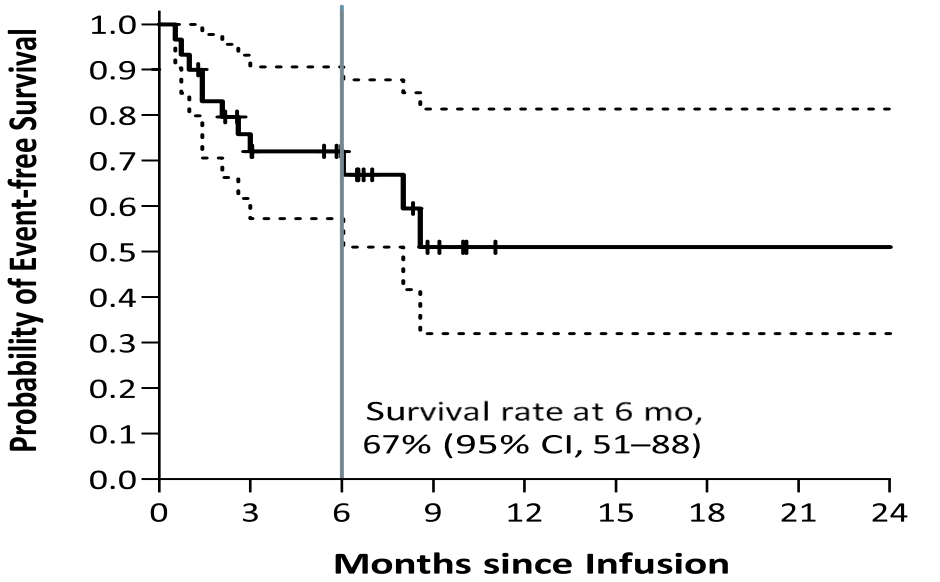
# Humanized CART19 (CTL119) Study Schema – NCT02374333

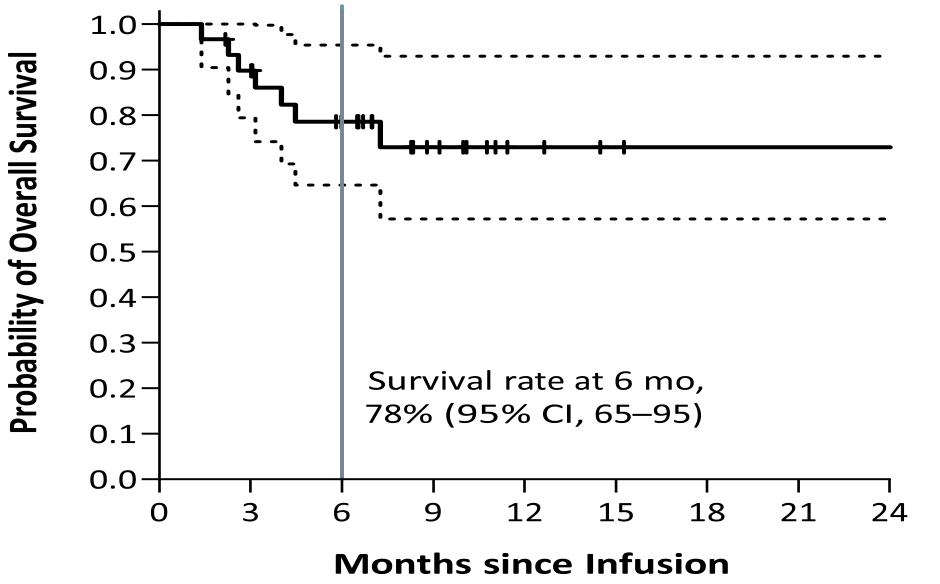



Children's Hospital of Philadelphia

Perelman School of Medicine University of Pennsylvania

# CAR T cell therapy in ALL




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

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# CAR T cell therapy in Diffuse Large B Cell Lymphoma

## *Agent efficacy and safety*

| | Tisagenlecleucel; Kymriah™, CTL019[1] | Axicabtagene Ciloleucel; Yescarta™, KTE-C19[2] | | Lisocabtagene maraleucel, Liso-cel™, JCAR017[3] |
|---|---|---|---|---|
| **Disease state** | r/r DLBCL | r/r DLBCL | r/r TFL/PMBCL | r/r DLBCL/FL3B/MCL |
| **Pts treated, n** | 81 | 77 | 24 | 69/1/5 |
| **Prior ASCT/ ≥3 lines/median Rx lines** | 47%/51%/3 | 21%/64%/NR | 21%/88%/NR | 46%/NR/3 |
| **Follow-up, median** | 5.6 mo | 15.4 mo | | 5.8 mo |
| **Efficacy** | | | | |
| ORR | 53% | 82% | 83% | 75% |
| CR | 39% | 38% | 71% | 56% |
| PR | 14% | 25% | 12% | NR |
| SD, PD, NE | 9% | 14% | 4% | NR |
| **Safety** | | | | |
| CRS | 23% grade ≥3 | 13% grade ≥3 | | 30% Any CRS ;1% grade 4 |
| Neurologic Events | 12% grade ≥3 | 28% grade ≥3 | | 20% grade 1/2; 10% grade 3/4 |

ASCT, Autologous stem cell transplant; CR, complete response; CRS, cytokine release syndrome; NE, Not evaluable; NR, not reported; ORR, overall response rate; PR, partial response; SD, stable disease

1. Schuster, SJ, et al. ASH 2017, abstract 577;. 2. Neelapu et al NEJM 2017; 3. Abramson JS, et al ASH 2017 abstract 581.

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# Patient selection criteria for CAR T Cell therapies

- Expression of the desired antigen for CAR T therapy
  - e.g. CD19 or CD22 expression
- Disease burden
  - CAR T trials: <30% to minimize the risk of cytokine release syndrome
- Presence of co-morbidities
  - e.g.  Presence of active autoimmune diseases which could be worsened



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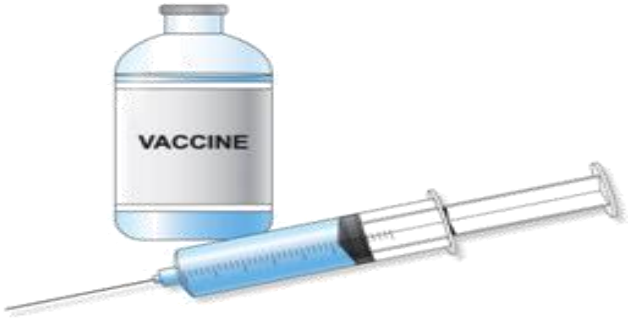
# Immunotherapies for Multiple Myeloma




- No approved checkpoint inhibitor therapies
  - KEYNOTE-183/185/023: discontinued due to risk/benefit profile

- Vaccine-based approaches
  - Non-Antigen Specific
    - Attenuated measles
    - Whole cell - GM-CSF
    - Dendritic – tumor fusions
    - (Blood and Marrow Transplant
    - Clinical Trials Network; BMT-CTN) 1401 Dendritic Cell Vaccine
  - Antigen Specific
    - Idiotype: RNA, DNA, protein
    - Pulsed dendritic cells
    - Tumor-specific peptides

