ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy of Hematologic Malignancies

Madhav Dhodapkar, MD

Professor

Yale School of Medicine

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Disclosures

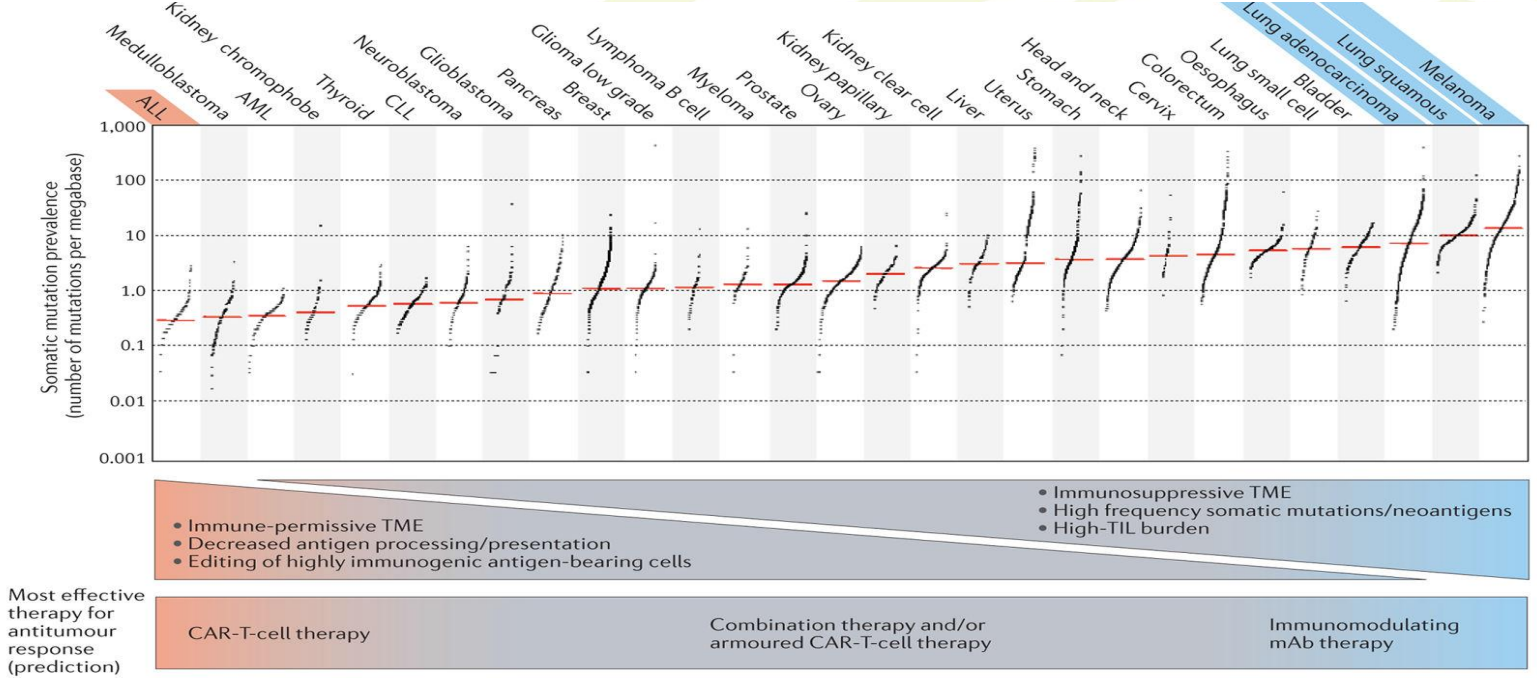
- Bristol-Myers Squibb, Genetech, Inc., Hoffmann-La Roche Ltd; Consulting Fees
- I will be discussing non-FDA approved indications during my presentation.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Diversity of Human Tumors



ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Some Examples of Immune Therapies in Hematologic Malignancies

- Antibodies
- Immunomodulatory drugs

- Immune checkpoint inhibitors
- Adoptive cell therapies, including CAR-T cells
- BiTEs

ADVANCES IN Cancer IMMUNOTHERAPY™

Patient Selection Criteria for Immune-Based Approaches

- Expression of the desired antigen for CAR-T therapy:
  - e.g. CD19 or BCMA for CAR-T cells
- Disease burden
  - <30% in certain CAR-T trials to minimize the risk of cytokine release syndromes
- Expression of the ligand for checkpoint inhibition
  - e.g. PD-L1 expression for anti-PD-1 therapy
- Presence of co-morbidities:

ACCC Association of Community Cancer Centers

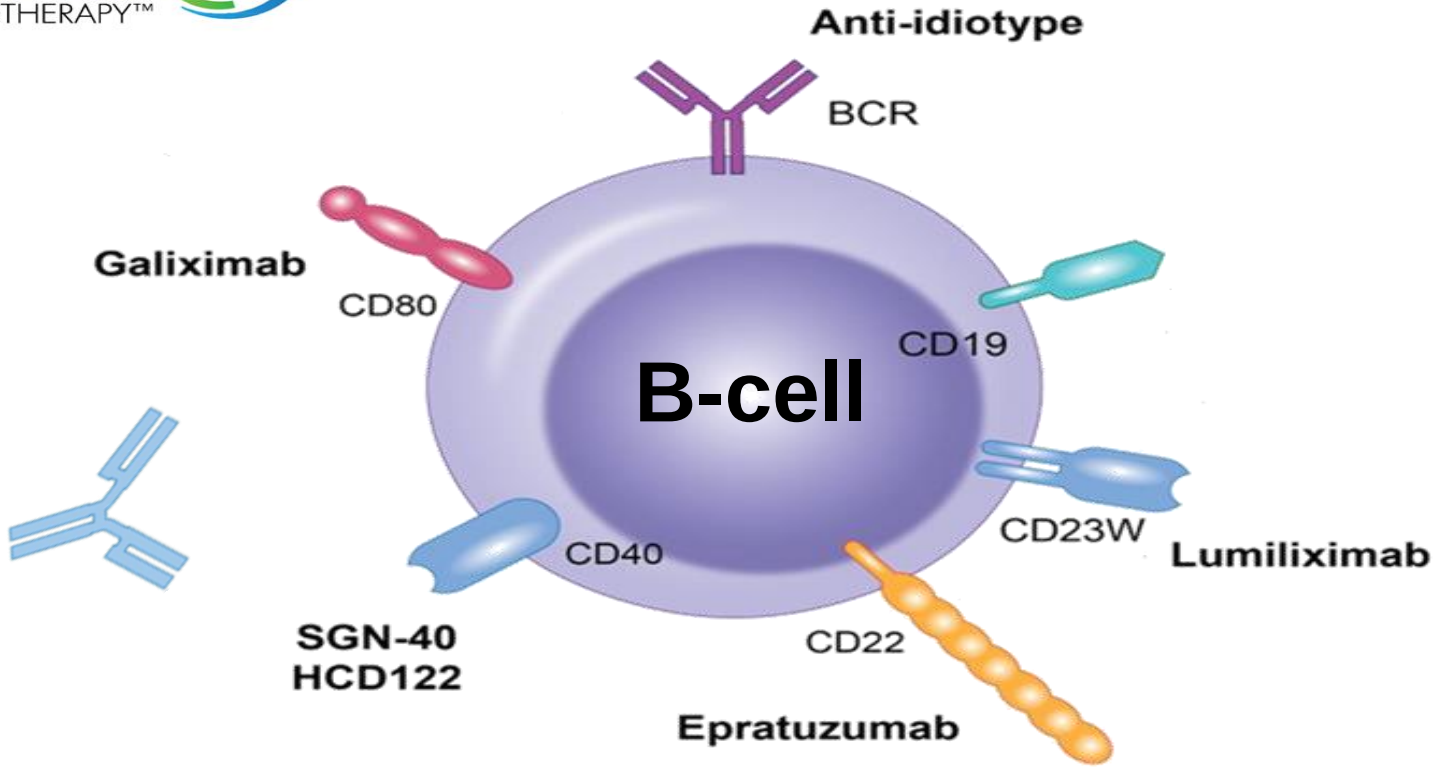
sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Lymphomas

