ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy of Hematologic Malignancies

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Medical University of South Carolina

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- No relevant financial relationships to disclose

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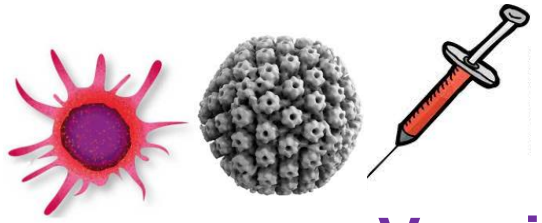
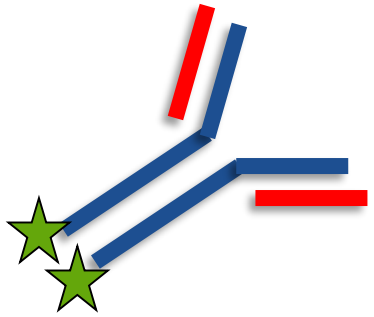
What is hot in immunotherapy?

CAR-T



Vaccine



Magic Bullet

Checkpoint blockade

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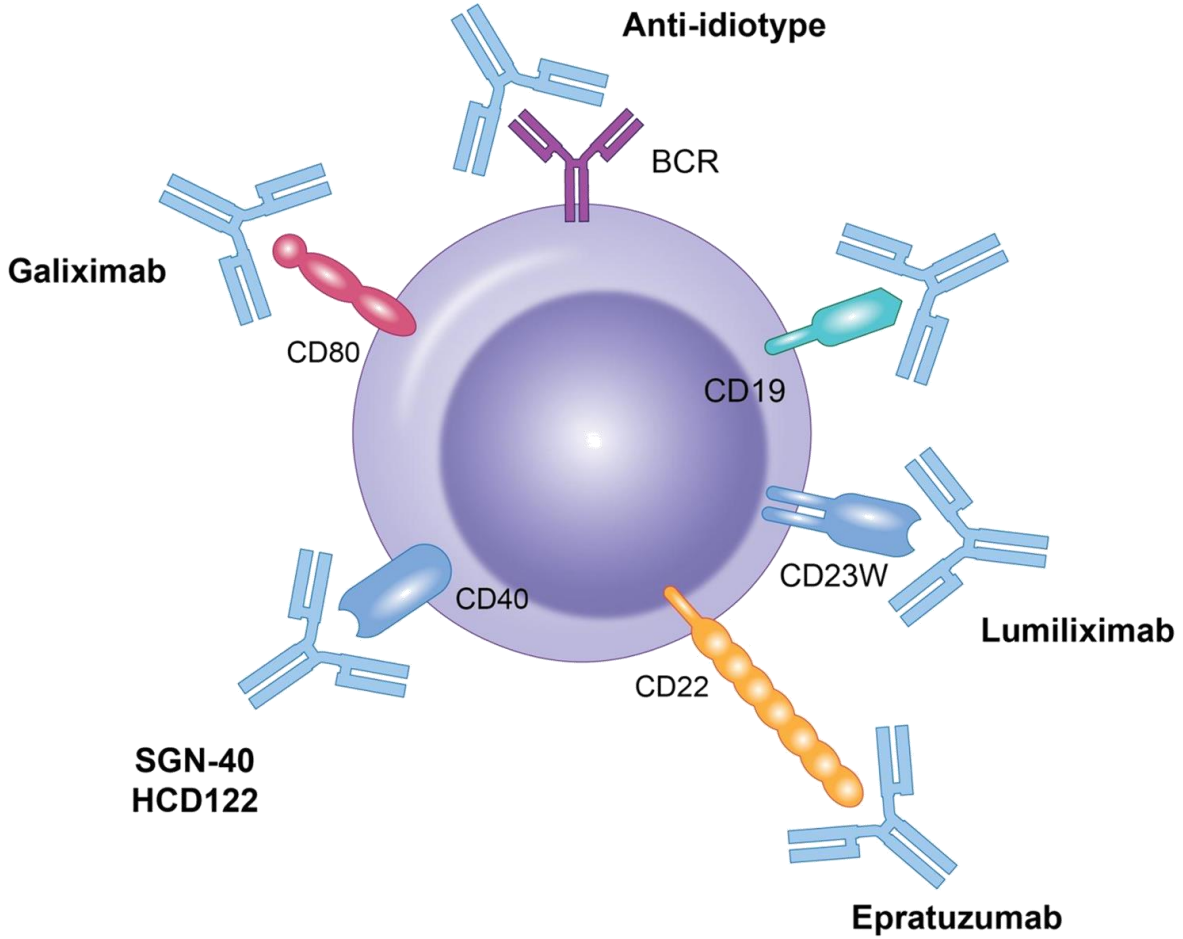
Monoclonal antibodies targeting B cell lymphomas



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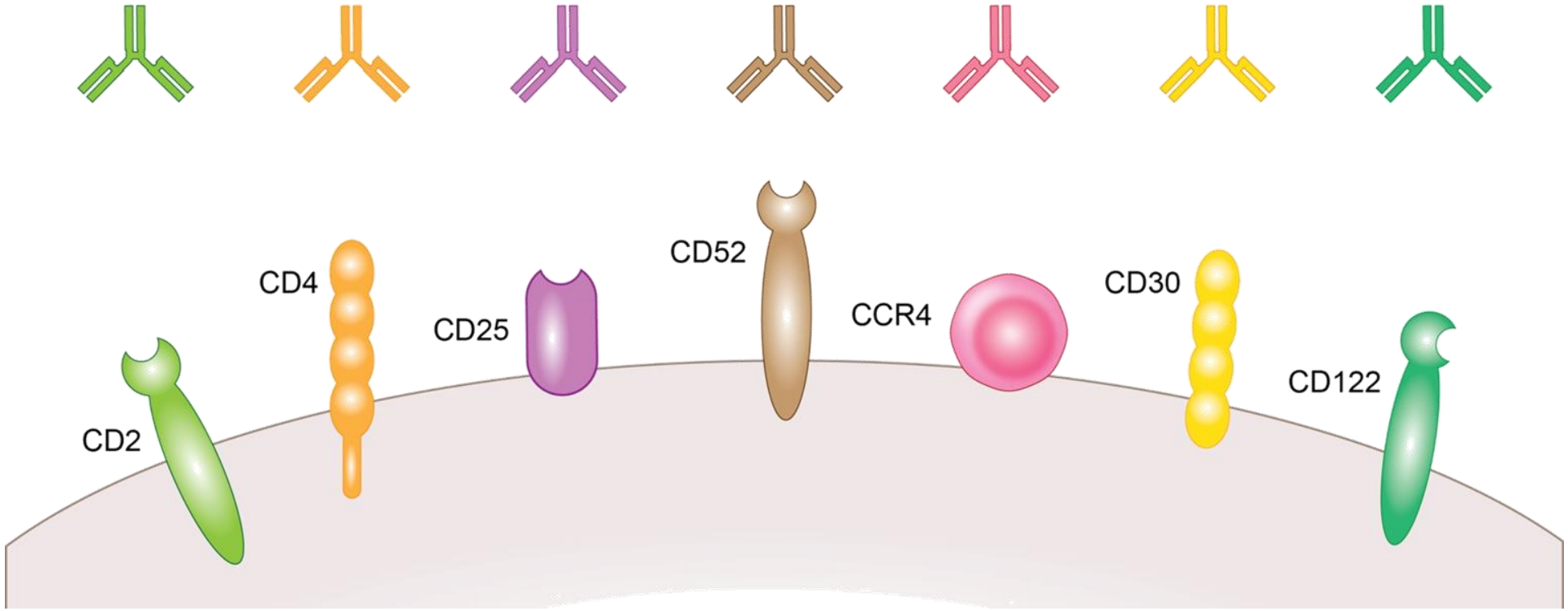
Monoclonal antibodies targeting T cell lymphomas



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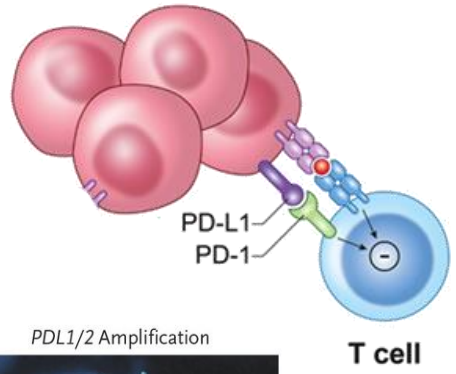
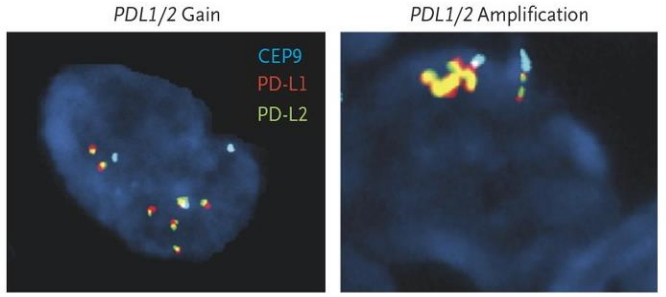
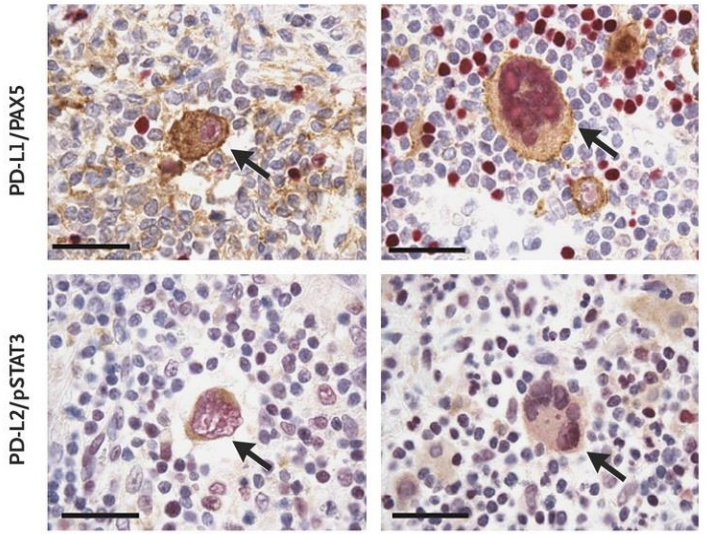
Checkpoint inhibitors

- 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

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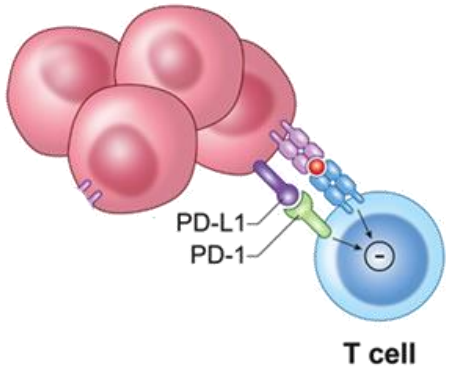

FDA-approved checkpoint inhibitors for hematologic malignancies

- 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 (anti-CD30 Ab linked to Monomethyl auristatin E)
  - 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

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Nivolumab in Hodgkin lymphoma

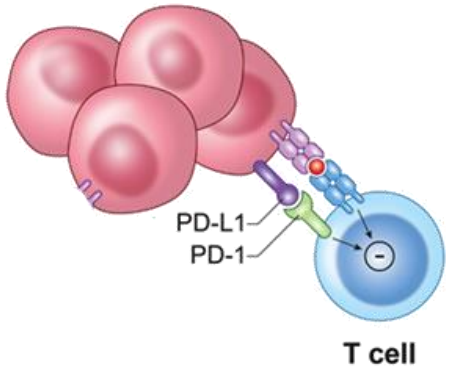

Table 3. Clinical Activity in Nivolumab-Treated Patients.*

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

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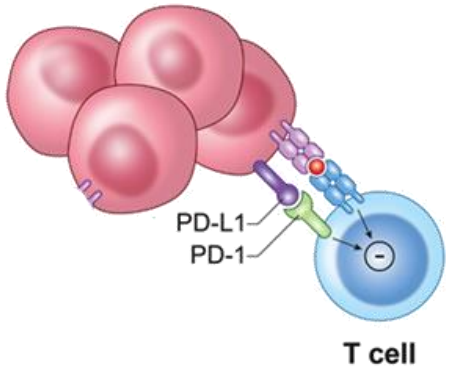
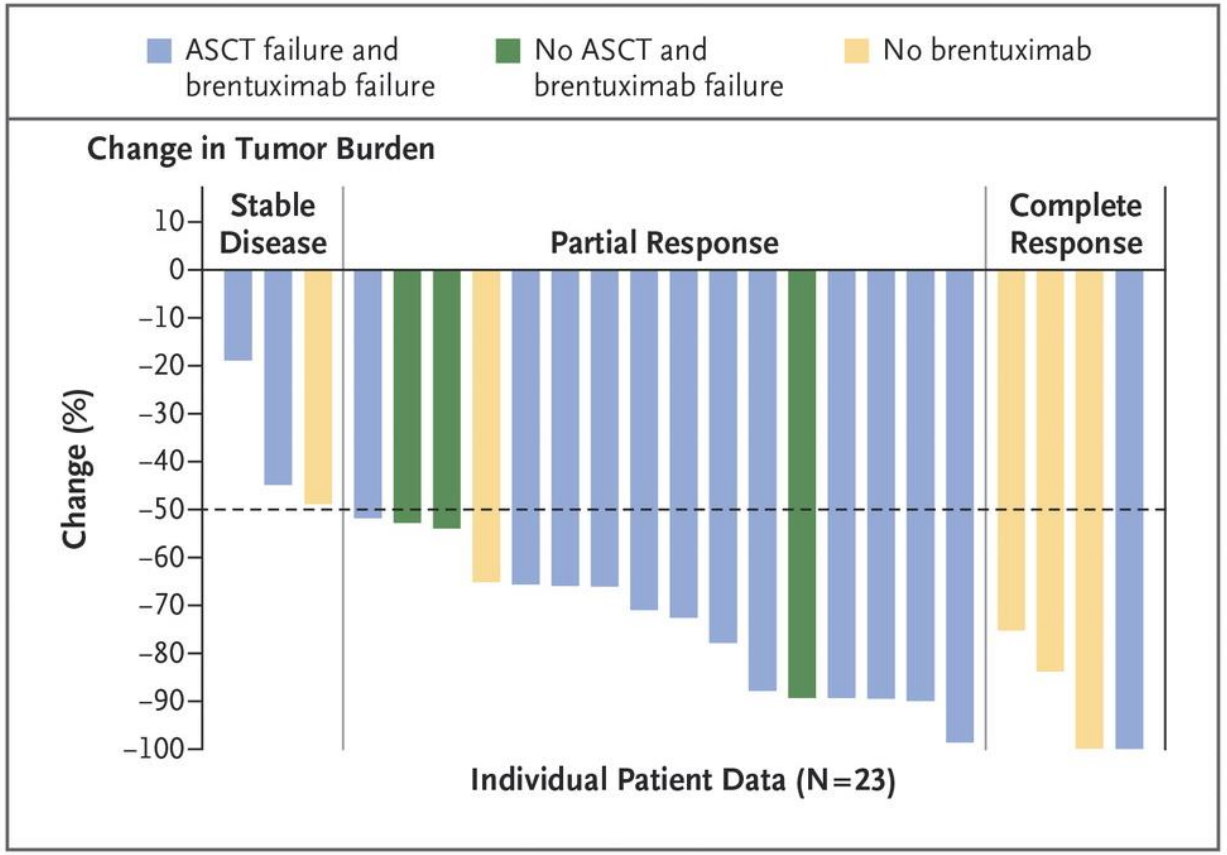


Nivolumab in Hodgkin lymphoma



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

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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

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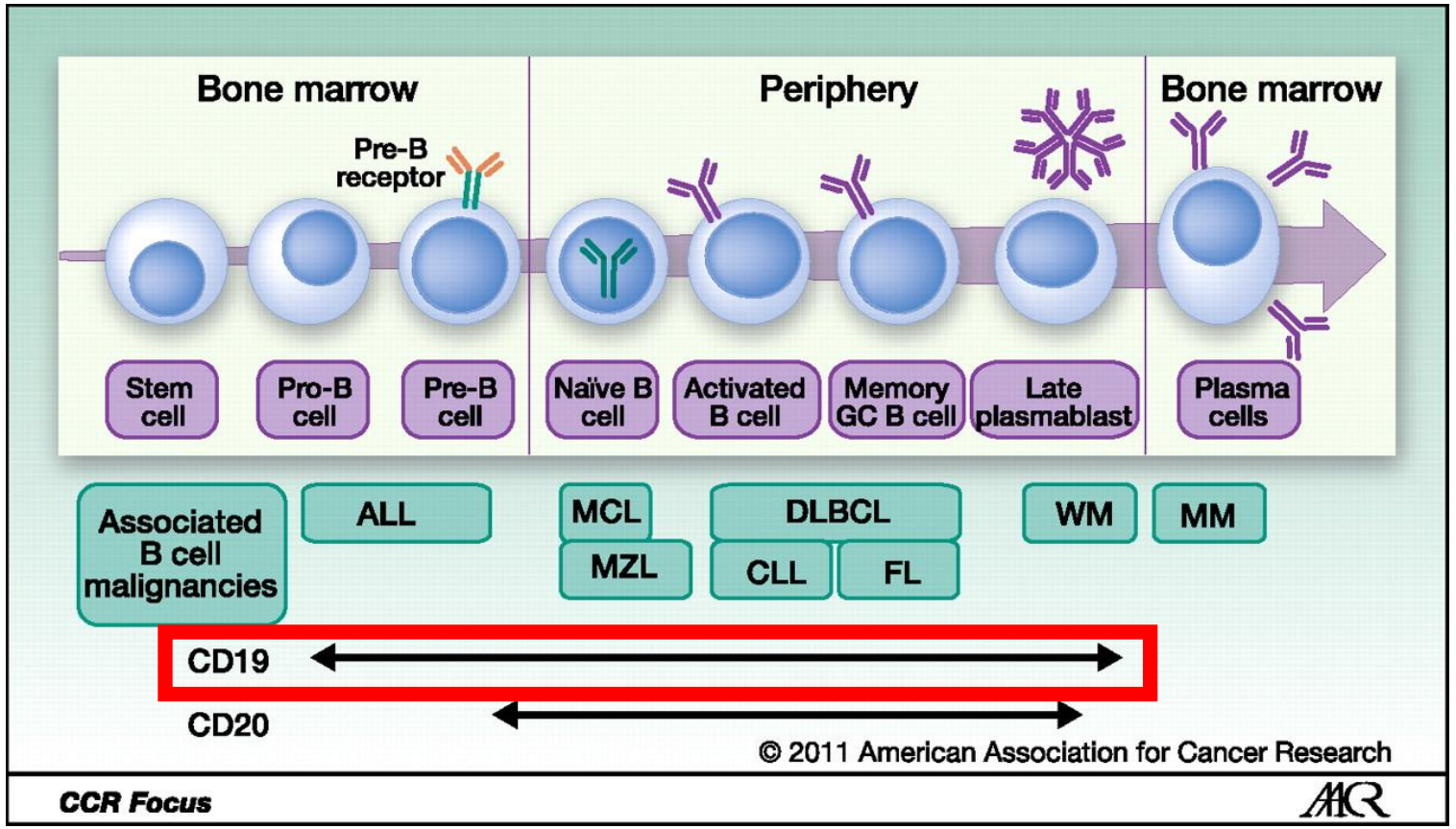
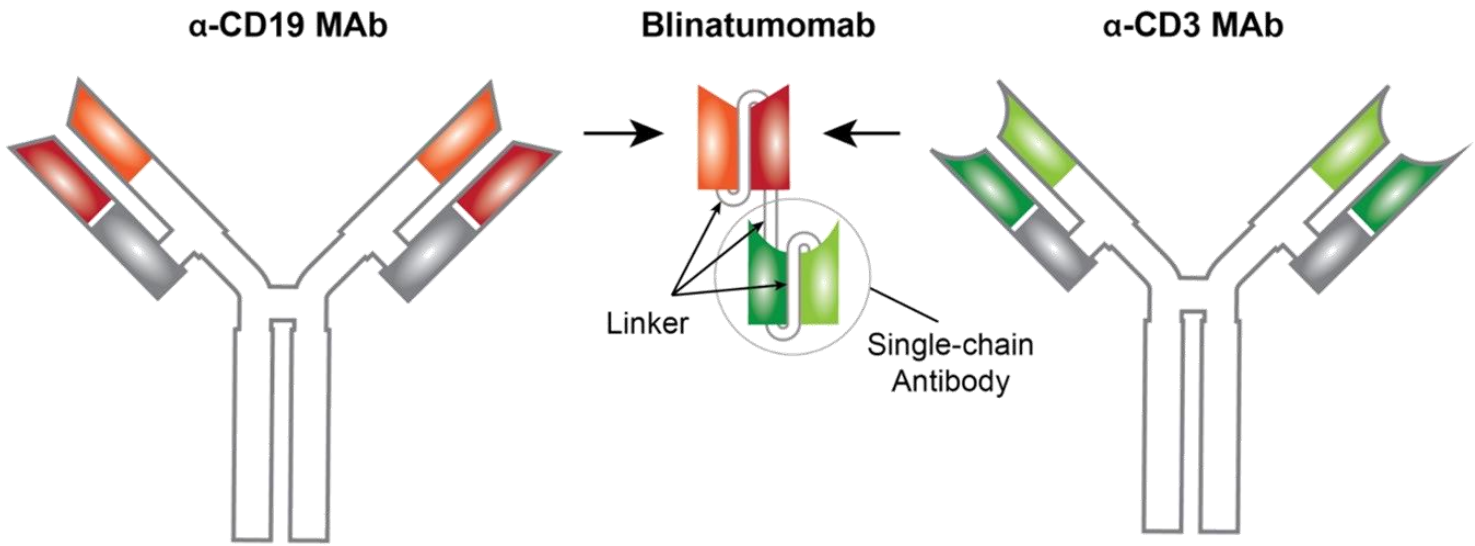
B cell malignancies are CD19+



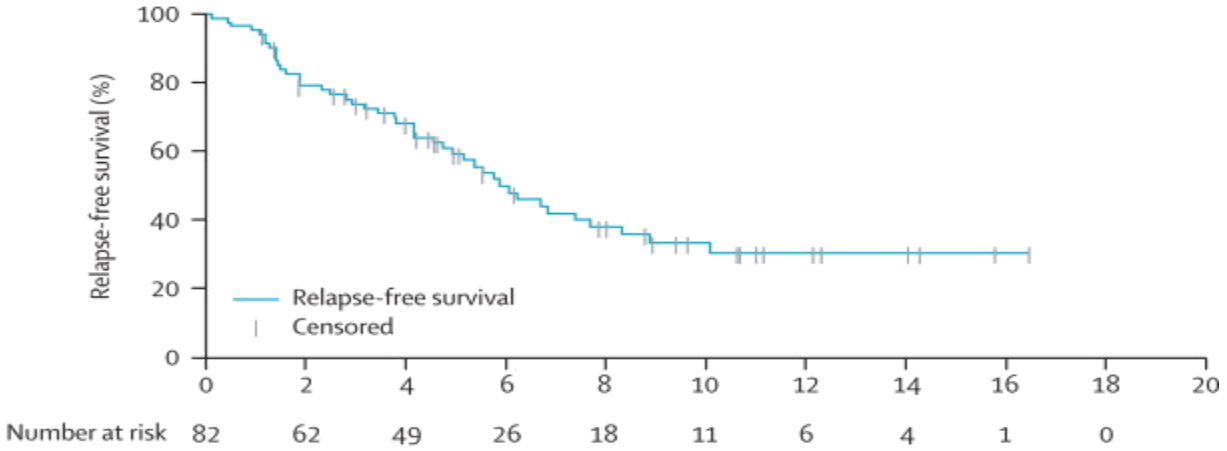
Blanc, V et al., Clinical Cancer Research, Volume 17 , Issue 20

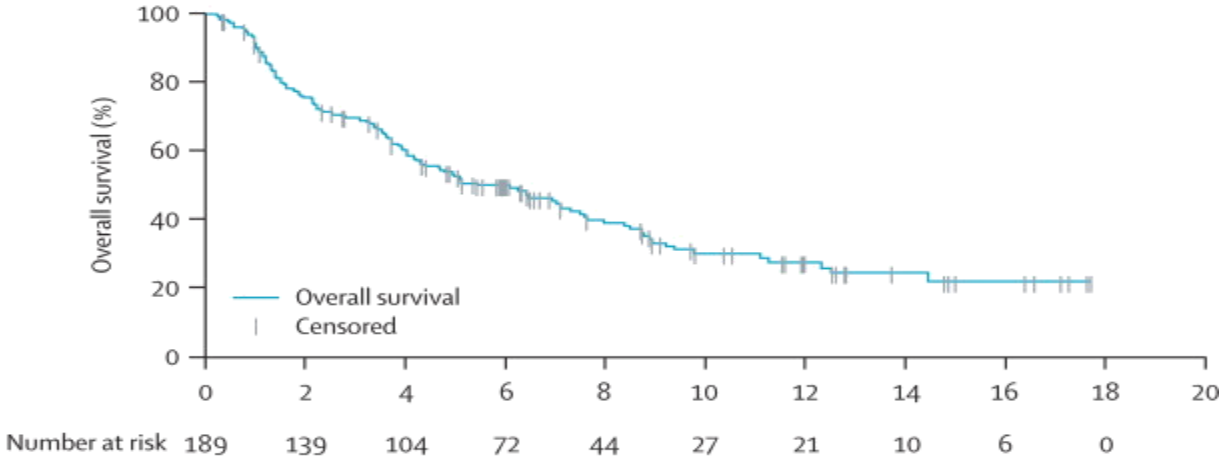
BiTE (blinatumumab) therapy

- 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



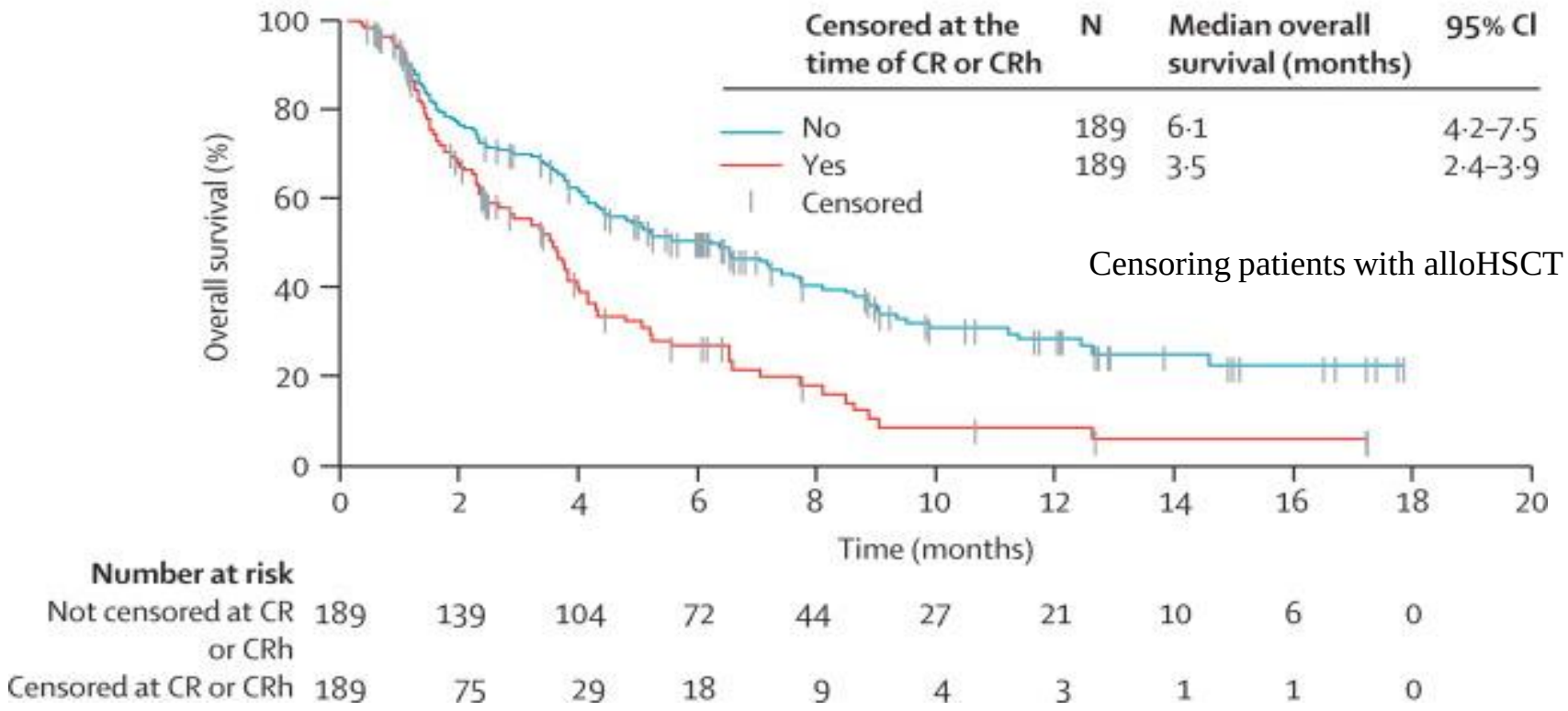
BiTE therapy in ALL





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

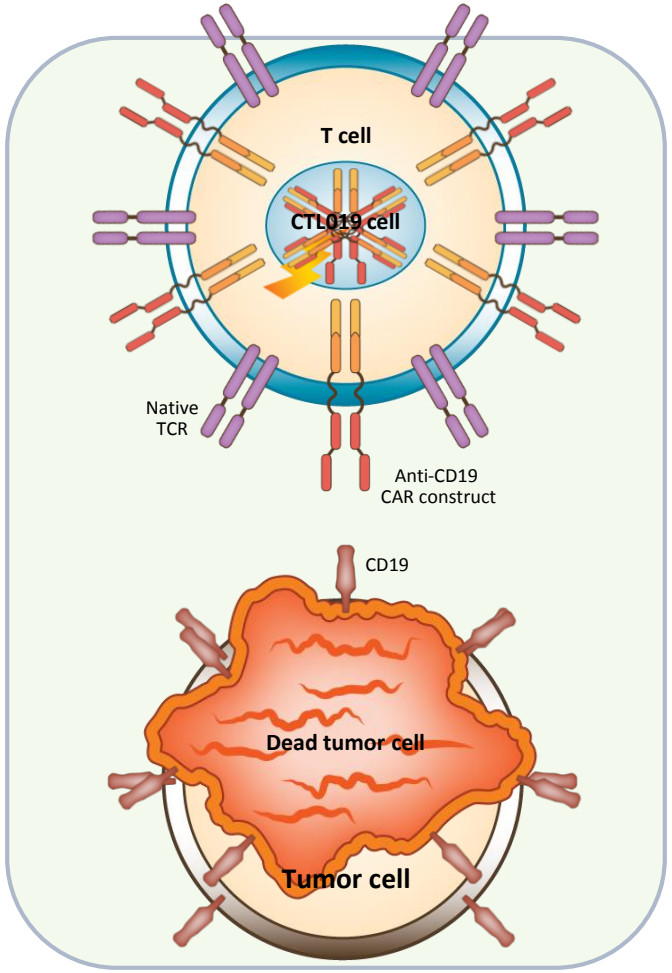
BiTE therapy in ALL



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.

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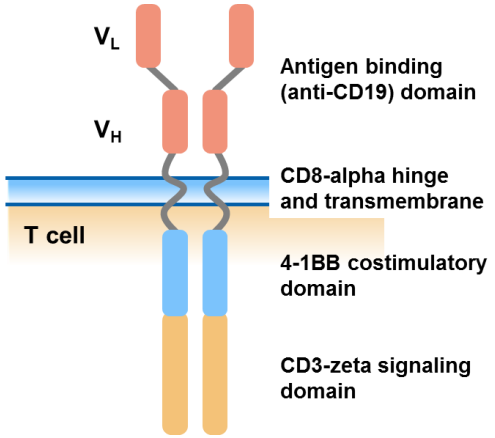
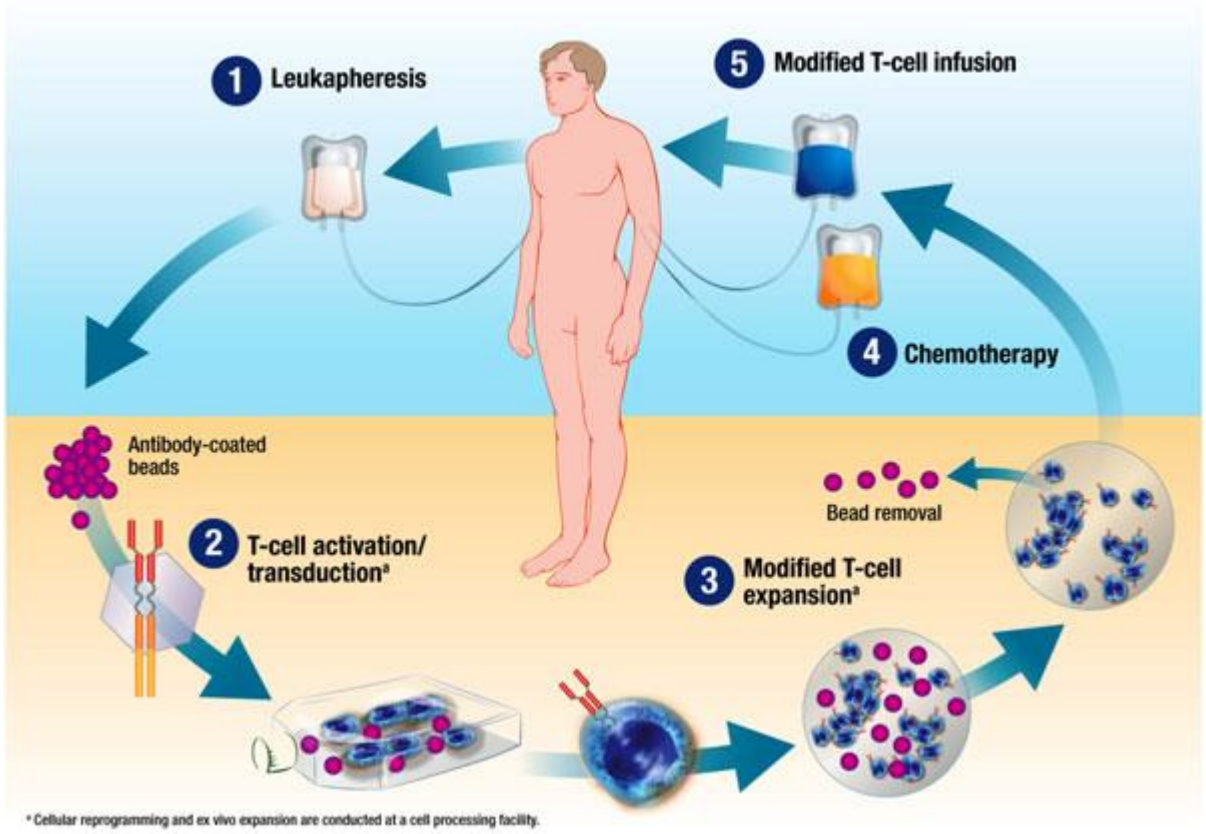
CAR T cell therapy





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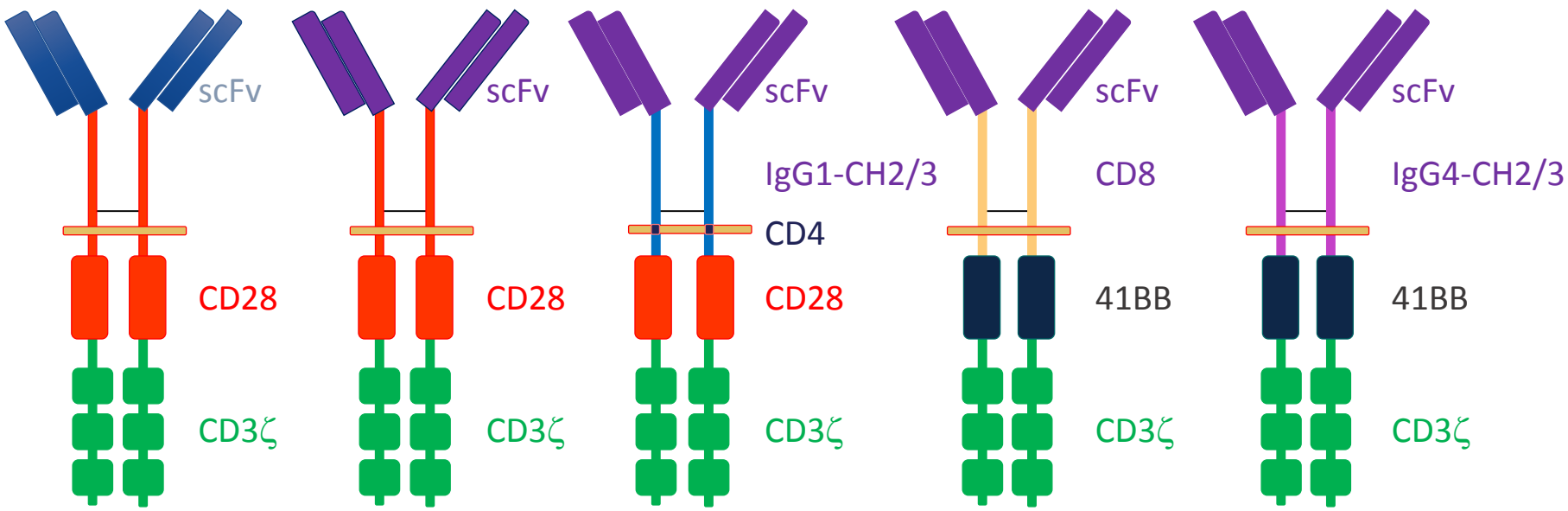
Many CAR Flavors



MSKCC NCI Baylor CHOP/UP FHCRC

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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

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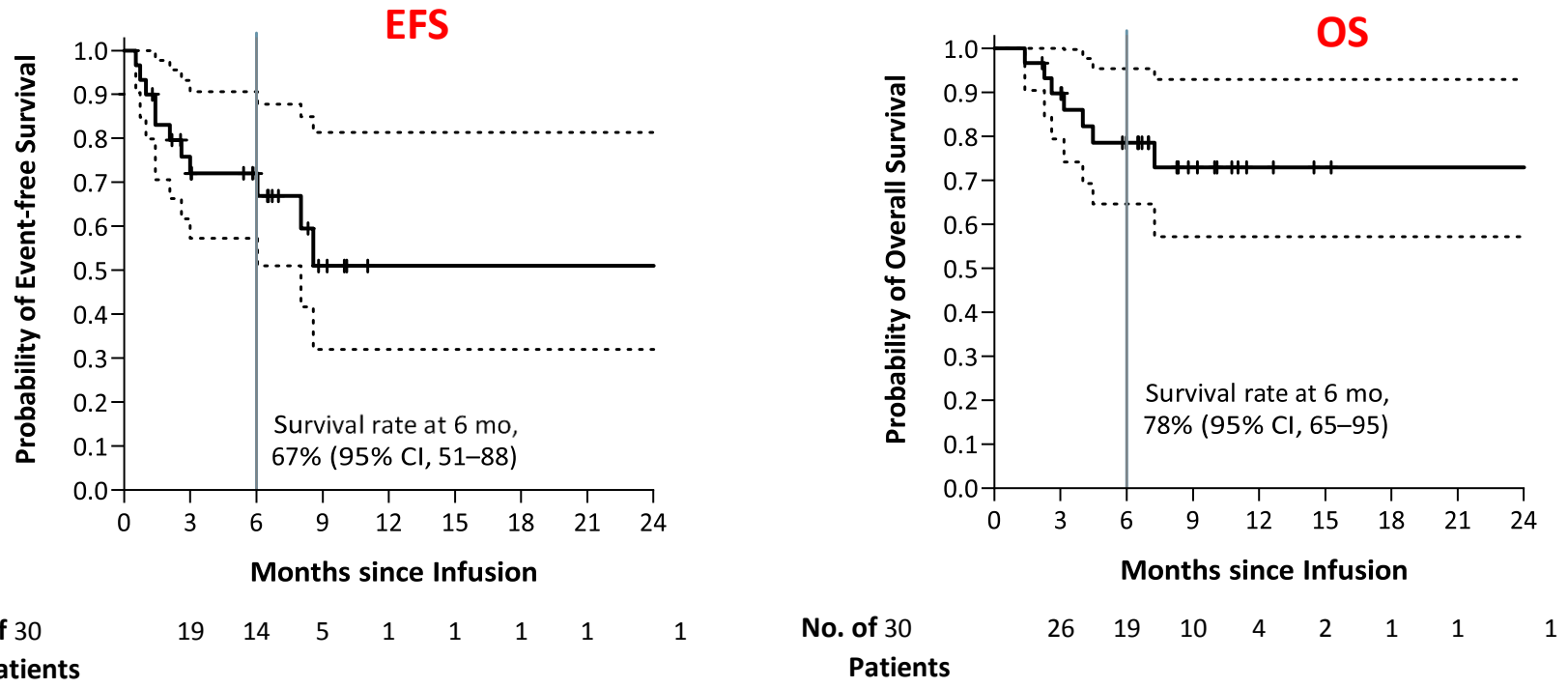
CAR T cell therapy in ALL



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

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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.

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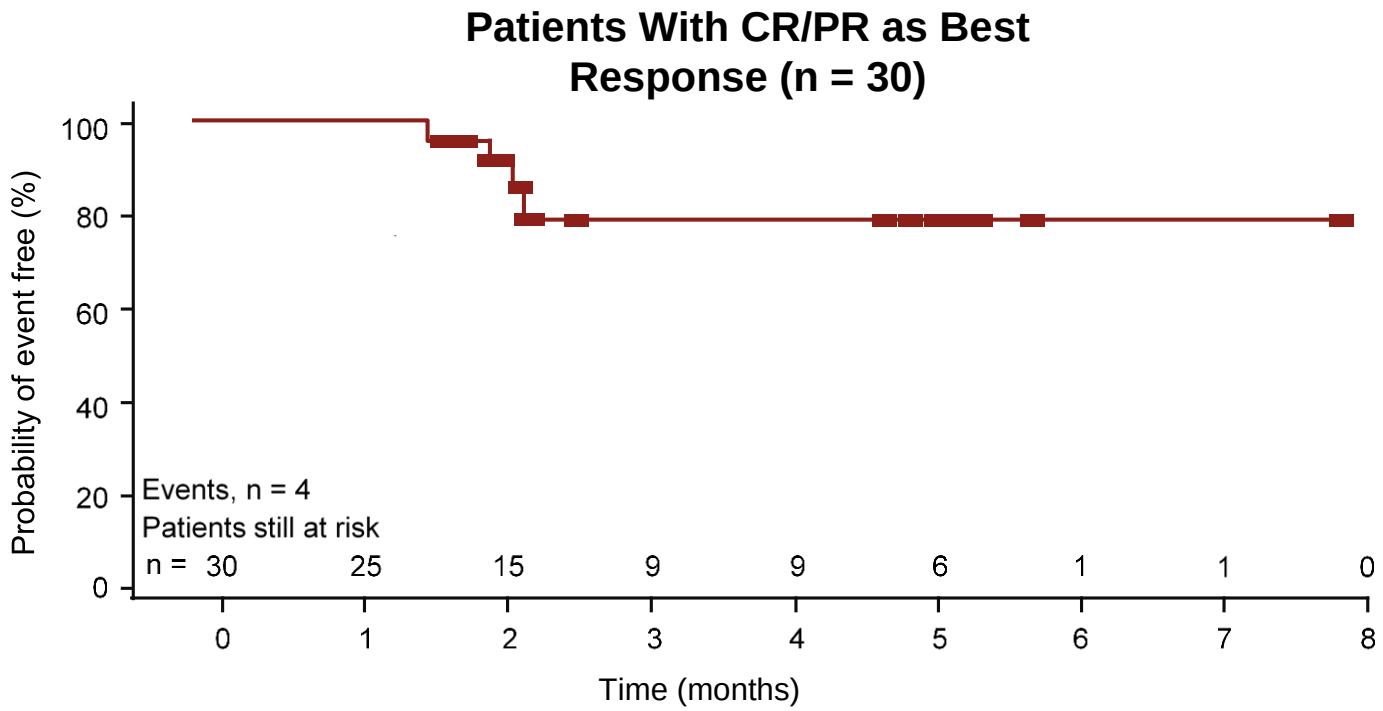
CAR T cell therapy in DLBCL

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

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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].

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CAR-T vs T cell engager

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

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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

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CD19-CAR-T update (2/7/2019)

Authors	Jae Park et al. NEJM 2018; 378:449-459	Maude et al. NEJM 2018; 378(5):439-448	Neelapu et al. NEJM 2017; 377(26):2531-2544
Product	19-28z MSKCC	tisagenlecleucel , 19-z4-1BB, phase 2, 25 sites, PENN	axicabtagene ciloleucel (axi-cel), CD19-z-28, multi-center phase 2, NCI
Indications (n)	adults with relapsed B-cell ALL (53)	pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL (75)	Refractory DLBL, 1^{o} mediastinal BCL, or transformed FL (111 enrolled, 101 treated)
Response (%)	CR: 83	CR: 81	Objective R: 82 CR: 54; OS at 18 m: 52
OS/MS (months)	mEFS: 6.1 m mOS: 12.9	EFS: 73%, OS: 90% at 6m EFS: 50%, OS: 76% at 12m	
CRS (%)	26	77	13
Neurotoxicity	No grade 5 or cerebral edema	No cerebral edema	28% were grade 3 or higher. No mention of cerebral edema

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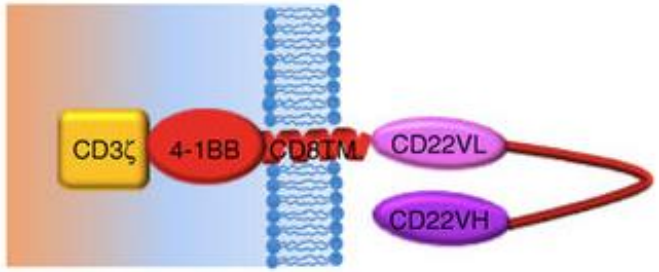
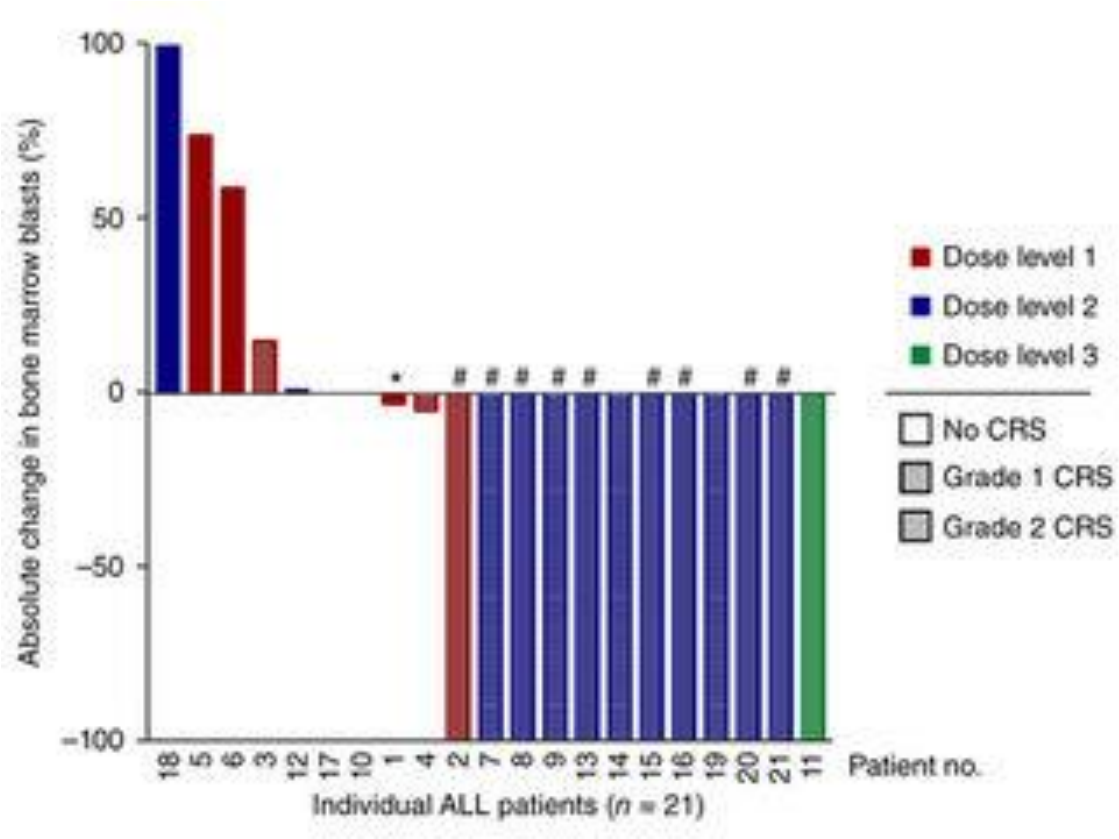
Ongoing trials with CAR T therapies for hematologic malignancies

- CD22+ CAR T cells effective in patients with relapsed, CD19- B-ALL



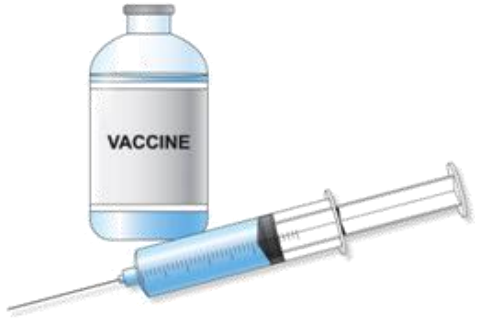


Fry, T.J. et al., Nature Medicine, 2017

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

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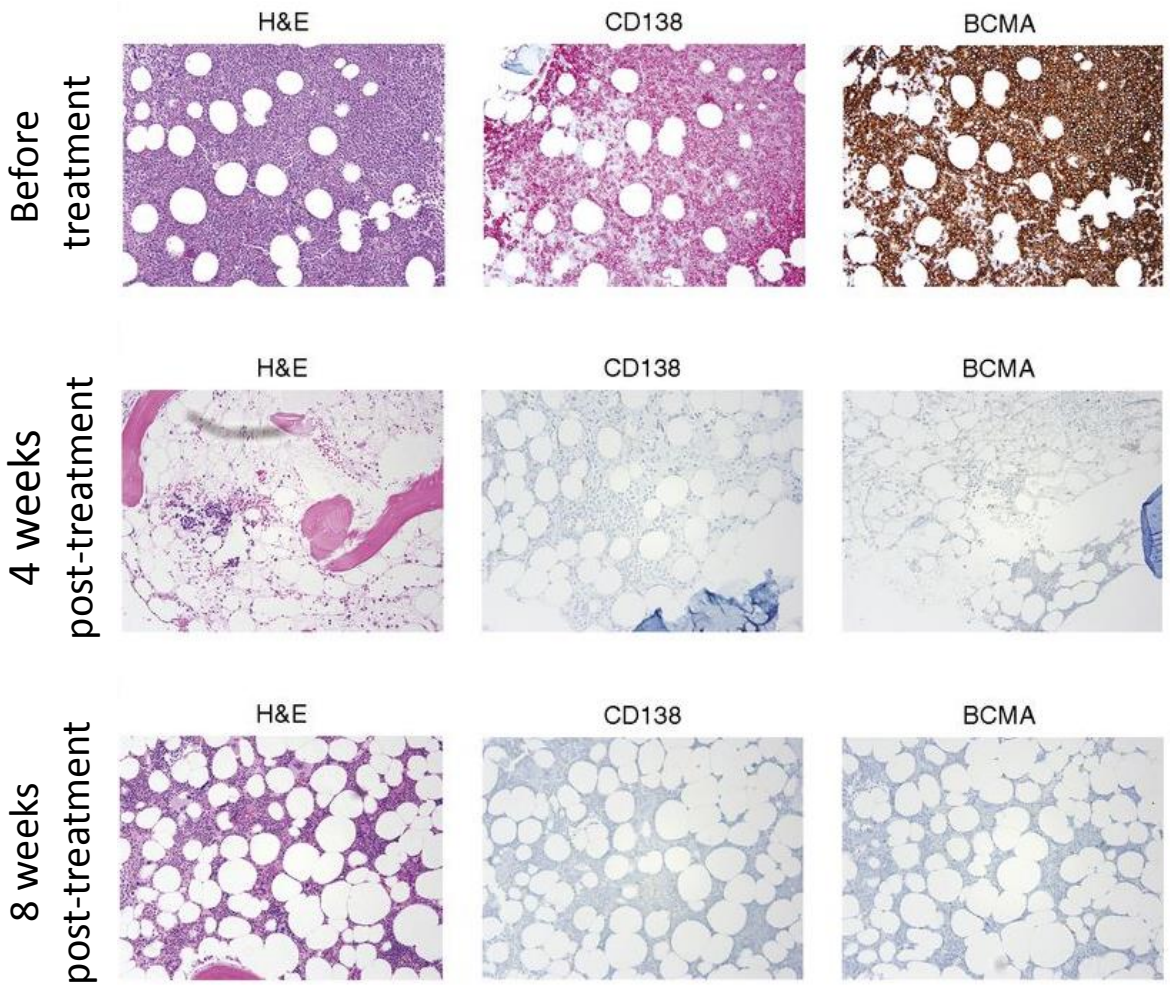
On the way: BCMA+ CAR T therapy for myeloma



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

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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

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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Thank you

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