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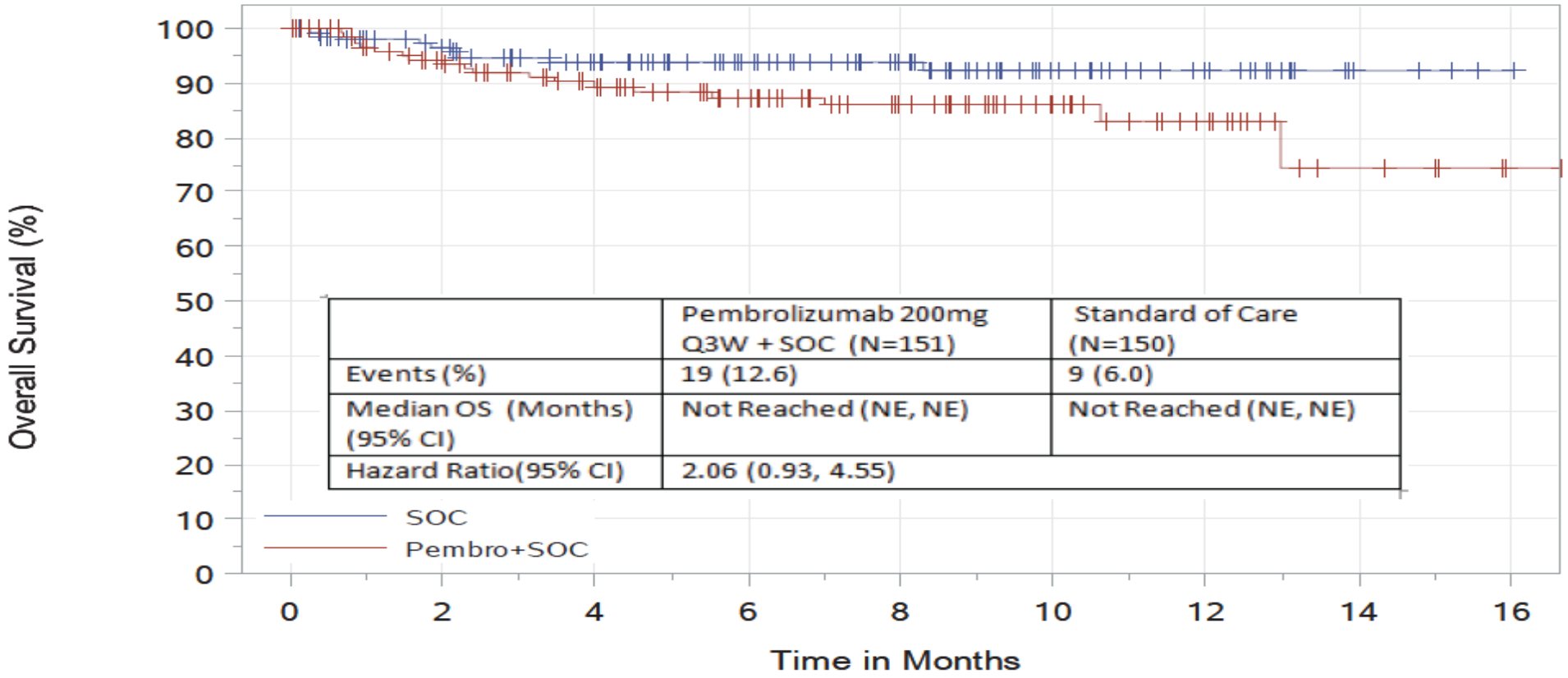
# Keynote 185: Phase 3, randomized, controlled trial of lenalidomide and low-dose dexamethasone +/- pembrolizumab in newly diagnosed multiple myeloma patients

- Data cutoff date: June 2, 2017 for safety & efficacy analysis of 301 randomized Transplant-ineligible NDMM patients
- Median follow-up 6.6 months
- OS: 19 deaths on the pembro/len/dex arm & 9 deaths on len dex arm, HR: 2.06 (95% CI: 0.93, 4.55), >2x RR of death compared to the control arm
- 22% increase of severe, grade 3-5 toxicity (72% vs. 50%, pembro/len/dex vs len/dex) & serious adverse events: 54% vs 39 %
- Non-disease progression causes of death in the pembro/len/dex arm: intestinal ischemia, cardio-respiratory arrest, suicide, pulmonary embolism, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure.
- https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm

# Keynote 185

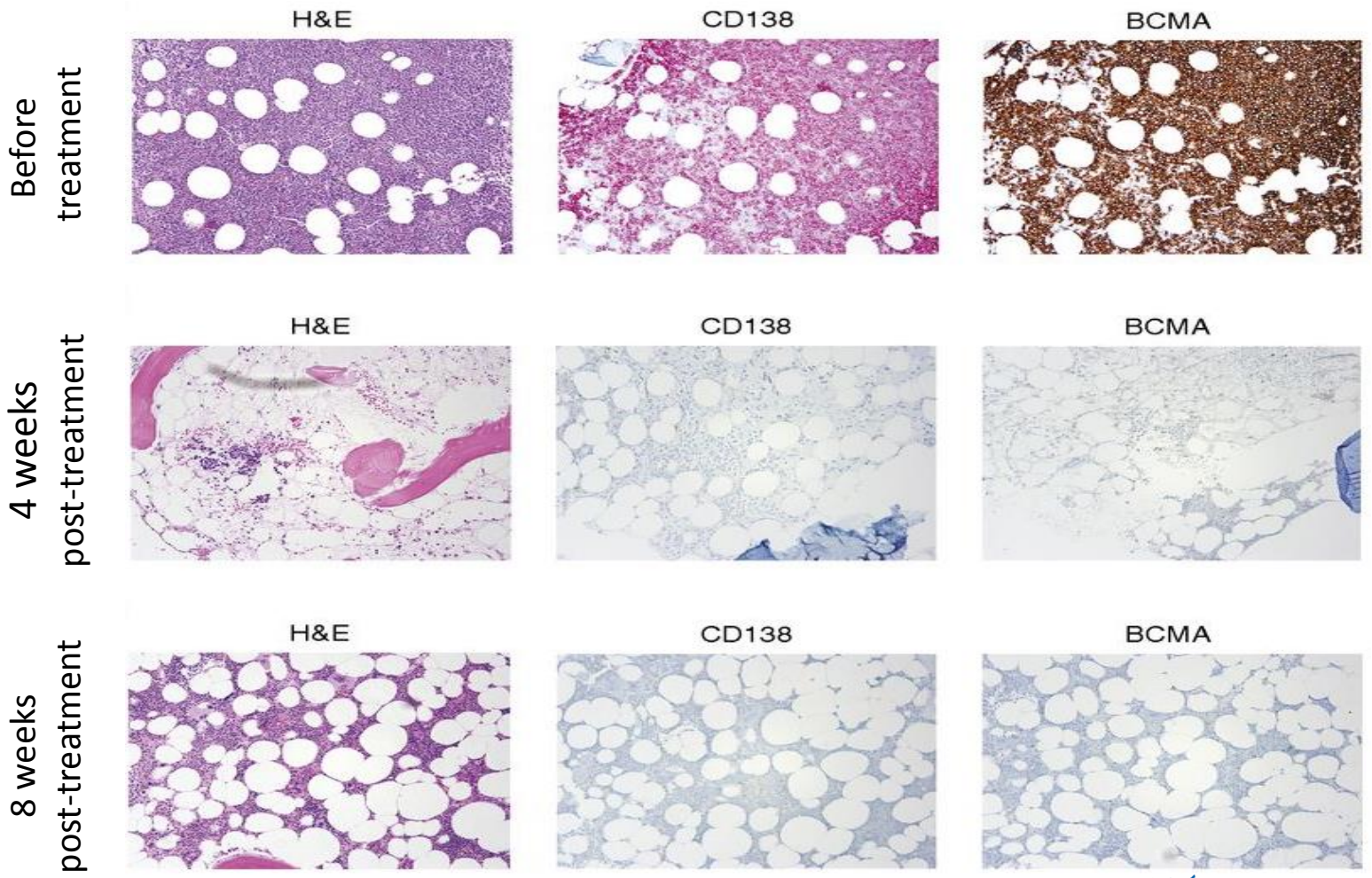



| | Pembrolizumab 200mg Q3W + SOC (N=151) | Standard of Care (N=150) |
|---|---|---|
| Events (%) | 19 (12.6) | 9 (6.0) |
| Median OS (Months) (95% CI) | Not Reached (NE, NE) | Not Reached (NE, NE) |
| Hazard Ratio(95% CI) | 2.06 (0.93, 4.55) | |

**Number of Subjects at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SOC | 150 | 124 | 102 | 82 | 56 | 31 | 19 | 5 | 1 |
| Pembro+SOC | 151 | 122 | 100 | 79 | 58 | 32 | 20 | 7 | 2 |

# BCMA+ CAR T therapy For Multiple Myeloma




Fan et al. LBA3001 ASCO 2017

- 100% ORR
- 33/35 patients in remission within 2 months after BCMA CAR T therapy

