ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy of Hematologic Malignancies

Lazaros Lekakis, MD
Associate Professor of Medicine,
BMT and Cellular Immunotherapy,
University of Miami

AMERICAN ACADEMY OF EMERGENCY MEDICINE

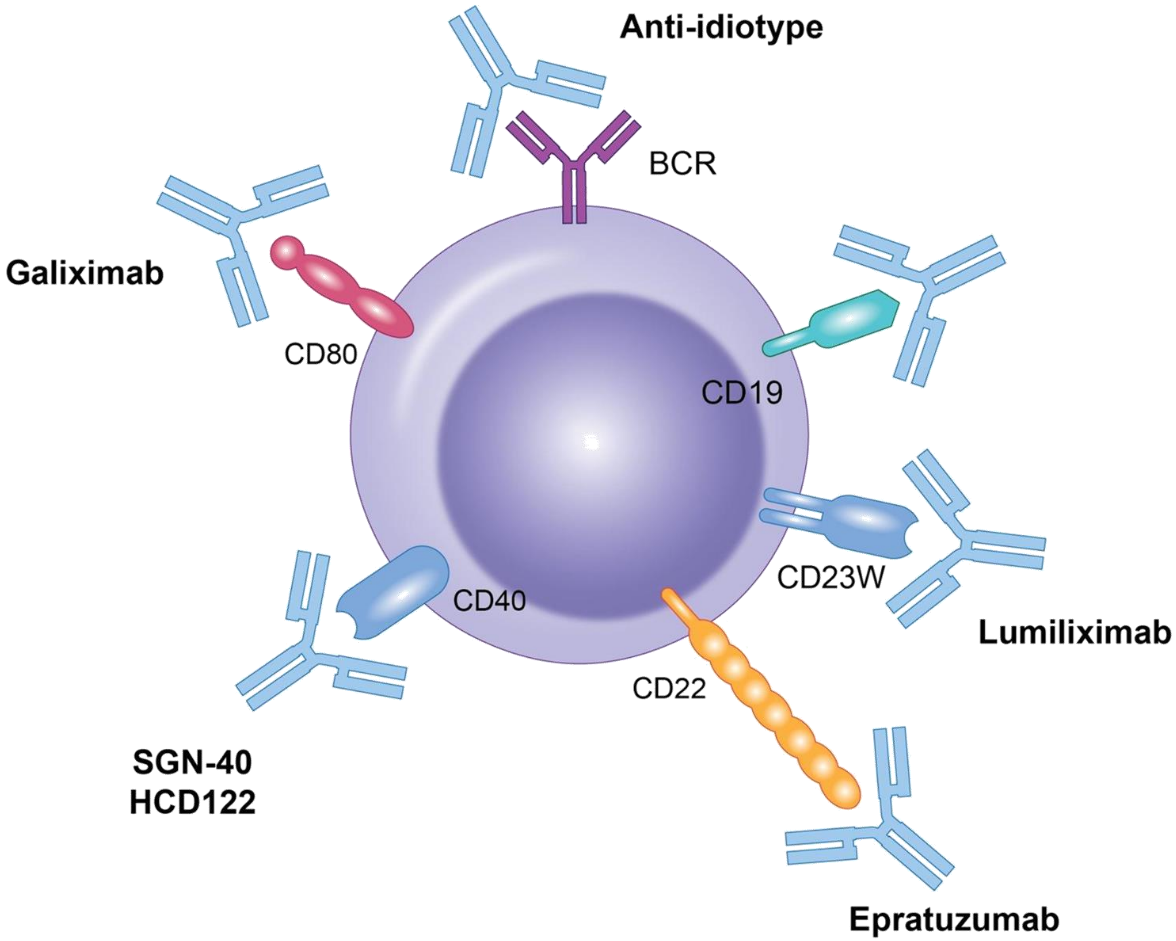
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Disclosures

- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

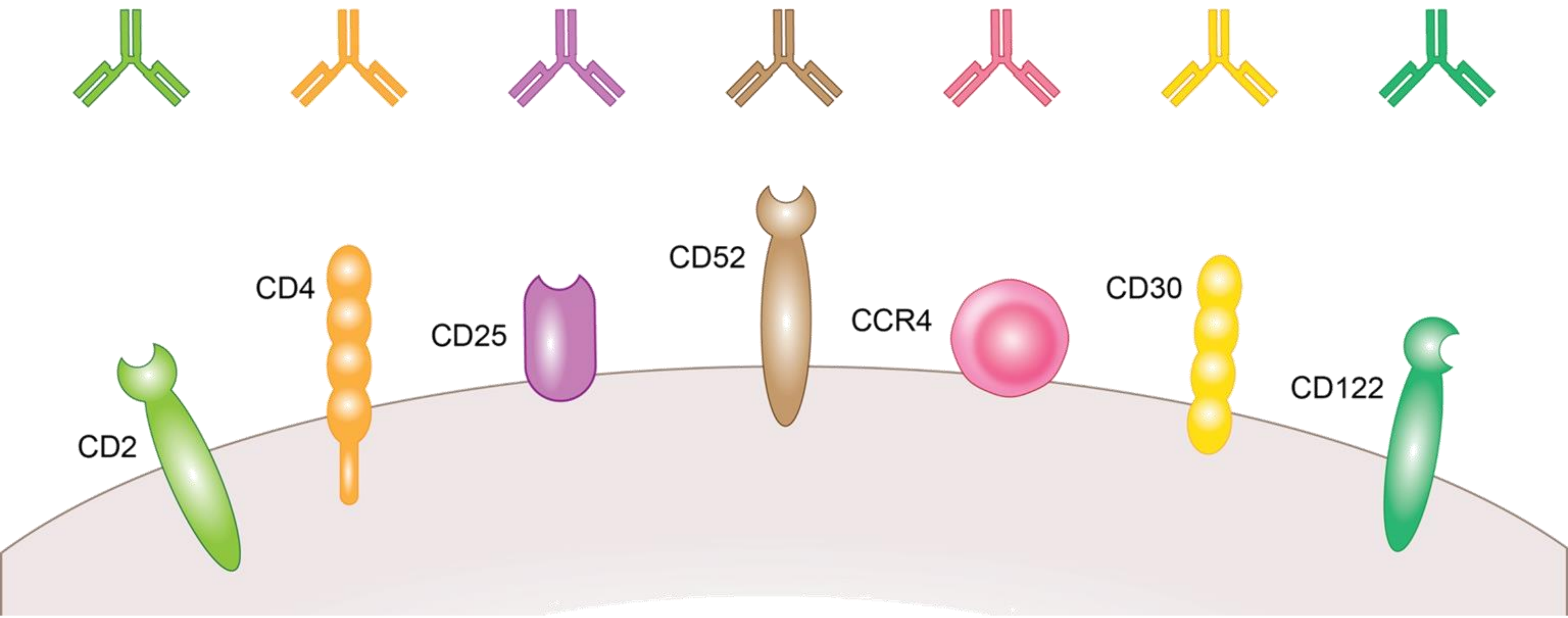
Monoclonal antibodies targeting B cell lymphomas



Monoclonal antibodies targeting B cell lymphomas

- Galiximab (a-CD80) failed in Hodgkin and not very impressive in FL.
- Lumiliximab (a-CD23) failed in a phase III in CLL.
- Anti-idiotype Abs due to labor intensiveness have lost ground.
- SGN40: Dacetuzumab (a-CD40): Negative phase IIB trial of RICE +/- dacetuzumab in relapsed DLBCL.
- Epratuzumab (a-CD22): Practically dead after approval of inotuzumab ozogamicin. Not very effective anyway.
- HCD122 (humanized a-CD40): Responses <15% in Hodgkin and in DLBCL.

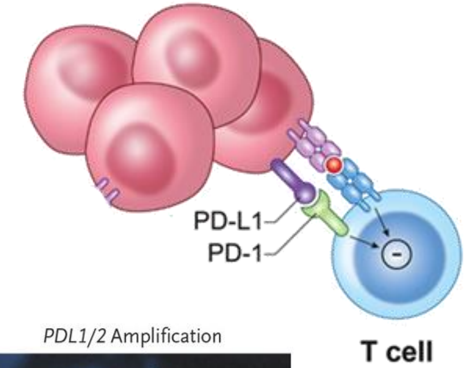
Monoclonal antibodies targeting T cell lymphomas



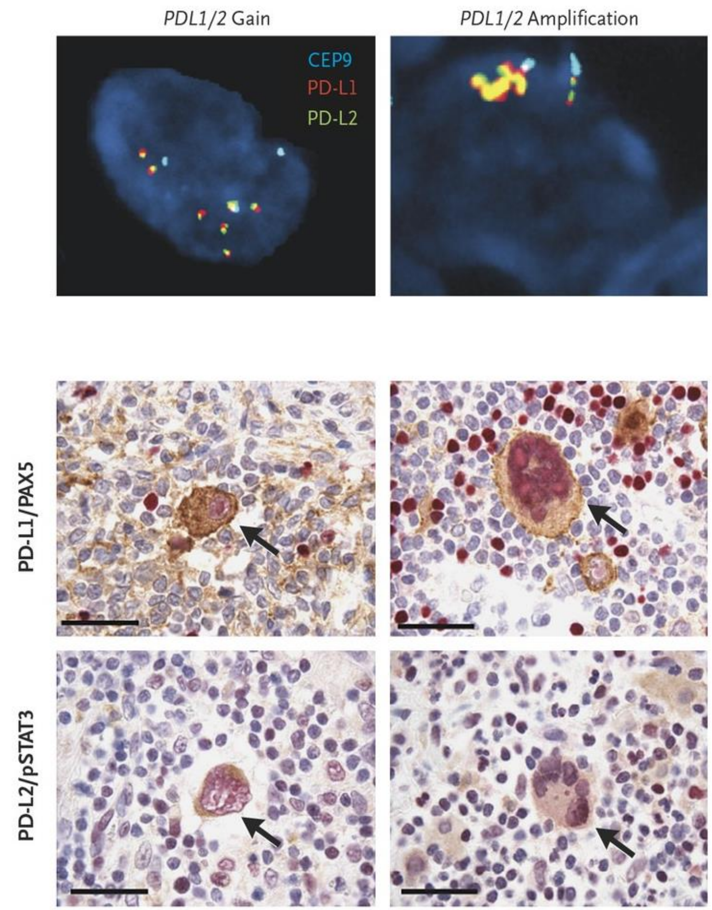
Monoclonal antibodies targeting T cell lymphomas

- Mogamulizumab (a-CCR4) is under FDA priority review for CTCL and is used in Japan alone or in combination for ATLL
- Denileukin diflitox (ONTAK, withdrawn: a-CD25 immunotoxin: some activity for ATLL, CTCL, GVHD)
- Basiliximab: a-CD25 Abs mainly for rejection prevention
- Alemtuzumab (a-CD52): Very effective for T-PLL, 17p- CLL, B-PLL, GVHD prevention (severe immunosuppression) and also for Sezary and refractory ATLL.
- Brentuximab vedotin (a-CD30 immunotoxin, very active in ALCL, HL and some cases of PTCL)

Checkpoint inhibitors

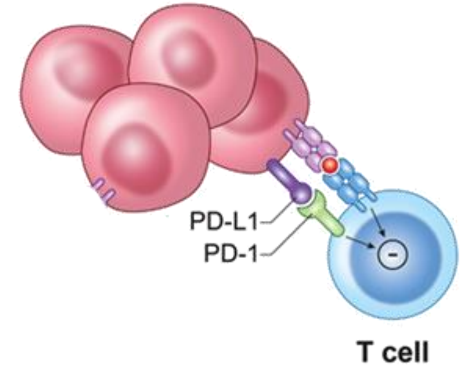


- Reed-Sternberg cells express both PD-L1 and PD-L2
- Expression of ligands increases with advanced disease
- Unclear whether PD-L1/L2 expression correlates with response to treatment



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

ADVANCES IN Cancer IMMUNOTHERAPY™



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

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Nivolumab in Hodgkin lymphoma

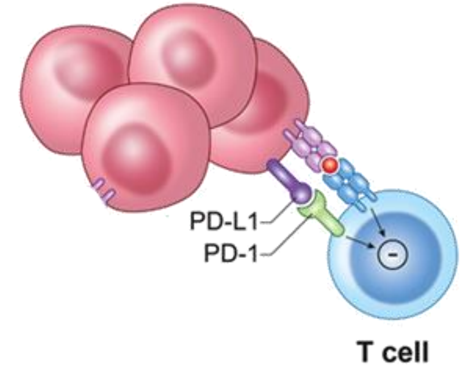


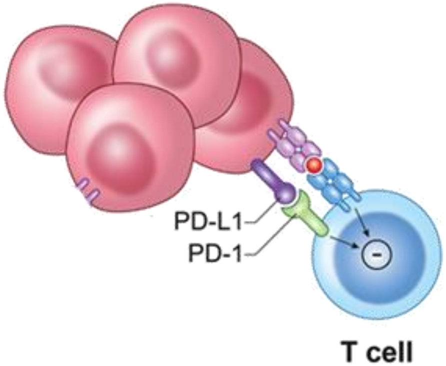
Table 3. Clinical Activity in Nivolumab-Treated Patients.*

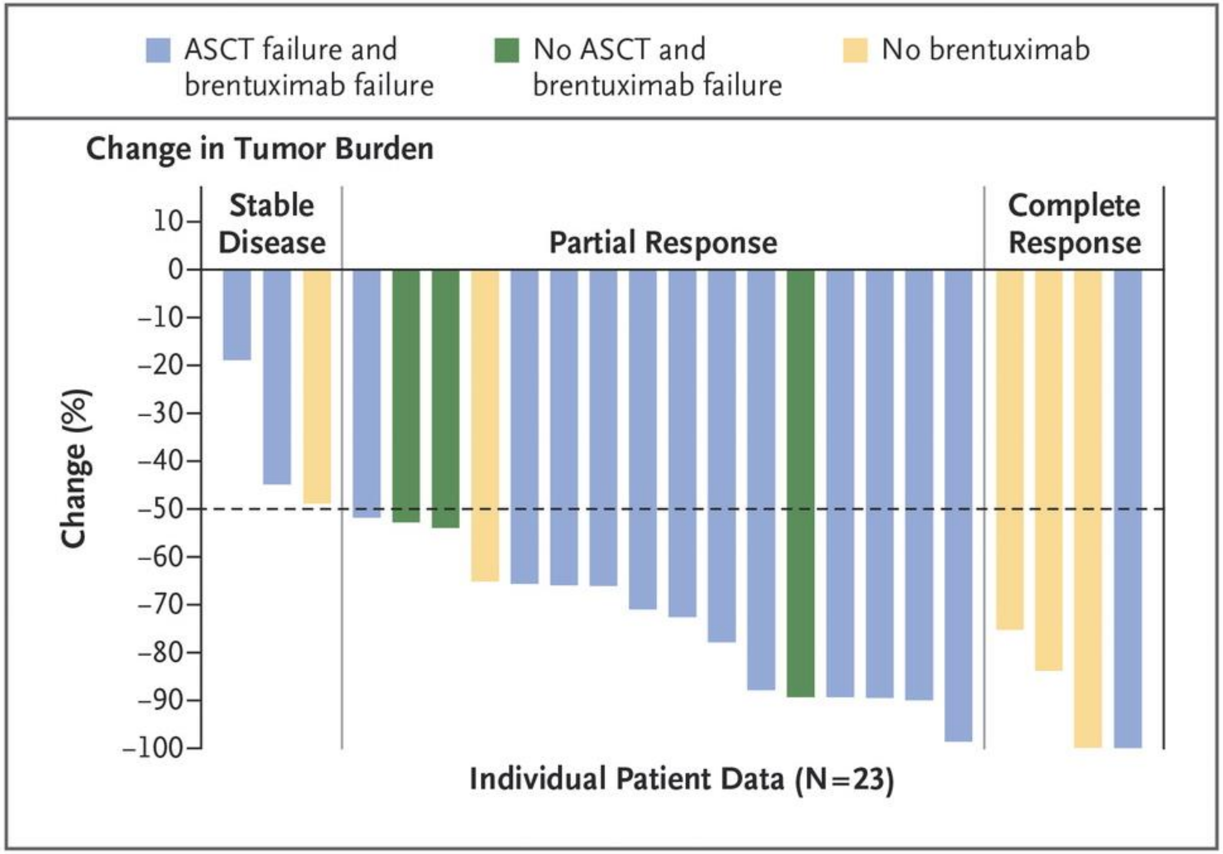
Variable	All Patients (N=23)	Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)	No Stem-Cell Transplantation and Failure of Brentuximab (N=3)	No Brentuximab Treatment (N=5)†
Best overall response — no. (%)				
Complete response	4 (17)	1 (7)	0	3 (60)
Partial response	16 (70)	12 (80)	3 (100)	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.

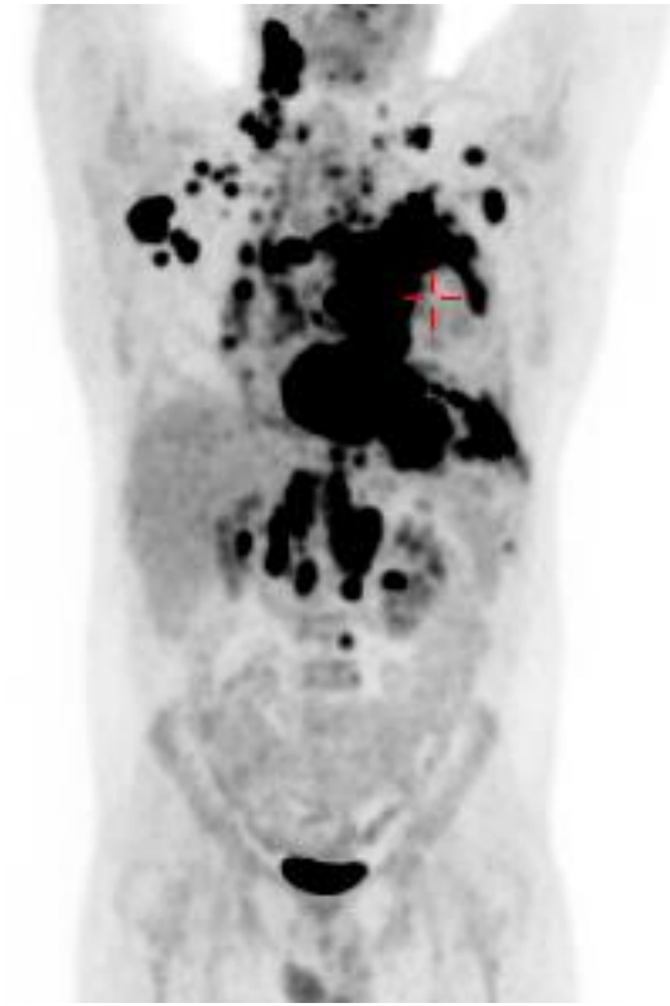
Ansell SM et al. N Engl J Med 2015;372:311-319

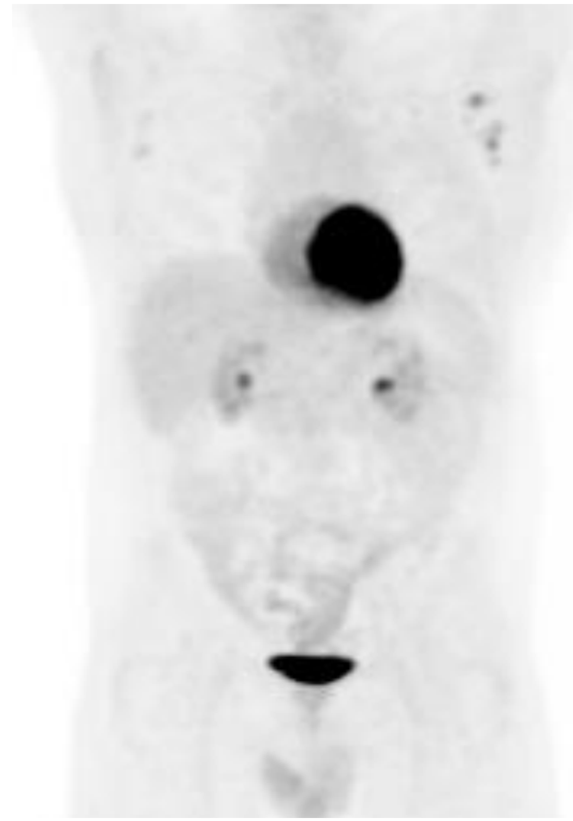
Nivolumab in Hodgkin lymphoma





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

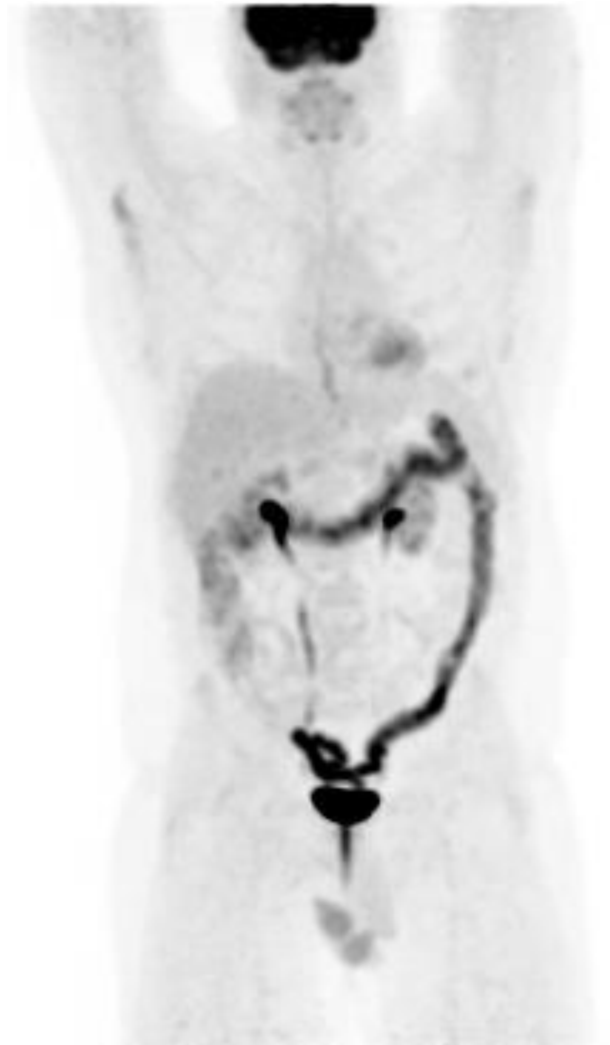




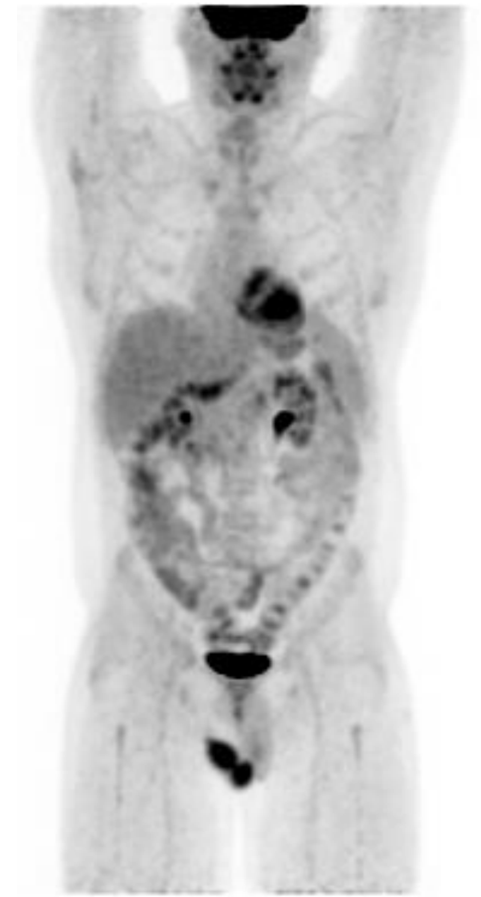
Post-BV

ADVANCES IN Cancer IMMUNOTHERAPY™

Post-auto

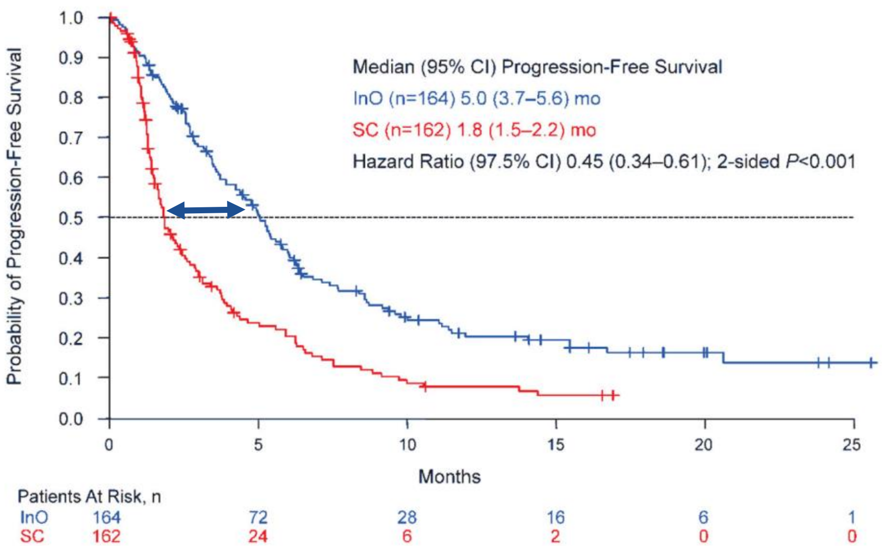


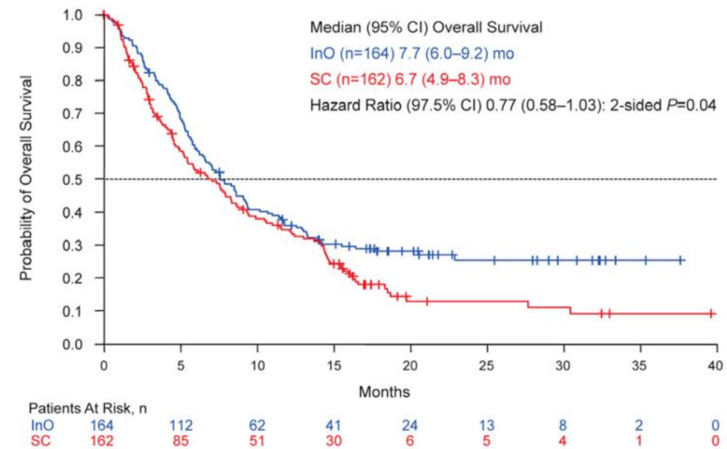
Post-nivo



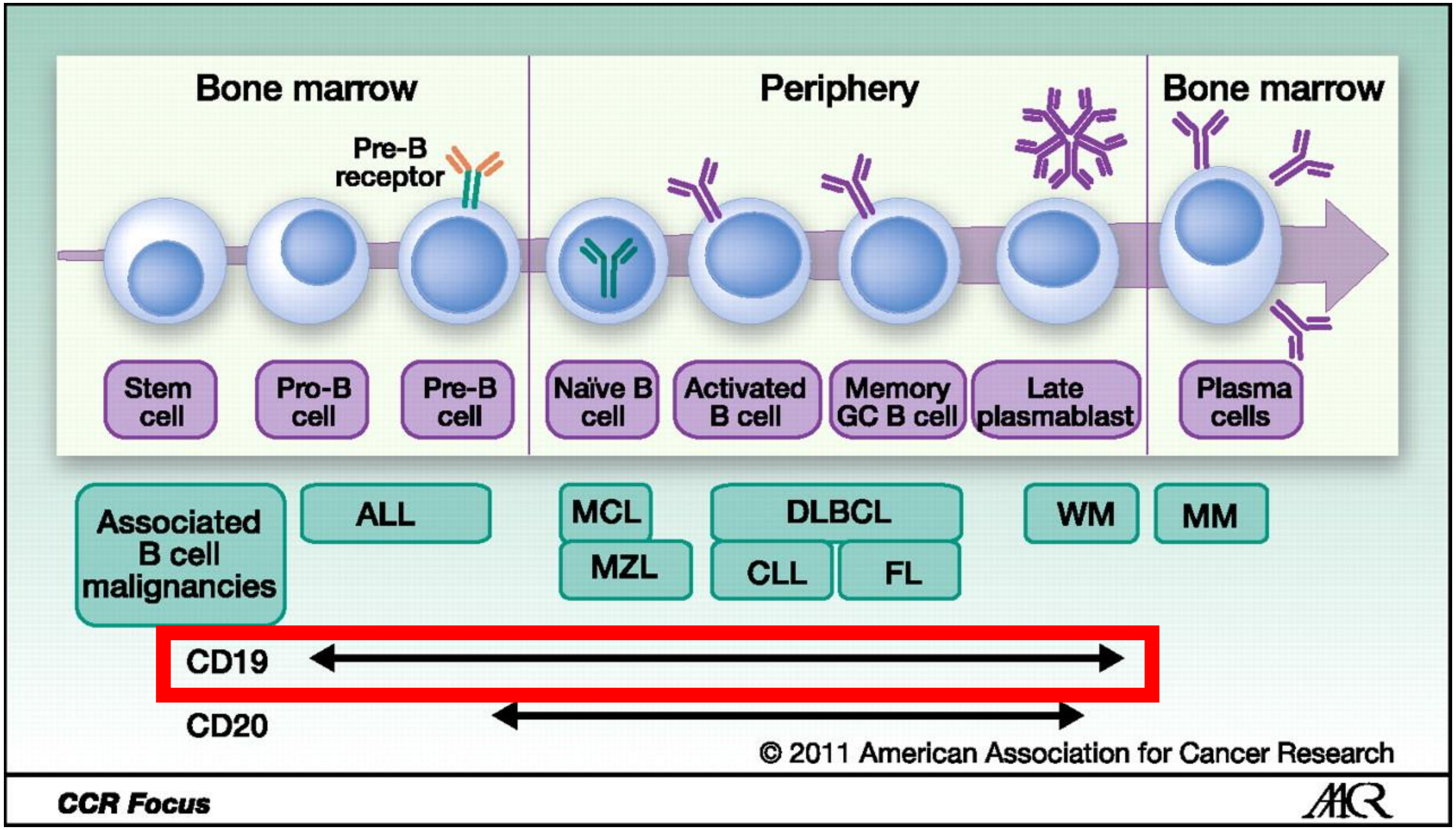
Post-allo

Inotuzumab vs. standard chemo for relapsed ALL





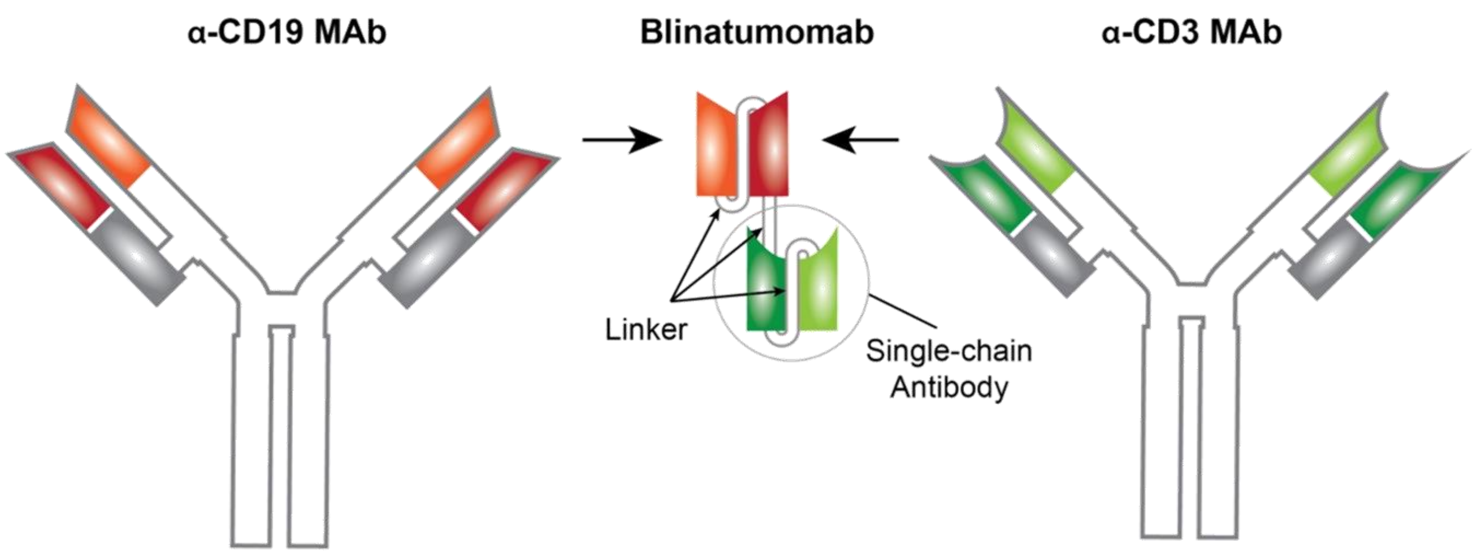
B cell malignancies are CD19+



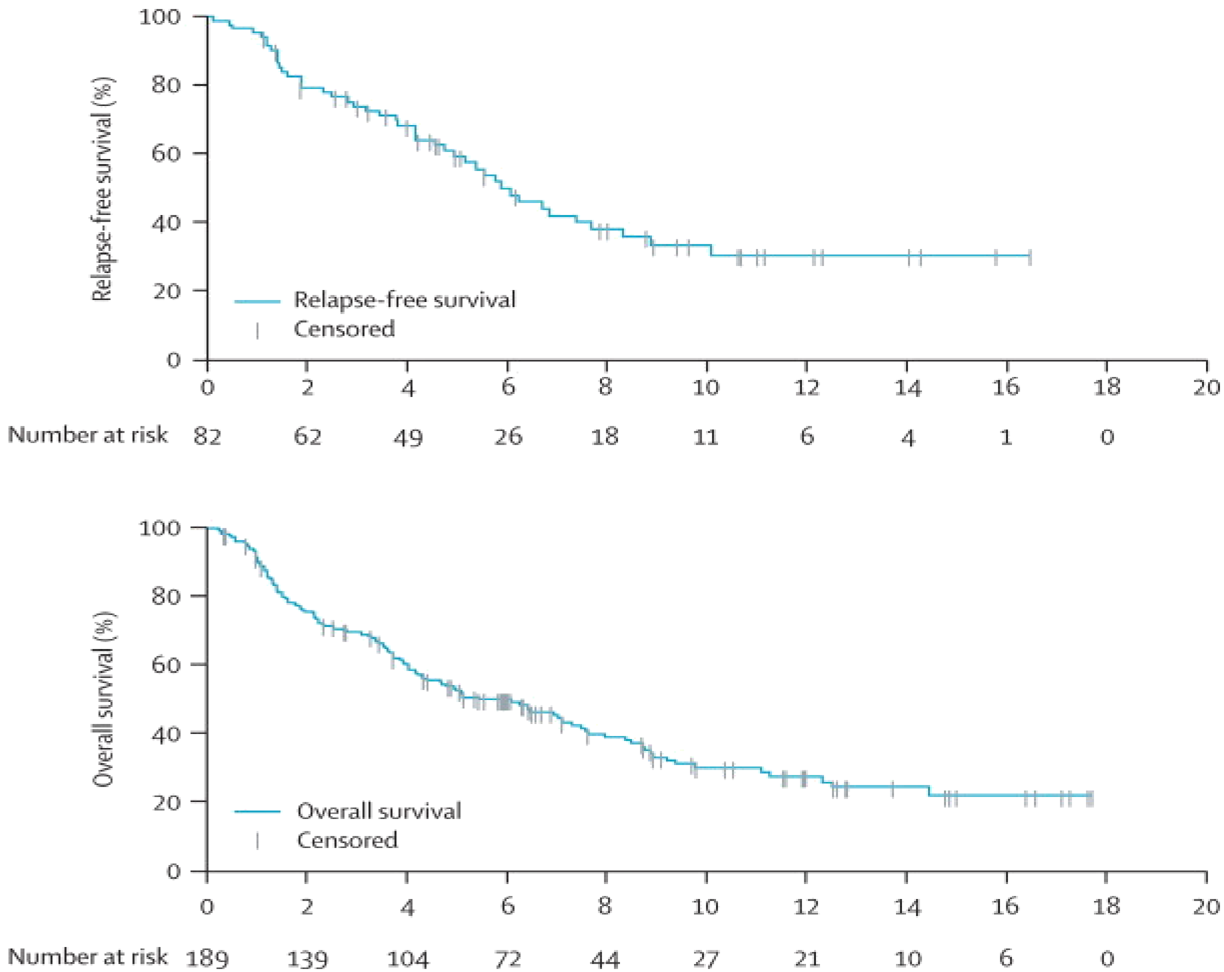
Blanc, V et al., Clinical Cancer Research, Volume 17 , Issue 20

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

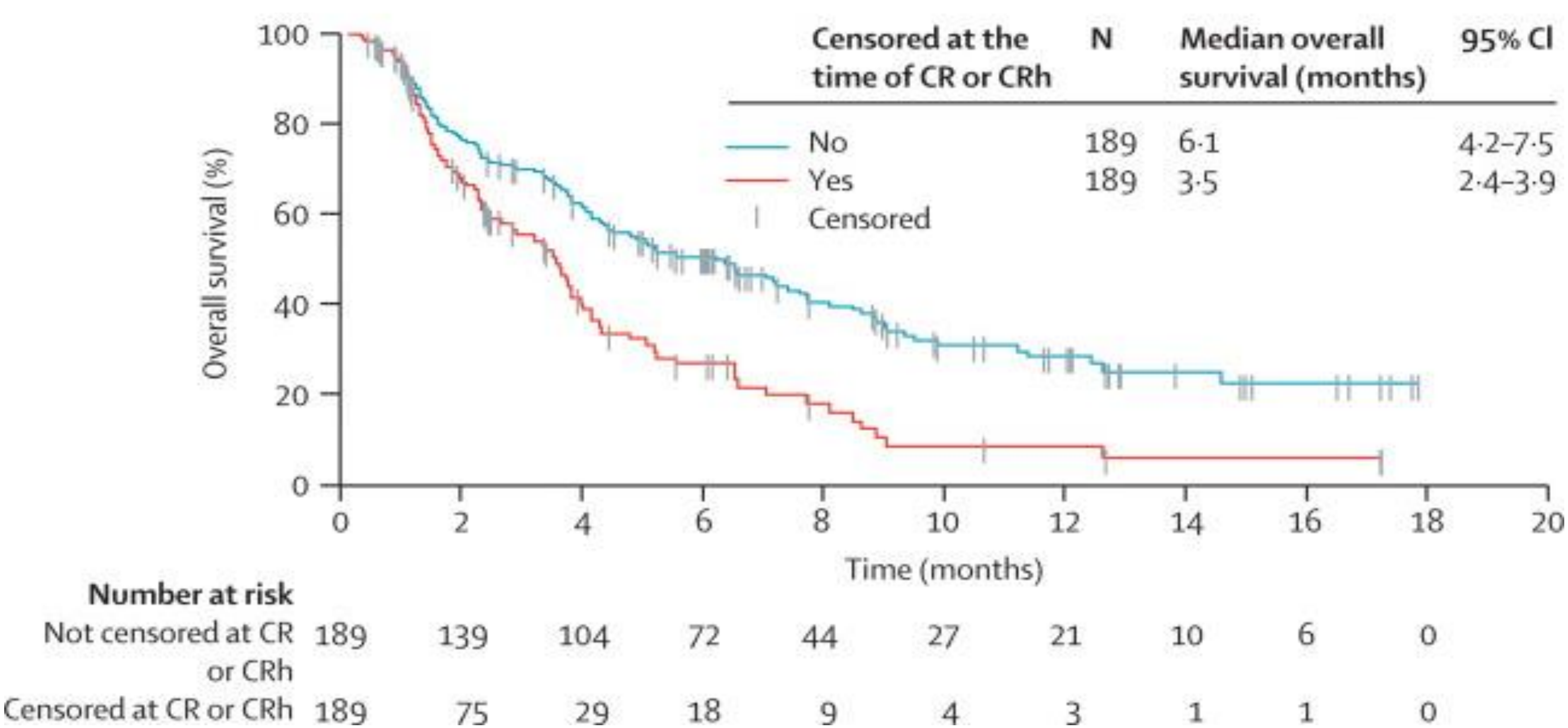


BiTE therapy in ALL



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

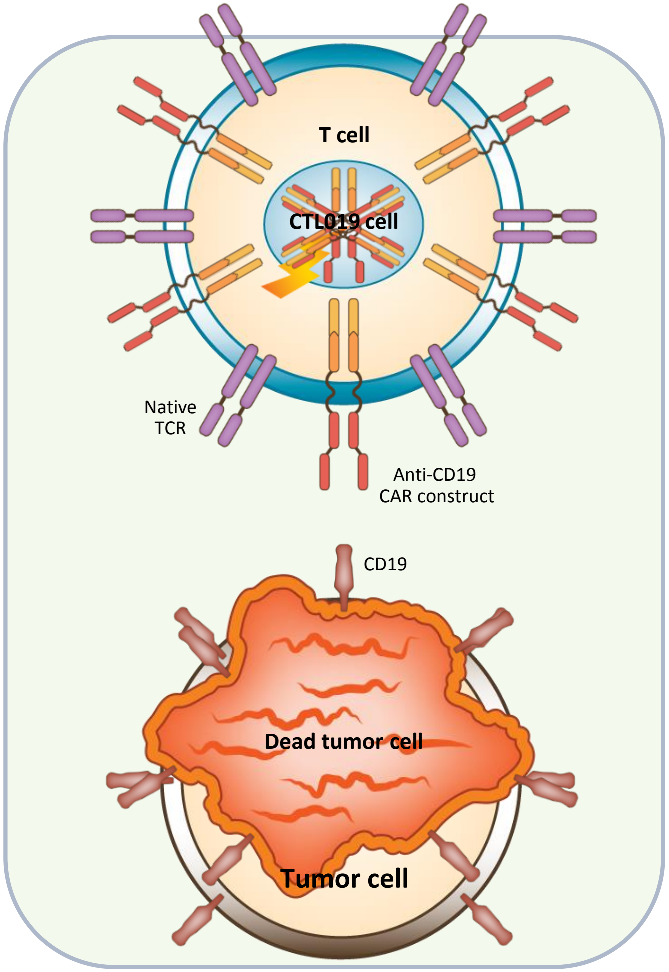
BiTE therapy in ALL



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

Chimeric Antigen Receptor (CAR) T cell therapy

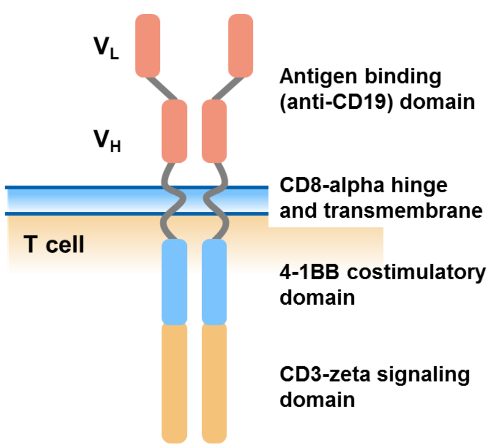
- Gene transfer technology stably expresses CARs on T cells[1,2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]
- **T cells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

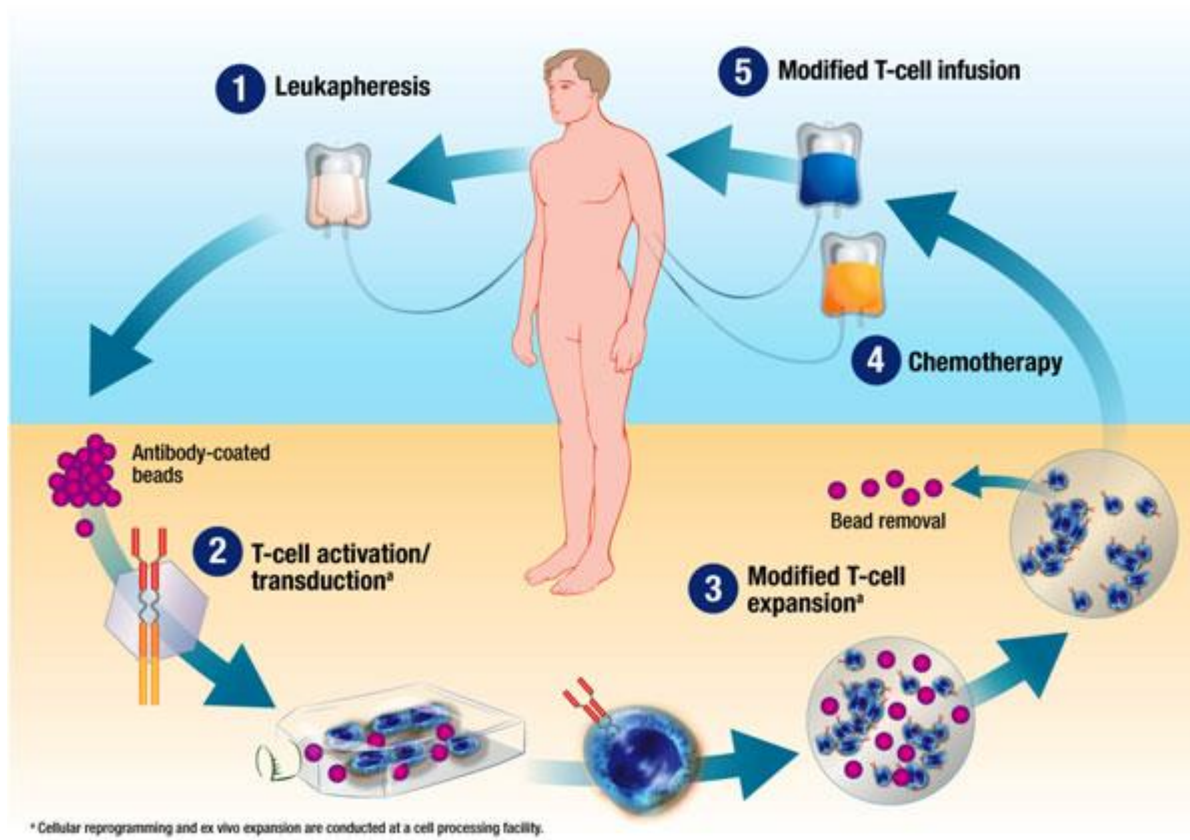


1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

ADVANCES IN Cancer IMMUNOTHERAPY™

CAR T cell therapy





ACCC Association of Community Cancer Centers

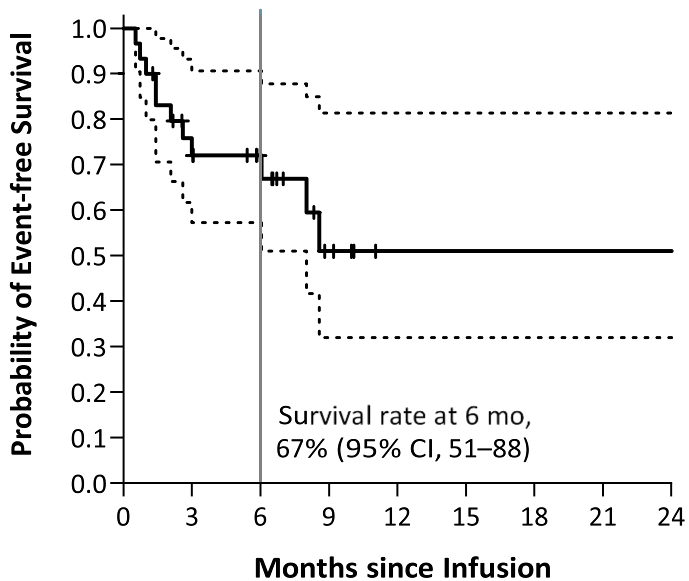
sitc Society for Immunotherapy of Cancer

FDA-approved CAR T cell therapies for hematologic malignancies

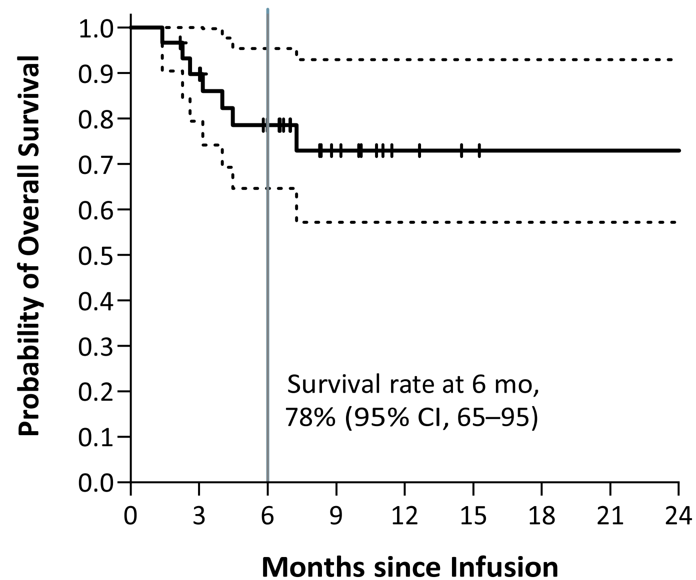
- Kymriah (tisagenlecleucel)
  - Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse
  - Accelerated approval – August 30th, 2017
- Yescarta (axicabtagene ciloleucel)
  - ZUMA-1: Adult patients with relapsed or refractory large B-cell lymphoma after 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

ADVANCES IN Cancer IMMUNOTHERAPY™

CAR T cell therapy in ALL



No. of Patients: 30, 19, 14, 5, 1, 1, 1, 1, 1



No. of Patients: 30, 26, 19, 10, 4, 2, 1, 1, 1

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

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

CAR T cell therapy in DLBCL

JULIET multi-institutional study

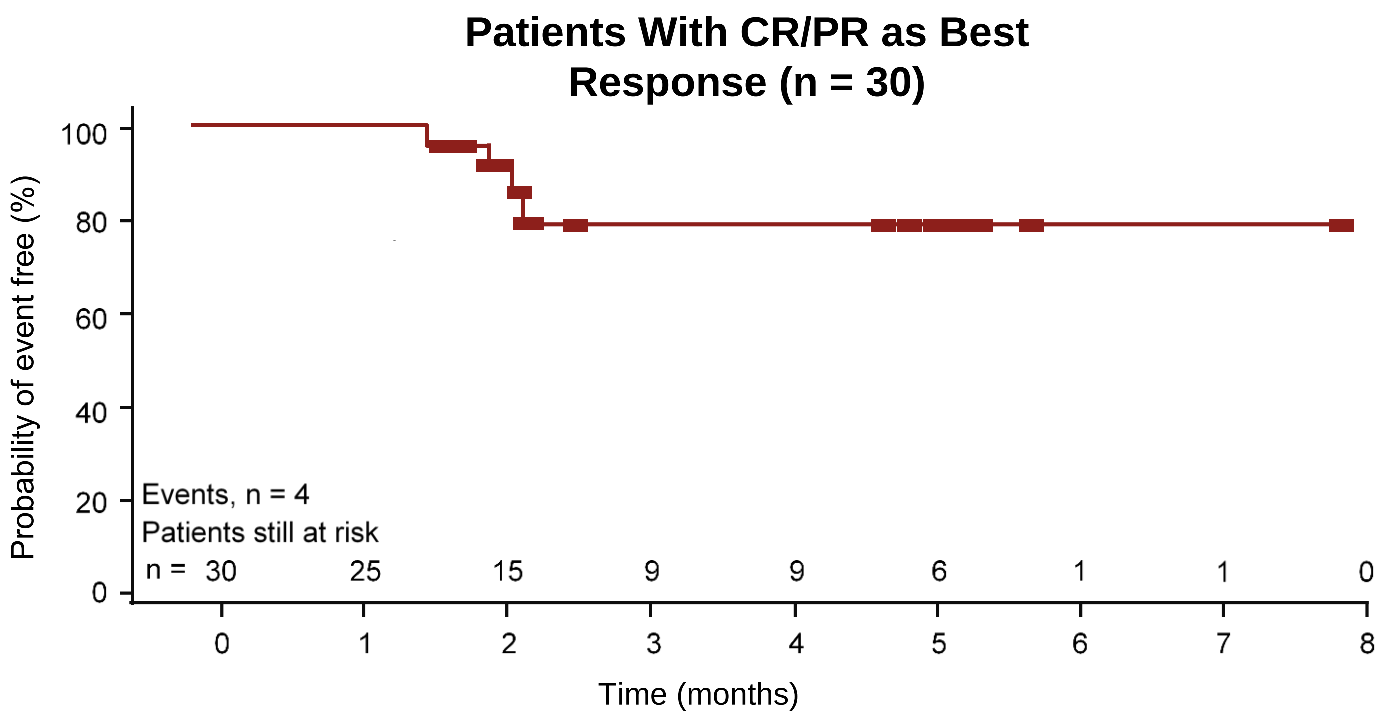
Response Rate	Patients (N = 51)[a]	
Best overall response (CR + PR)	59%	P < .0001[b] (95% CI, 44-72)
CR[1]	43%	
PR[1]	16%	
SD[1]	12%	
PD[1]	24%	
Overall response rate (CR + PR) at 3 months	45%	
CR[1]	37%	
PR[1]	8%	

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

ADVANCES IN Cancer IMMUNOTHERAPY™

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

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

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

[a]20 pts with DLBCL were evaluated for efficacy.

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

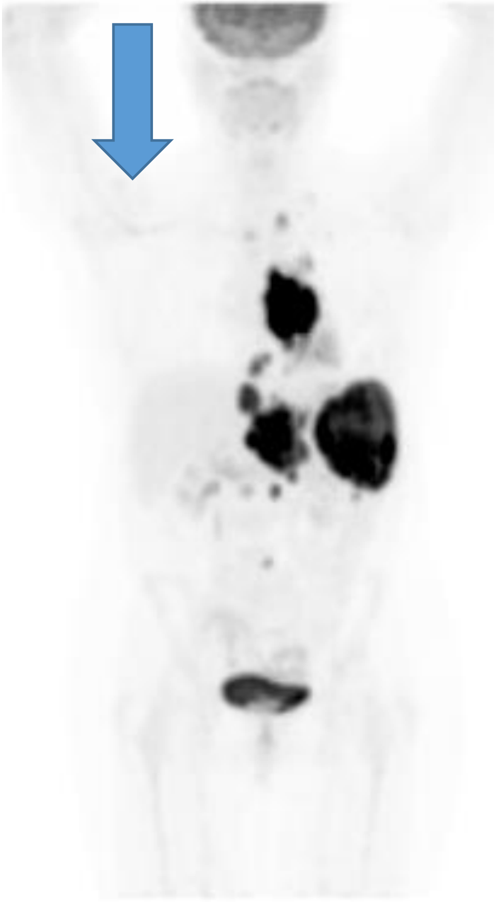
1. Schuster, SJ, et al. ICML 2017 [abstract 007]. 2. Locke FL, et al. AACR 2017 [abstract CT019]; 3. Locke FL, et al. ASCO 2017 [abstract 7512]; 4. Abramson JS, et al. *Blood*. 2016;128(22) [abstract 4192]; 5. Abramson JS, et al. ASCO 2017 [abstract 7513].

Antigen-specific approaches in ALL

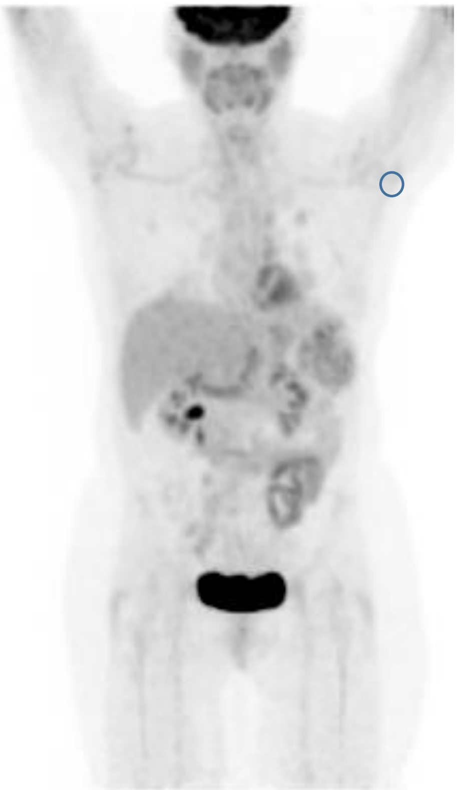
Technology:	CAR T cells	BiTE
Example	tisagenlecleucel (CAR(CD19) T)	blinatumumab (anti-CD3/CD19)
Dosing	One infusion	Continuous 28 days
Complete Response	90%	66%
Survival	78% 6 mos OS	9 mos median
Major toxicity	Cytokine release	Cytokine release
Antigen loss relapse?	Yes	Yes
Challenges	Complex manufacturing,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

Gill Immunol Rev Dec 2014

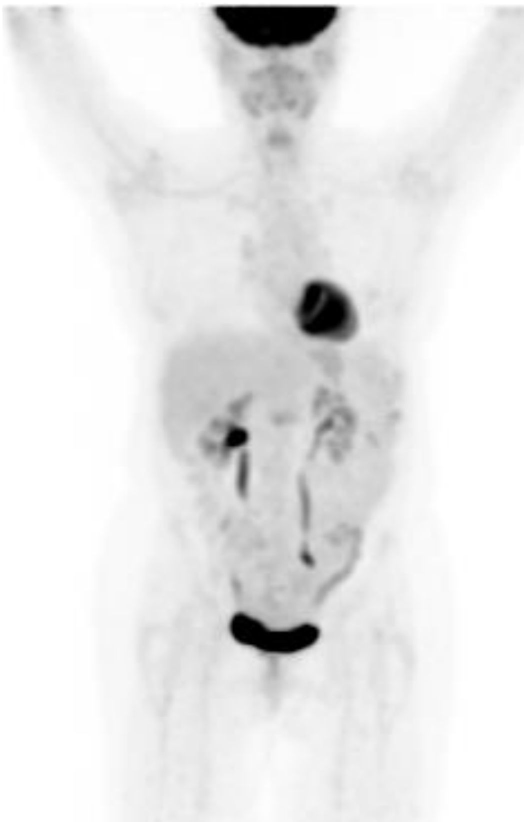
CD19-CART



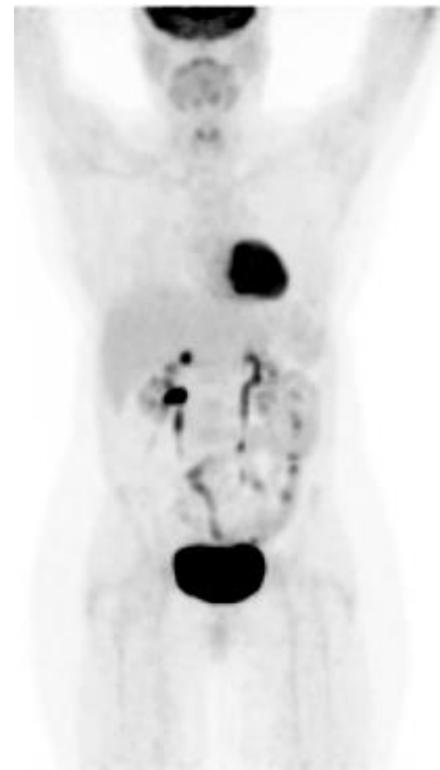
DEC 2015



FEB 2016



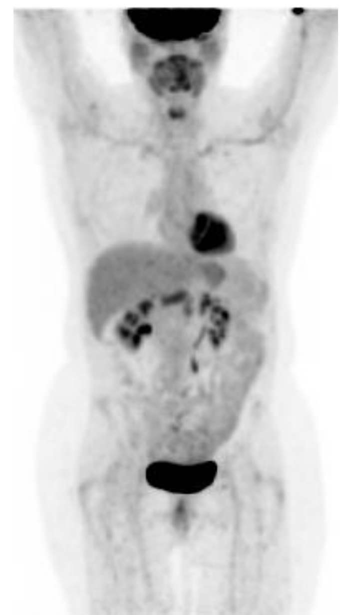
April 2016



June 2016

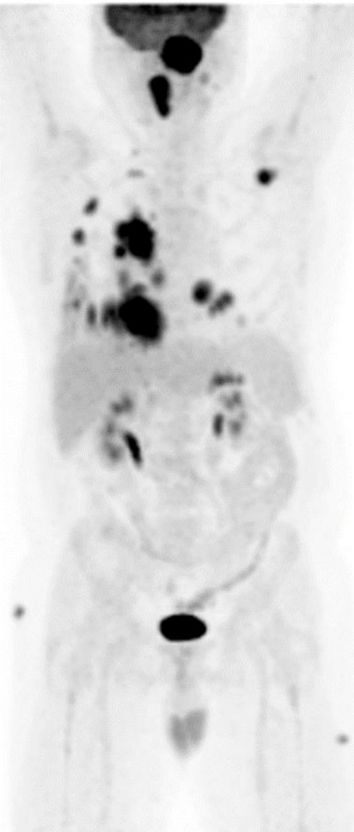
REPEATED infusion

AUG 2016



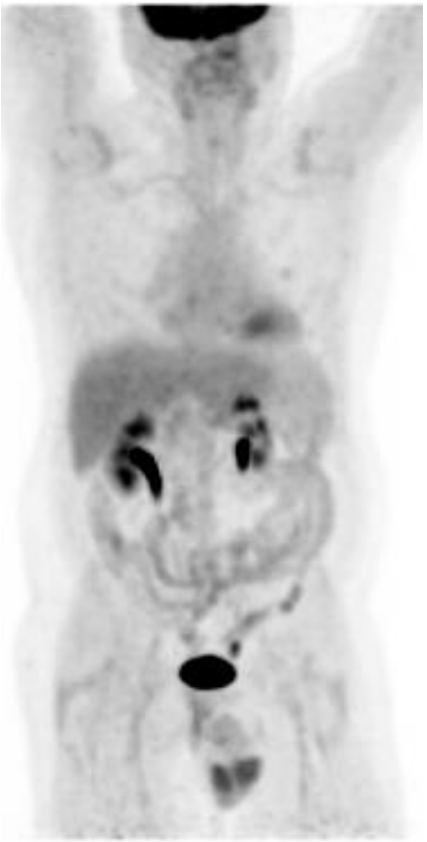
SEP 2016

CD19-CART: 2nd case

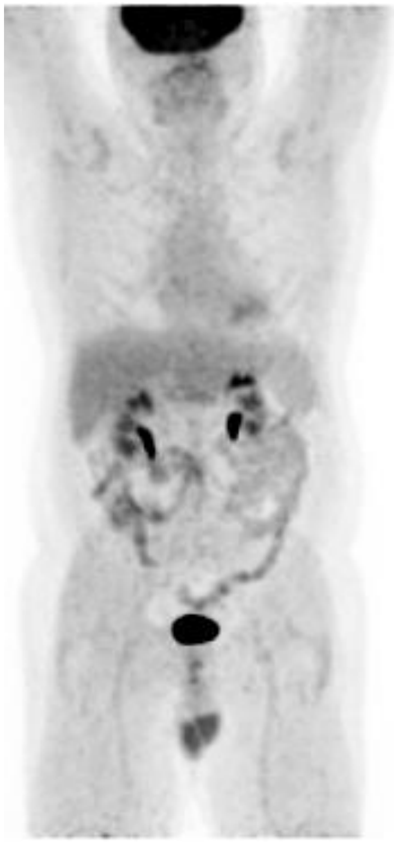


APRIL 2016

CAR-T infusion



MAY 2016

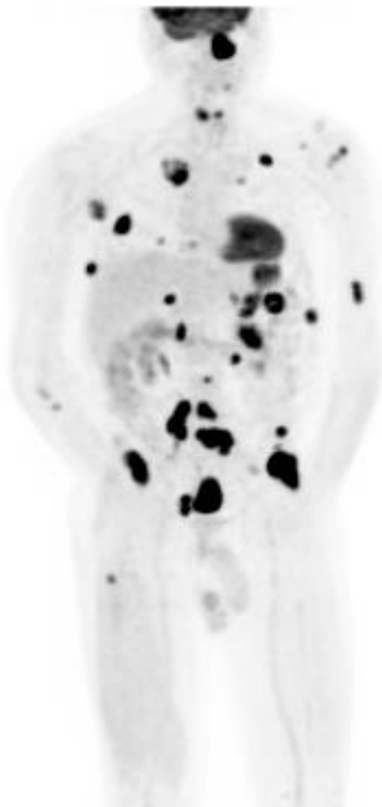


JULY 2016

APRIL 2016

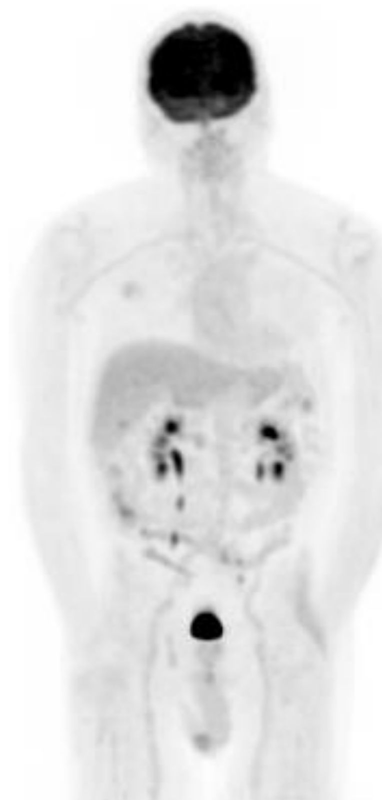
JULY 2016

CD19 CAR-T: 3rd case

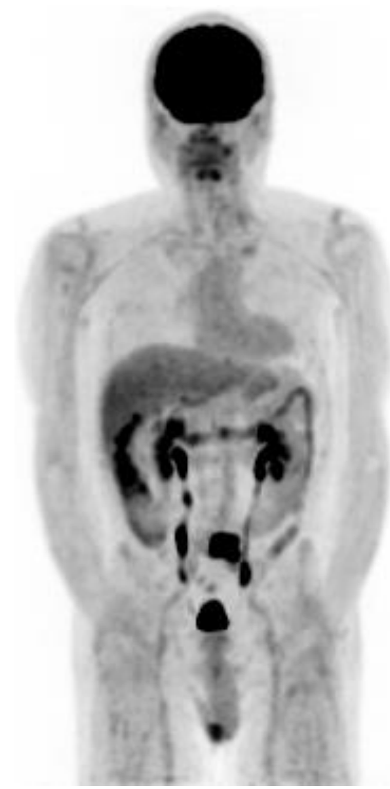


APRIL 2016

CAR-T



MAY 2016



JULY 2016

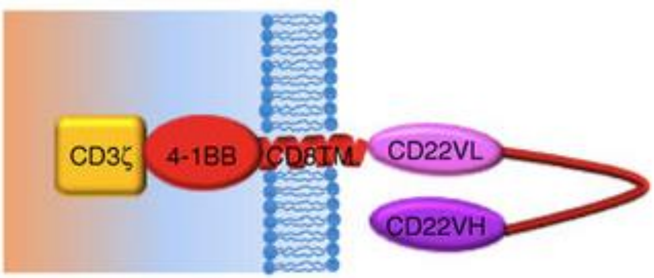
XRT AND ALLO-HCT

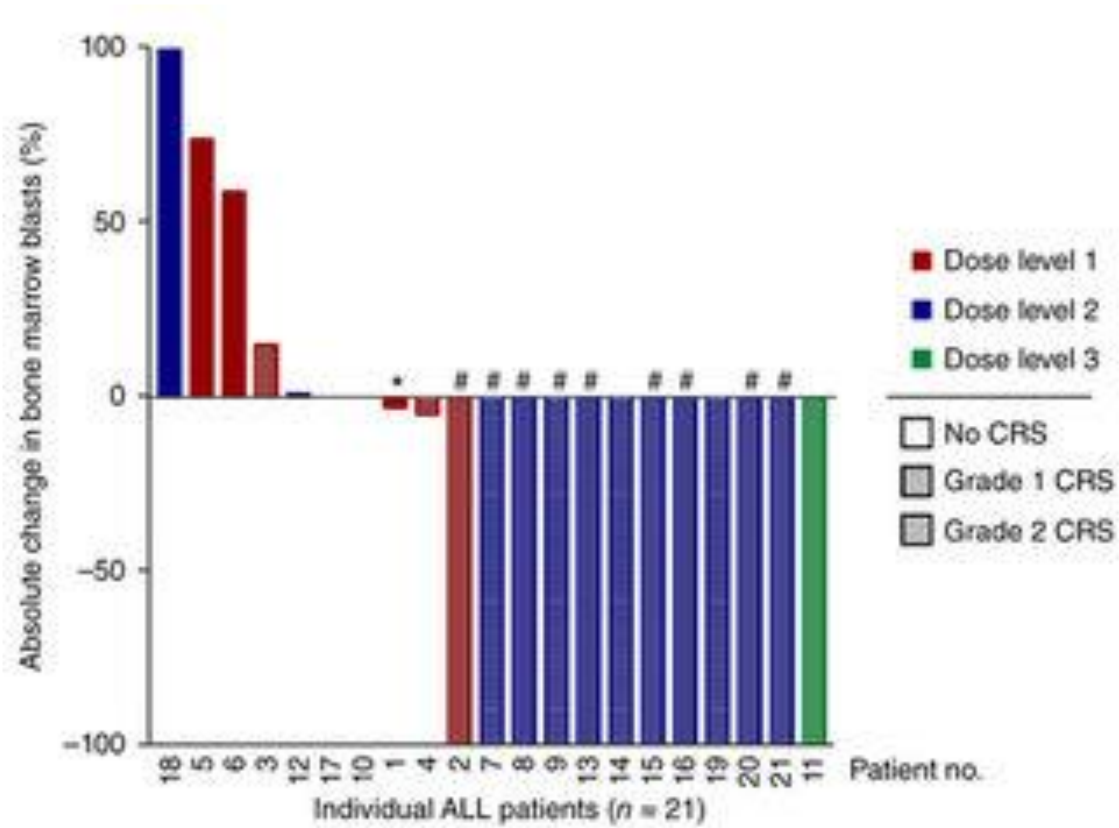
Patient selection criteria for CAR T therapies

- 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





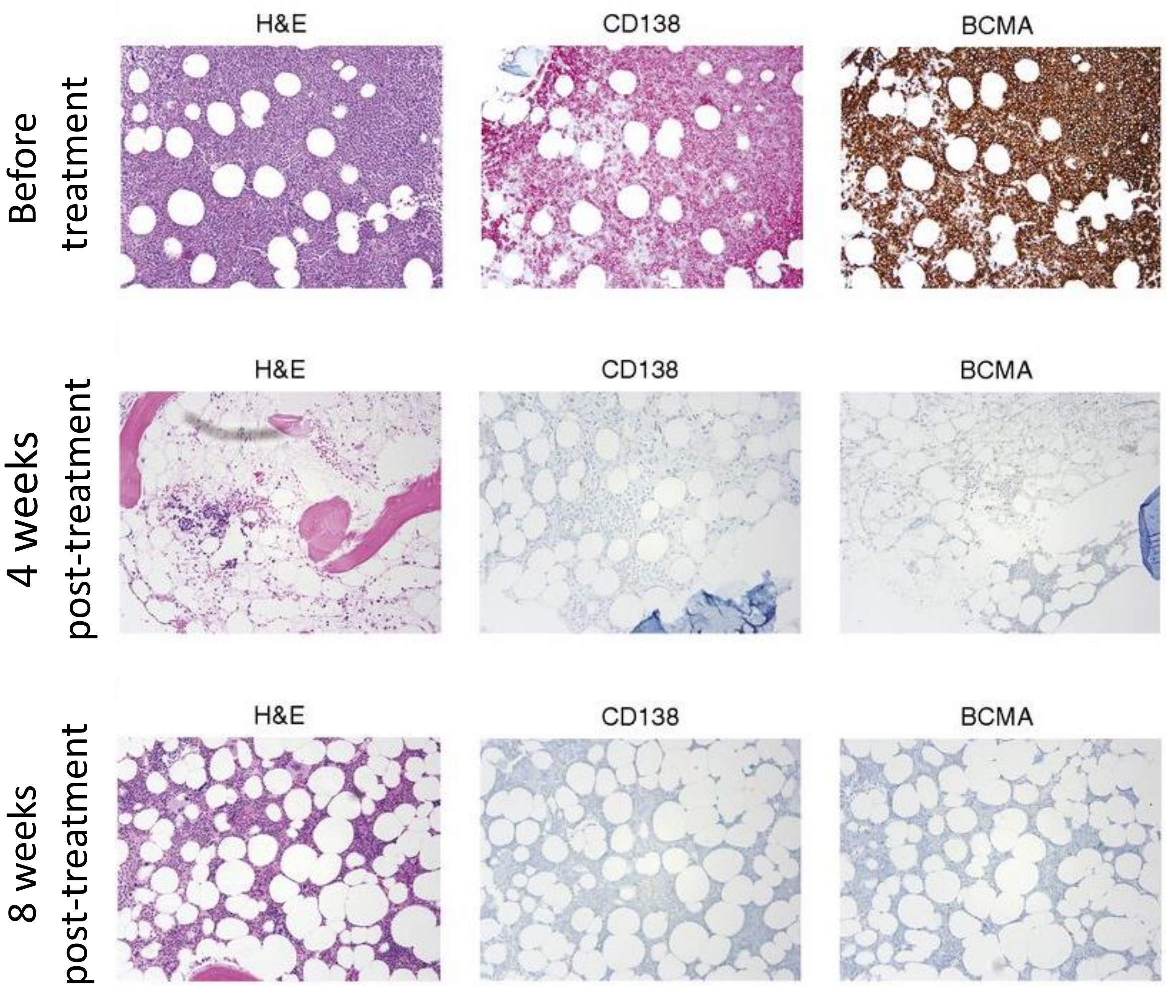
Fry, T.J. et al., Nature Medicine, 2017

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
    - Idiotype: 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 17th, 2017 FDA Breakthrough Designation

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**

CrossMark

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*]

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer