

ADVANCES IN
Cancer
IMMUNOTHERAPY™



Immunotherapy of Hematologic Malignancies

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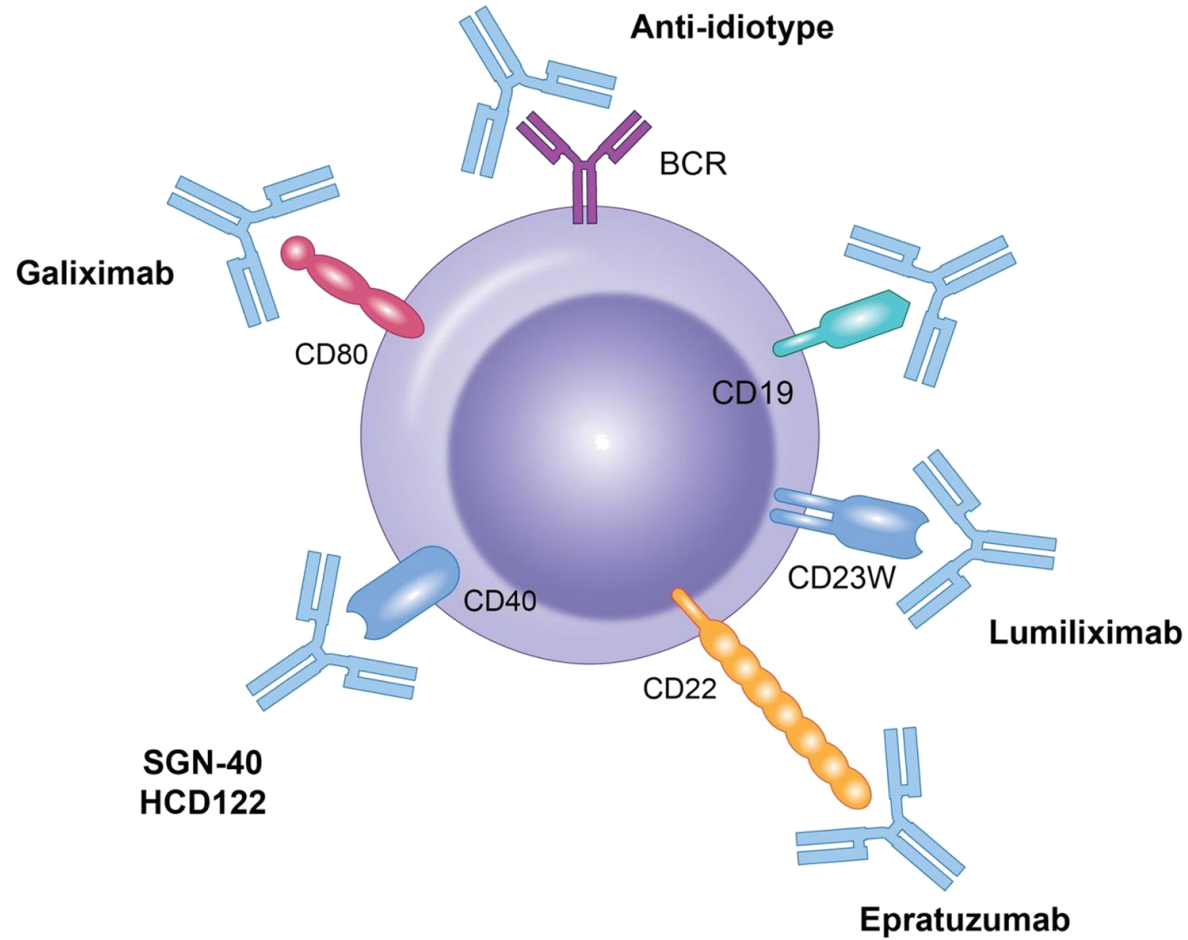


Society for Immunotherapy of Cancer

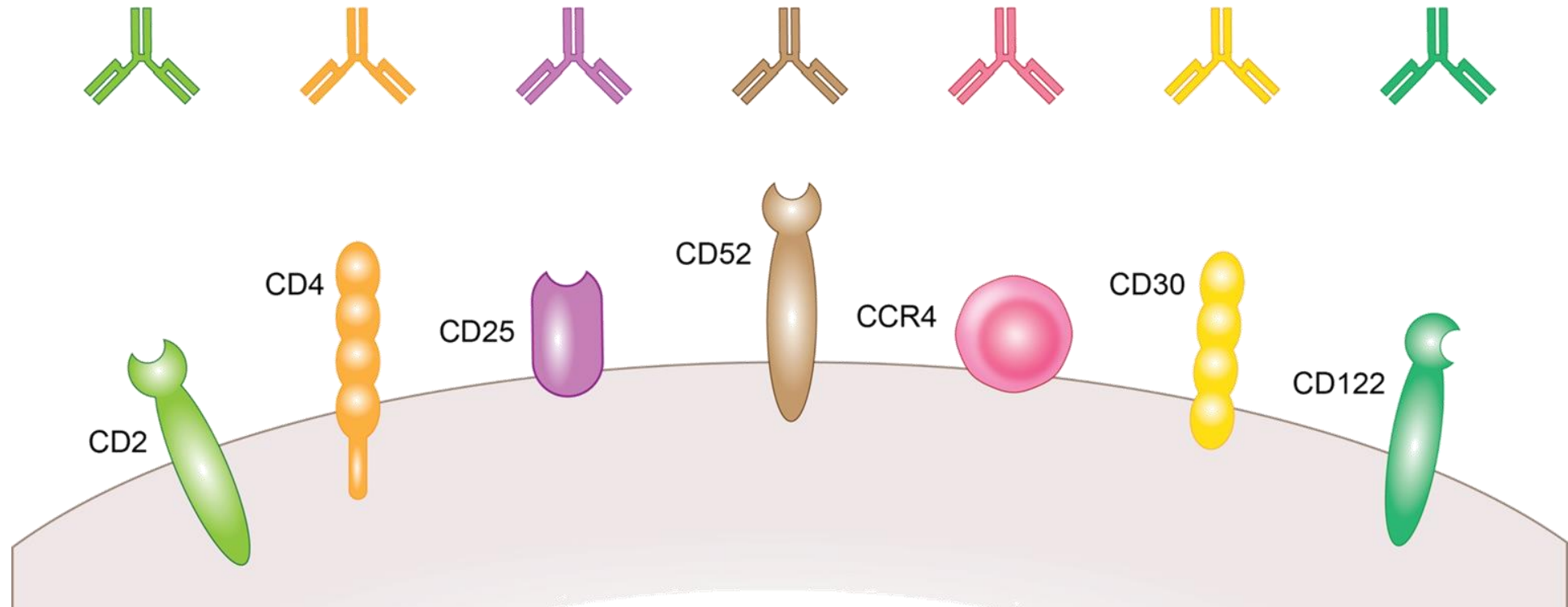
Disclosures

- Takeda, Amgen, and Celgene Speaker's Bureau
- I will be discussing non-FDA approved indications during my presentation.

Monoclonal antibodies targeting B cell lymphomas

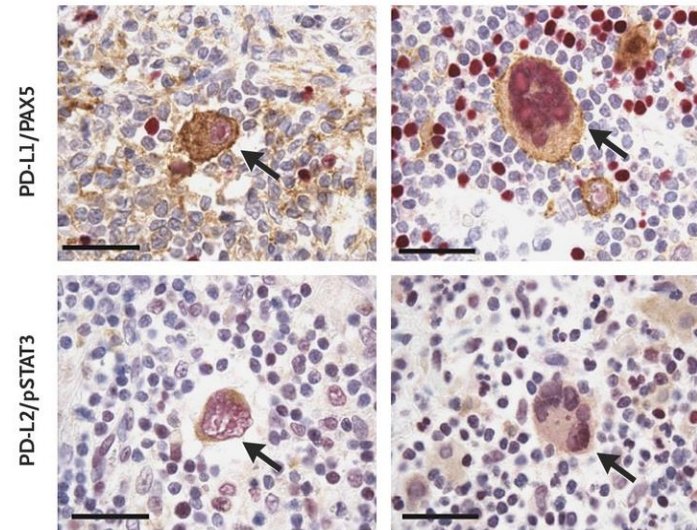
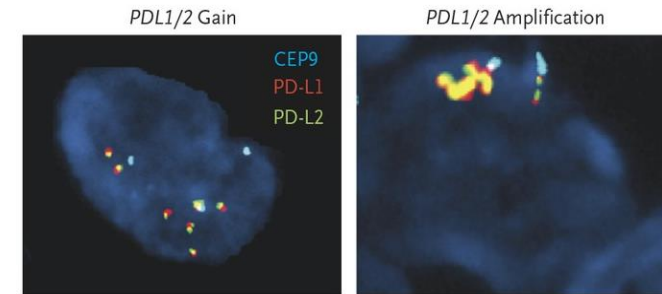
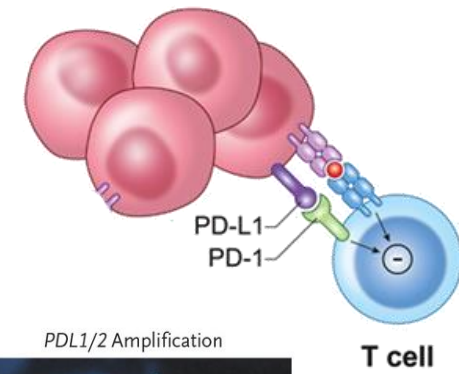


Monoclonal antibodies targeting T cell lymphomas



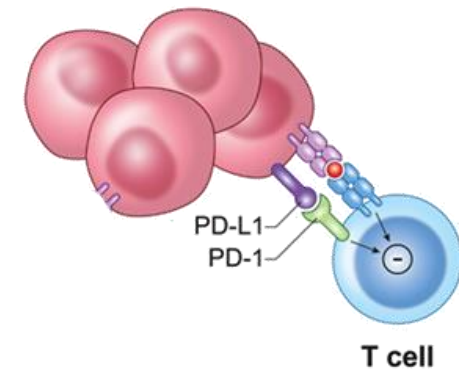
Checkpoint inhibitors

- 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

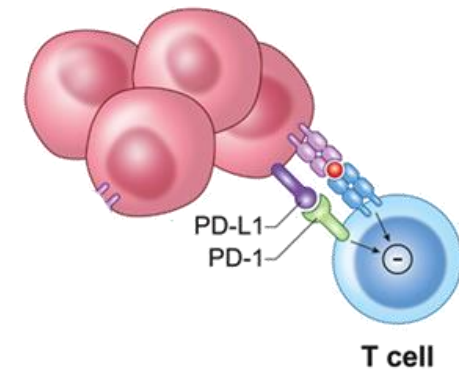


Ansell SM et al. N Engl J Med 2015;372:311-319

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 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



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

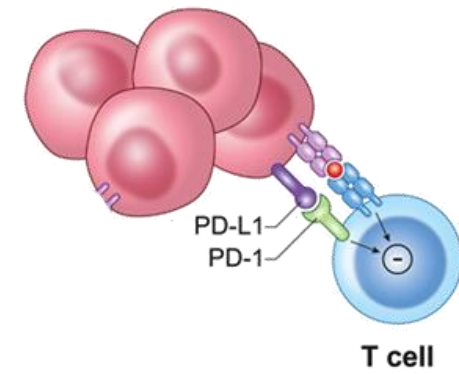
* NC denotes not calculated, and NR not reached.

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

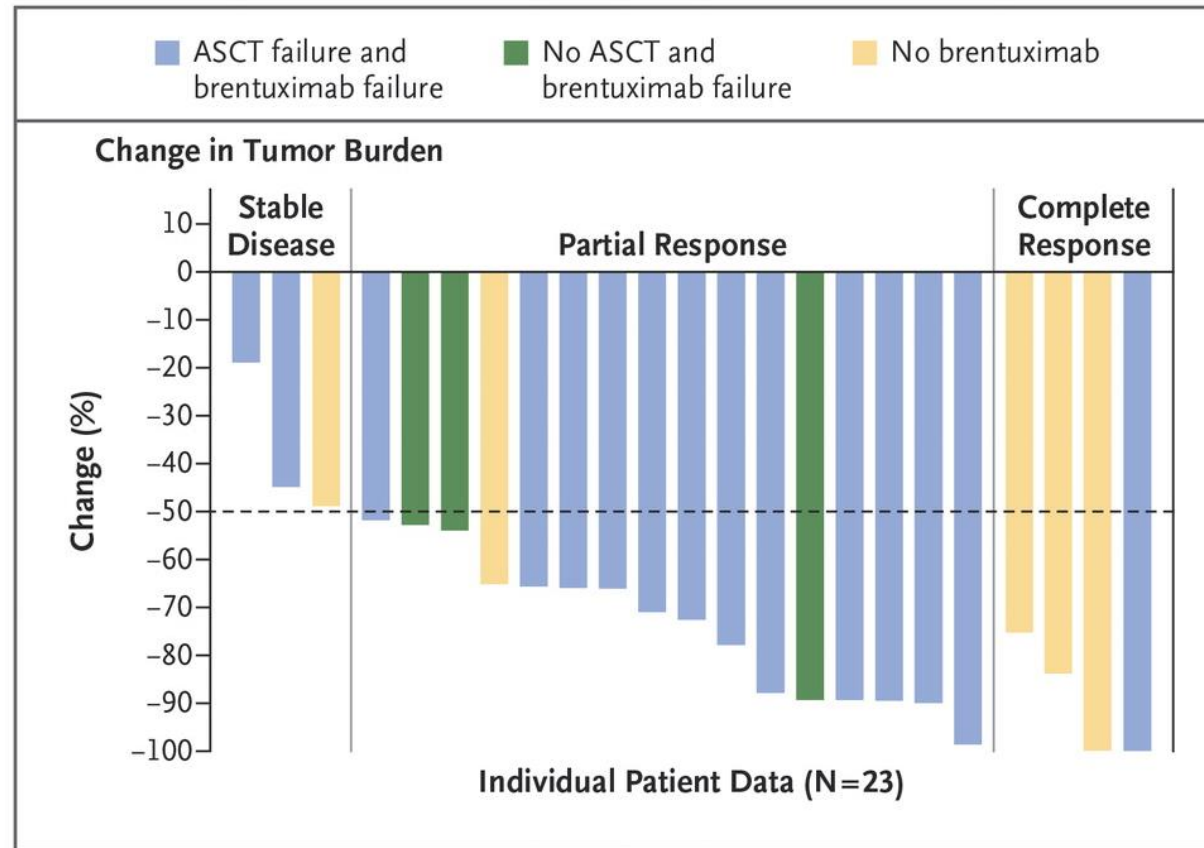
‡ Point estimates were derived from Kaplan–Meier analyses; 95% confidence intervals were derived from Greenwood's formula.

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

¶ Responses were ongoing in 11 patients.



Nivolumab in Hodgkin lymphoma

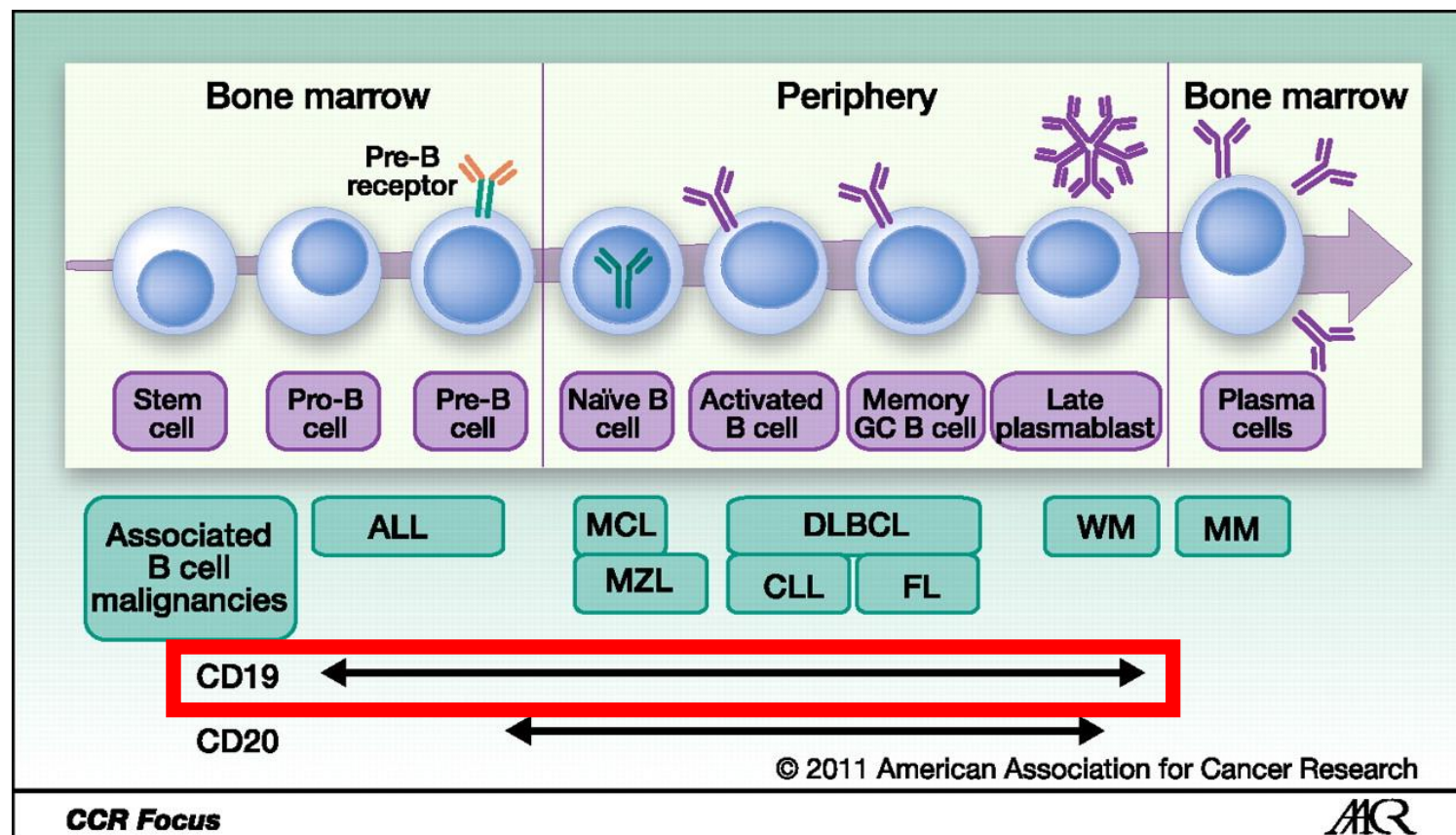


Ansell SM et al. N Engl J Med 2015;372:311-319

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

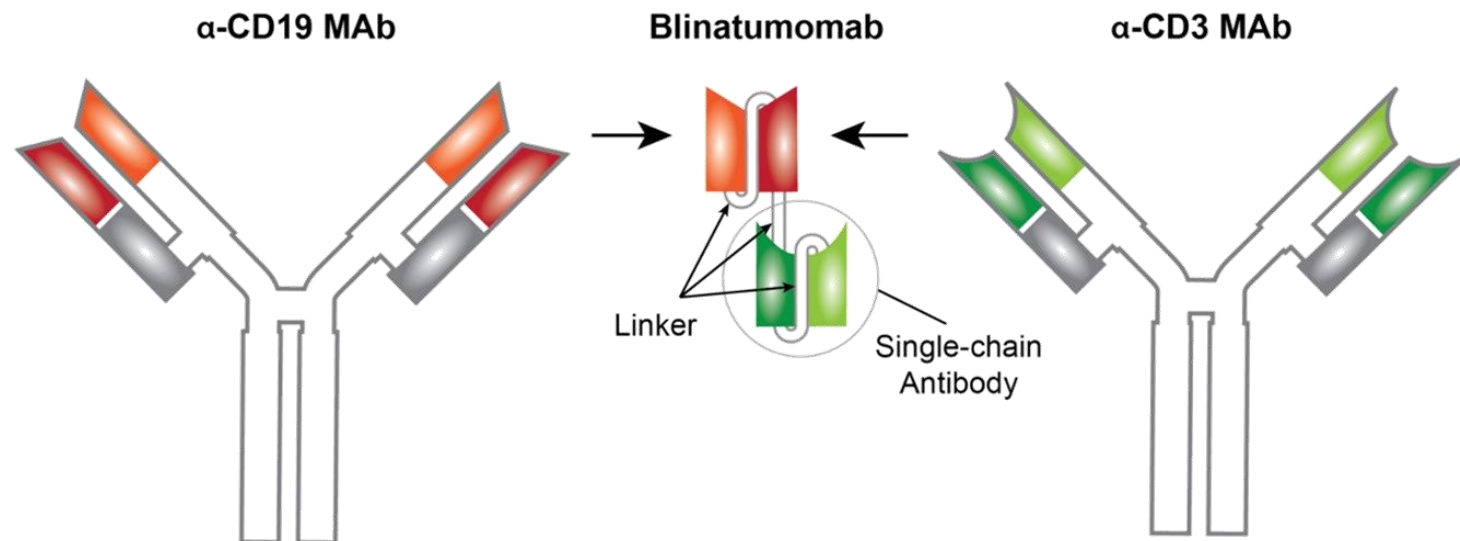
B cell malignancies are CD19+



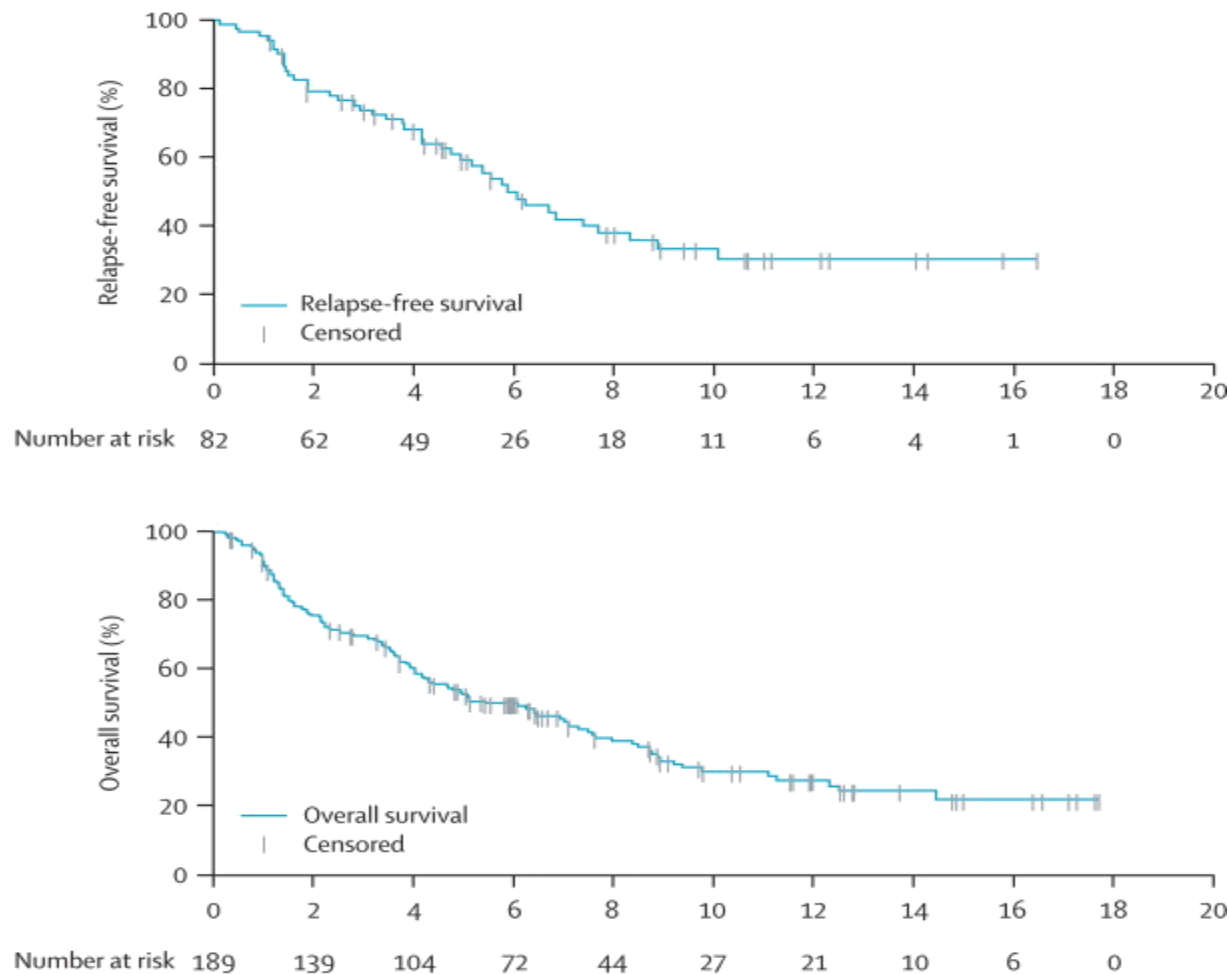
Blanc, V et al., Clinical Cancer Research, Volume 17 , Issue 20

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 11th, 2017



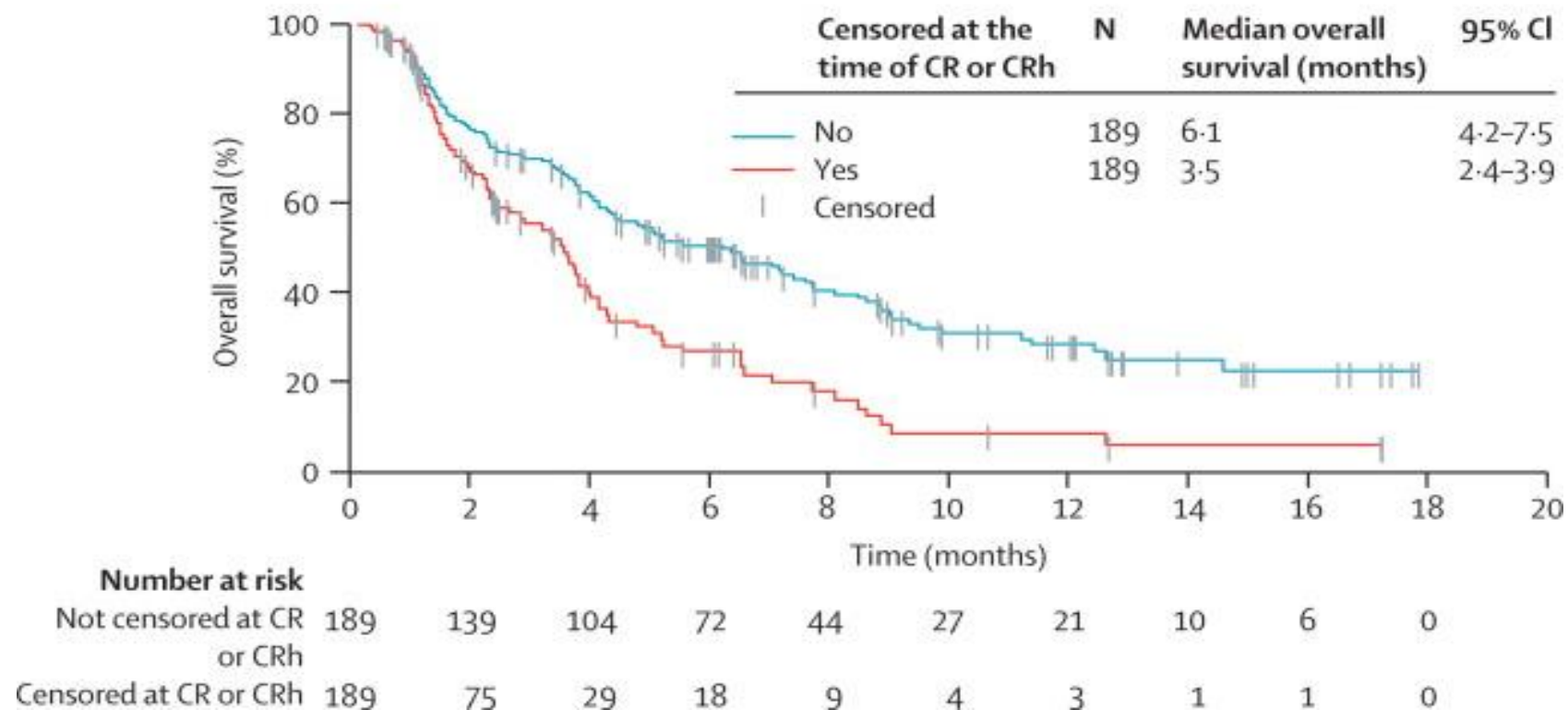
BiTE therapy in ALL



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



BiTE therapy in ALL



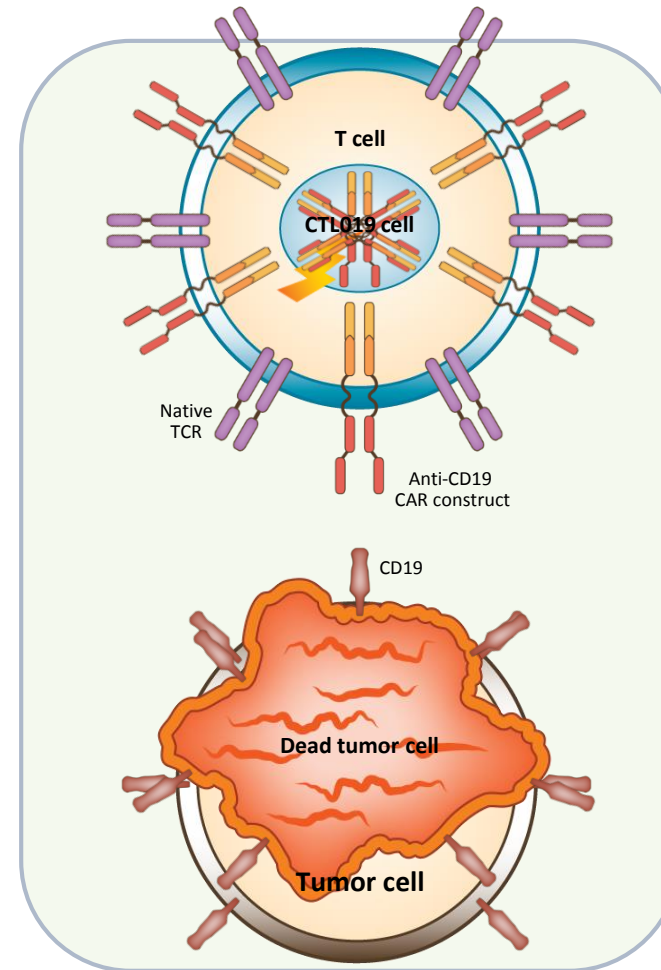
Topp, Max S et al., The Lancet Oncology , Volume 16 , Issue 1 , 57 - 66



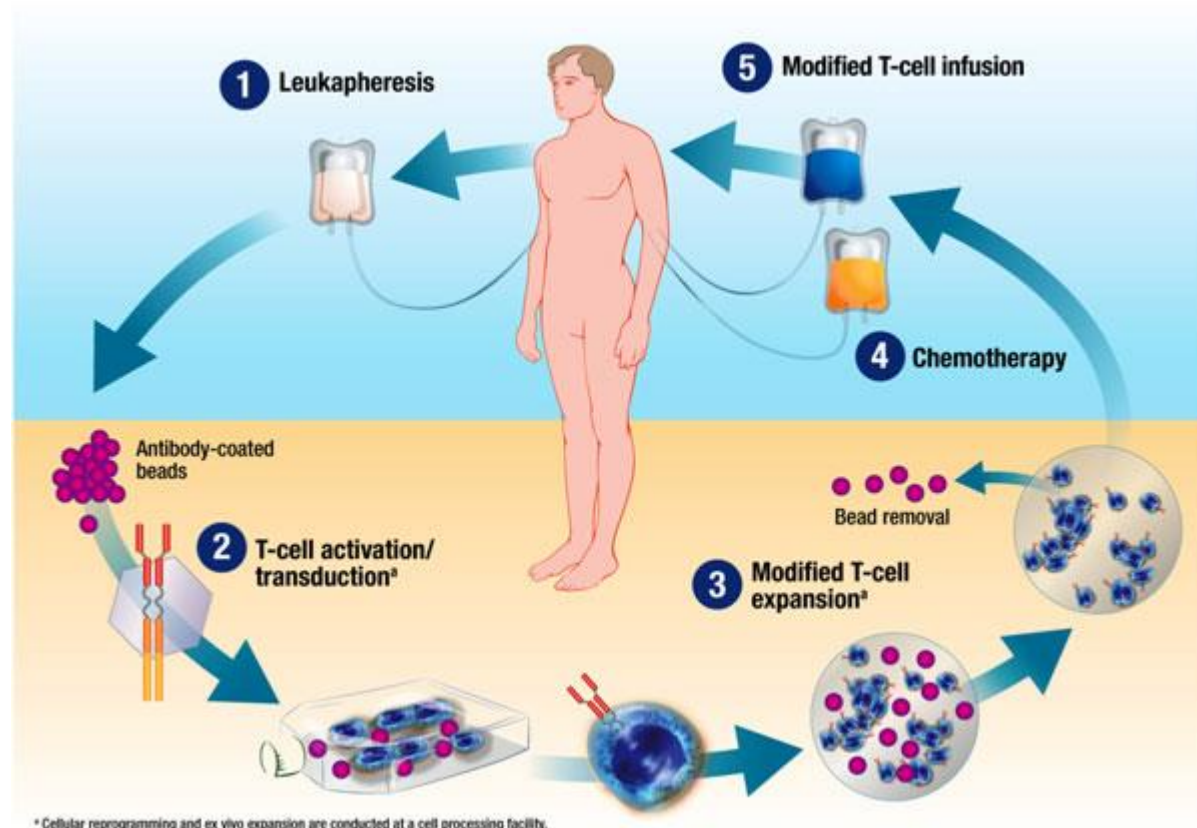
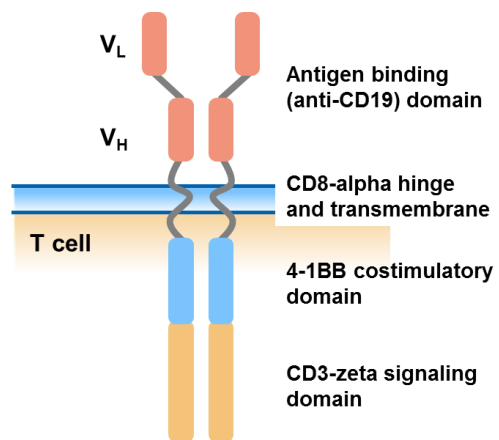
Chimeric Antigen Receptor (CAR) T cell therapy

- Gene transfer technology stably expresses CARs on T cells^{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}
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells³
- **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.



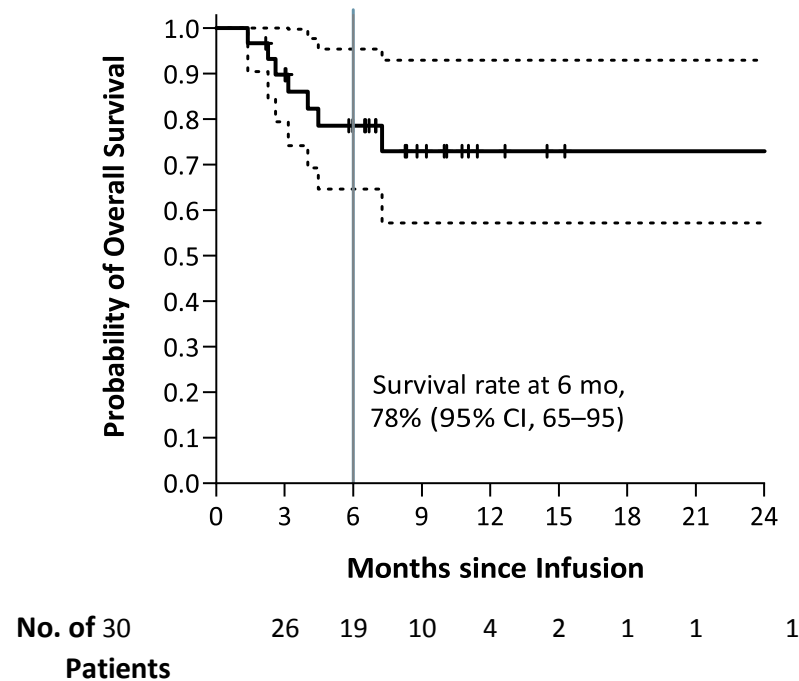
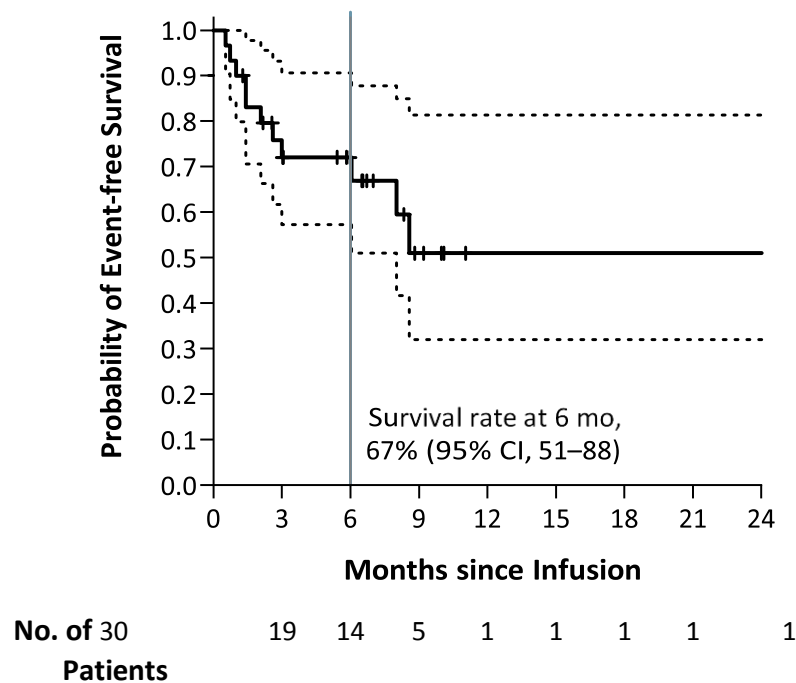
CAR T cell therapy



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 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

CAR T cell therapy in ALL



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

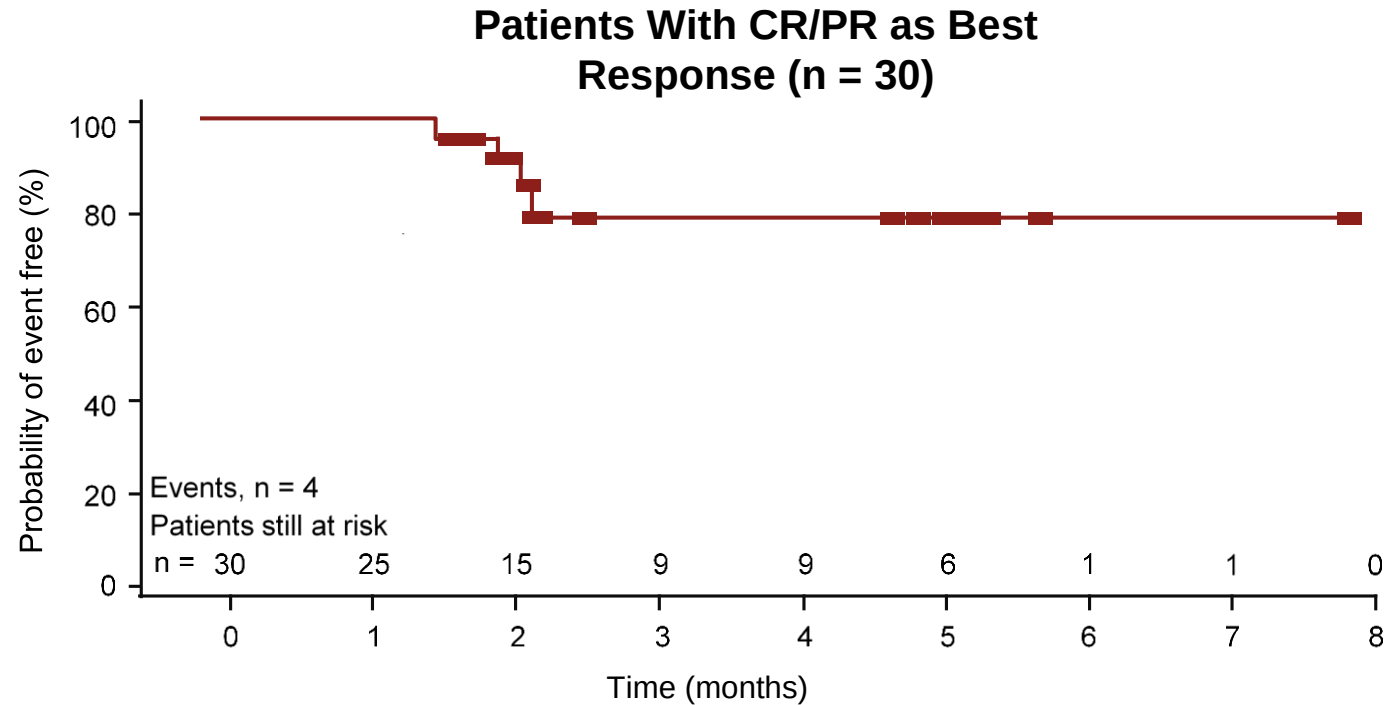


CAR T cell therapy in DLBCL

JULIET multi-institutional study

Response Rate	Patients (N = 51) ^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.



- 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 ¹	KTE-C19 ^{2,3}		JCAR017 ^{4,5}
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% ^a
CR (best response)	43%	54%	71%	60% ^a
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

^a20 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

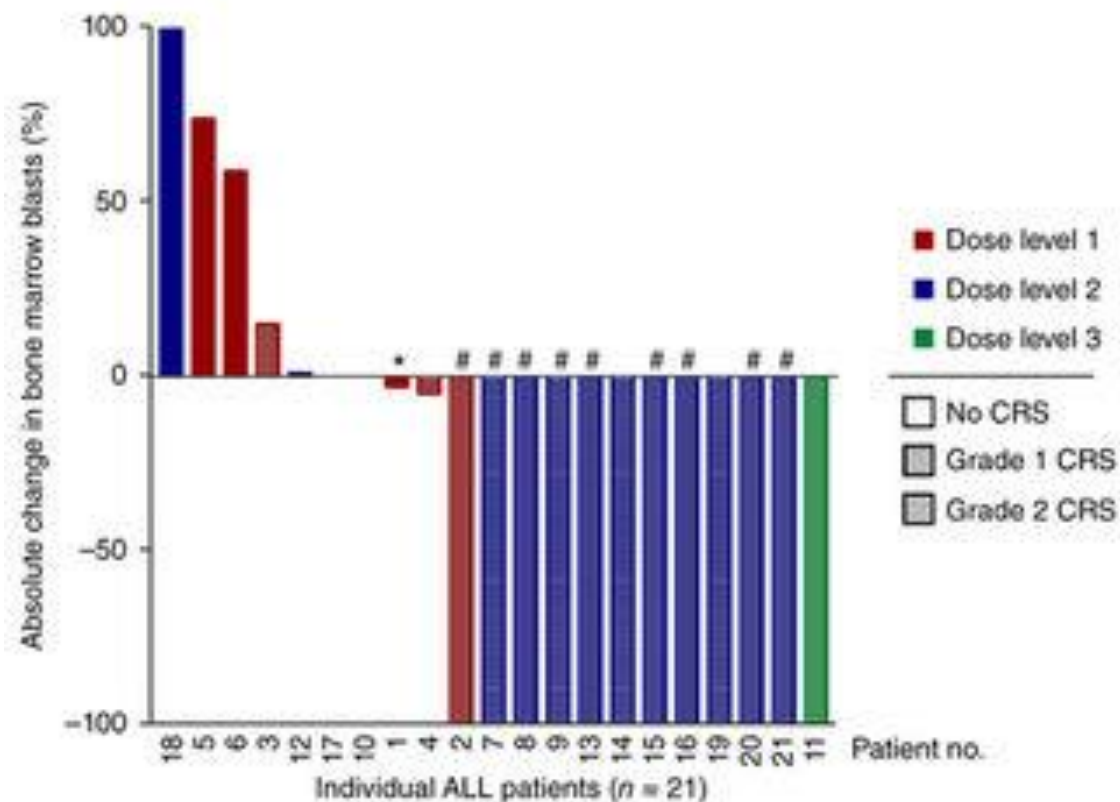
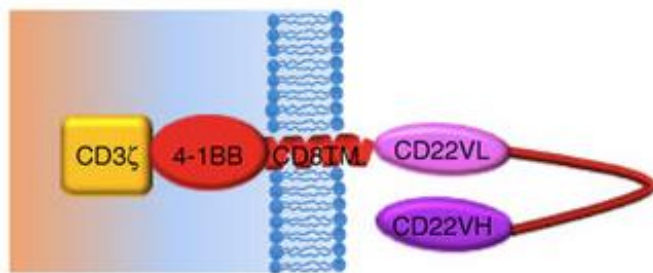
Technology:	CAR T cells	BiTE
Example	tisagenlecleucel (CAR(CD19) T)	blinatumumab (anti-CD3/CD19)
Dosing	One infusion	Continuous 28 days
Complete Response	90%	66%
Survival	78% 6 mos OS	9 mos median
Major toxicity	Cytokine release	Cytokine release
Antigen loss relapse?	Yes	Yes
Challenges	Complex manufacturing,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

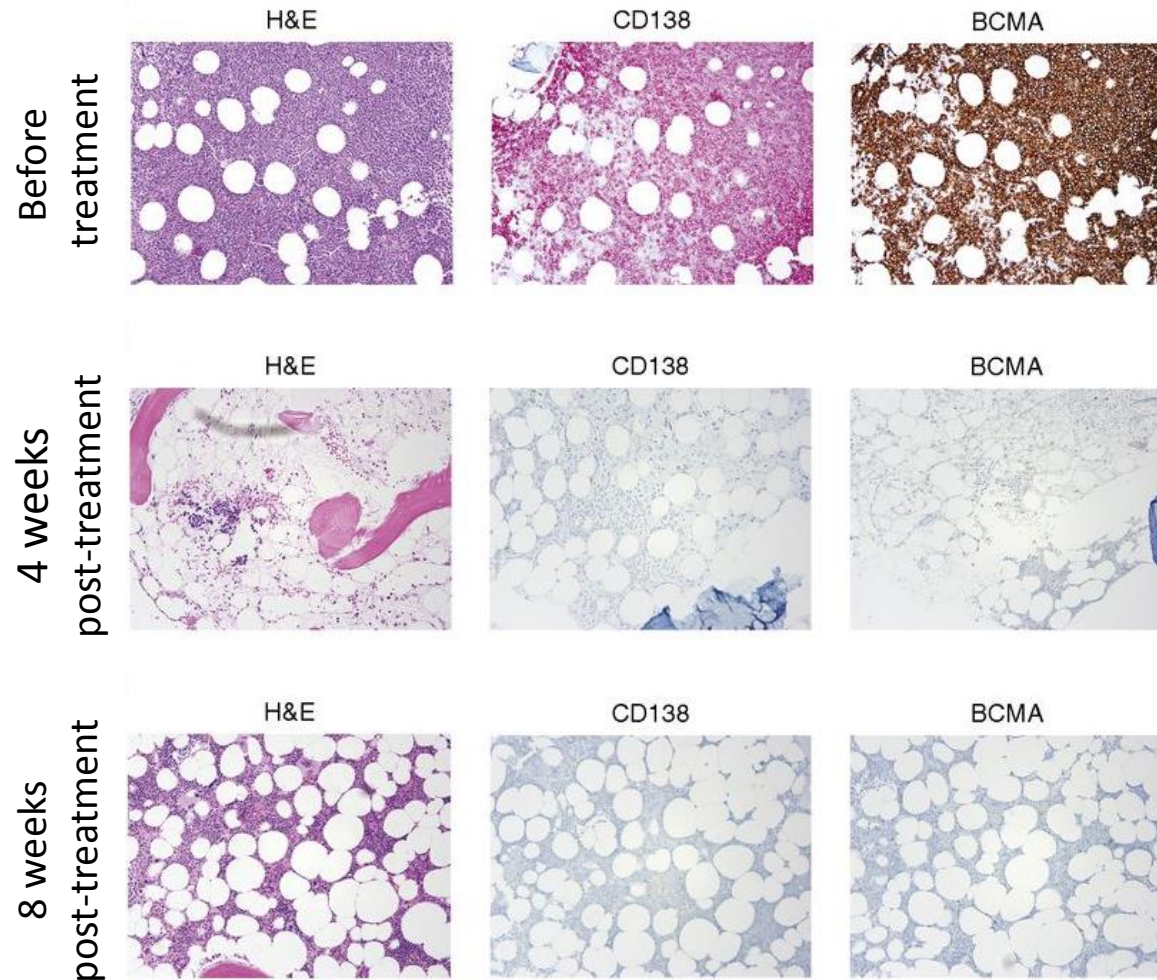
- No approved checkpoint inhibitor therapies
 - KEYNOTE-183/185/023: halted or discontinued due to risk/benefit profile
- Monoclonal Antibodies: 2 FDA Approved
 - **Daratumumab**: Anti-CD38
 - Combined with Bortezomib OR Lenalidomide as 2nd line Rx
 - **Elotuzumab**: Anti-SLAMF7
 - Combined with Lenalidomide as 2nd line Rx
- Vaccine-based approaches

Attenuated measles
Dendritic – tumor fusions
Pulsed dendritic cells

Whole cell - GM-CSF
Idiotypic: RNA, DNA, protein
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 of BCMA CAR T therapy

Berdeja et al BB2121 ASH '17

- 94% ORR, 56% CR

U Penn and NIH studies also promising (NIH data here)

UTSW participating in Phase 2 Celgene/ BlueBird Bio study (KarMMa, now open)

- November 17th, 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^{1†}, Michael R. Bishop^{2†}, Rafat Abonour³, Kenneth C. Anderson⁴, Stephen M. Ansell⁵, David Avigan⁶, Lisa Barbarotta⁷, Austin John Barrett⁸, Koen Van Besien⁹, P. Leif Bergsagel¹⁰, Ivan Borrello¹¹, Joshua Brody¹², Jill Brufsky¹³, Mitchell Cairo¹⁴, Ajai Chari¹², Adam Cohen¹⁵, Jorge Cortes¹⁶, Stephen J. Forman¹⁷, Jonathan W. Friedberg¹⁸, Ephraim J. Fuchs¹⁹, Steven D. Gore²⁰, Sundar Jagannath¹², Brad S. Kahl²¹, Justin Kline²², James N. Kochenderfer²³, Larry W. Kwak²⁴, Ronald Levy²⁵, Marcos de Lima²⁶, Mark R. Litow²⁷, Anuj Mahindra²⁸, Jeffrey Miller²⁹, Nikhil C. Munshi³⁰, Robert Z. Orlowski³¹, John M. Pagel³², David L. Porter³³, Stephen J. Russell⁵, Karl Schwartz³⁴, Margaret A. Shipp³⁵, David Siegel³⁶, Richard M. Stone⁴, Martin S. Tallman³⁷, John M. Timmerman³⁸, Frits Van Rhee³⁹, Edmund K. Waller⁴⁰, Ann Welsh⁴¹, Michael Werner⁴², Peter H. Wiernik⁴³ and Madhav V. Dhodapkar^{44*}