Berdeja et al ASH 2017 Abs 740

- 85% ORR

- November 17th, 2017

FDA Breakthrough Designation

Syed Abbas Ali et al. Blood 2016;128:1688-1700

http://www.cellectis.com/sites/default/files/cellectis_therapeutics_150414.pdf

# Lead Product Candidate: UCART19 intended for ALL and CLL

## Cell Development Process:

1. Start from healthy, unmodified donor T-Cells

**Insert a marker for tracking (CD34)**

2. Insertion of single-chain CAR construct and suicide gene

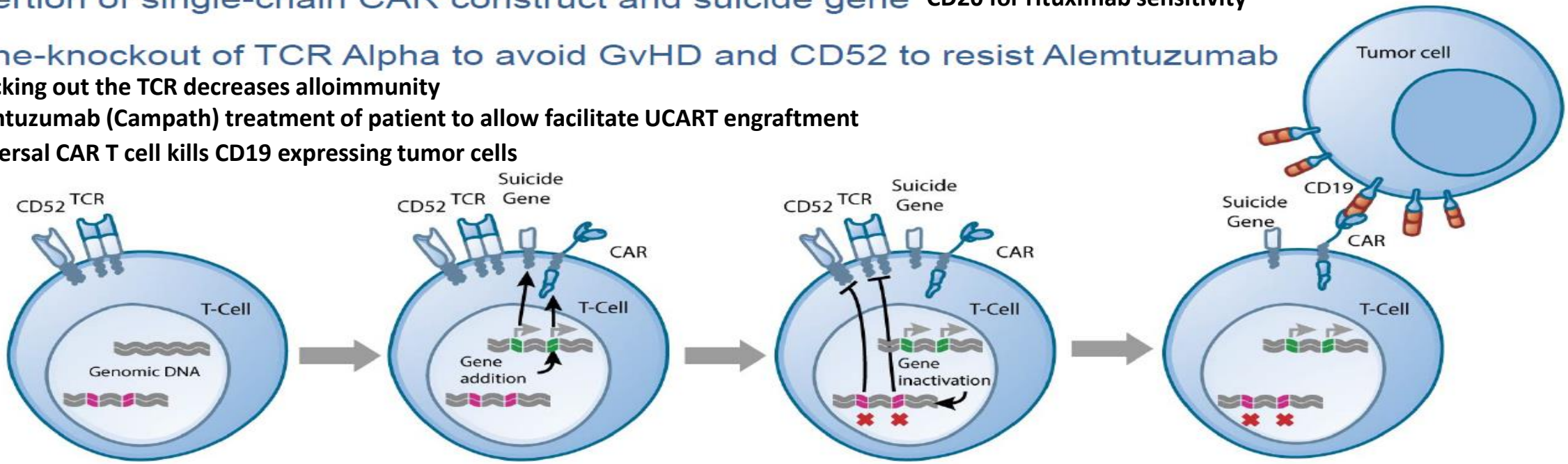
**CD20 for rituximab sensitivity**

3. Gene-knockout of TCR Alpha to avoid GvHD and CD52 to resist Alemtuzumab

**Knocking out the TCR decreases alloimmunity**

**Alemtuzumab (Campath) treatment of patient to allow facilitate UCART engraftment**

**Universal CAR T cell kills CD19 expressing tumor cells**




| Normal T-cell | Gene Insertion | Gene Knockout (KO) | UCART19 |
|---|---|---|---|
| Normal unmodified T-cell from a healthy donor. | We first insert a CAR and a suicide gene. | We then inactivate the TCR and CD52 genes. | UCART19 is the fully modified CART-cell |

Qasim W et al. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. Sci Transl Med. 2017 Jan 25;9(374). pii: eaaj2013.

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# Further resources

Boyiadzis *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:90
DOI 10.1186/s40425-016-0188-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

## The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia

Michael Boyiadzis[1†], Michael R. Bishop[2†], Rafat Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borrello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12], Adam Cohen[15], Jorge Cortes[16], Stephen J. Forman[17], Jonathan W. Friedberg[18], Ephraim J. Fuchs[19], Steven D. Gore[20], Sundar Jagannath[12], Brad S. Kahl[21], Justin Kline[22], James N. Kochenderfer[23], Larry W. Kwak[24], Ronald Levy[25], Marcos de Lima[26], Mark R. Litzow[27], Anuj Mahindra[28], Jeffrey Miller[29], Nikhil C. Munshi[30], Robert Z. Orlowski[31], John M. Pagel[32], David L. Porter[33], Stephen J. Russell[5], Karl Schwartz[34], Margaret A. Shipp[35], David Siegel[36], Richard M. Stone[4], Martin S. Tallman[37], John M. Timmerman[38], Frits Van Rhee[39], Edmund K. Waller[40], Ann Welsh[41], Michael Werner[42], Peter H. Wiernik[43] and Madhav V. Dhodapkar[44*]

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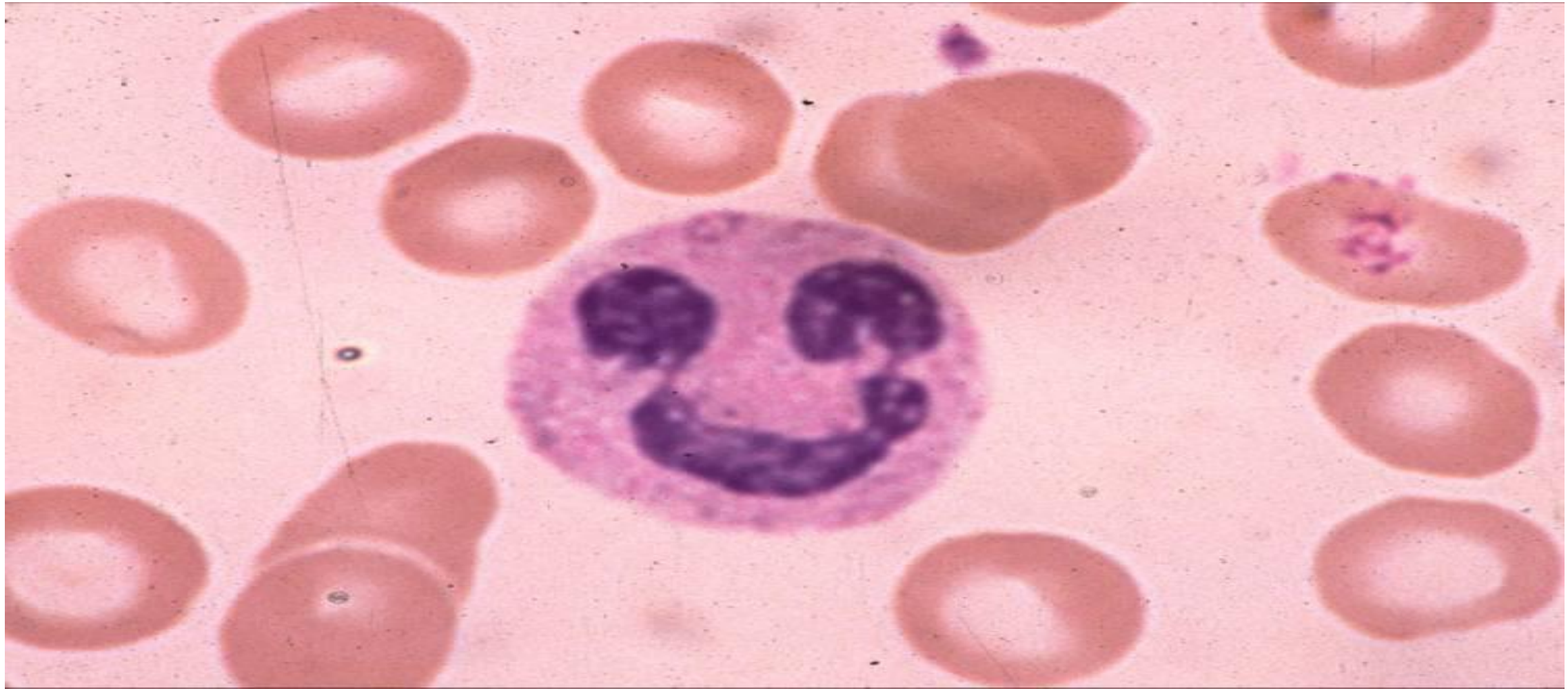
# Thank you very much



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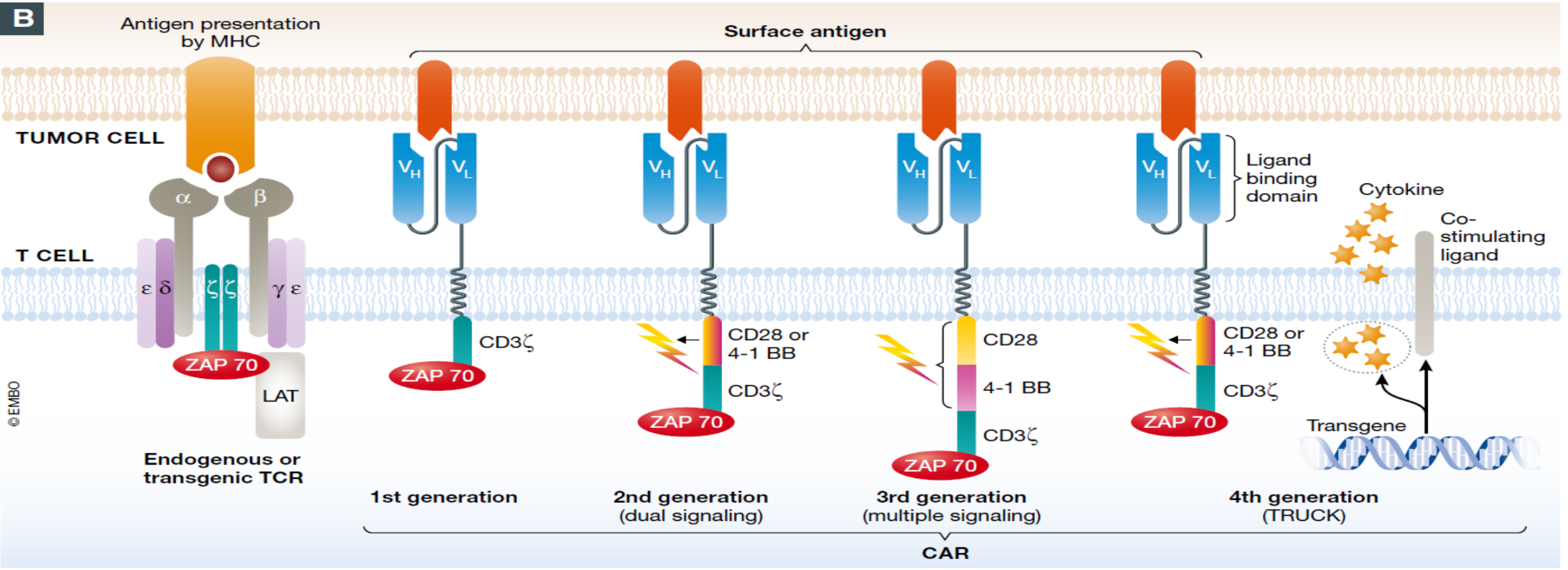
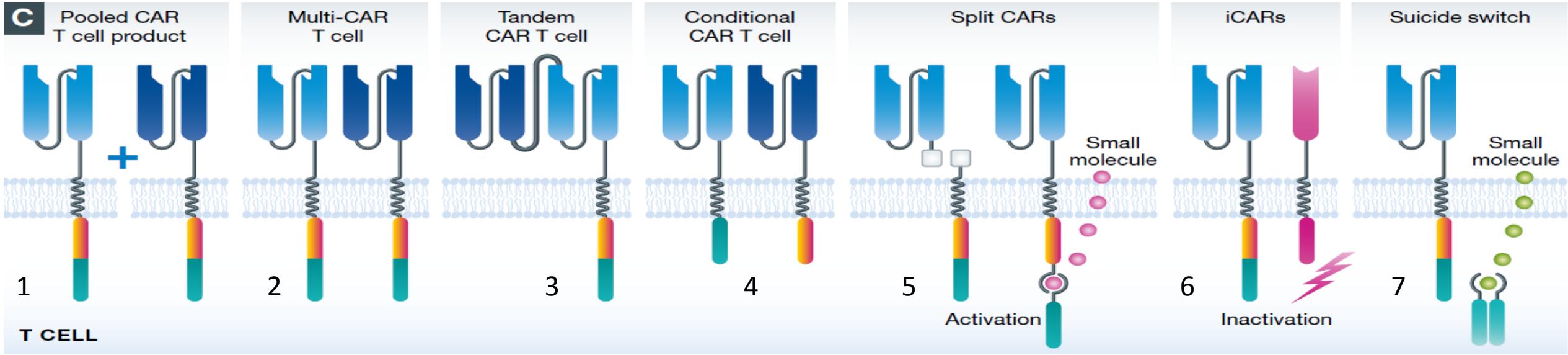
# TCR and 4 types of CARs




Hartmann J et al EMBO Molecular Medicine 2017

# Overview of “smart” CAR T cells




1) Pooled CAR T cell products: 2 or more single-targeting CAR T cell types with distinct antigen specificities.
2) Multi-CAR T cells harbor several CAR molecules with different antigen specificities.
3) Tandem CAR T cell expresses a CAR construct harboring 2 ligand-binding domains with different antigen specificities.
4) Conditional CAR T cell activation and co-stimulation are separated on two CAR constructs recognizing different target antigens.
5) Split CAR construct the ligand-binding or signaling domain is physically separated allowing controlled CAR T cell activation.
6) iCAR T cells additionally express a receptor engineered to recognize an antigen expressed on normal tissue to provide an inhibitory signal in turn.
7) CAR T cells can be equipped with suicide genes or switches (e.g., iCasp9) allowing ablation of CAR T cells.

Hartmann J et al EMBO Molecular Medicine 2017

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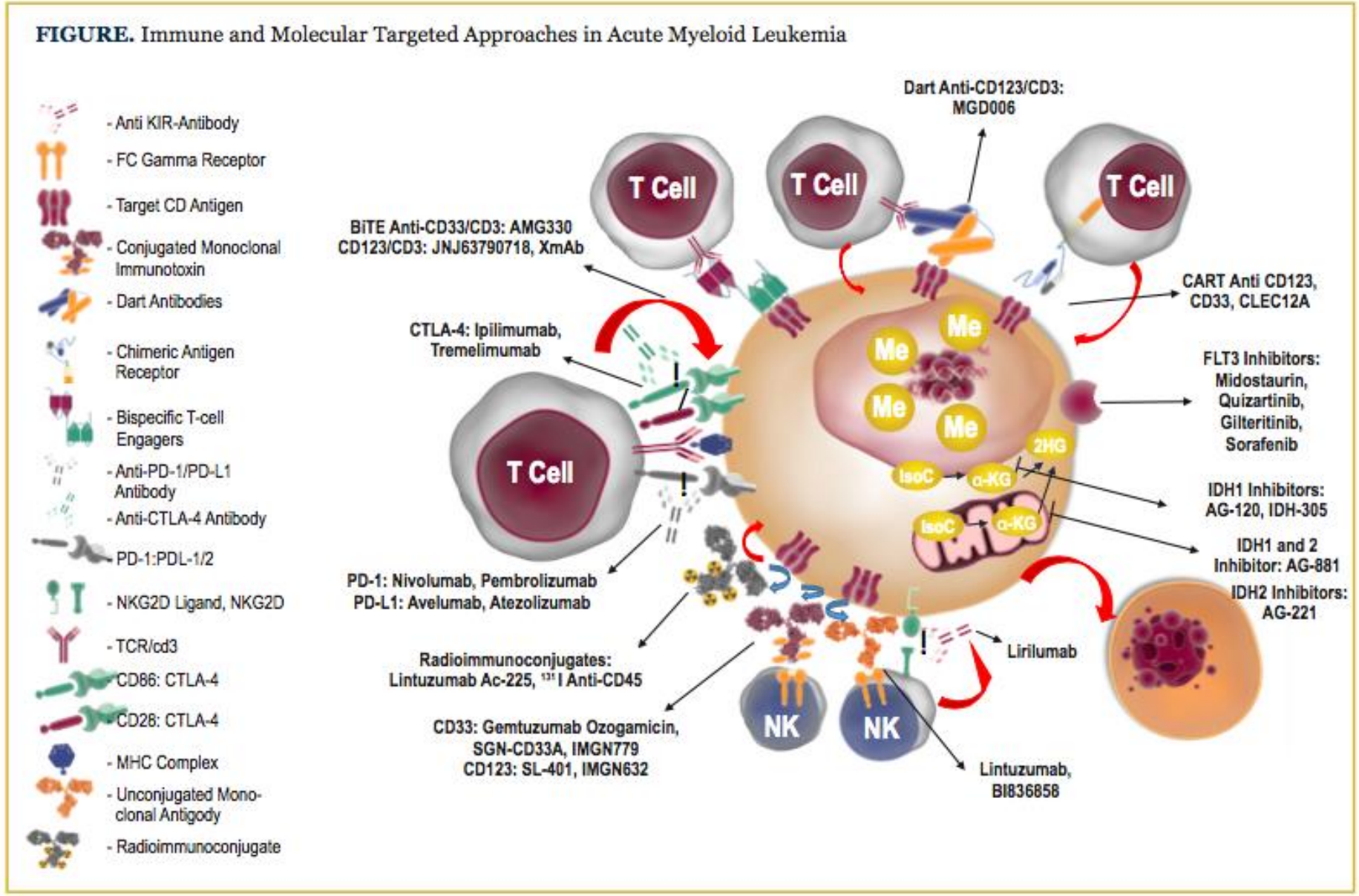
**FIGURE.** Immune and Molecular Targeted Approaches in Acute Myeloid Leukemia




http://www.gotoper.com/publications/ajho/2017/2017apr/emerging-molecular-and-immune-therapies-in-acute-myeloid-leukemia

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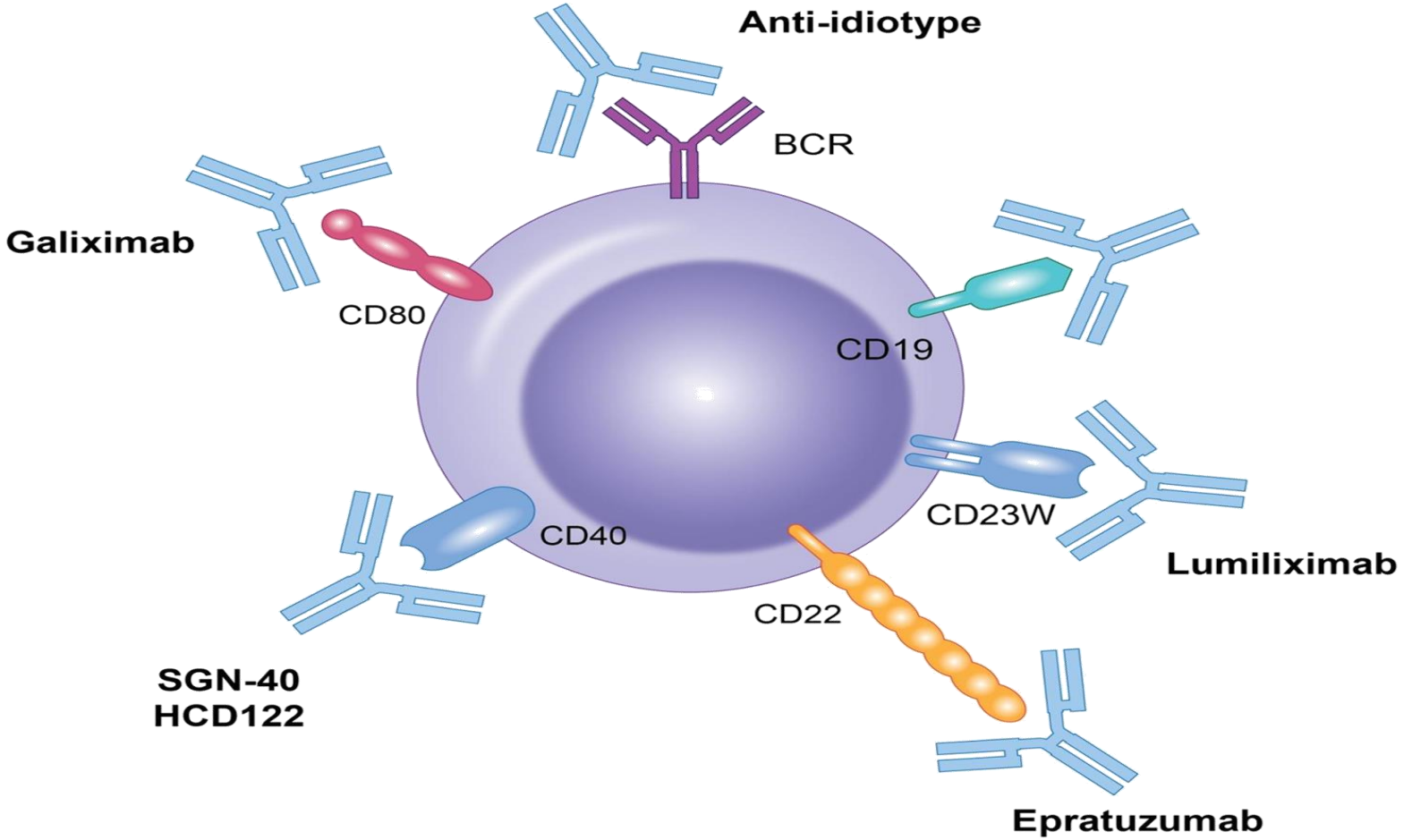
# Monoclonal antibodies targeting B cell lymphomas



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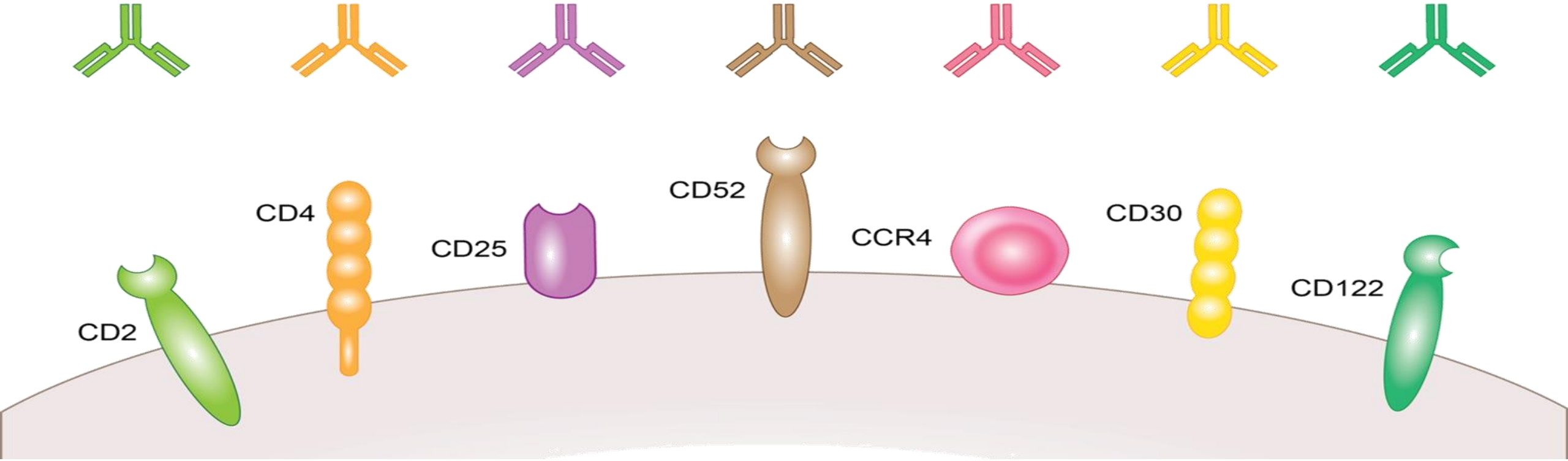
# Monoclonal antibodies targeting T cell lymphomas



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# Antigen-specific approaches in ALL

| Technology: | CAR T cells | BiTE |
|---|---|---|
| Example | tisagenlecleucel (CAR(CD19) T) | blinatumumab (anti-CD3/CD19) |
| Dosing | One infusion | Continuous 28 days |
| Complete Response | 90% | 66% |
| Survival | 78% 6 mos OS | 9 mos median |
| Major toxicity | Cytokine release | Cytokine release |
| Antigen loss relapse? | Yes | Yes |
| Challenges | Complex manufacturing, individualized | Burdensome infusion |

Gill Immunol Rev Dec 2014



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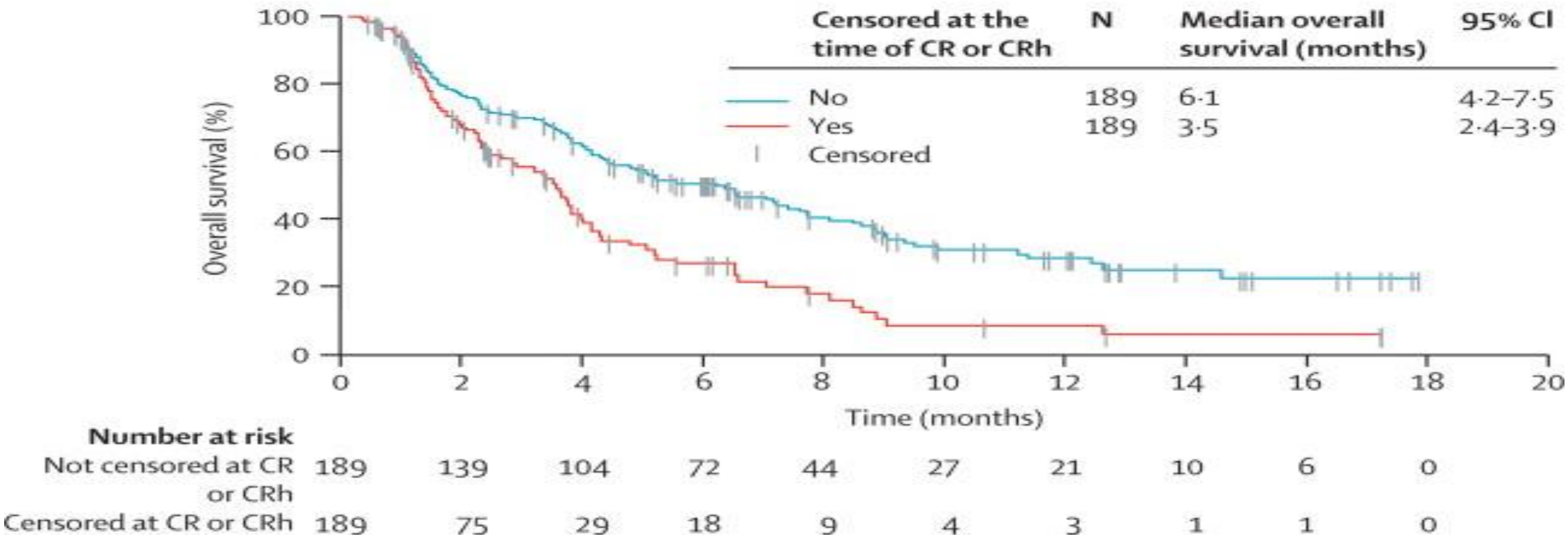
# BiTE therapy in ALL




Topp, Max S et al., The Lancet Oncology, 2015 , Volume 16 , Issue 1 , 57 - 66

# CAR T cell therapy in DLBCL

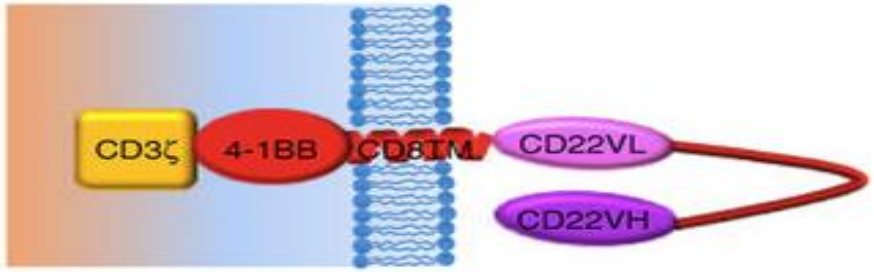
*JULIET multi-institutional study*

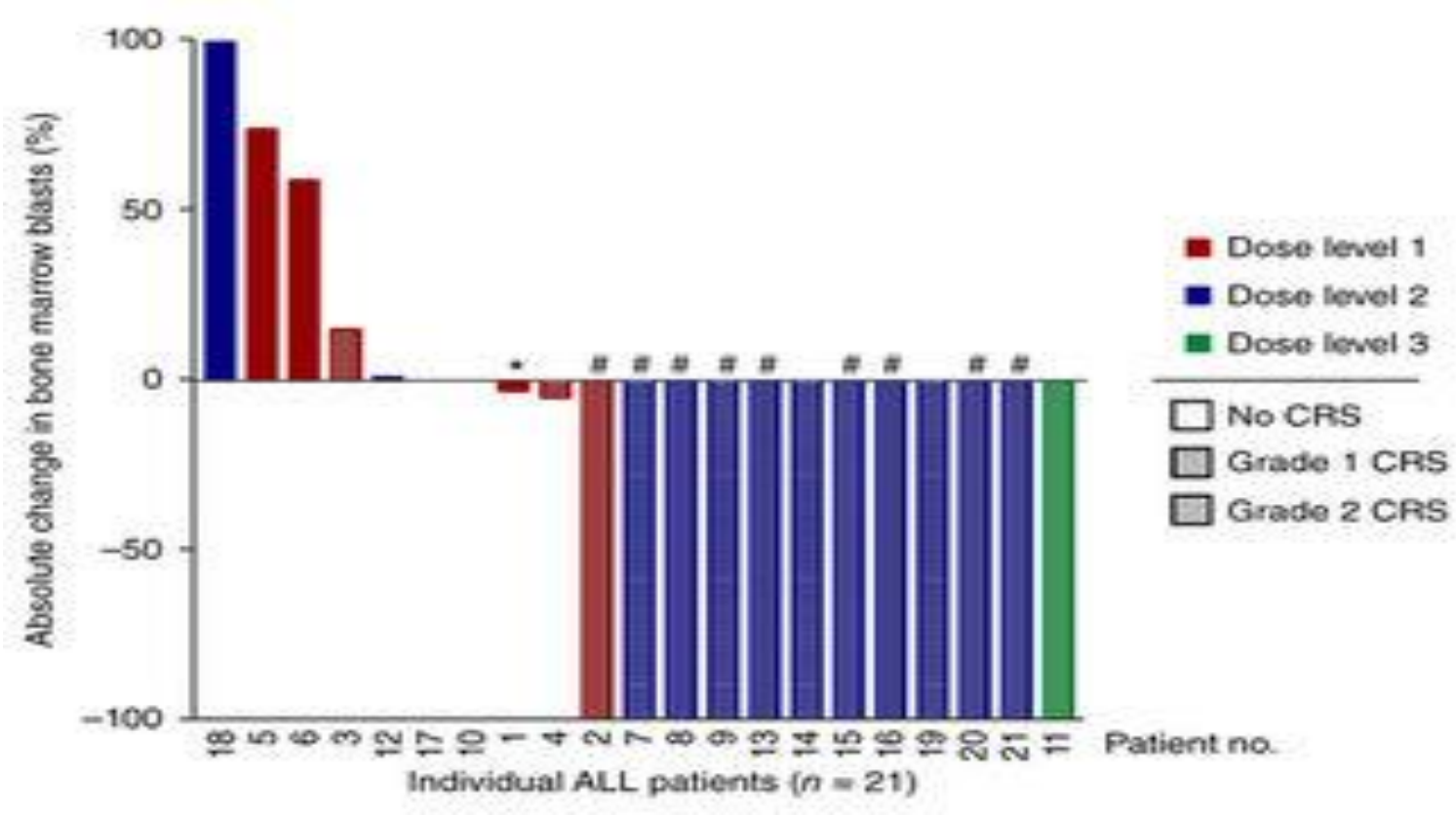
| Response Rate | Patients (N = 51)[a] | |
|---|---|---|
| Best overall response (CR + PR) | 59% | P < .0001[b] (95% CI, 44-72) |
| CR[1] | 43% | |
| PR[1] | 16% | |
| SD[1] | 12% | |
| PD[1] | 24% | |
| | | |
| Overall response rate (CR + PR) at 3 months | 45% | |
| CR[1] | 37% | |
| PR[1] | 8% | |

CI, confidence interval; CR, complete remission; ORR, overall remission rate; PD, progressive disease; PR, partial remission; SD, stable disease.

# Ongoing trials with CAR T therapies for hematologic malignancies

- CD22+ CAR T cells effective in patients with relapsed, CD19- B-ALL

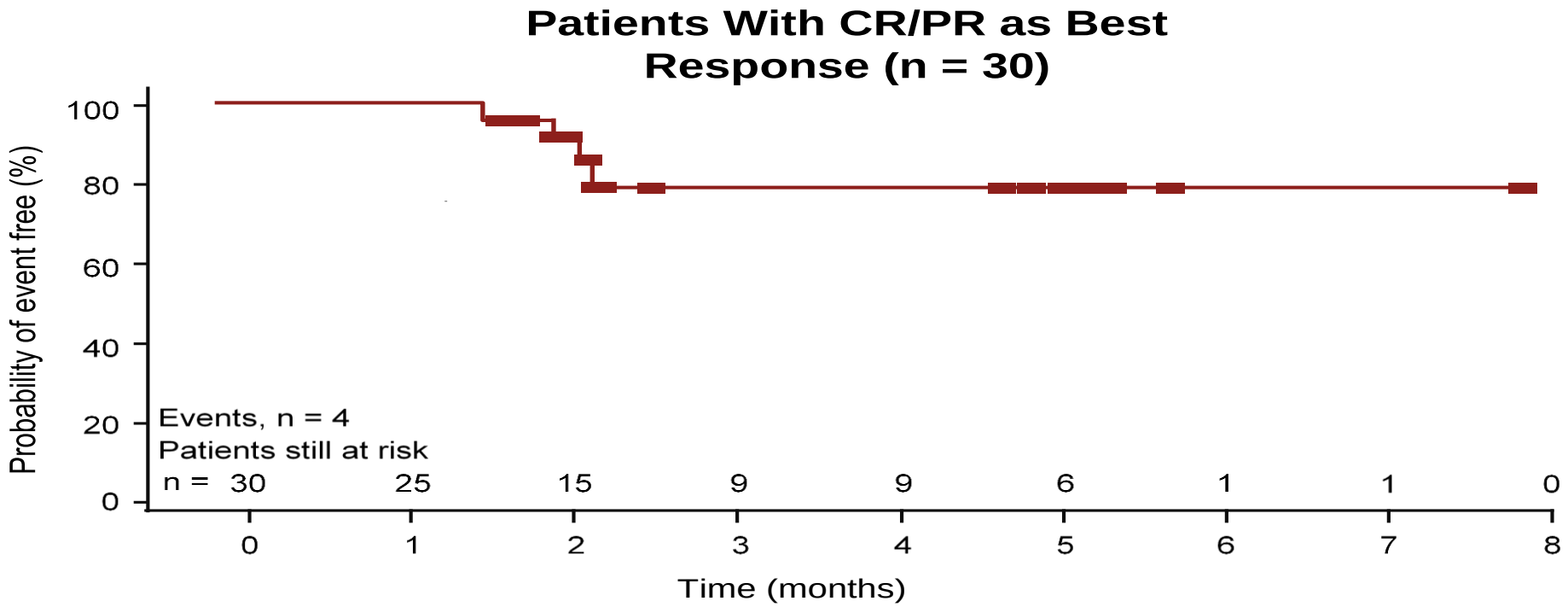



Fry, T.J. et al., Nature Medicine, 2017

# CAR T cell therapy in DLBCL

*JULIET multi-institutional study*




- All responses at 3 months were ongoing at the time of cut-off
  - No responding patients went on to SCT
- Median DOR and OS not reached

# KEYNOTE-183: Phase 3, randomized, controlled trial of pomalidomide & low-dose dexamethasone +/- pembrolizumab (anti-PD-1)in relapsed refractory multiple myeloma patients with ≥2 prior therapy lines

- At a data cutoff date of June 2, 2017, safety and efficacy evaluation of 249 randomized RRMM patients
- Median follow-up of 8.1 months.
- OS: 29 deaths on the pembro/pom/dex & 21 deaths on the pom/dex arm. HR: 1.61 (95% CI: 0.91-2.85), increasing RR of death by > 50% compared to control arm
- 18% increase of severe, grade 3-5 toxicity (83% vs. 65%, pembro/pom/dex vs. pom/dex ) with an incidence of serious adverse events: 63% vs 46%
- Non-disease progression causes of death on the pembro/pom/dex arm: myocarditis, Stevens-Johnson syndrome, myocardial infarction, pericardial hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, multiple organ dysfunction, respiratory failure, and unknown.
- https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm

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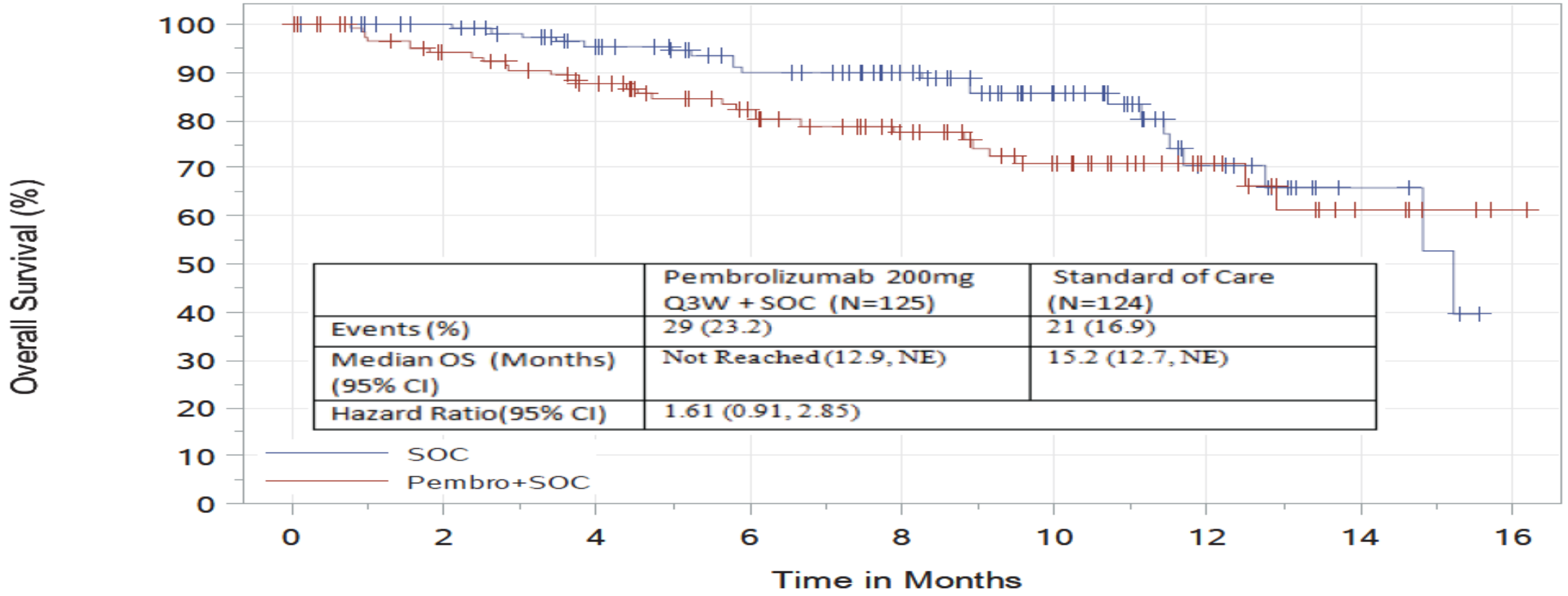
# Keynote 183




| | Pembrolizumab 200mg Q3W + SOC (N=125) | Standard of Care (N=124) |
|---|---|---|
| Events (%) | 29 (23.2) | 21 (16.9) |
| Median OS (Months) (95% CI) | Not Reached (12.9, NE) | 15.2 (12.7, NE) |
| Hazard Ratio (95% CI) | 1.61 (0.91, 2.85) | |

**Number of Subjects at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SOC | 124 | 115 | 99 | 83 | 67 | 42 | 18 | 6 | 0 |
| Pembro+SOC | 125 | 105 | 91 | 73 | 53 | 37 | 18 | 7 | 1 |

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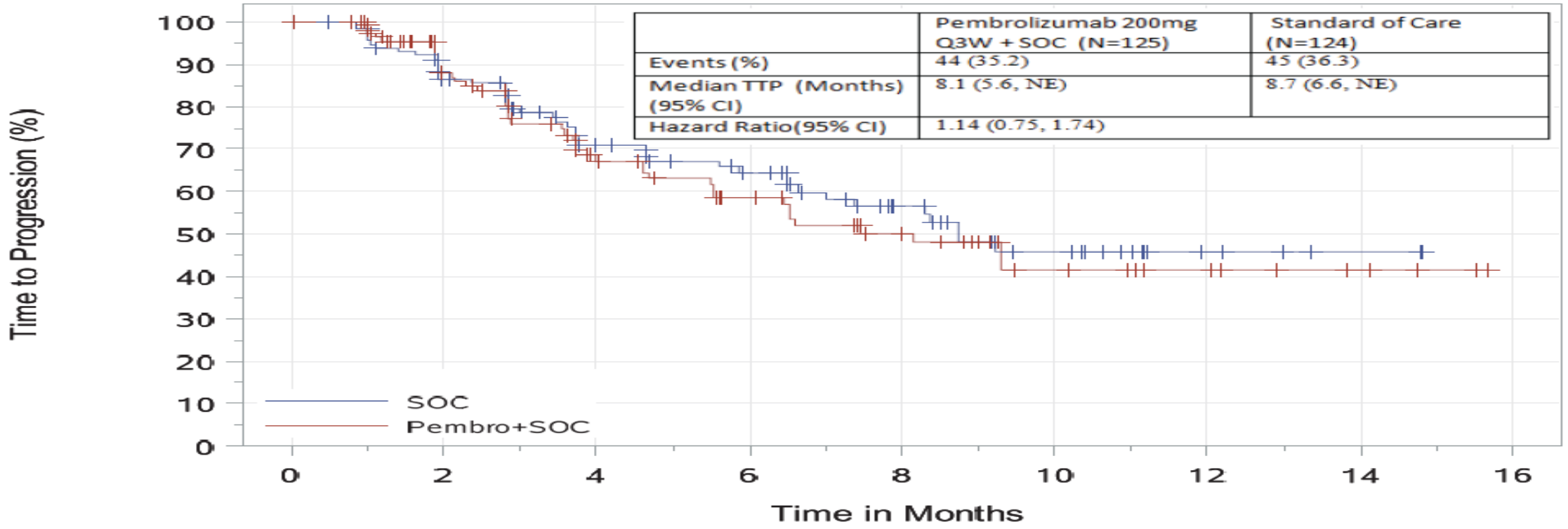
# Keynote 183




| | Pembrolizumab 200mg Q3W + SOC (N=125) | Standard of Care (N=124) |
|---|---|---|
| Events (%) | 44 (35.2) | 45 (36.3) |
| Median TTP (Months) (95% CI) | 8.1 (5.6, NE) | 8.7 (6.6, NE) |
| Hazard Ratio(95% CI) | 1.14 (0.75, 1.74) | |

**Number of Subjects at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SOC | 124 | 91 | 61 | 46 | 29 | 17 | 5 | 2 | 0 |
| Pembro+SOC | 125 | 81 | 50 | 37 | 24 | 12 | 8 | 4 | 0 |

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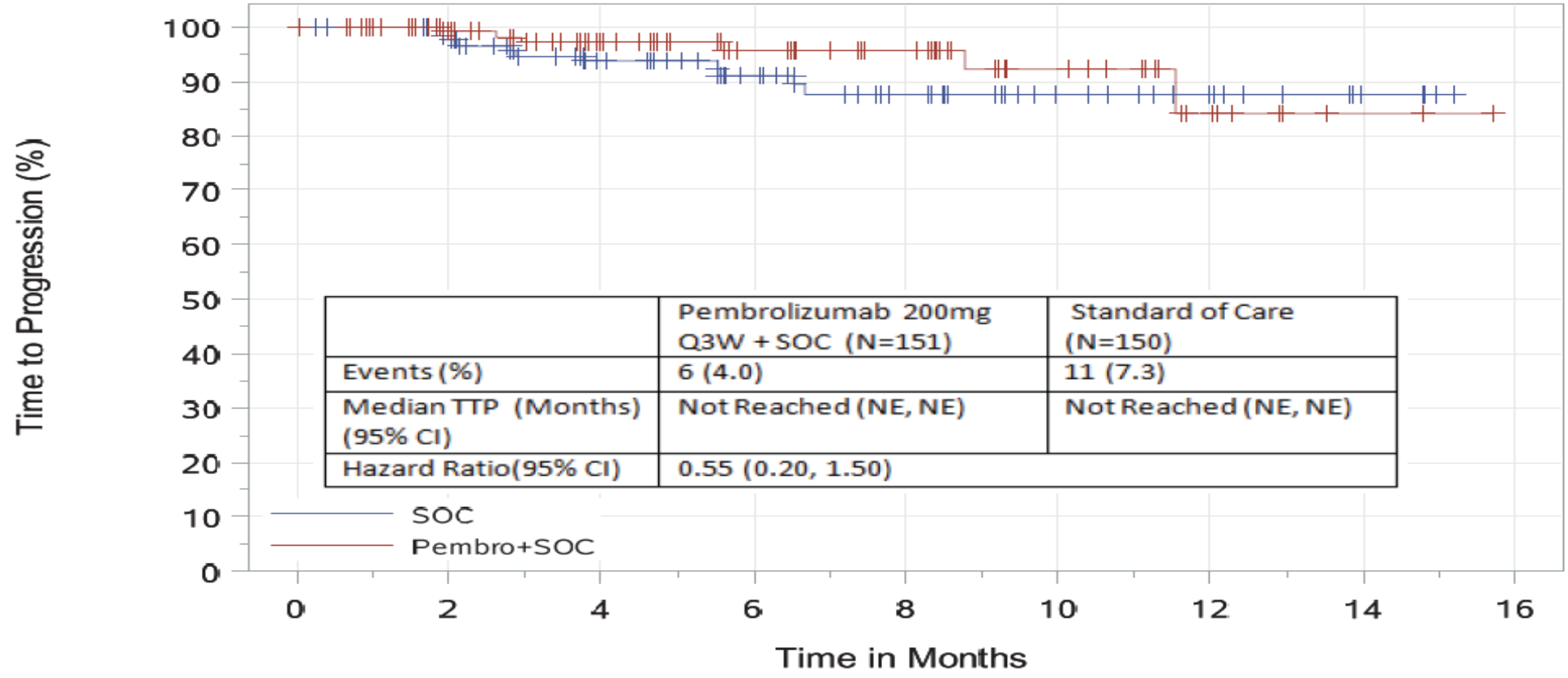
# Keynote 185




| | Pembrolizumab 200mg Q3W + SOC (N=151) | Standard of Care (N=150) |
|---|---|---|
| Events (%) | 6 (4.0) | 11 (7.3) |
| Median TTP (Months) (95% CI) | Not Reached (NE, NE) | Not Reached (NE, NE) |
| Hazard Ratio(95% CI) | 0.55 (0.20, 1.50) | |

**Number of Subjects at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SOC | 150 | 114 | 82 | 59 | 38 | 20 | 12 | 4 | 0 |
| Pembro+SOC | 151 | 108 | 80 | 57 | 45 | 19 | 8 | 2 | 0 |

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