ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy of Hematologic Malignancies

Alex Herrera, MD

City of Hope

Association of Community Cancer Centers

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Disclosures

- Bristol-Myers Squibb, Genentech, Inc., Merck & Co., Inc., Pharmacyclics LLC, Consulting Fees
- I *will* be discussing non-FDA approved indications during my presentation.

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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:
  - e.g. Presence of active autoimmune diseases which could be worsened

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Lymphomas

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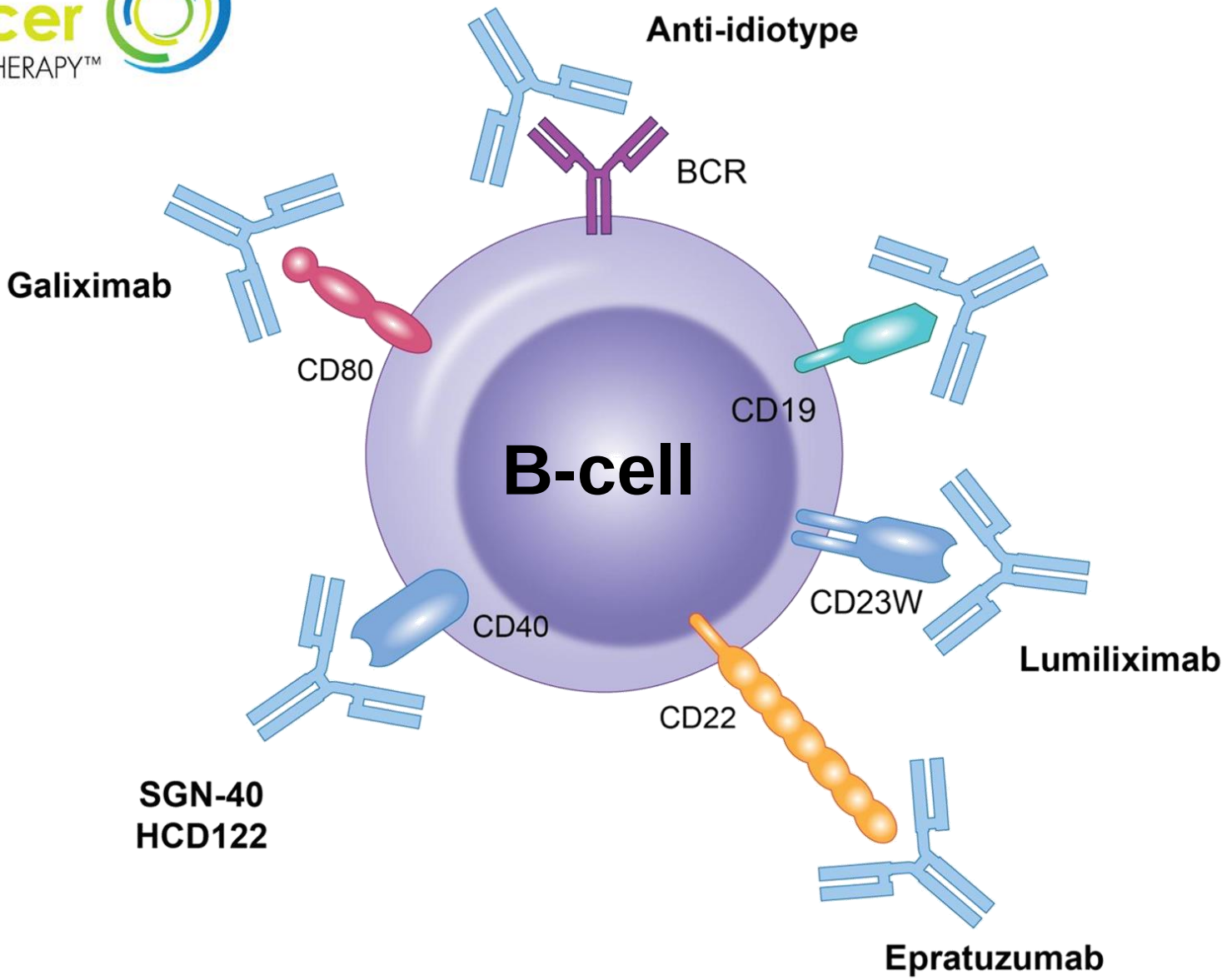
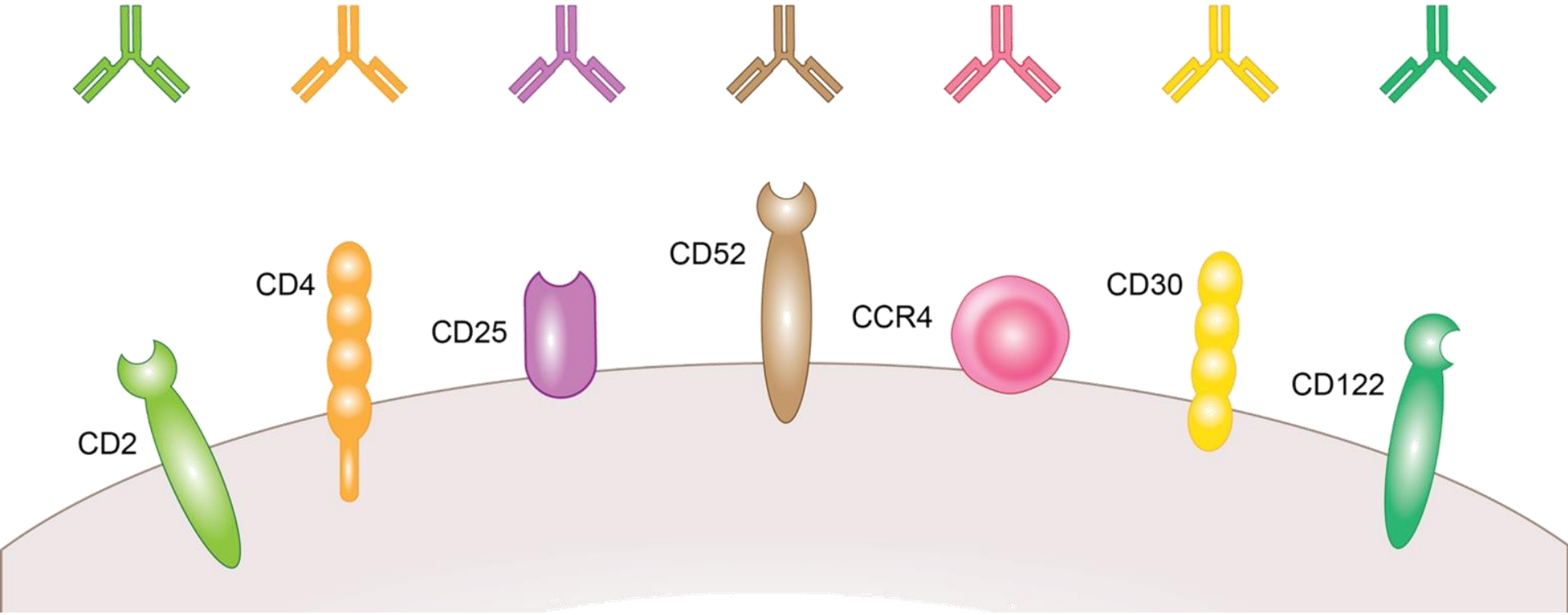
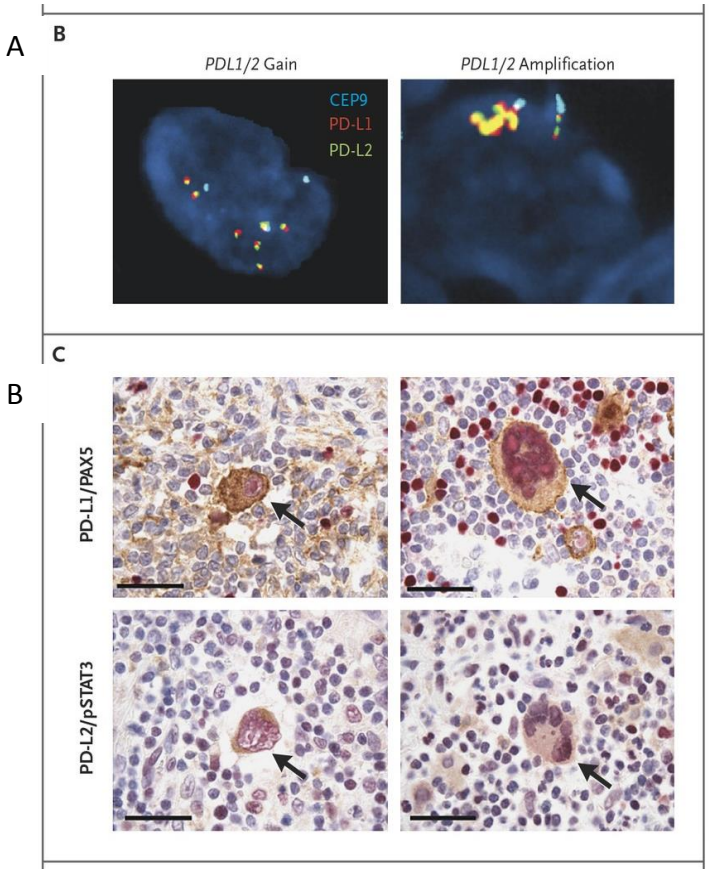

Anti-idiotype
BCR
Galiximab
CD80
CD19
B-cell
CD23W
Lumiliximab
CD40
CD22
SGN-40
HCD122
Epratuzumab

Several monoclonal antibodies targeting T-cell lymphomas



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

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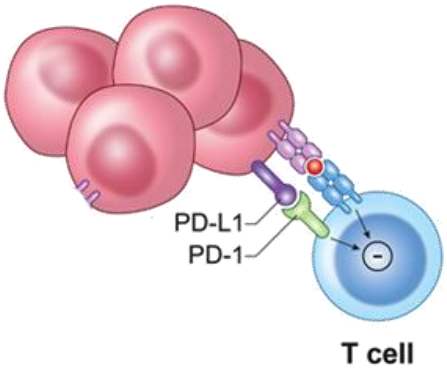

Anti-PD-1 in Hodgkin's Lymphoma

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.

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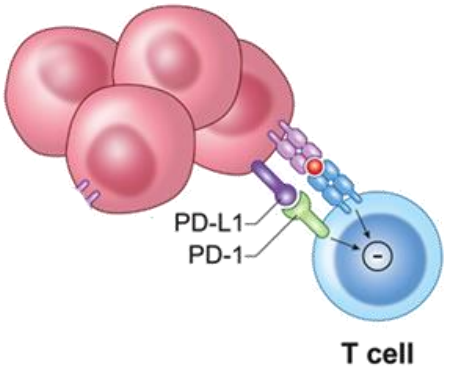

Anti-PD-1 in Hodgkin's Lymphoma

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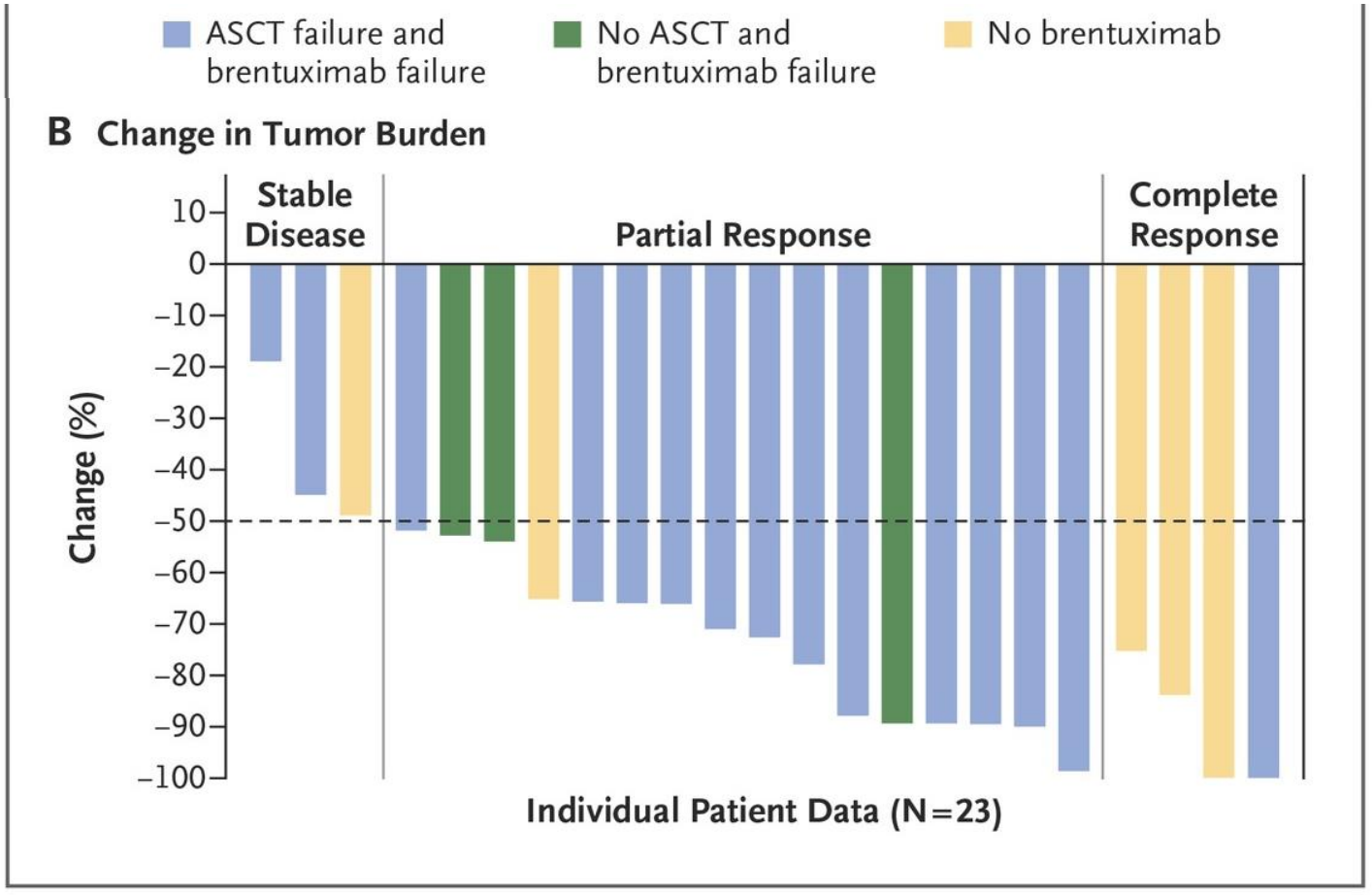

* NC de
† In this
‡ Point e
§ The estimate was not calculated when the percentage of data censoring was above 25%.
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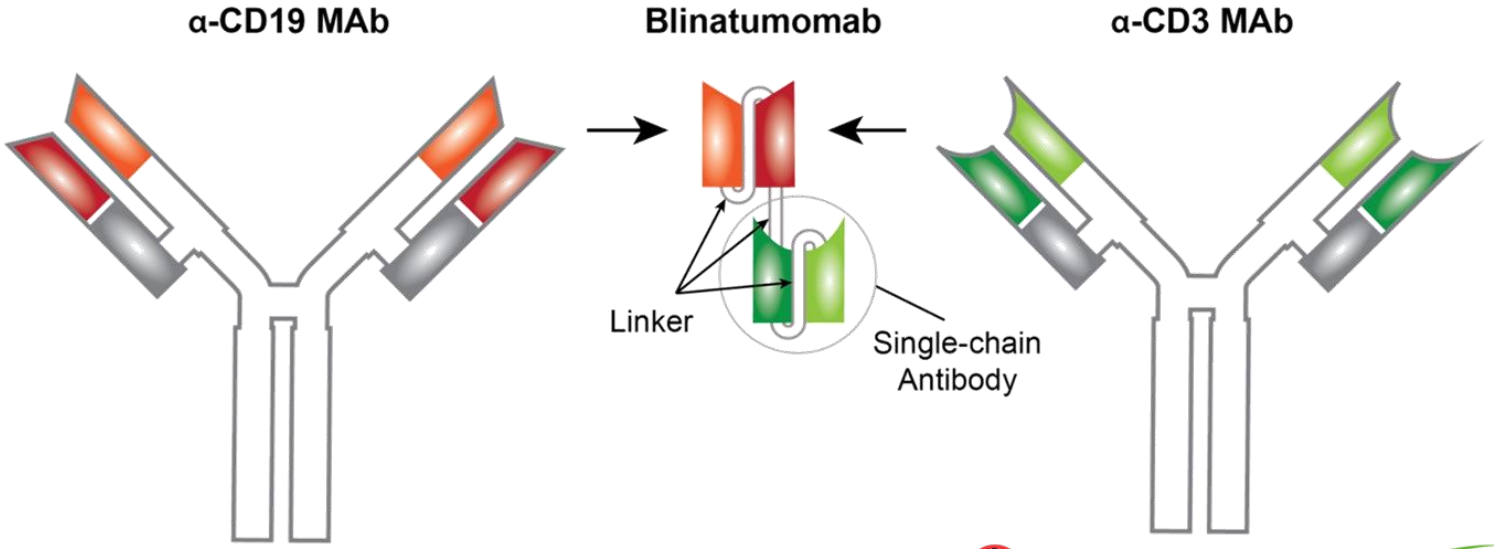
Nivolumab in R/R B Cell Malignancies: Efficacy

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)

BiTE: Blinatumumab

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



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Case Study #1

- 24 year-old male with a history of stage IIIB classical Hodgkin lymphoma who entered PET-negative remission after ABVD x 6. Relapsed within one year and underwent ICE salvage therapy x 3 with PR followed by ASCT then received brentuximab vedotin maintenance until 7 months after ASCT when B symptoms recur. PET shows FDG-avid disease above the diaphragm, biopsy confirms relapse.

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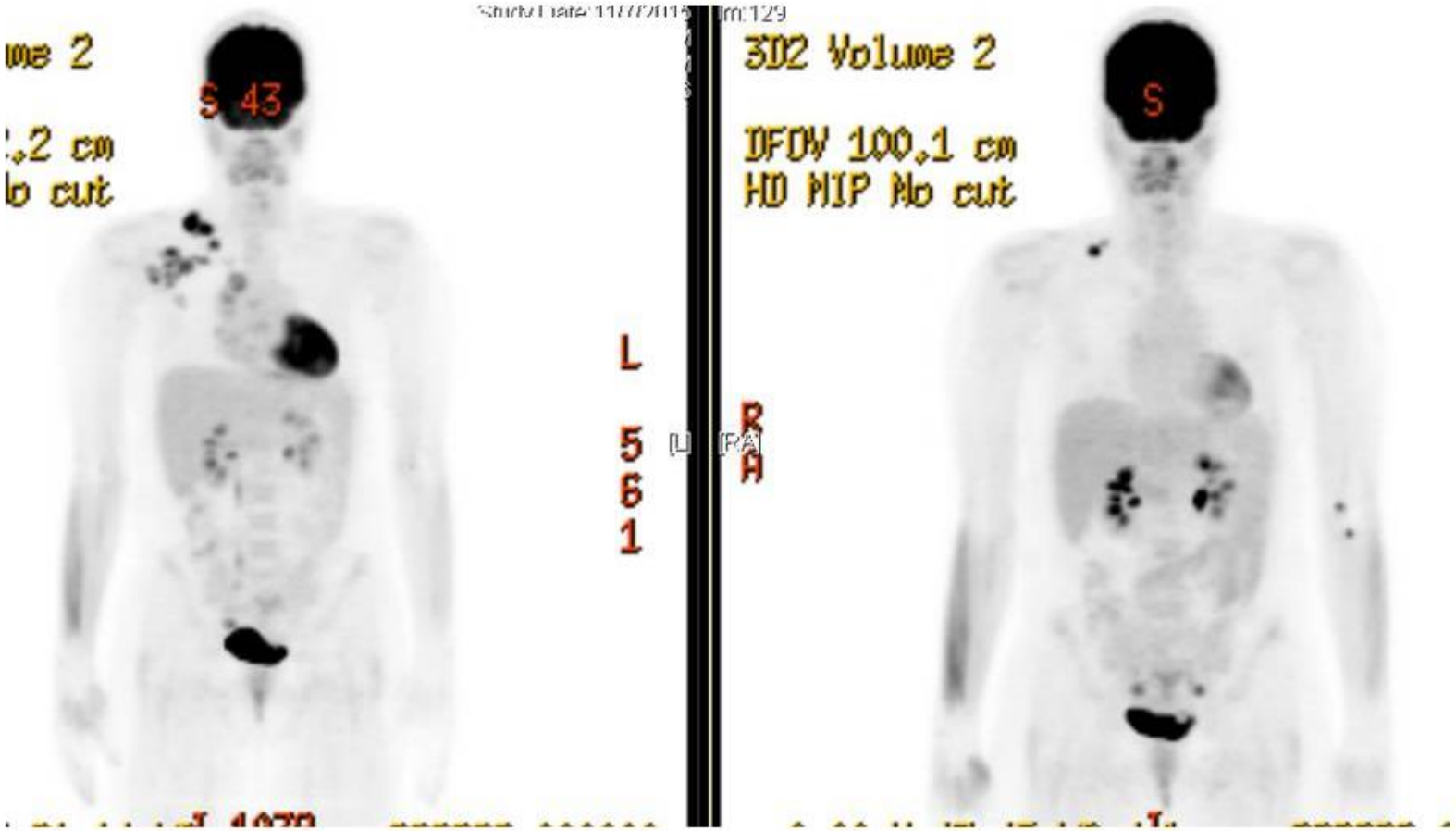
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Which of the following is true?

- A. Most patients with HL will achieve PET-negative remission with a PD-1 inhibitor
- B. Most patients with HL will respond, but a minority of patients will achieve PET-negative remission with a PD-1 inhibitor
- C. Pembrolizumab but not Nivolumab is FDA-approved for this indication
- D. Nivolumab is approved only for patients with PD-L1 expression in a tumor sample

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Leukemia

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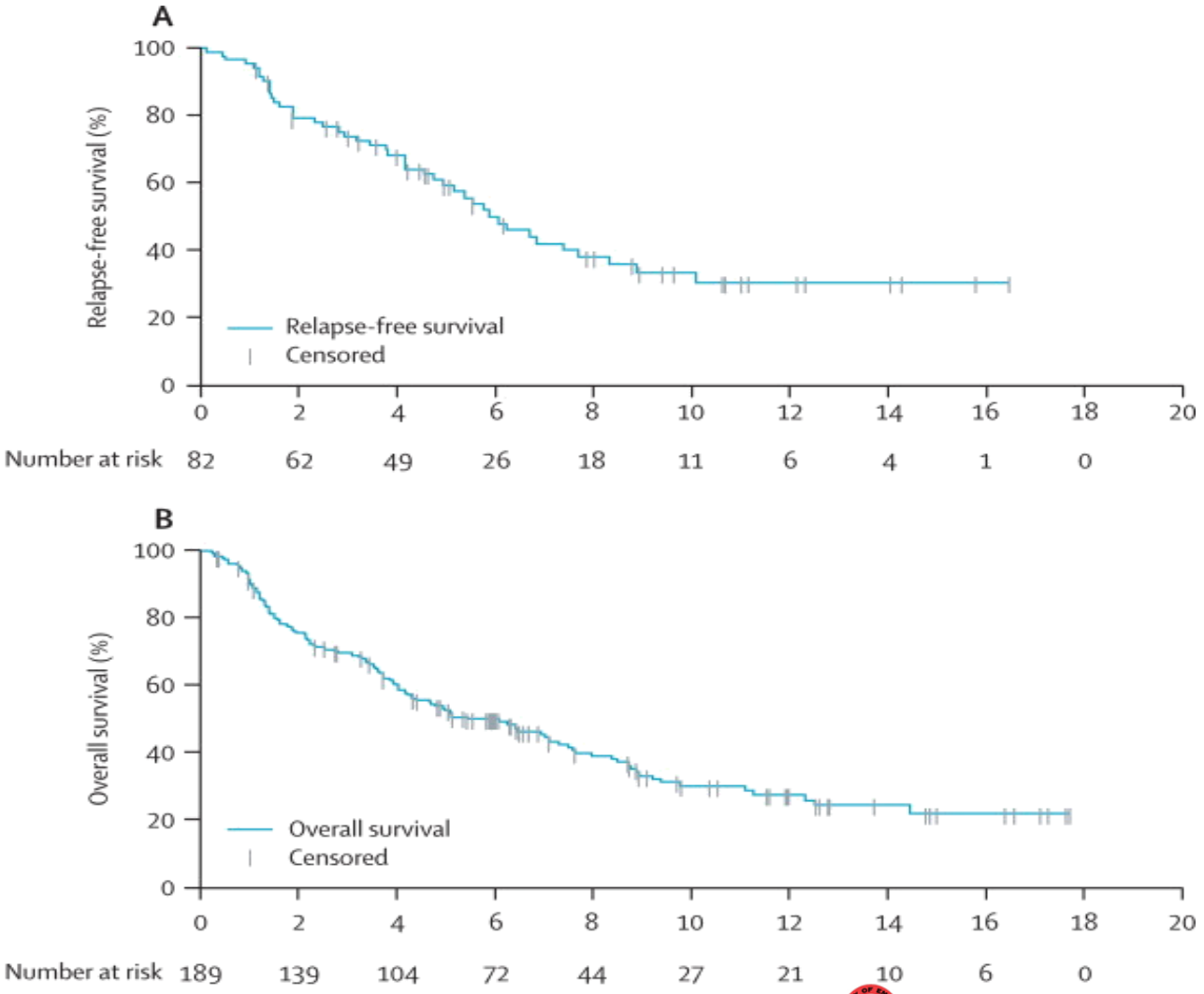
Blinatumumab in ALL



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

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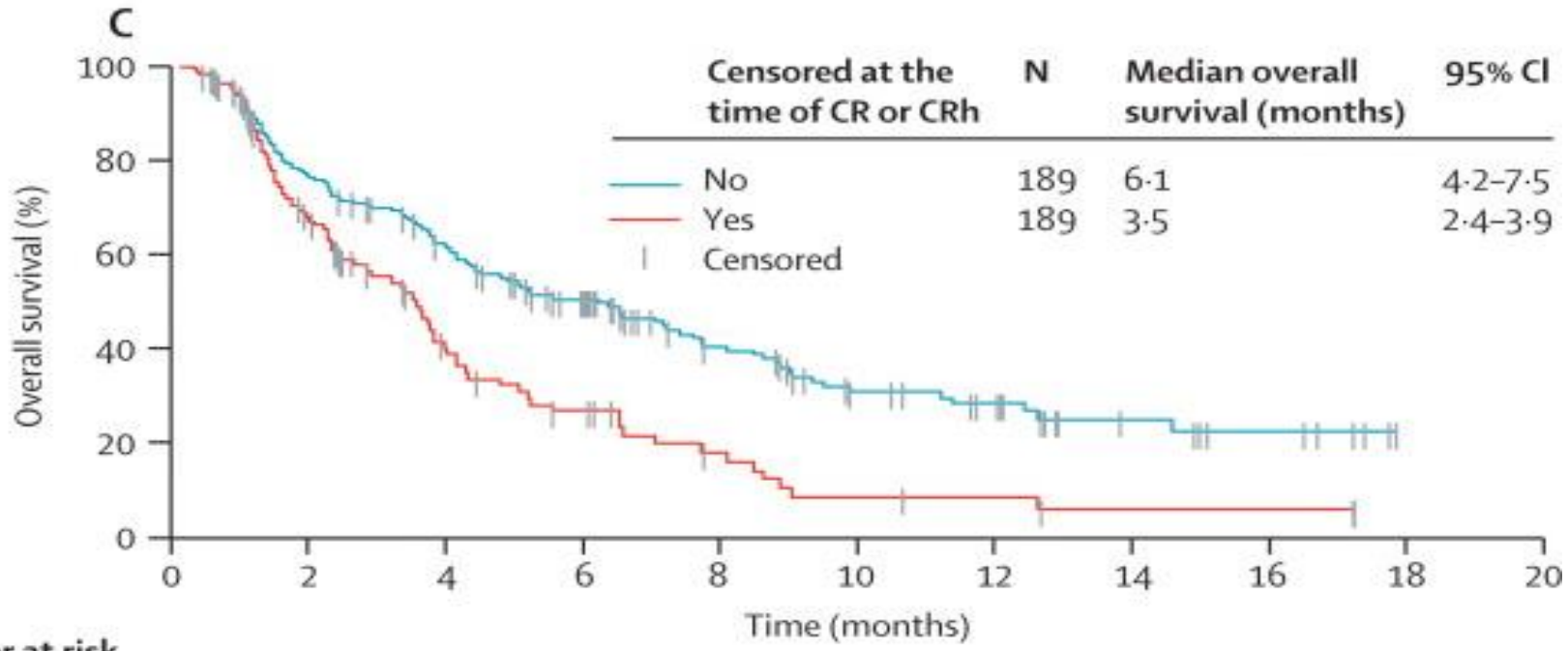
Blinatumumab in ALL



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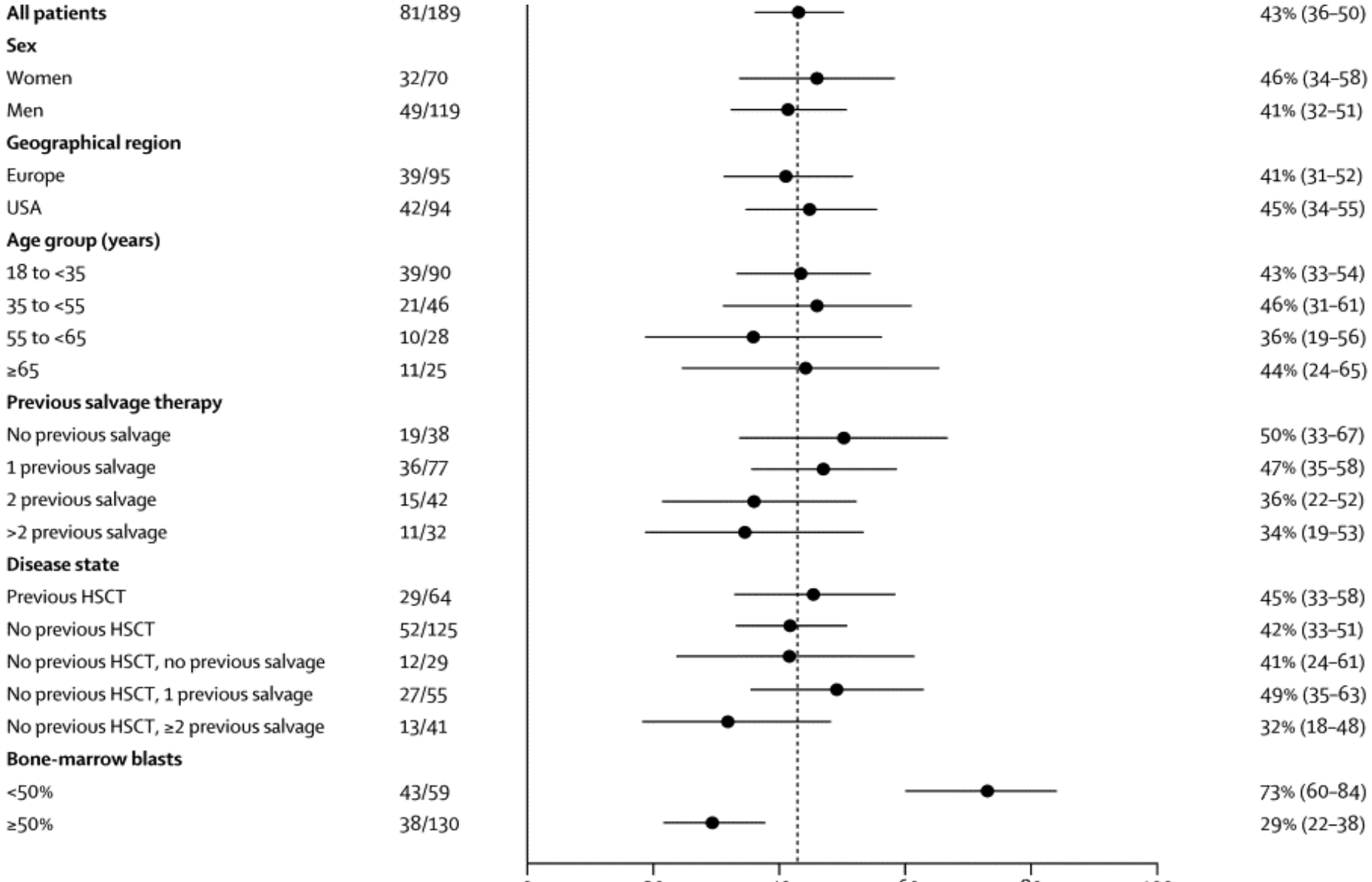
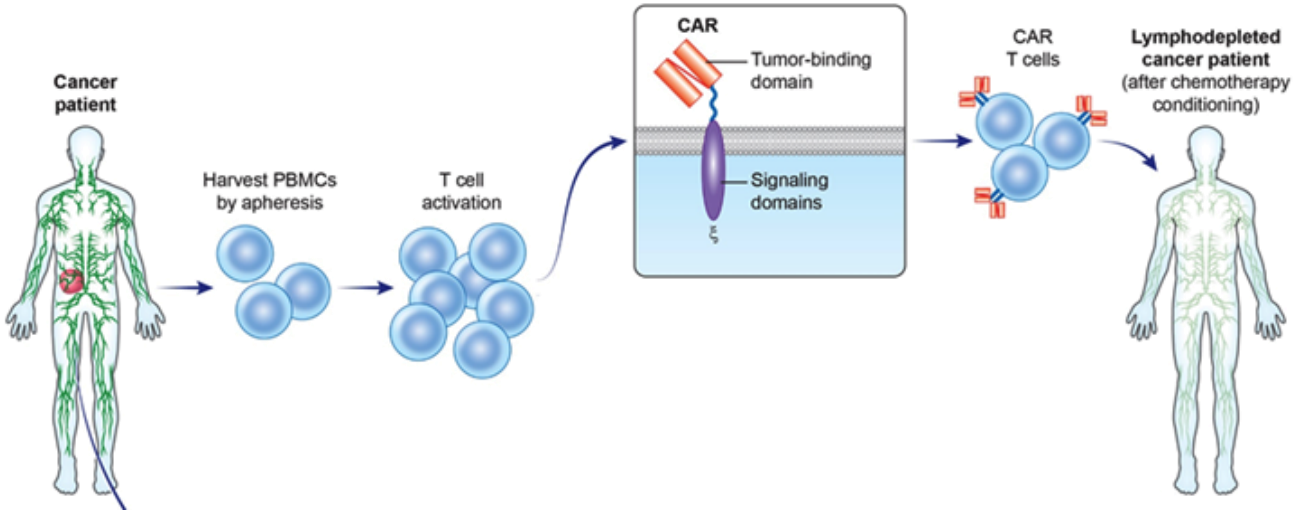
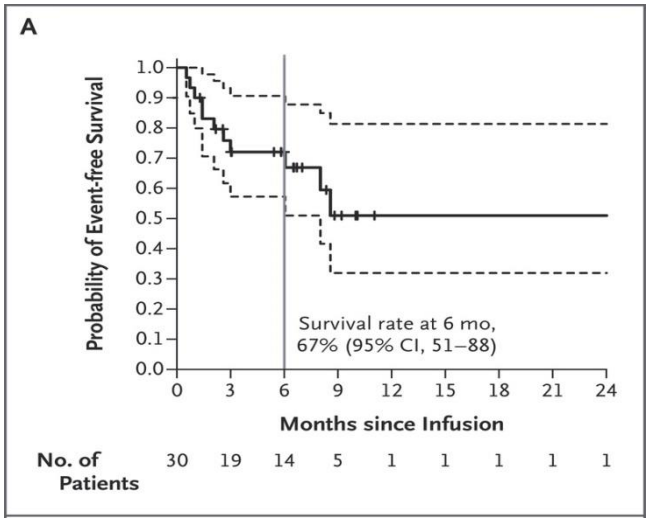
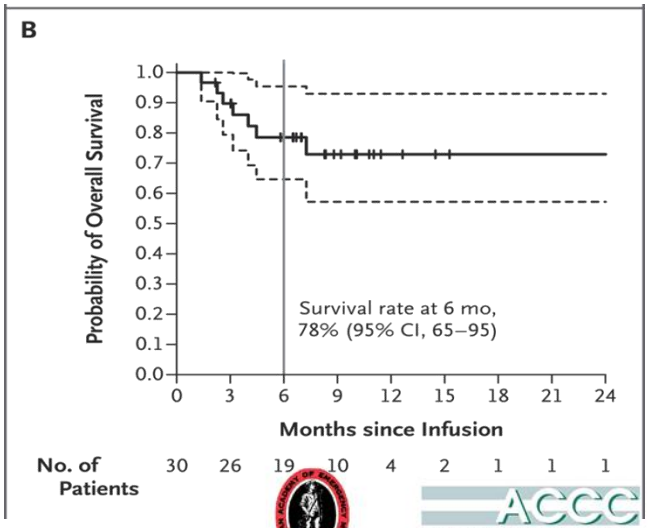


CD-19 CAR-T in ALL

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







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

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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

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Myeloma

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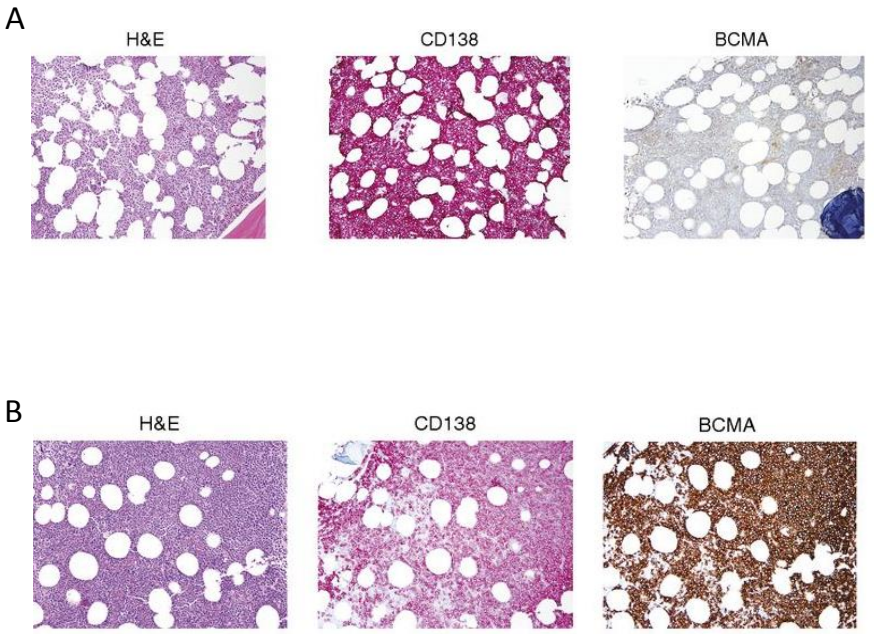
Case Study #2

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

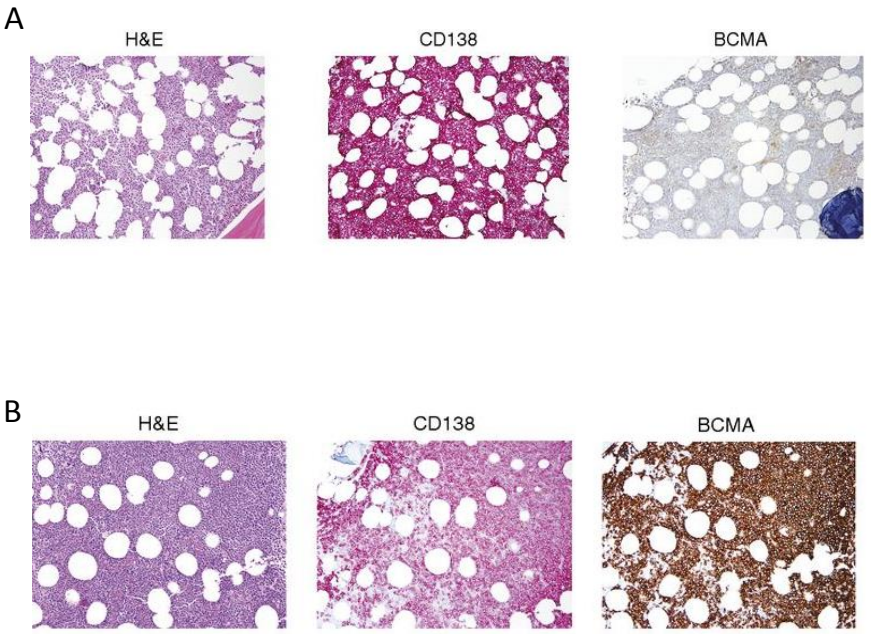
Which of the following statements is true?

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

D.CRS is only seen in ALL



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Combination Therapies

Pembrolizumab + Lenalidomide: Prior Therapies

	Pembro + Len + Dex N = 50
Prior therapies, median (range)	4 (1-5)
≥3 Lines of therapy, n (%)	36 (**72**)
Prior therapies, n, (%) Lenalidomide Bortezomib Pomalidomide Carfilzomib	 48 (**96**) 48 (**96**) 13 (**26**) 11 (**22**)
Prior ASCT, n (%)	43 (**86**)

	Pembro + Len + Dex N = 50
Refractory to lenalidomide, n (%)*	38 (**76**)
Double refractory	15 (30)
Triple refractory	6 (12)
Quadruple refractory	4 (8)
	50%
Refractory to bortezomib, n (%)	32 (64)
Refractory, last line, n (%)	40 (**80**)
Refractory to lenalidomide as last line, n (%)	10 (20)

*Double refractory = Len/Bort
Triple refractory = Len/Bort/Pom or Len/Bort/Carf
Quadruple refractory = Len/Bort/Pom/Carf

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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.

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Baseline Patients' Demographics

Characteristic	N=33
Age – yr	
Median (Range)	65 (42-81)
Sex – no. (%)	
Male	24 (73%)
Female	9 (27%)
Race – no (%)	
Caucasians	17 **(52%)**
African Americans	13 **(39%)**
Others (Hispanic, Asian)	3 **(9%)**
Isotype – no.(%)	
IgG	18 **(55%)**
IgA	7 **(21%)**
Light chain	8 **(24%)**
LDH – Median (range)	415 (148- 4800)
Cytogenetics – no. (%)	
High risk [del 17p, t(4:14) and/or t(14:16)]	14 **(42%)**
del 13q	16 **(48%)**
1q+	23 **(70%)**

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Best Response to Treatment (IMWG Criteria)

Evaluable Pts (n=27)

	All N=27	Double refractory N=20	High risk cytogenetics N=12
ORR (≥ PR), %	**60%**	**55%**	**50%**
sCR	1	0	0
CR	0	0	0
VGPR	4	2	1
PR	11	9	5
Stable Disease	**8 (30%)**	**6 (30%)**	**5 (42%)**
Progressive disease	**3 (10%)**	**3 (15%)**	**1 (8%)**

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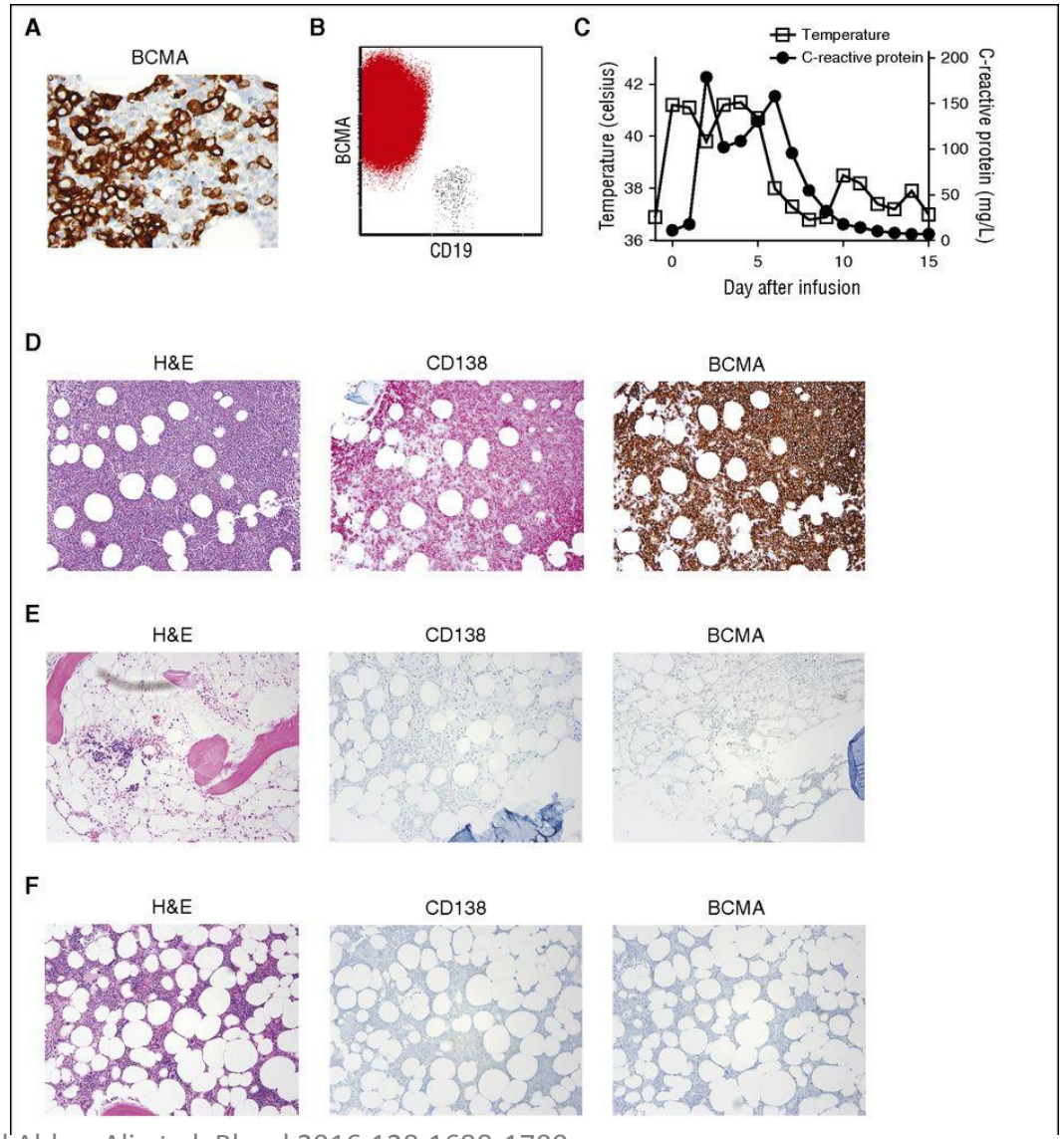
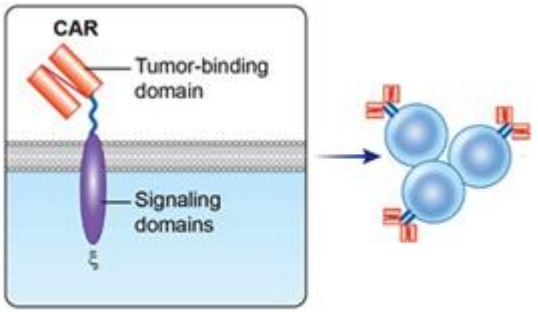
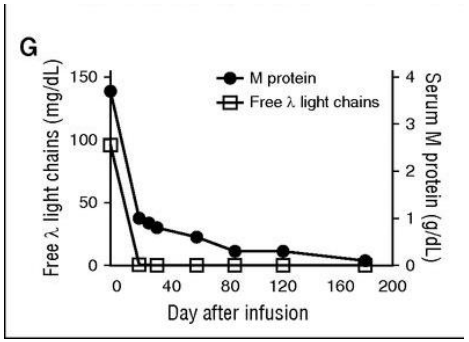
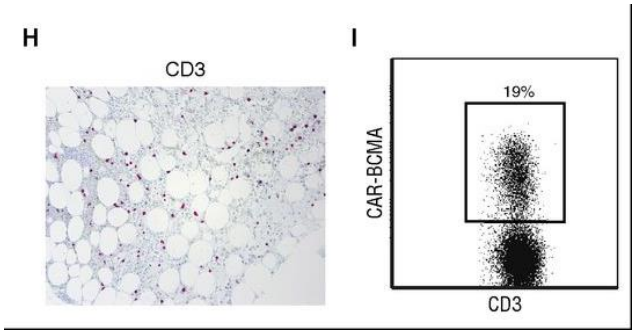
Efficacy of BCMA CAR-T in Myeloma









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

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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

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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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