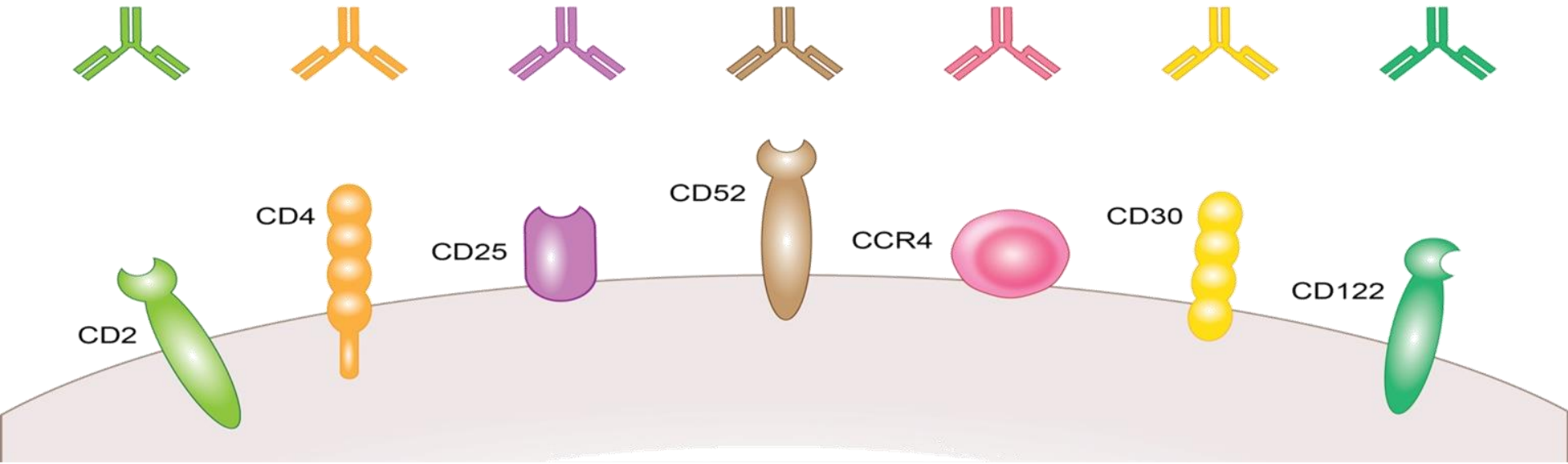
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer


Anti-idiotype
BCR
Galiximab
CD80
CD19
B-cell
CD23W
Lumiliximab
CD40
SGN-40
HCD122
CD22
Epratuzumab

ADVANCES IN Cancer IMMUNOTHERAPY™

Several monoclonal antibodies targeting T-cell lymphomas



ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Case Study #1

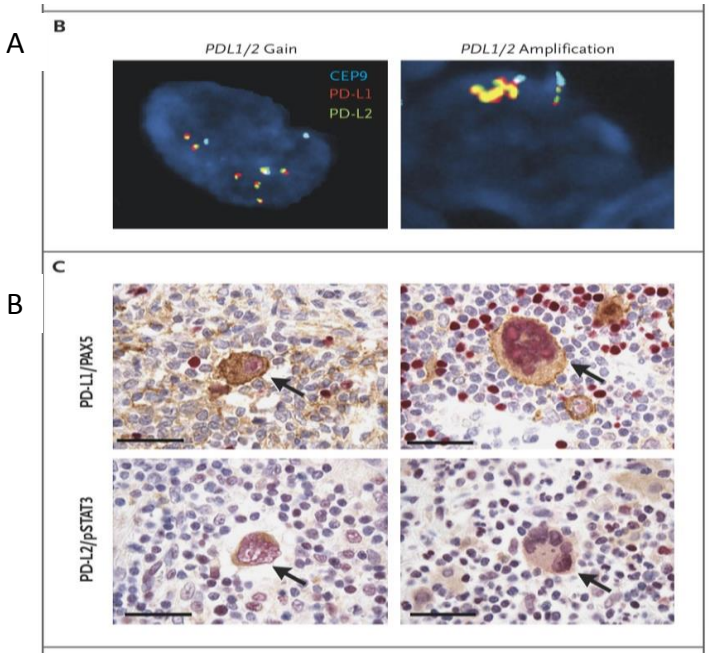
19-year-old female with a history of Hodgkin's lymphoma with two prior relapses including ABVD and an autologous stem cell transplant now presents with fevers, night sweats and shortness of breath. Chest CT confirms a large mediastinal mass with axillary adenopathy. Biopsy of a lymph node confirms disease recurrence.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

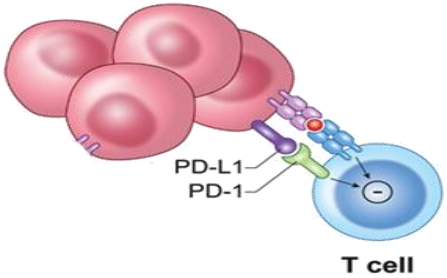
PD-L1 Expression in Hodgkin's Lymphoma

- 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™



Anti-PD-1 in Hodgkin's Lymphoma

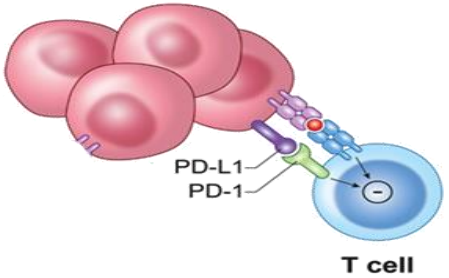
Table 3. Clinical Activity in Nivolumab-Treated Patients.*

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

ADVANCES IN Cancer IMMUNOTHERAPY™



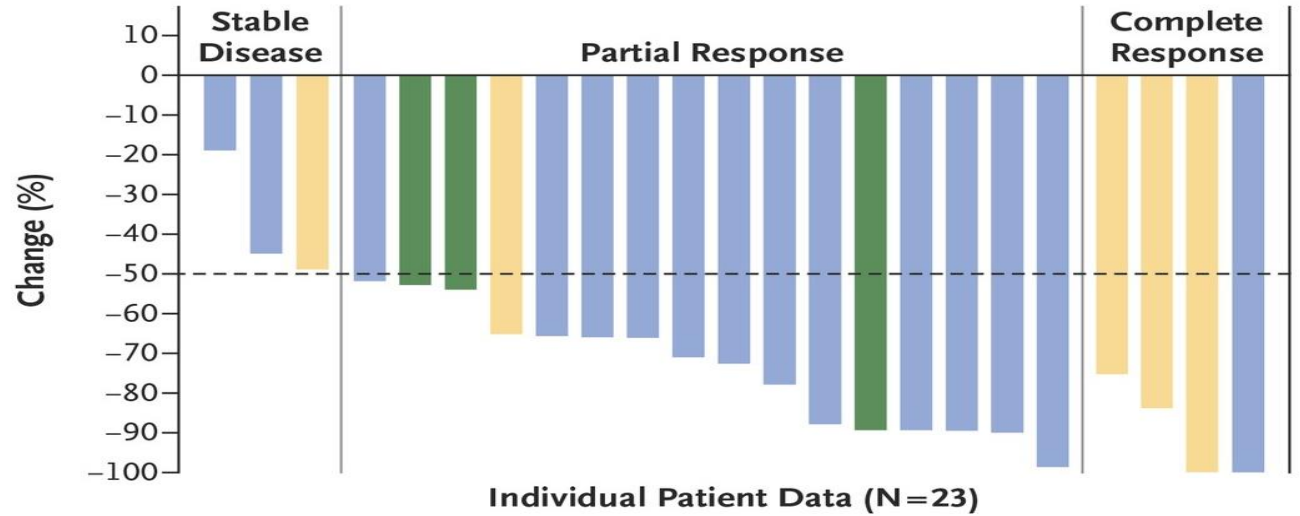
Anti-PD-1 in Hodgkin's Lymphoma

Table

Variab
Best o
Co
Pa
Sta
Pro
Object
No
Pe
Progre
Overal
Me
Ra

ASCT failure and brentuximab failure
No ASCT and brentuximab failure
No brentuximab

B Change in Tumor Burden



uximab
nent
)†
50)
20)
20)
–99)
–97)
50

* NC de
† In this
‡ Point e
§ 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

ADVANCES IN Cancer IMMUNOTHERAPY™

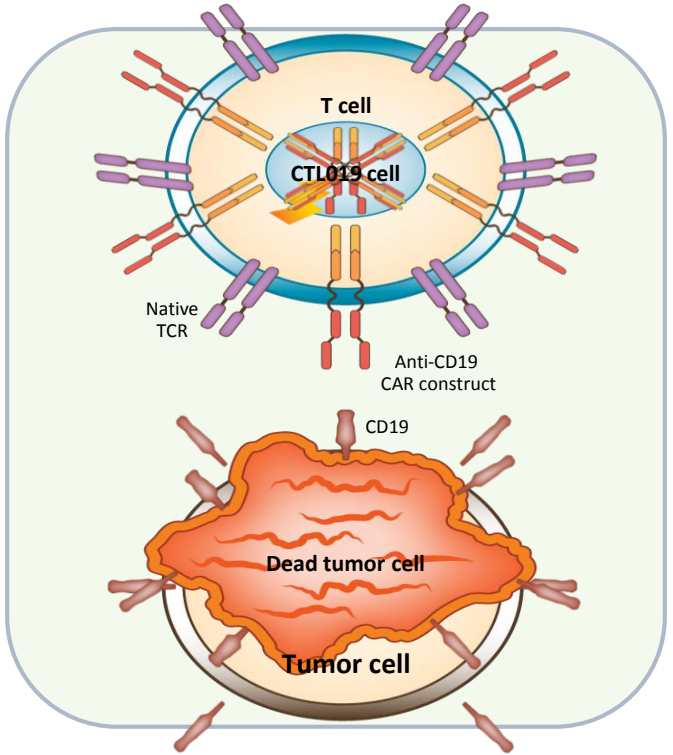
Nivolumab in R/R B Cell Malignancies: Efficacy

Types	N	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)
B cell lymphoma	29	8 (28)	2 (7)	6 (21)	14 (48)
DLBCL	11	4 (36)	1 (9)	3 (27)	3 (27)
FL	10	4 (40)	1 (10)	3 (30)	6 (60)
T cell lymphoma	23	4 (17)	0	4 (17)	10 (43)
Mycosis fungoides	13	2 (15)	0	2 (15)	9 (69)
PTCL	5	2 (40)	0	2 (40)	0
Multiple myeloma	27	0	0	0	18 (67)
Primary mediastinal B-cell lymphoma	2	0	0	0	2 (100)

ADVANCES IN Cancer IMMUNOTHERAPY™

Redirecting the Specificity of T cells

- 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**

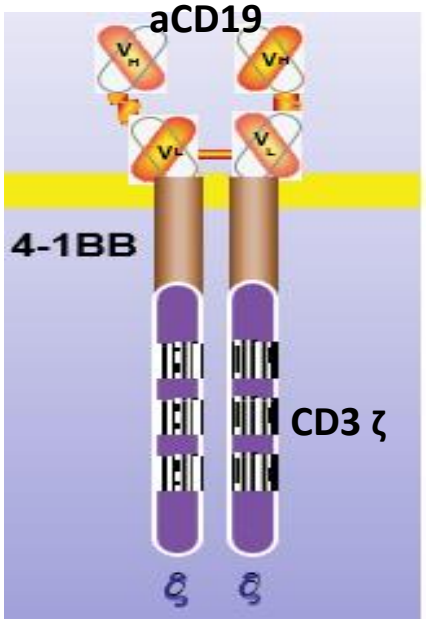


1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Chimeric Antigen Receptor for CD19 (CTL019)



Extracellular domain
- FMC63 **mouse** hybridoma derivative

Intracellular domain
- Fusion protein

ADVANCES IN Cancer IMMUNOTHERAPY™

CAR T-cell therapies in DLBCL

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].

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

CAR T-cell therapies in DLBCL

UPENN Single Institution Study

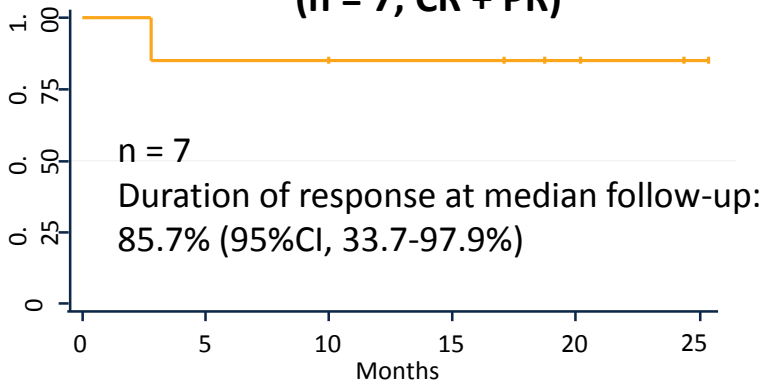
- Results from a single-center, phase 2 study at the University of Pennsylvania showed durable remissions with a single infusion of CTL019 in r/r DLBCL (Cohort A)[1,2]
  - No patient in CR at 6 months has relapsed (median follow-up, 23.3 months)

Response Rates
(N = 15)

	Month 3	Month 6
ORR	7 (47%)	7 (47%)
CR	3 (20%)	6 (40%)
PR	4 (27%)	1 (7%)

CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response.

Duration of Response
(n = 7; CR + PR)



1. Schuster SJ, et al. *Blood*. 2015;126(23):[abstract 183].
2. Schuster SJ, et al. *Blood*. 2016;128(22):[abstract 3026].

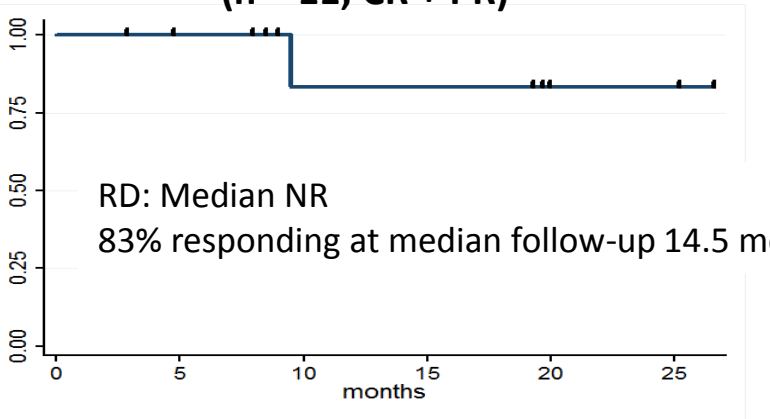
CAR T-cell therapies in FL

UPENN Single Institution Study

FL: ORR at 3 mo. 79% (N = 14)		FL: Best Response Rate 79% (N = 14)	
- CR: 7 - PR: 4 - PD: 3	(50%)	- CR: 10 - PR: 1 - PD: 3	(71%)

- 3 patients with PRs by anatomic criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months who remained in PR at 6 and 9 months had PD

Duration of Response
(n = 11; CR + PR)



Chong EA, et al. *Blood*. 2016;128:abstract1100.

ADVANCES IN Cancer IMMUNOTHERAPY™

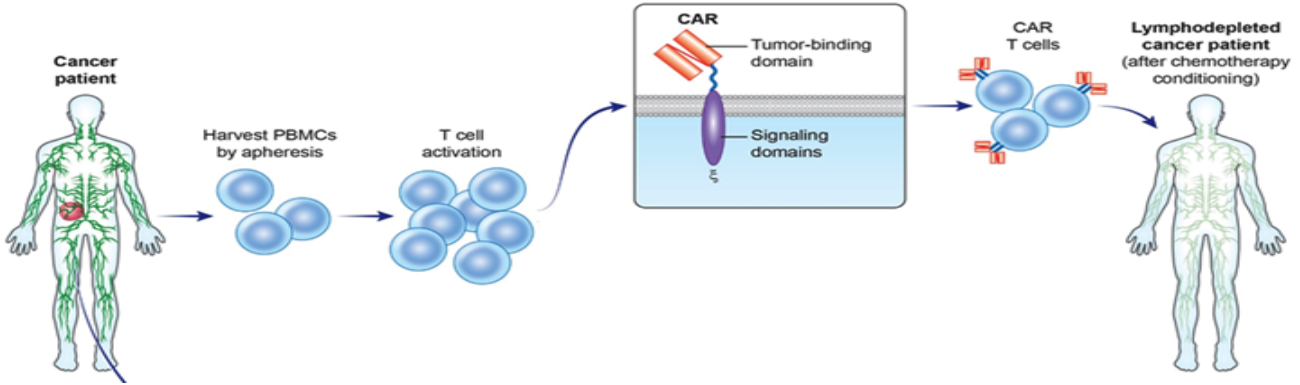
Leukemia

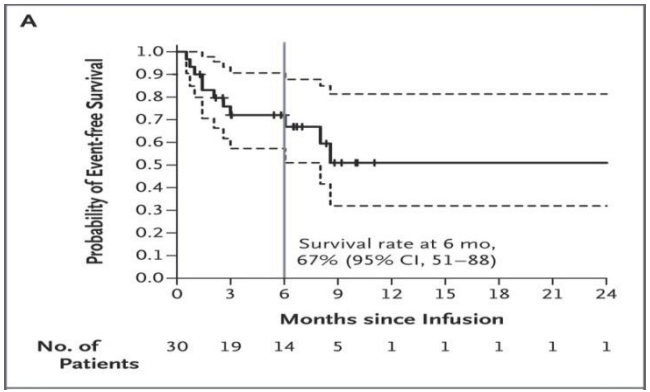
ACCC Association of Community Cancer Centers

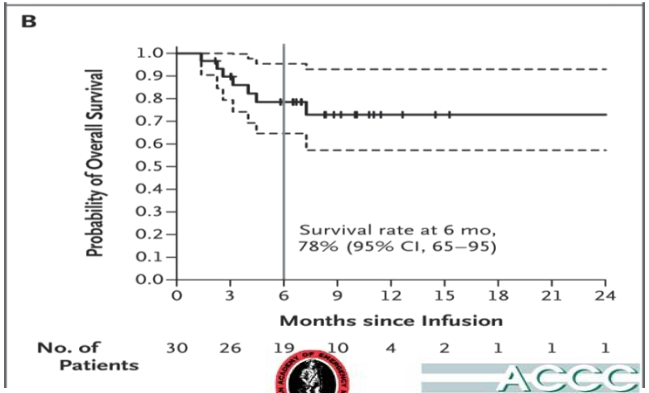
sitc Society for Immunotherapy of Cancer

CD-19 CAR-T in ALL

Probability of Event-Free and Overall Survival at Six Months.







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

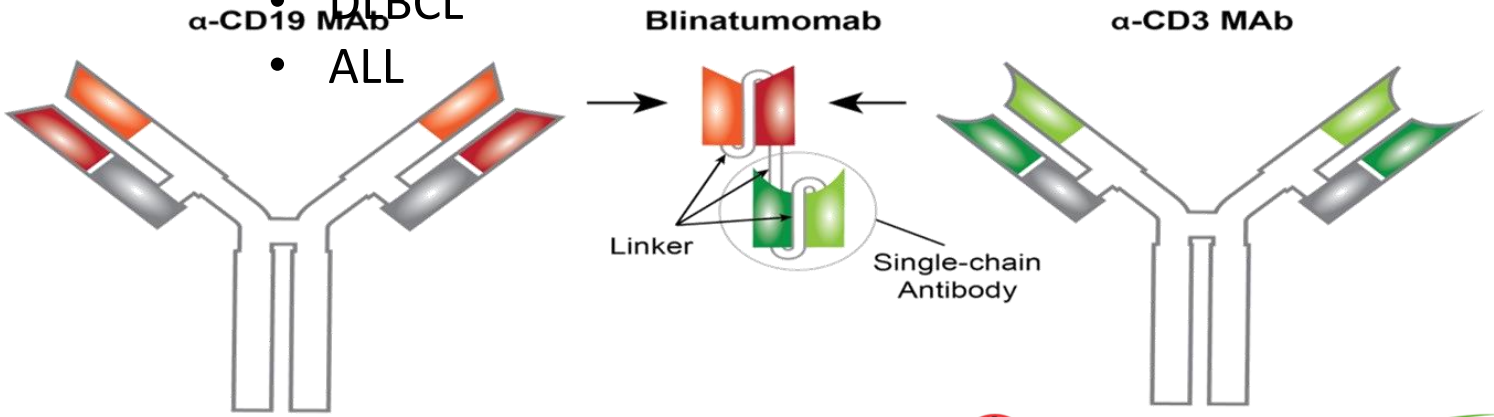
Eliana Trial- CTL-019 in ALL

- Phase II Pivotal Trial of CTL-019 (tisagenlecleucel; KYMRIAH) in relapsed/refractory pediatric/young adult ALL.
- Global enrollment across 25 centers.
- CR / CR with incomplete hem recovery): 83%
- RFS: 75% at 6 months; 64% at 12 months
- OS: 89% at 6 months; 79% at 12 months
- 47% G3 or 4 CRS

Grupp et al. EHA June 2017

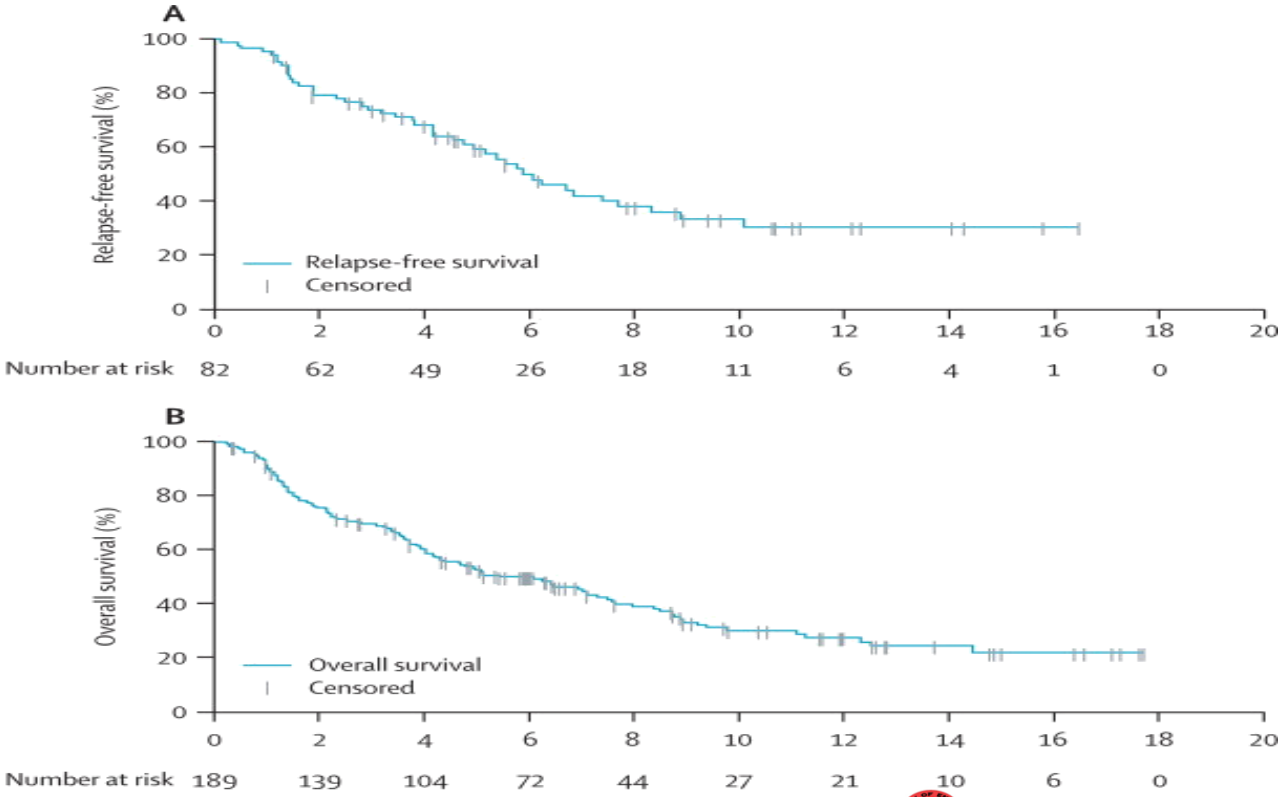
BiTE: Blinatumumab

- Combines the F(ab) of an antibody with an anti-CD3 F(ab)
- Lacks the Fc region
- Requires continuous infusions
- Shown considerable activity in:
  - Follicular NHL
  - DLBCL
  - ALL



ADVANCES IN Cancer IMMUNOTHERAPY™

Blinatumumab in ALL

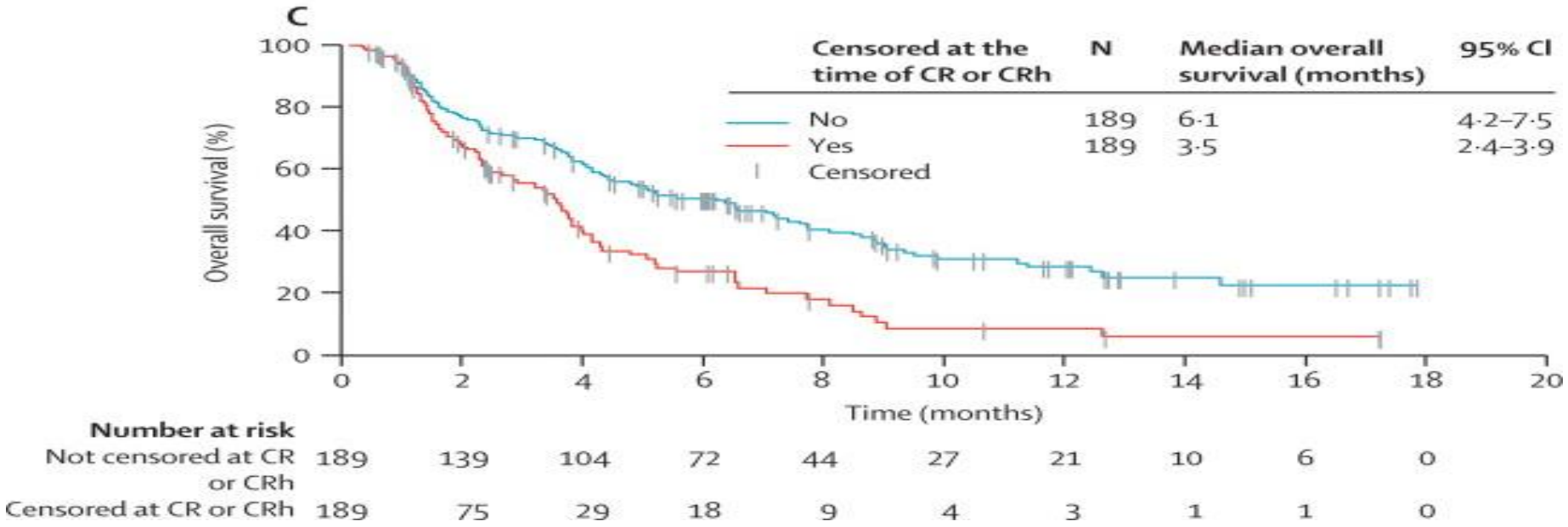


Topp, Max S et al., The Lancet Oncology , Volume 16 , Issue 1 , 57 - 66

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Blinatumumab in ALL

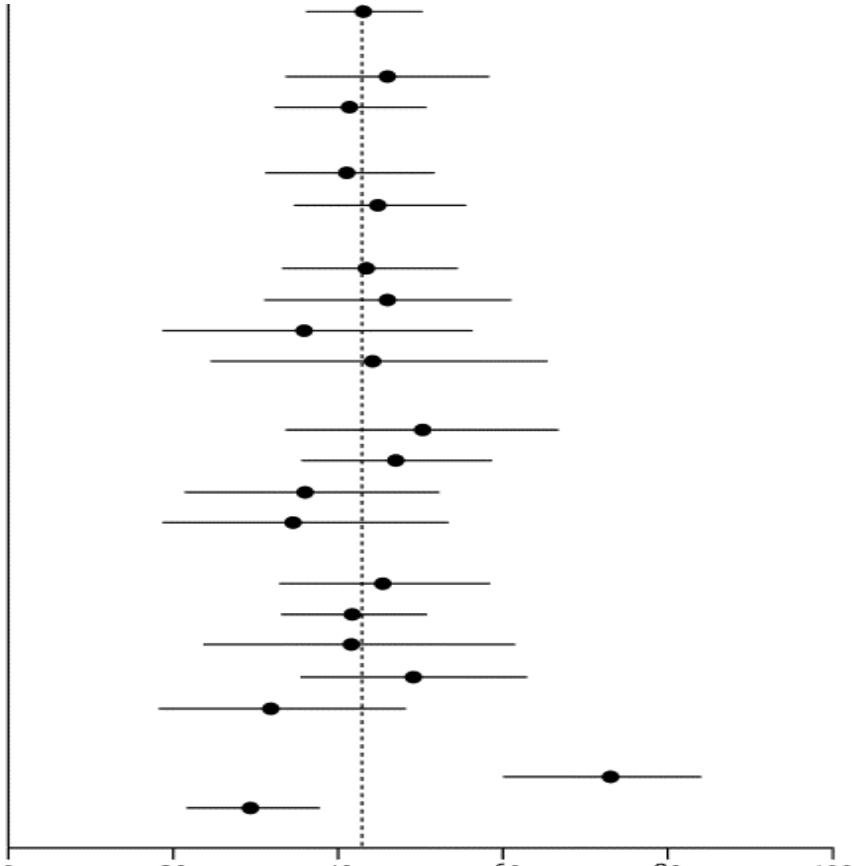


Topp, Max S et al., The Lancet Oncology , Volume 16 , Issue 1 , 57 - 66

ADVANCES IN Cancer IMMUNOTHERAPY™

Blinatumumab in ALL

All patients	81/189	43% (36–50)
Sex		
Women	32/70	46% (34–58)
Men	49/119	41% (32–51)
Geographical region		
Europe	39/95	41% (31–52)
USA	42/94	45% (34–55)
Age group (years)		
18 to <35	39/90	43% (33–54)
35 to <55	21/46	46% (31–61)
55 to <65	10/28	36% (19–56)
≥65	11/25	44% (24–65)
Previous salvage therapy		
No previous salvage	19/38	50% (33–67)
1 previous salvage	36/77	47% (35–58)
2 previous salvage	15/42	36% (22–52)
>2 previous salvage	11/32	34% (19–53)
Disease state		
Previous HSCT	29/64	45% (33–58)
No previous HSCT	52/125	42% (33–51)
No previous HSCT, no previous salvage	12/29	41% (24–61)
No previous HSCT, 1 previous salvage	27/55	49% (35–63)
No previous HSCT, ≥2 previous salvage	13/41	32% (18–48)
Bone-marrow blasts		
<50%	43/59	73% (60–84)
≥50%	38/130	29% (22–38)



ADVANCES IN Cancer IMMUNOTHERAPY™

Antigen-specific Approaches in ALL

Technology:	CART	ADC	BiTE
Example	CART-19	Inotuzumab (anti-CD22 + toxin)	Blinatumumab (anti-CD3/CD19)
Dosing	One infusion	Every 3 weeks	Continuous 28 days
Complete Response	90%	19%	66%
Survival	78% 6 mos OS	5-6 months median	9 mos median
Major toxicity	Cytokine release	Hepatotoxicity	Cytokine release
Antigen loss relapse?	Yes	No	Yes
Challenges	Complex manufacturing, individualized	Lower response rates	Burdensome infusion

Gill Immunol Rev Dec 2014

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Myeloma

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Combination Therapies

Pembrolizumab + Lenalidomide: Response Rates

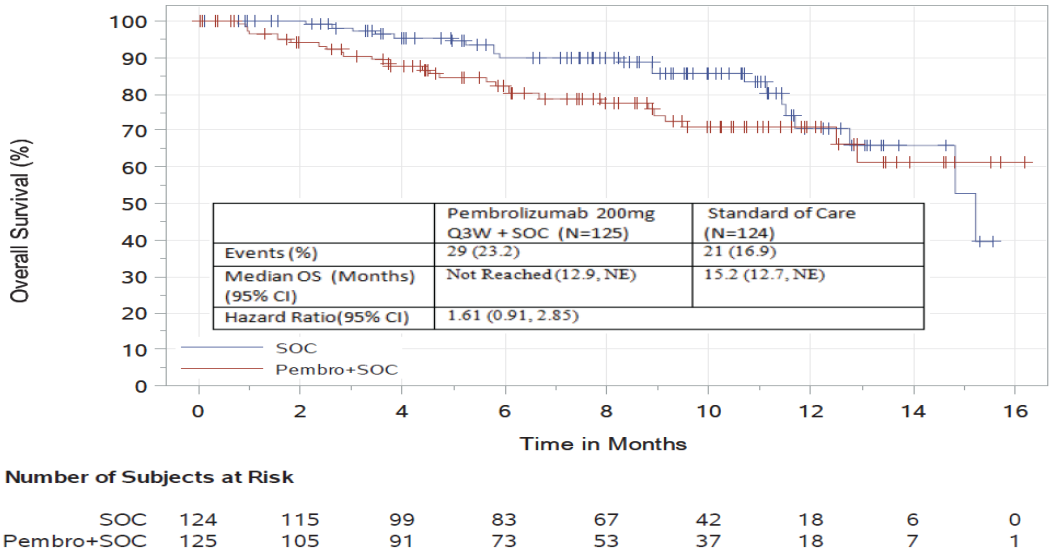
N (%)	Total N = 17	Len Refractory* N = 9
Overall Response Rate	13 (**76**)	5 (**56**)
Very Good Partial Response	4 (**24**)	2 (**22**)
Partial Response	9 (**53**)	3 (**33**)
Disease Control Rate†	15 (**88**)	7 (**78**)
Stable Disease	3 (**18**)	3 (**33**)
Progressive Disease	1 (**6**)	1 (**11**)

*3 patients double refractory and 1 triple refractory (Len/Bor +Pom)
†Disease Control Rate = CR +VGPR + PR + SD >12 weeks.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

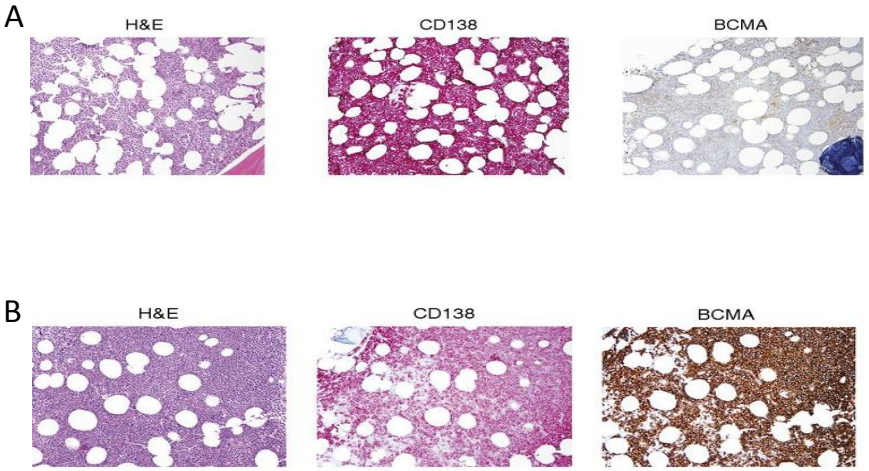
FDA Alert: Pembro in combination with IMiDs; Aug 2017



FDA website

Case Study #2

Two patients with multiply relapsed myeloma considering participation in a BCMA CAR-T cell trial.

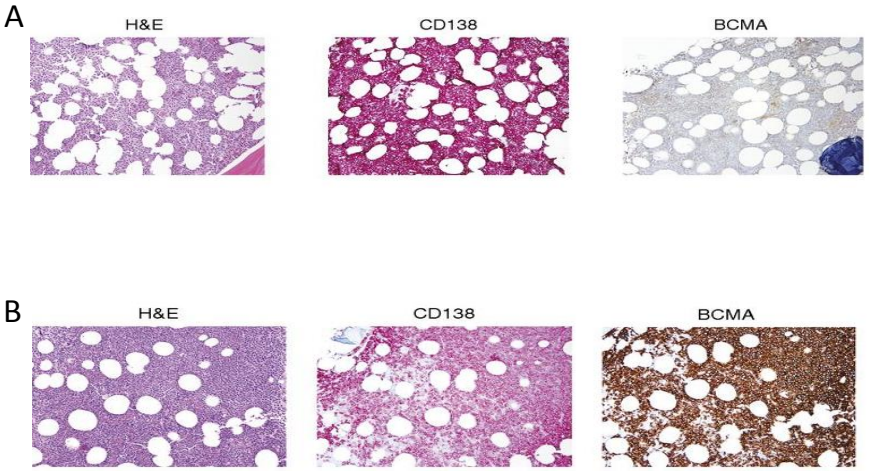


Enrollment BM biopsy shows the following staining

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

Case Study #2

Which of the following statements is true?



A.Pt A more likely to respond to BCMA CAR-T cell therapy

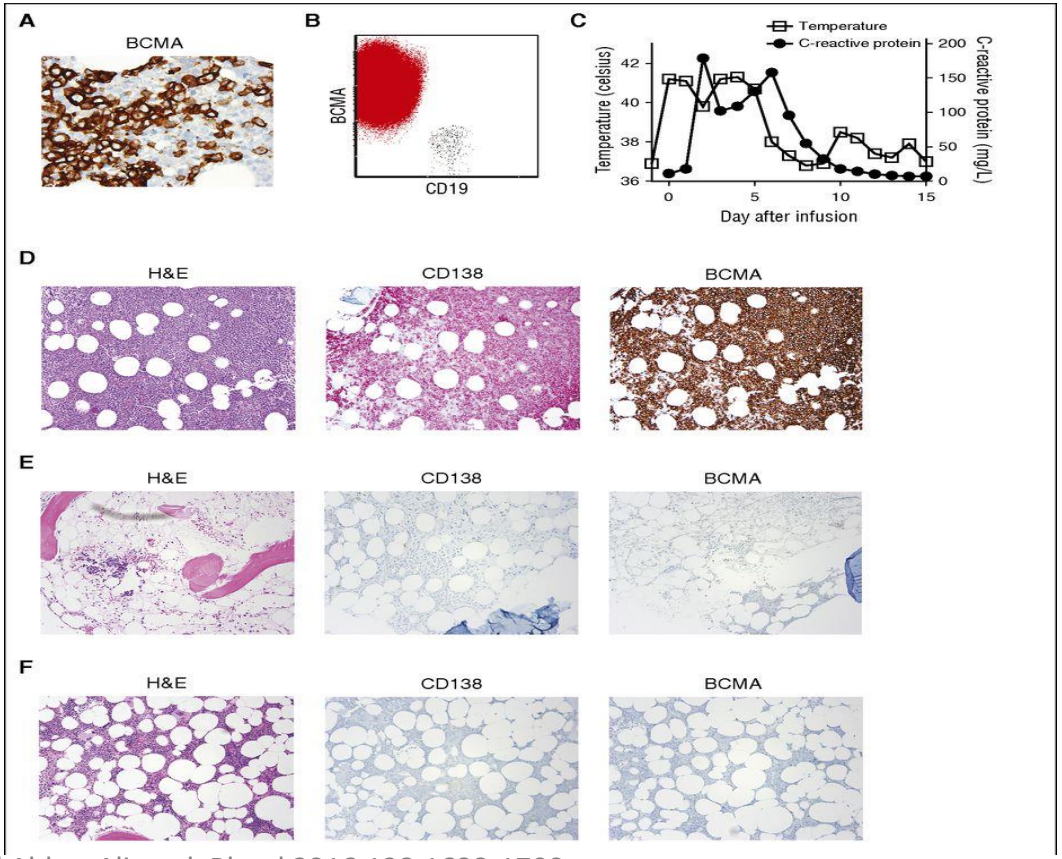
B.Pt B more likely to suffer from cytokine release syndrome (CRS) following BCMA CAR-T cell therapy

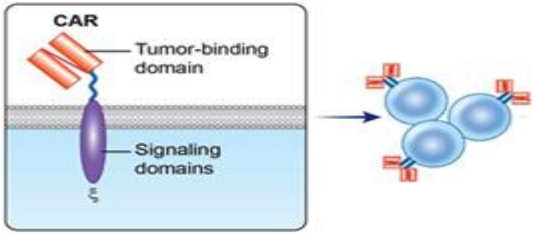
C.CRS is independent of disease burden

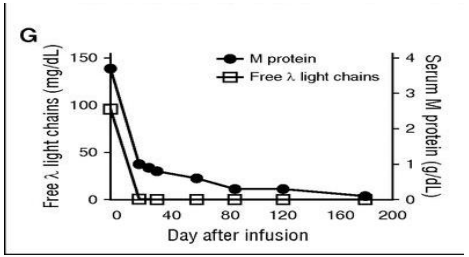
Syed Abbas Ahmed Blood 2018;132:1307

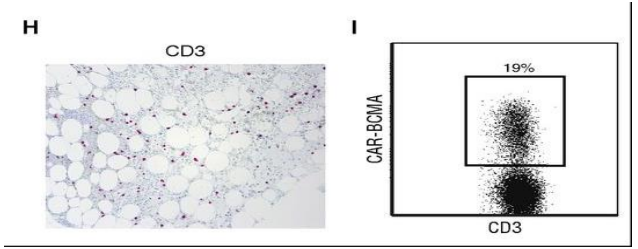
ADVANCES IN Cancer IMMUNOTHERAPY™

Efficacy of BCMA CAR-T in Myeloma









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

ADVANCES IN Cancer IMMUNOTHERAPY™

Types of Vaccines Used in Myeloma

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

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

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*]

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer