

ADVANCES IN  
**Cancer**  
IMMUNOTHERAPY™



# Immunotherapy of Hematologic Malignancies

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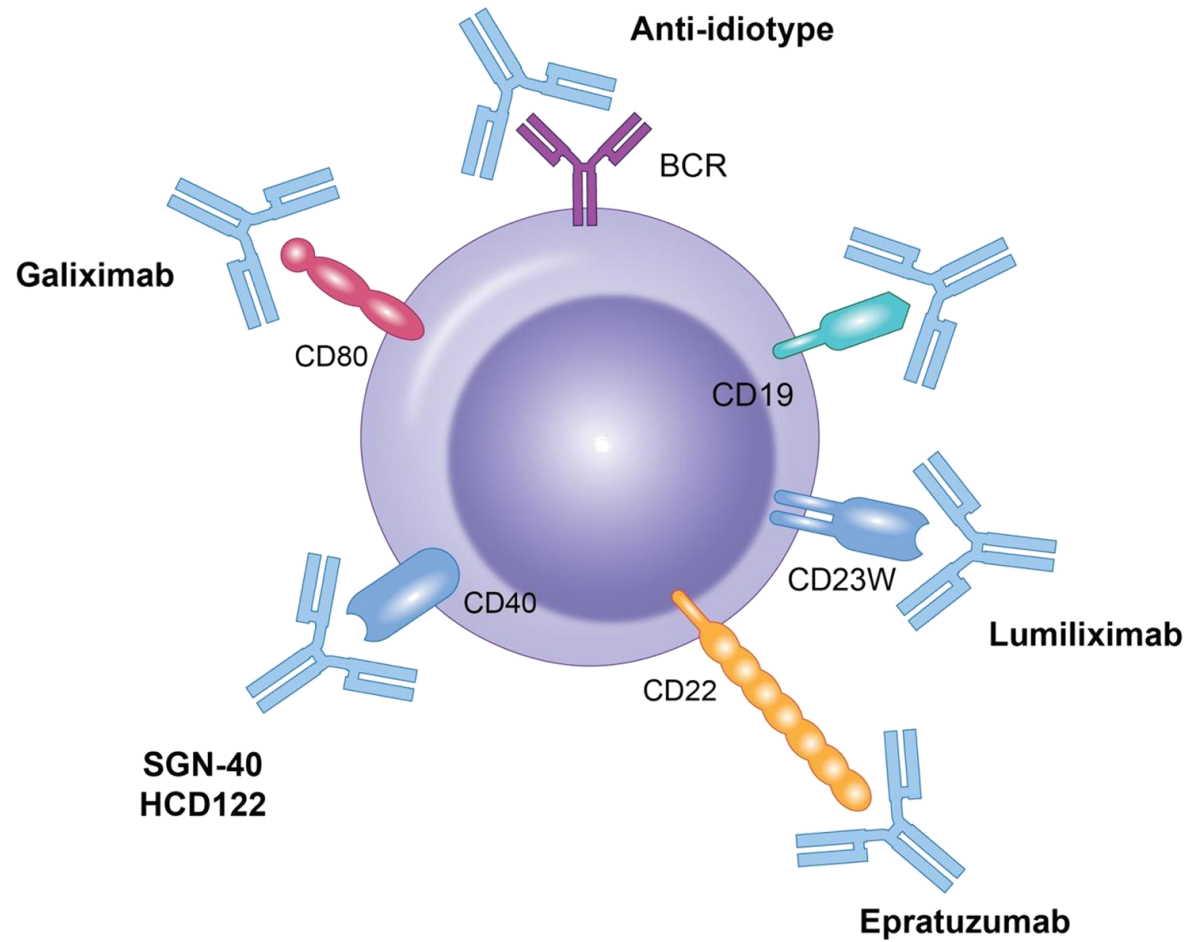


Society for Immunotherapy of Cancer

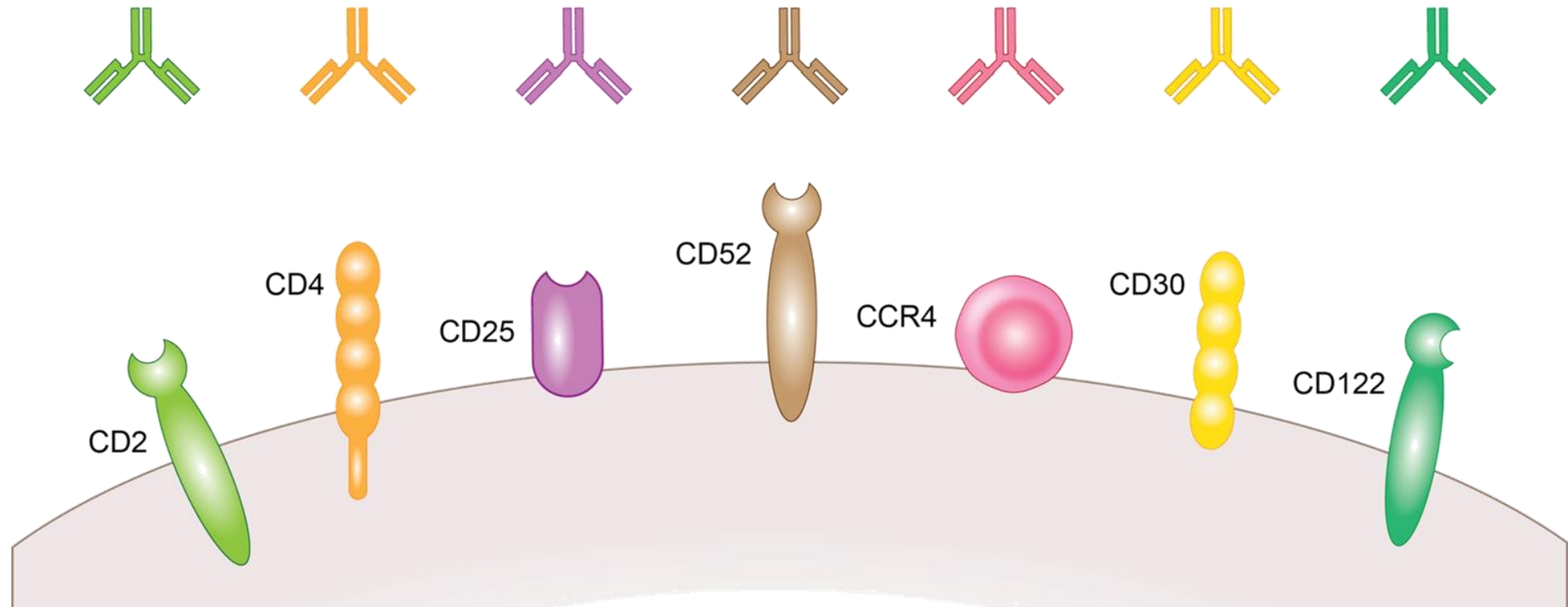
# Disclosures

- Speaker for Incyte, Gilead, Seattle Genetics, Spectrum
- Advisory Boards for Novartis, BMS, Bayer, Pfizer, Gilead, Incyte, Seattle Genetics, Teva, JAZZ, Otsuka, Spectrum, Kite, Daichii, Sanofi
- I will be discussing non-FDA approved indications during my presentation.

# Monoclonal antibodies targeting B cell lymphomas

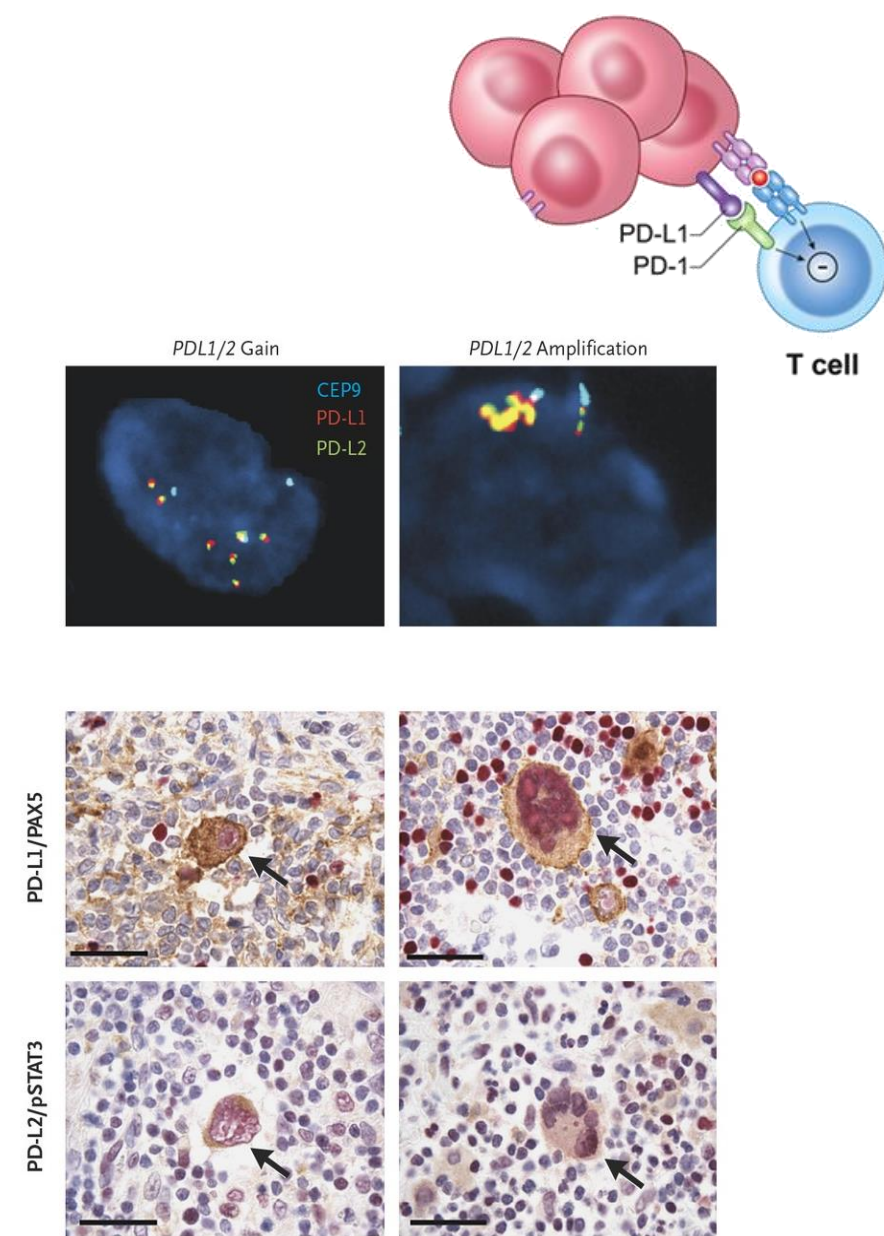


# Monoclonal antibodies targeting T cell lymphomas



## Checkpoint inhibitors

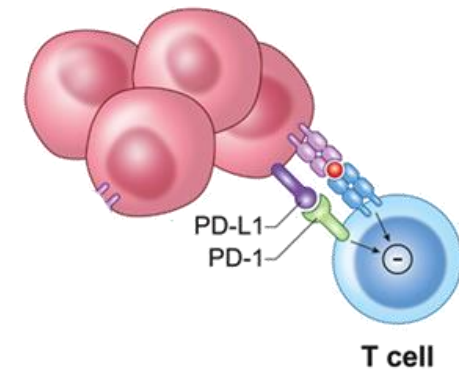
- Reed-Sternberg cells express both PD-L1 and PD-L2
- Expression of ligands increases with advanced disease
- Unclear whether PD-L1/L2 expression correlates with response to treatment



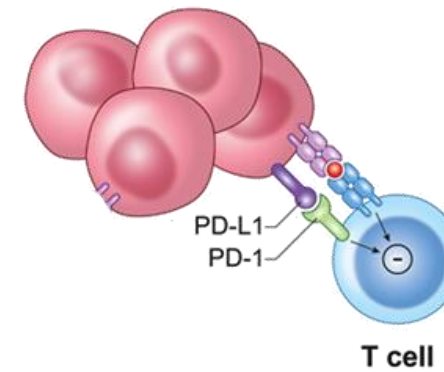
Ansell SM et al. N Engl J Med 2015;372:311-319



## 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 17<sup>th</sup>, 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 14<sup>th</sup>, 2017



## Nivolumab in Hodgkin lymphoma

**Table 3. Clinical Activity in Nivolumab-Treated Patients.\***

Variable	All Patients (N=23)	Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)	No Stem-Cell Transplantation and Failure of Brentuximab (N=3)	No Brentuximab Treatment (N=5)†
Best overall response — no. (%)				
Complete response	4 (17)	1 (7)	0	3 (60)
Partial response	16 (70)	12 (80)	3 (100)	1 (20)
Stable disease	3 (13)	2 (13)	0	1 (20)
Progressive disease	0	0	0	0
Objective response				
No. of patients	20	13	3	4
Percent of patients (95% CI)	87 (66–97)	87 (60–98)	100 (29–100)	80 (28–99)
Progression-free survival at 24 wk — % (95% CI)‡	86 (62–95)	85 (52–96)	NC§	80 (20–97)
Overall survival — wk				
Median	NR	NR	NR	NR
Range at data cutoff¶	21–75	21–75	32–55	30–50

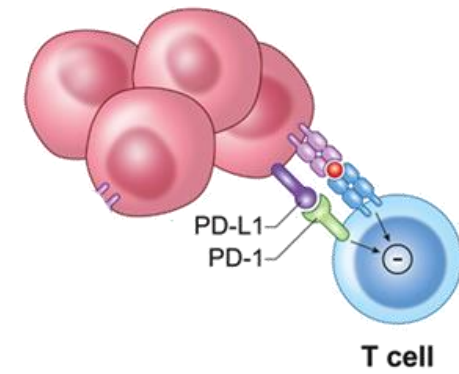
\* NC denotes not calculated, and NR not reached.

† In this group, two patients had undergone autologous stem-cell transplantation and three had not.

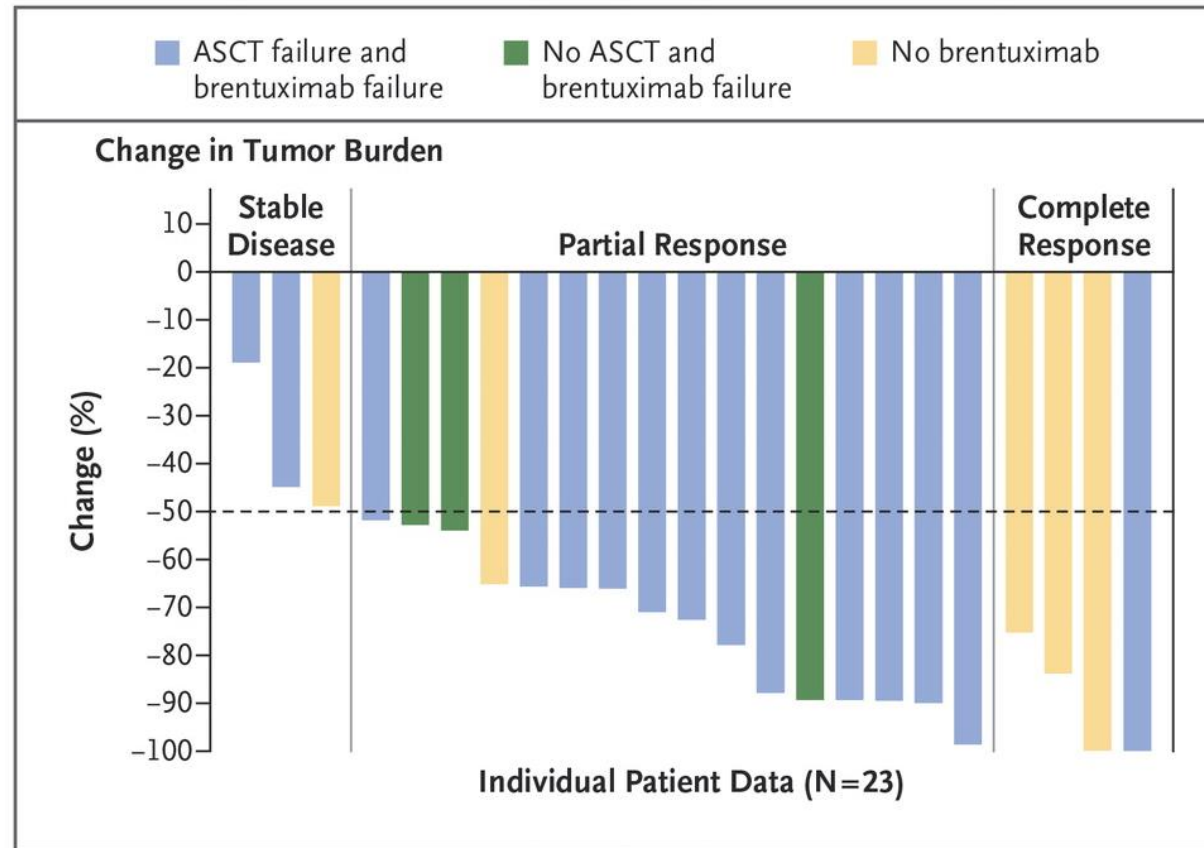
‡ Point estimates were derived from Kaplan–Meier analyses; 95% confidence intervals were derived from Greenwood's formula.

§ The estimate was not calculated when the percentage of data censoring was above 25%.

¶ Responses were ongoing in 11 patients.



## Nivolumab in Hodgkin lymphoma



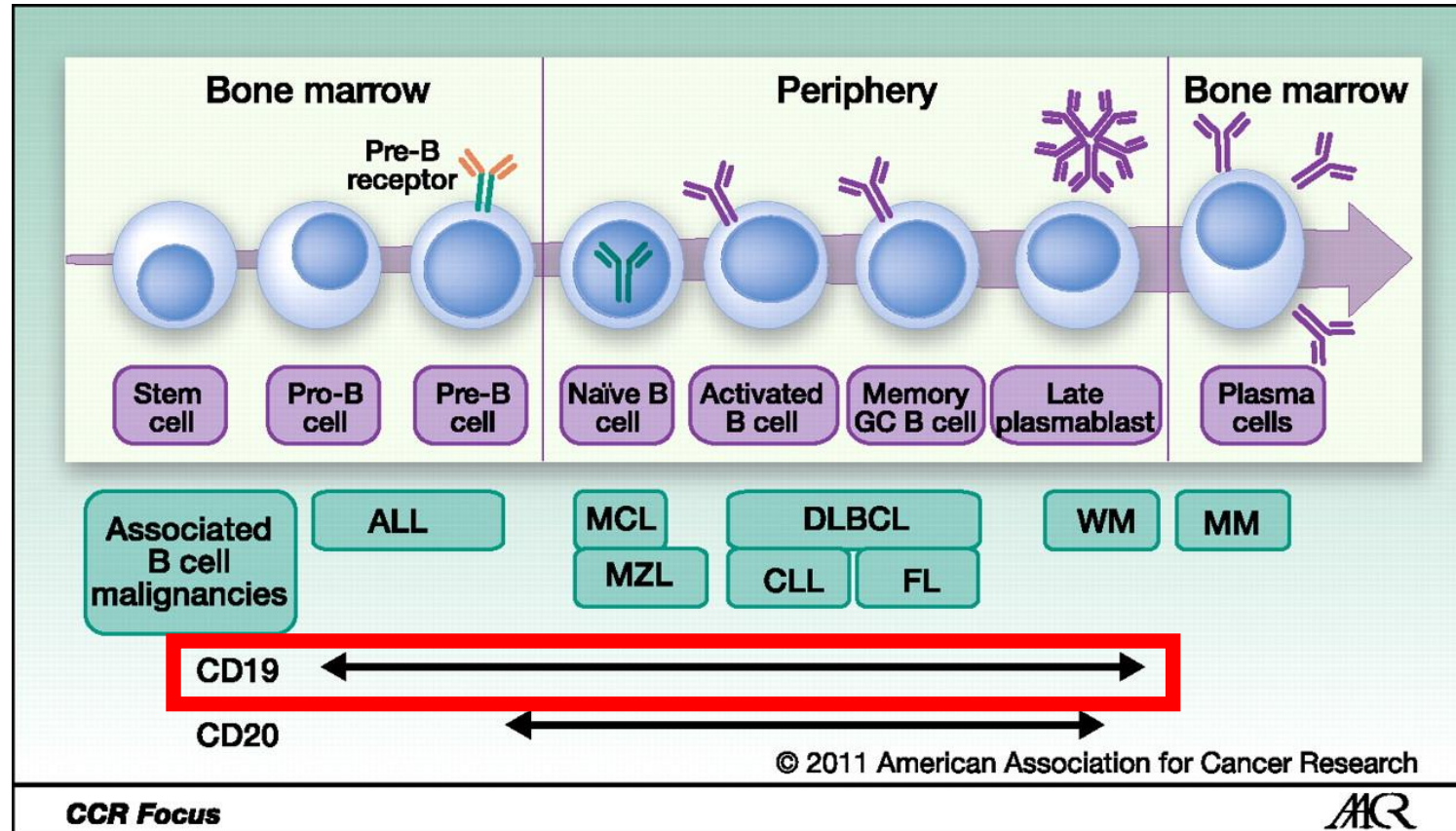
Ansell SM et al. N Engl J Med 2015;372:311-319



## Patient selection criteria for checkpoint inhibitor therapies

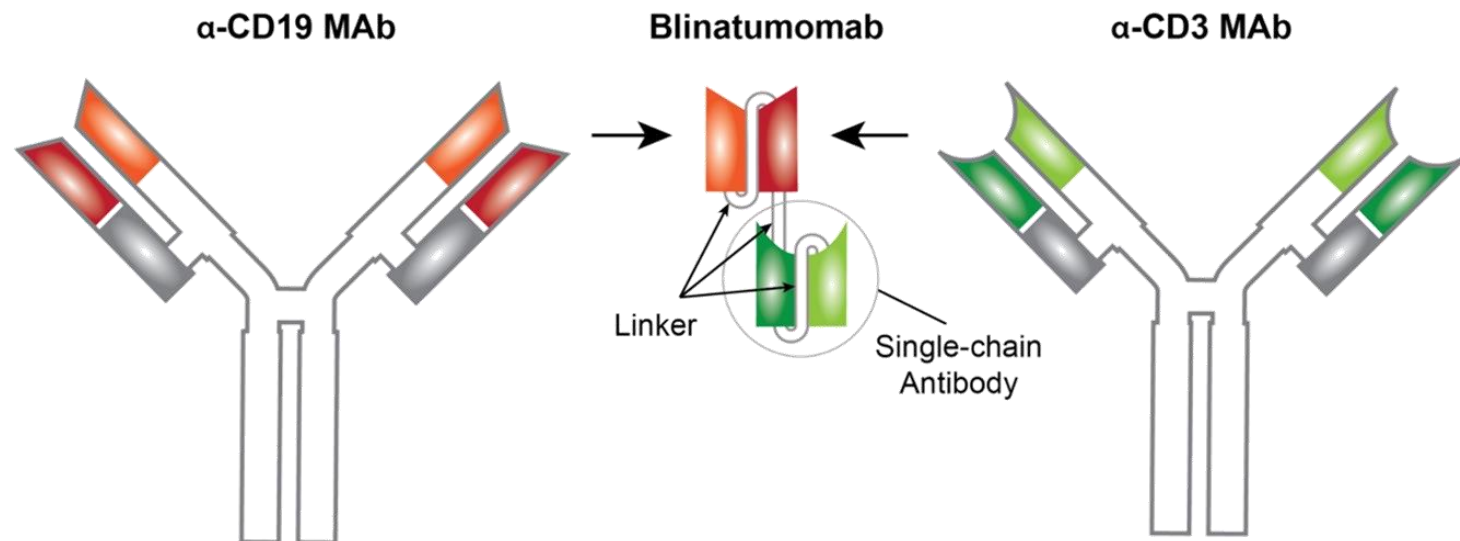
- Expression of the ligand for checkpoint inhibition
  - e.g. PD-L1 expression for anti-PD-1 therapy
- Relapse or progression after previous therapies
  - Nivolumab: After prior HSCT and brentuximab therapy
  - Pembrolizumab: Relapse after three prior treatments
- Presence of co-morbidities:
  - e.g.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

# B cell malignancies are CD19+

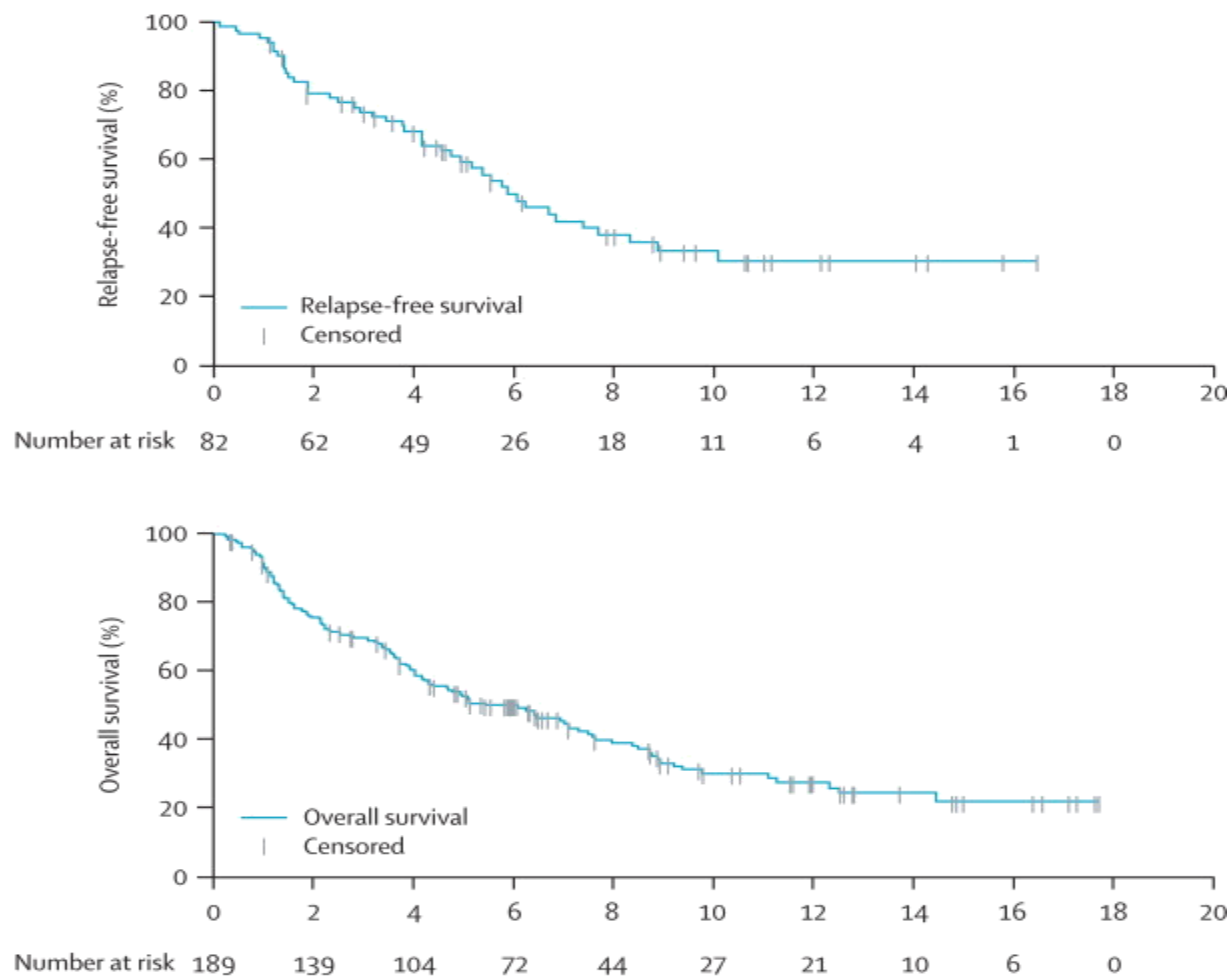


## BiTE (blinatumumab) therapy

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



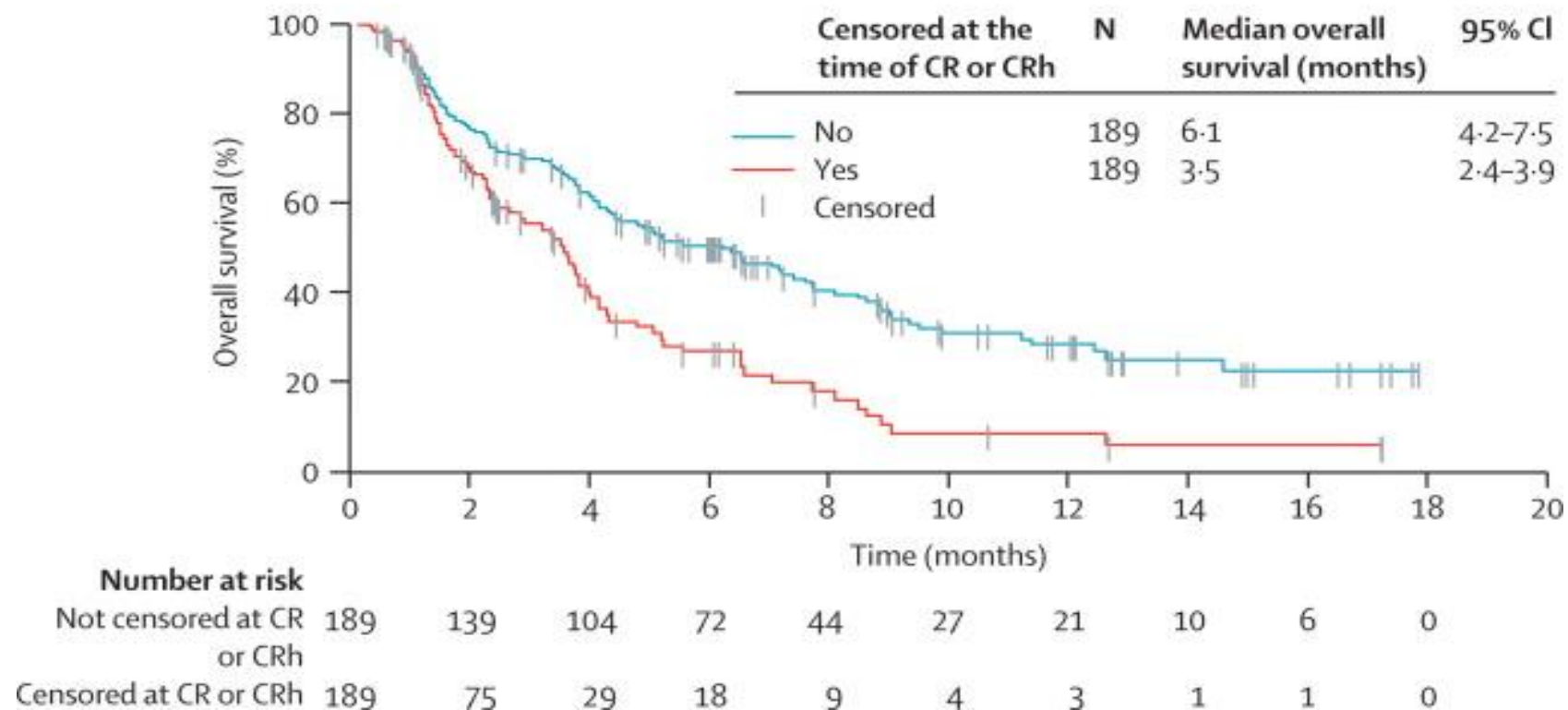
# BiTE therapy in ALL



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



# BiTE therapy in ALL



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

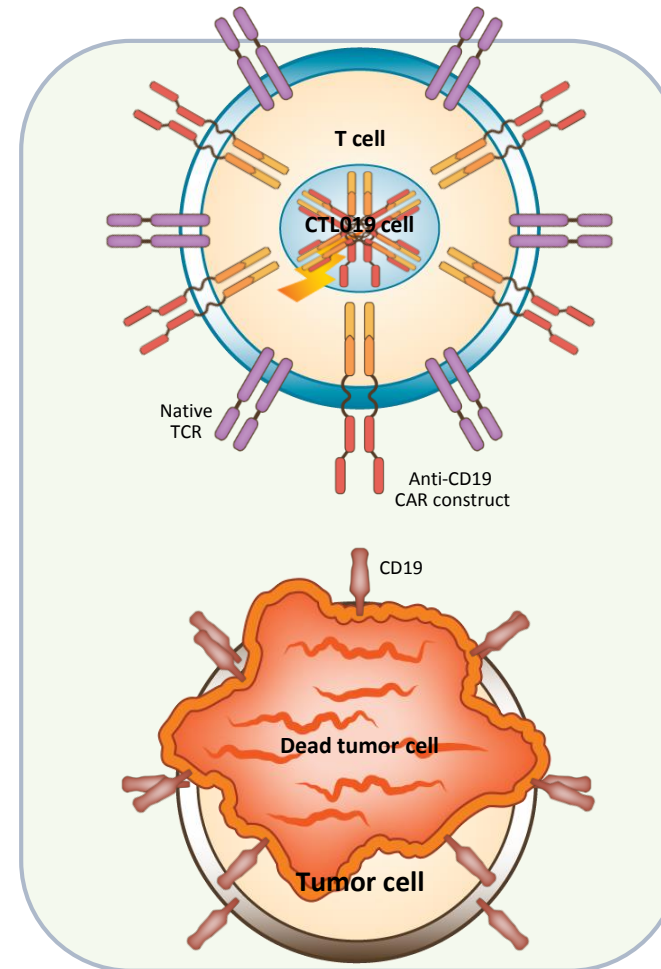




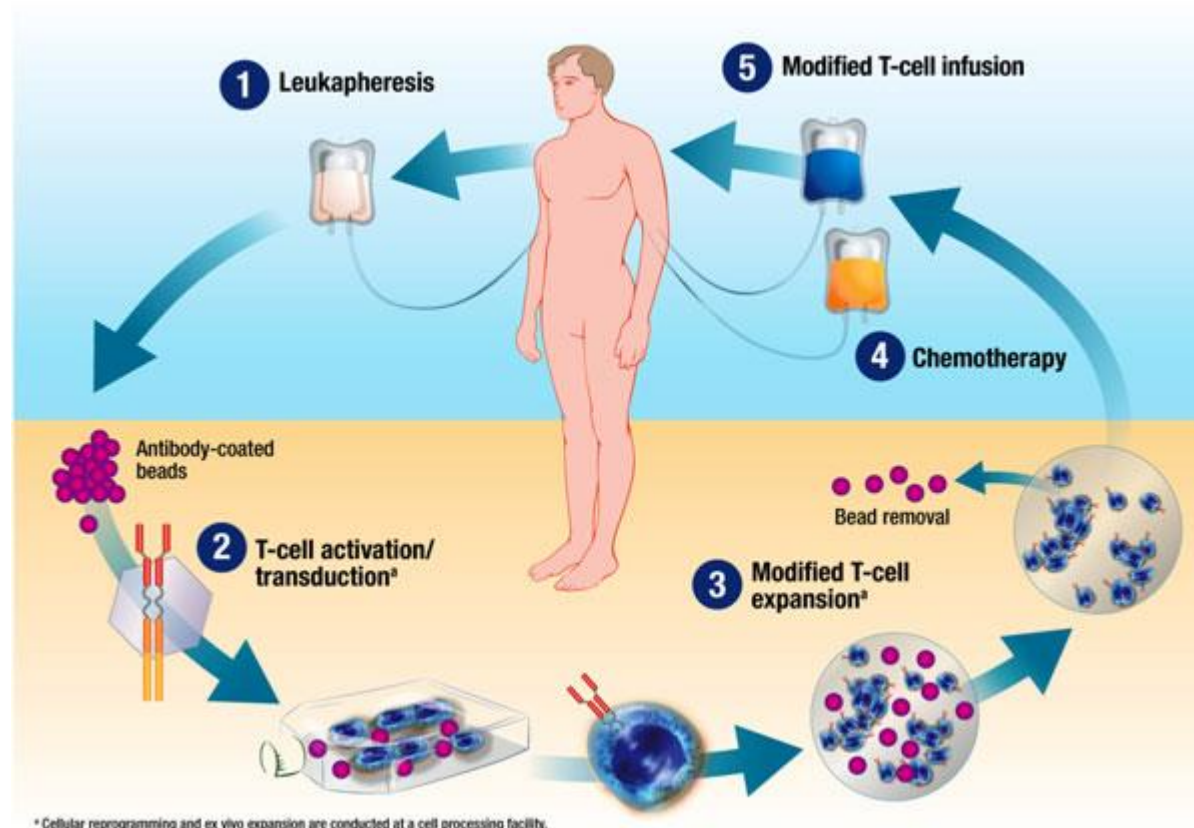
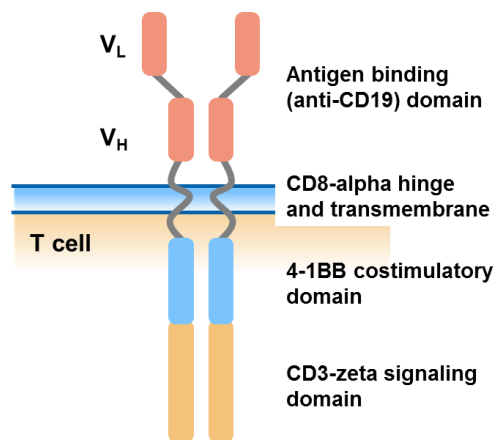
# Chimeric Antigen Receptor (CAR) T cell therapy

- Gene transfer technology stably expresses CARs on T cells<sup>1,2</sup>
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner<sup>1,3</sup>
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells<sup>3</sup>
- **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.



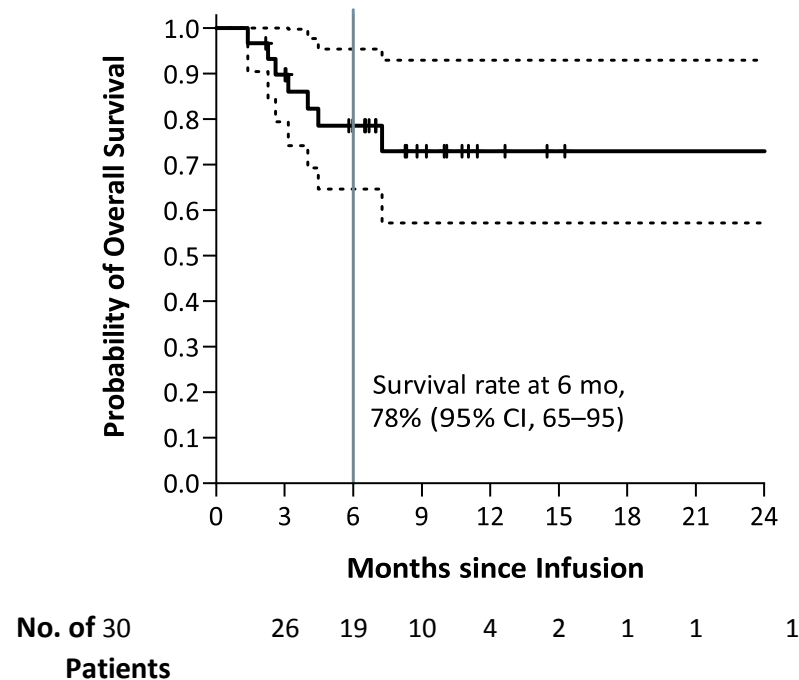
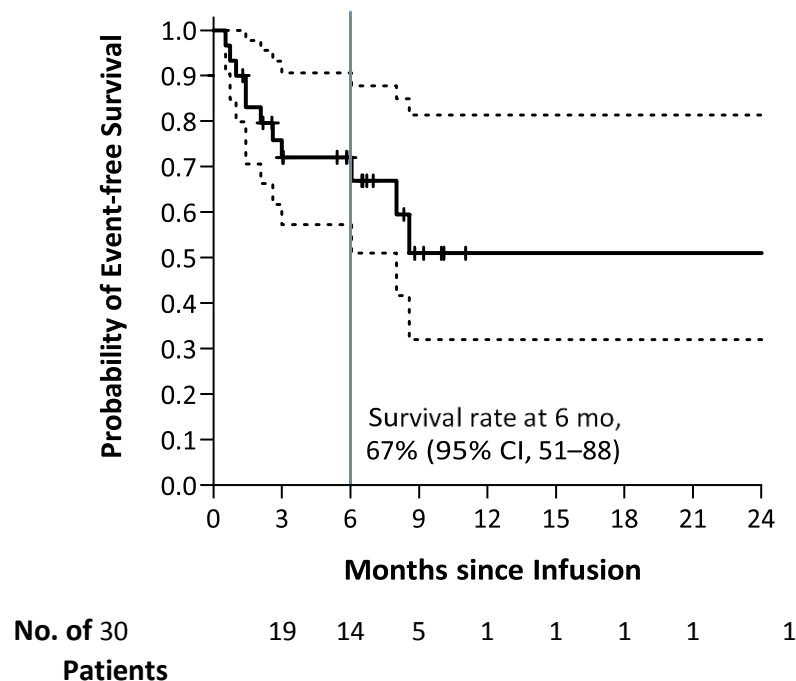
# CAR T cell therapy



# FDA-approved CAR T cell therapies for hematologic malignancies

- Kymriah (tisagenlecleucel)
  - Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse
  - Accelerated approval – August 30<sup>th</sup>, 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 18<sup>th</sup>, 2017

# CAR T cell therapy in ALL



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



# CAR T cell therapy in DLBCL

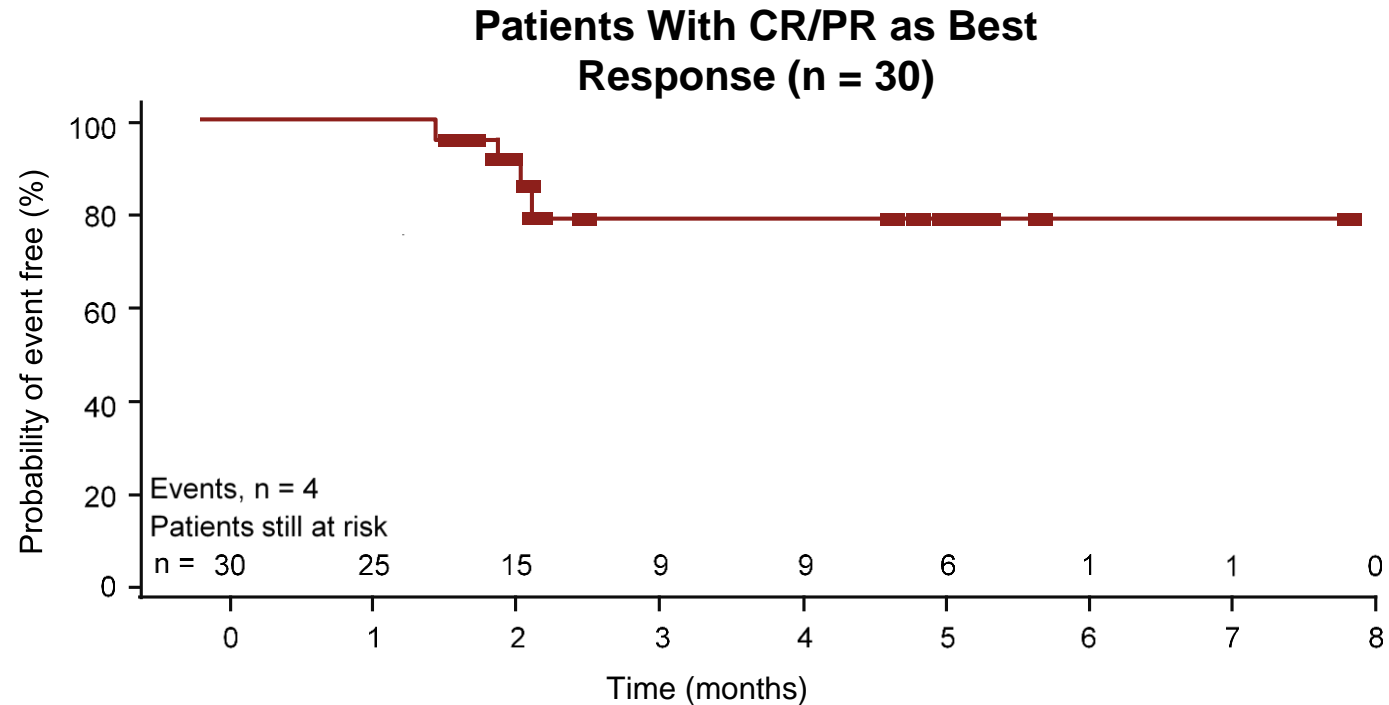
## *JULIET multi-institutional study*

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

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







- 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

# CAR T cell therapy in DLBCL

## *Agent efficacy and safety*

	CTL019 <sup>1</sup>	KTE-C19 <sup>2,3</sup>		JCAR017 <sup>4,5</sup>
Disease state	r/r DLBCL	r/r DLBCL	r/r TFL/PMBCL	r/r DLBCL, NOS, tDLBCL, FL3B
Pts treated, n	85	77	24	28
Follow-up, median	NR	8.7 mo		NR
Efficacy				
ORR (best response)	59%	82%	83%	80% <sup>a</sup>
CR (best response)	43%	54%	71%	60% <sup>a</sup>
CR (3 months)	37%	NR	NR	45%
CR (6 months)	NR	31%	50%	NR
Safety				
CRS	31% grade 1/2; 26% grade 3/4	13% grade ≥3		36% grade 1/2; 0% grade 3/4
Neurotoxicity	13% grade 3/4	28% grade ≥3		4% grade 1/2; 14% grade 3/4

<sup>a</sup>20 pts with DLBCL were evaluated for efficacy.

CR, complete response; CRS, cytokine release syndrome; NR, not reported; ORR, overall response rate.

1. Schuster, SJ, et al. ICML 2017 [abstract 007]. 2. Locke FL, et al. AACR 2017 [abstract CT019]; 3. Locke FL, et al. ASCO 2017 [abstract 7512]; 4.

Abramson JS, et al. *Blood*. 2016;128(22) [abstract 4192]; 5. Abramson JS, et al. ASCO 2017 [abstract 7513].



## Antigen-specific approaches in ALL

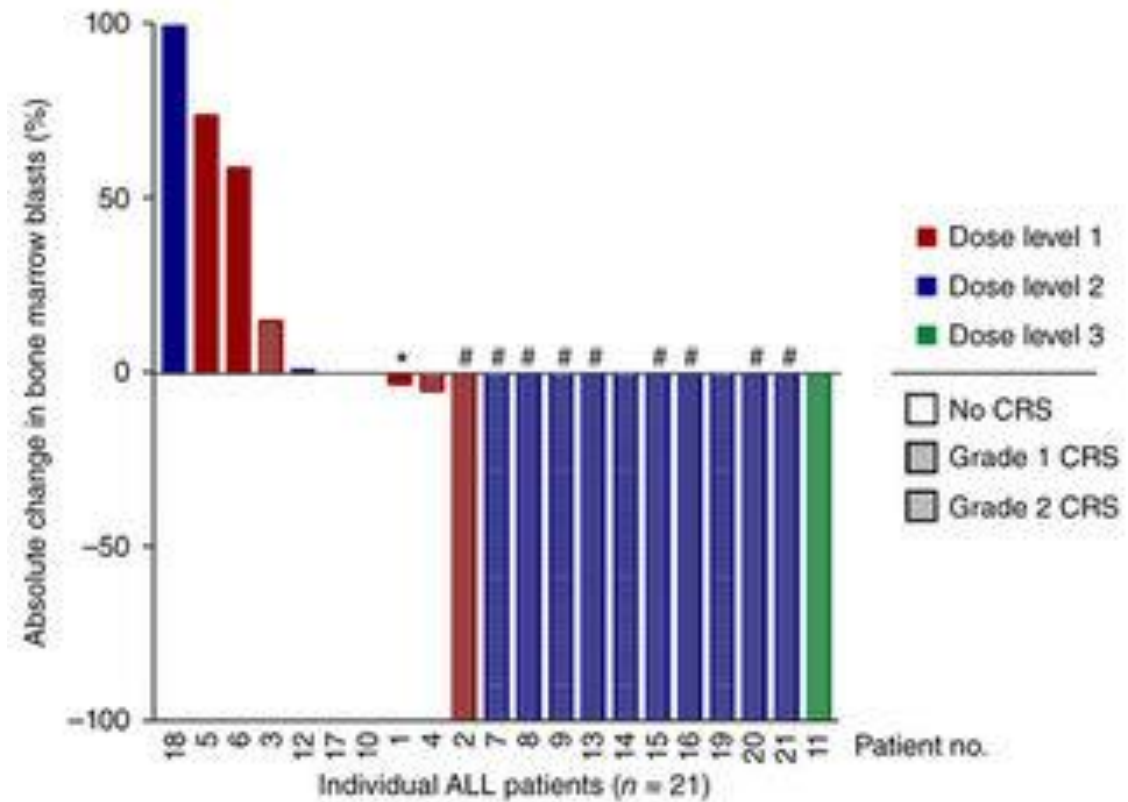
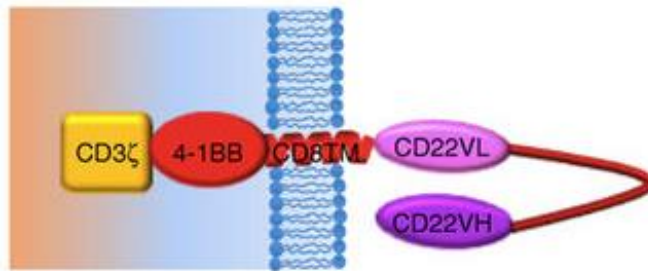
Technology:	CAR T cells	BiTE
Example	tisagenlecleucel (CAR(CD19) T)	blinatumumab (anti-CD3/CD19)
Dosing	One infusion	Continuous 28 days
Complete Response	90%	66%
Survival	78% 6 mos OS	9 mos median
Major toxicity	Cytokine release	Cytokine release
Antigen loss relapse?	Yes	Yes
Challenges	Complex manufacturing,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

# Patient selection criteria for CAR T 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

# 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



# Immunotherapies for myeloma

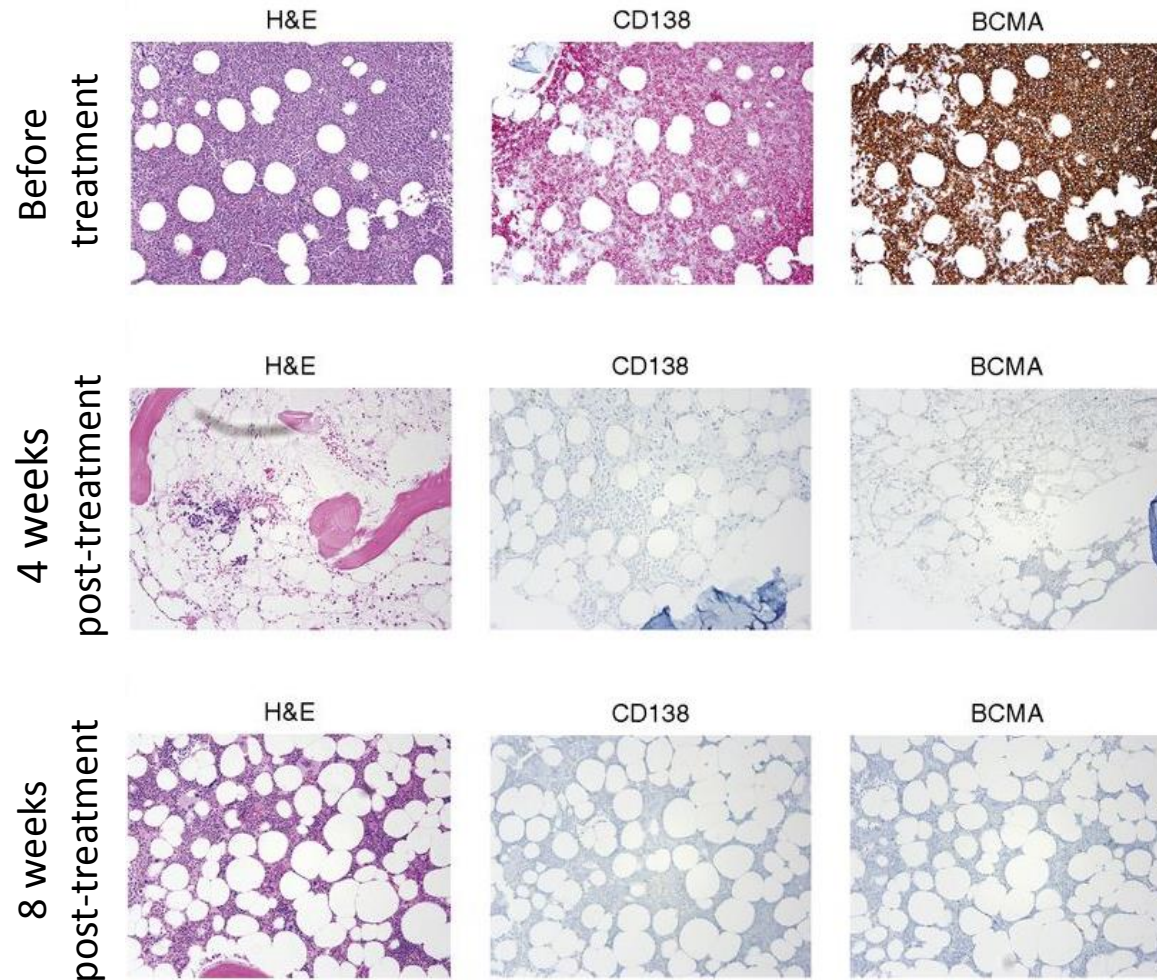
- No approved checkpoint inhibitor therapies
  - KEYNOTE-183/185/023: halted or discontinued due to risk/benefit profile

- Vaccine-based approaches



- Non-Antigen Specific
  - Attenuated measles
  - Whole cell - GM-CSF
  - Dendritic – tumor fusions
- Antigen Specific
  - Idiotypic: RNA, DNA, protein
  - Pulsed dendritic cells
  - Tumor-specific peptides

# On the way: BCMA+ CAR T therapy for myeloma



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

- Fan et al. LBA3001  
ASCO 2017
- 100% ORR
- 33/35 patients in remission within 2 months after BCMA CAR T therapy
- November 17<sup>th</sup>, 2017  
FDA Breakthrough Designation

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

