Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hematologic Malignancies

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

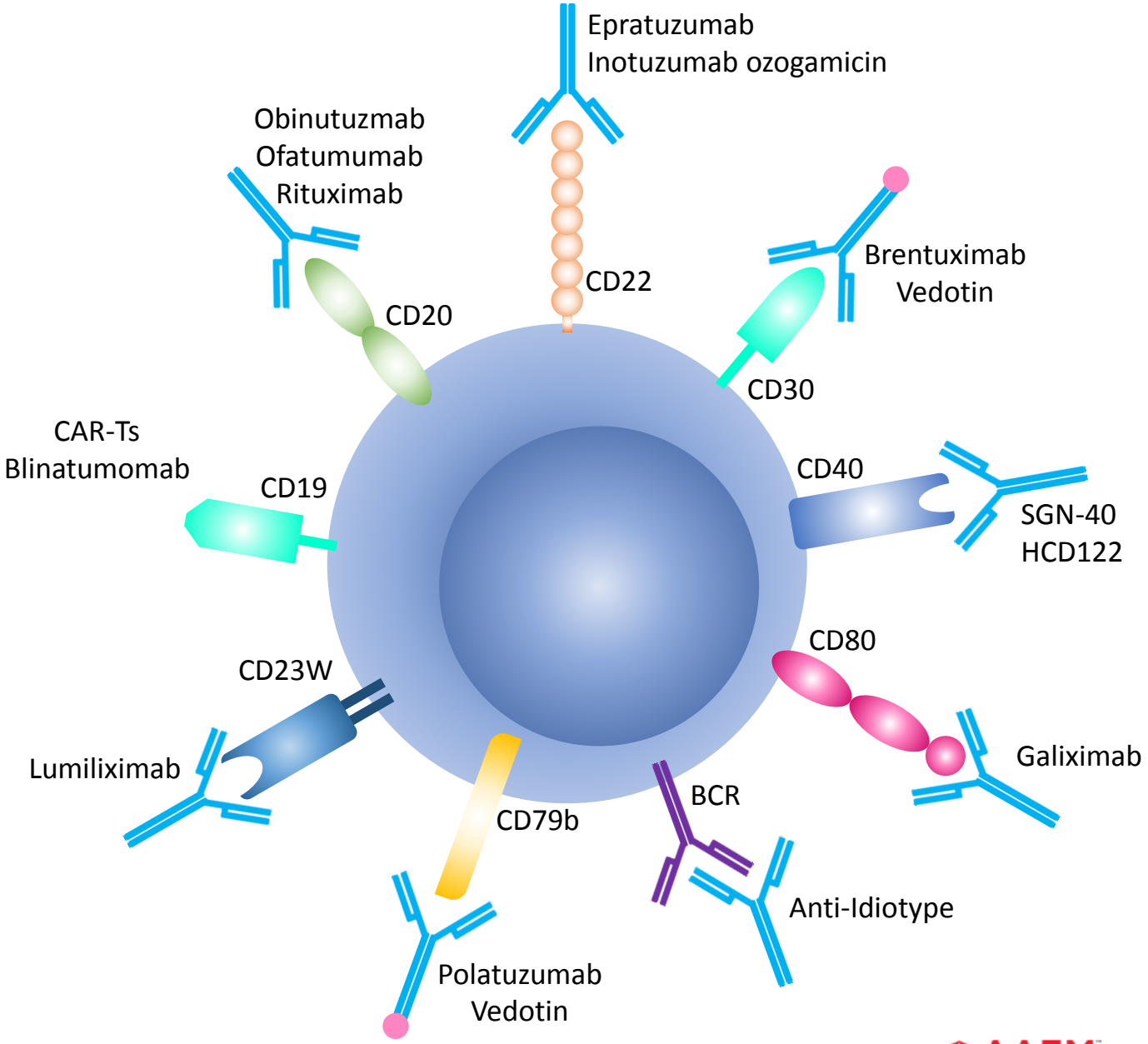
ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

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



Checkpoint inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

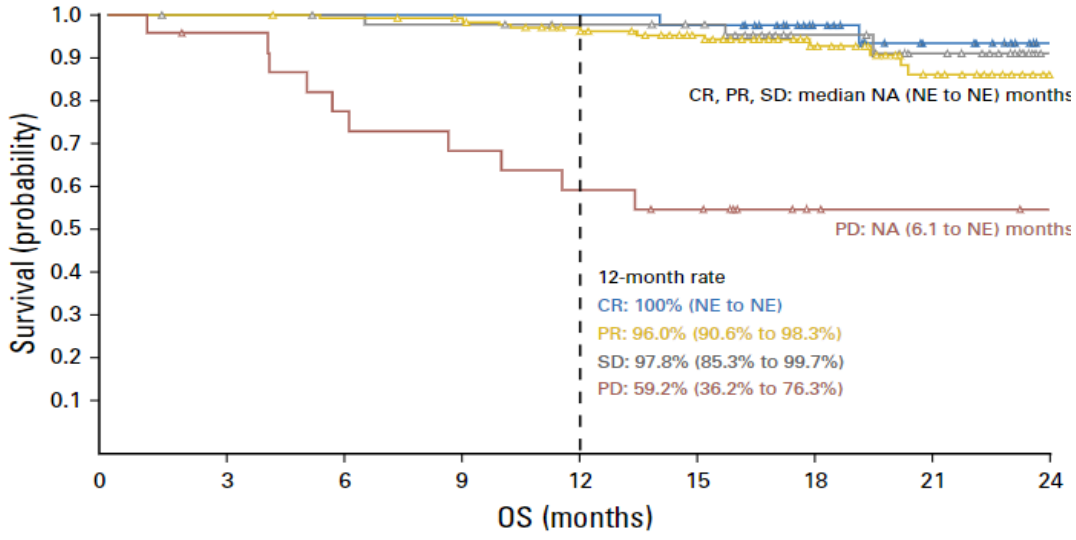
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg (up to 200 mg) q3w (pediatric)
Pembrolizumab	2018	Adult/pediatric refractory primary mediastinal large B-cell lymphoma or relapsed after 2 previous therapies	200 mg q3W adults 2 mg/kg (up to 200 mg) q3w (pediatric)

Checkpoint inhibitors: Hodgkin Lymphoma

Checkmate-205

ORR = 69%

CR = 16%



No. at risk:

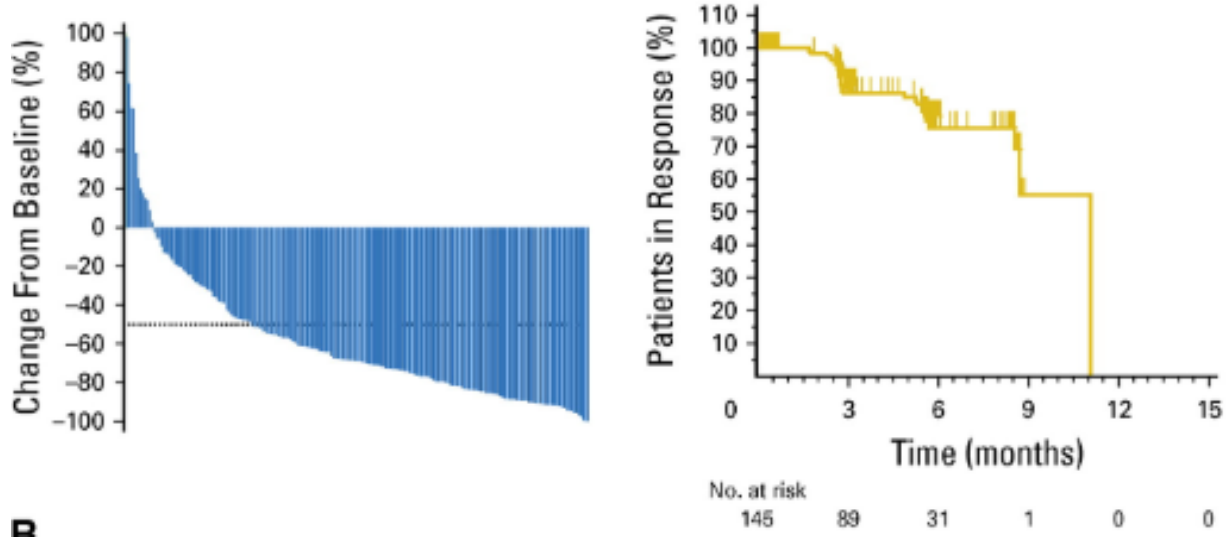
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

CR = 22.4%

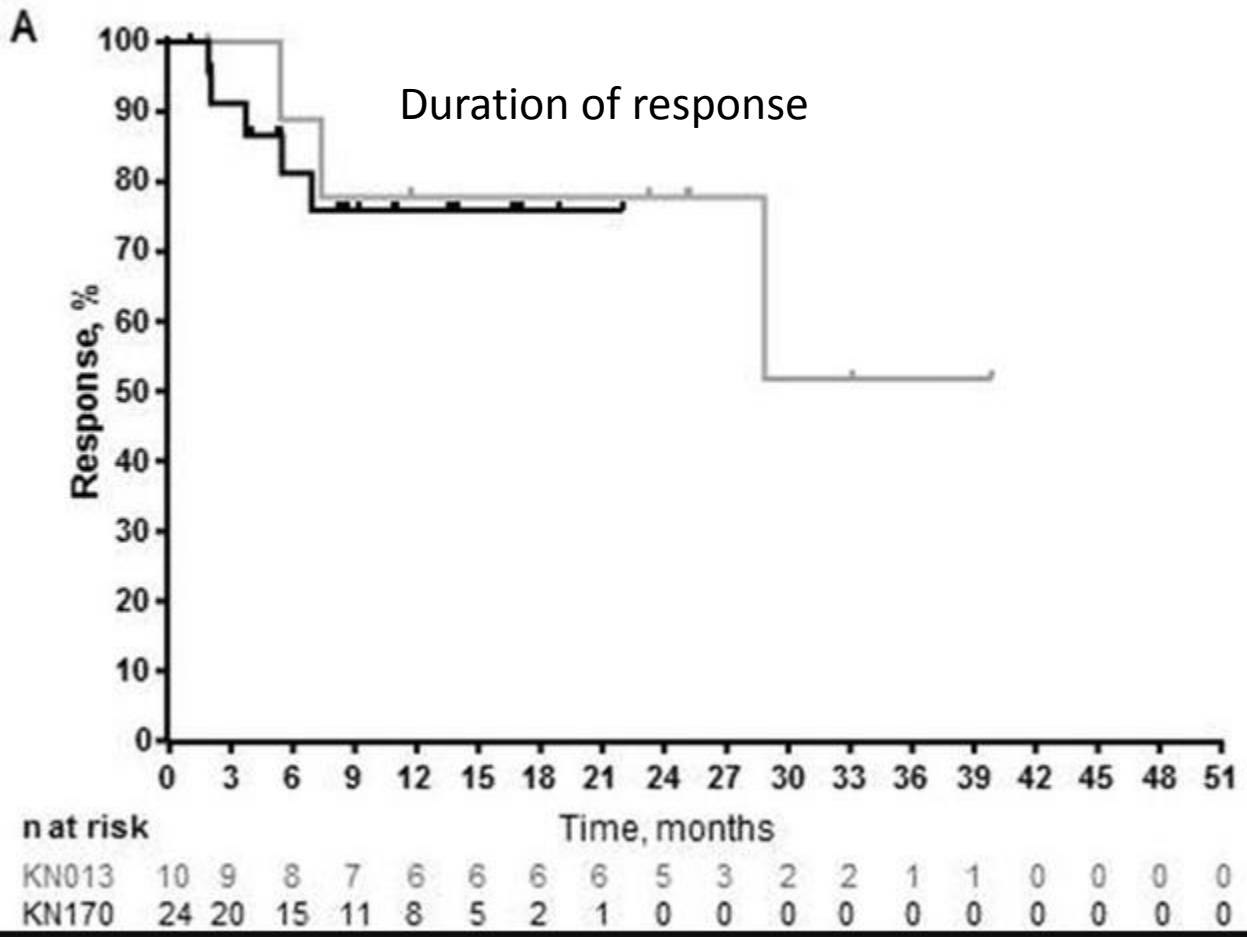
Activity seen regardless of PD-L1 expression

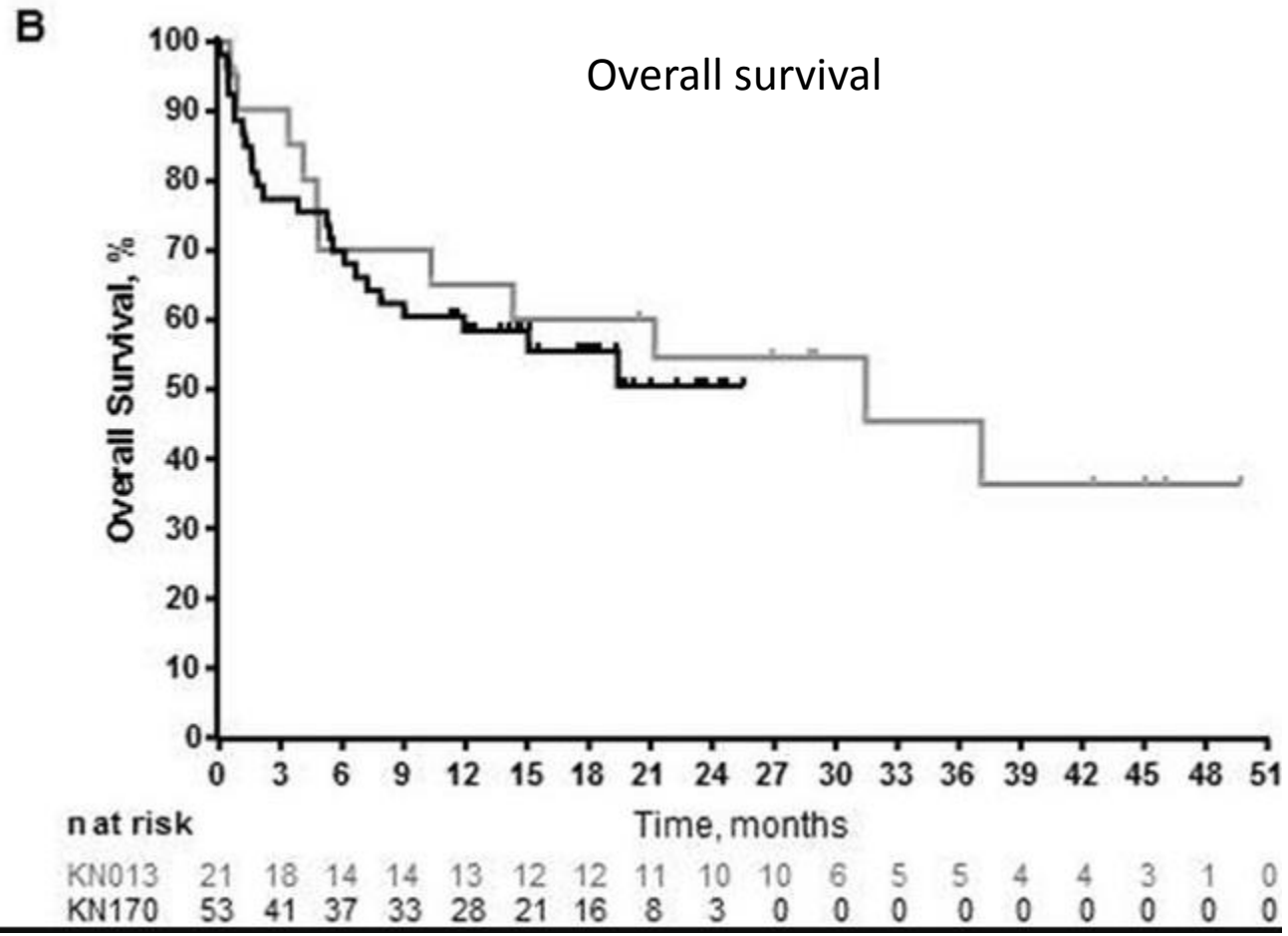


Armand, J Clin Oncol 2018.

Chen, J Clin Oncol 2017.

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

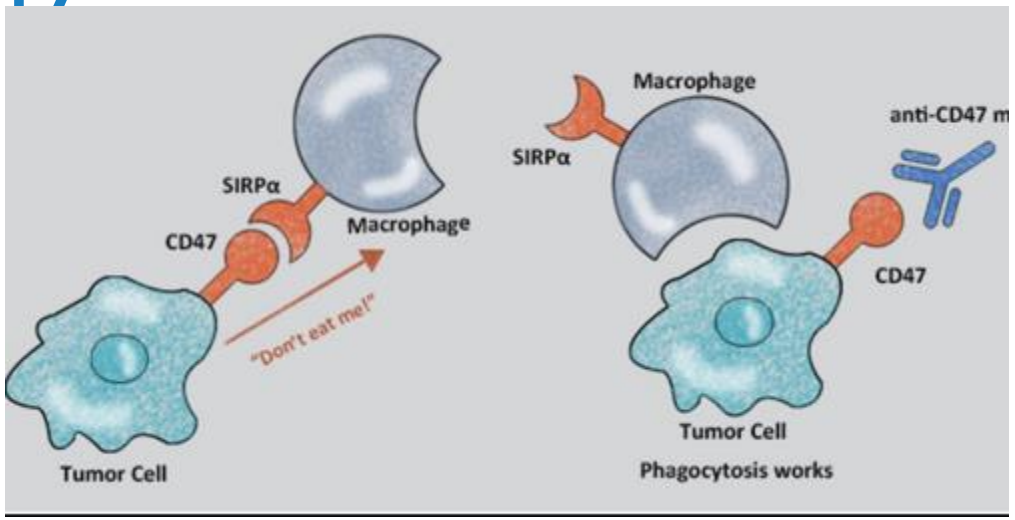


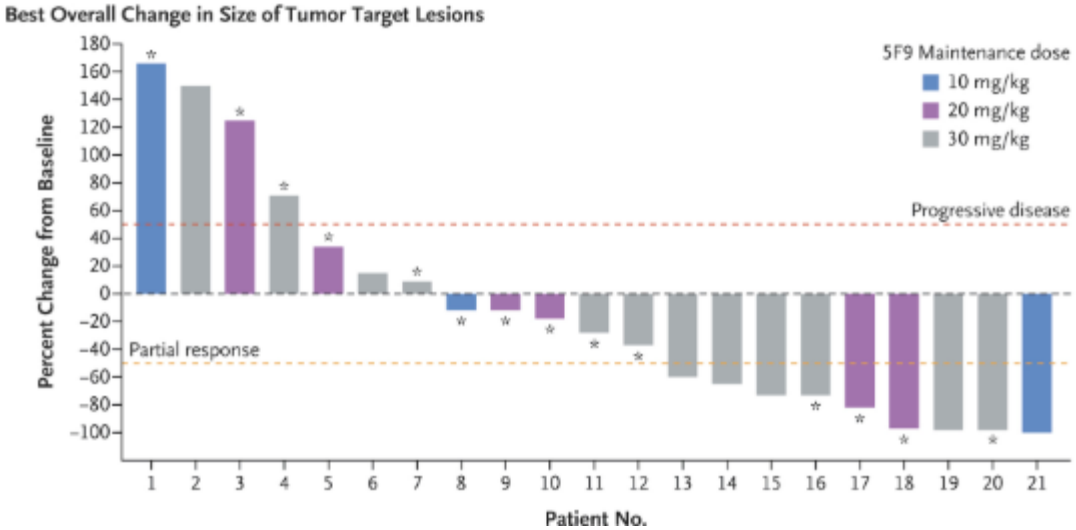


Armand, Blood 2018.

In development: Macrophage checkpoint: CD47

- Phase 1b: Hu5F9-G4 + rituximab in rituximab refractory disease
- DLBCL – ORR = 40%, CR = 33%
- Follicular lymphoma – ORR = 71%, CR = 43%



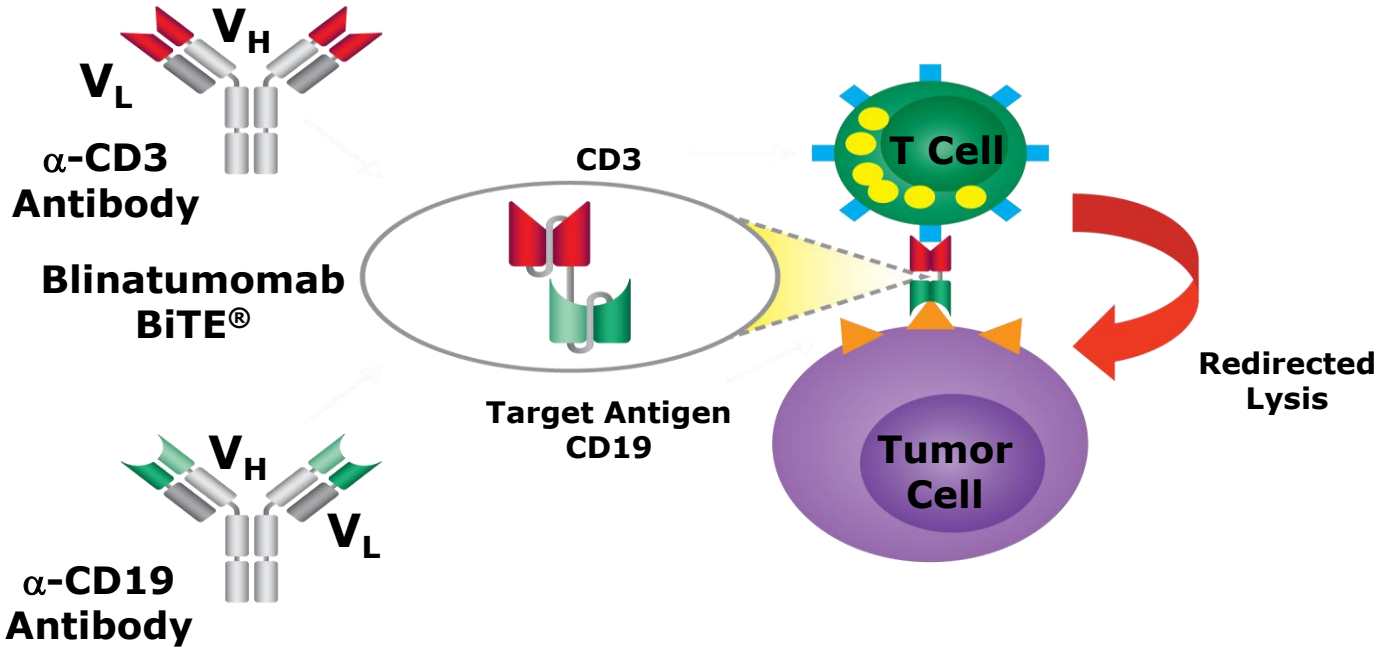


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

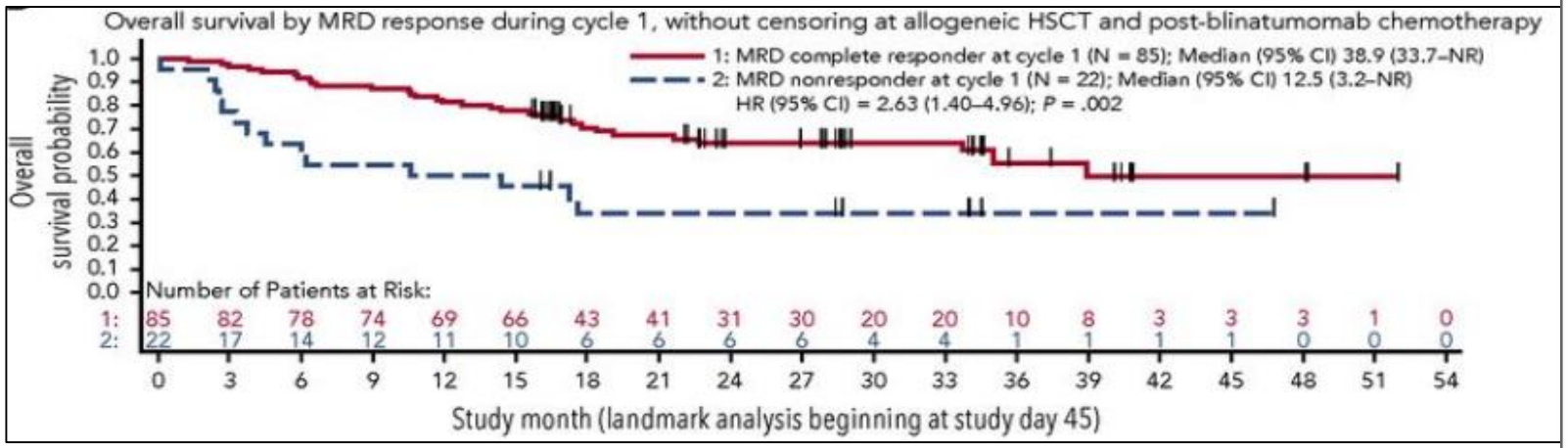
BiTE (Blinatumomab) Therapy

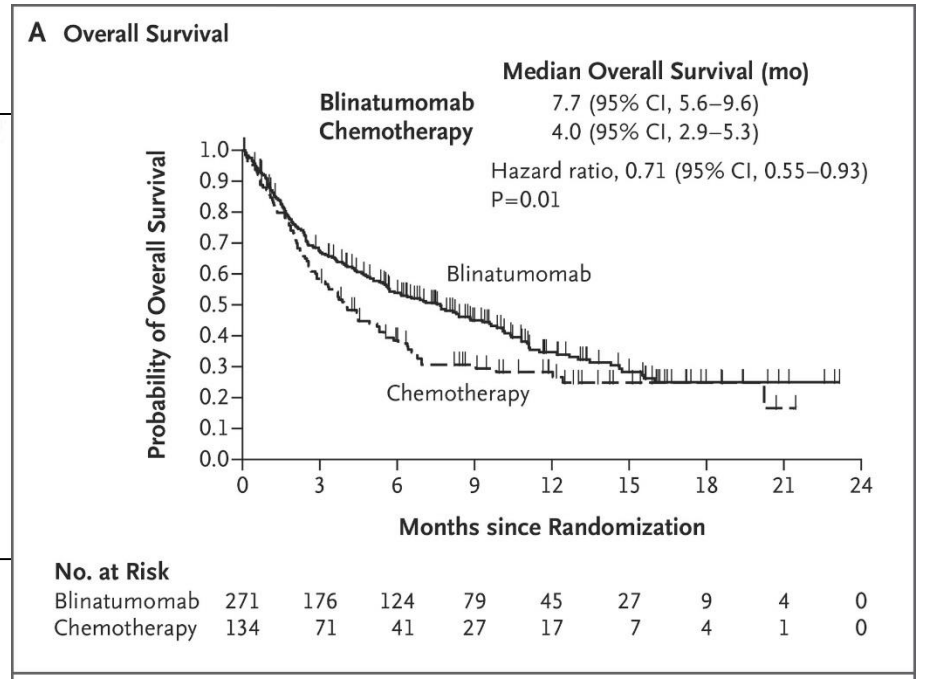
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





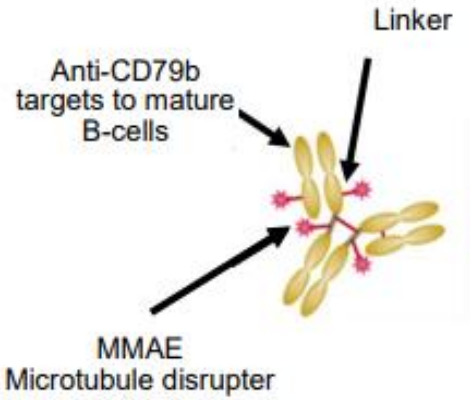
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

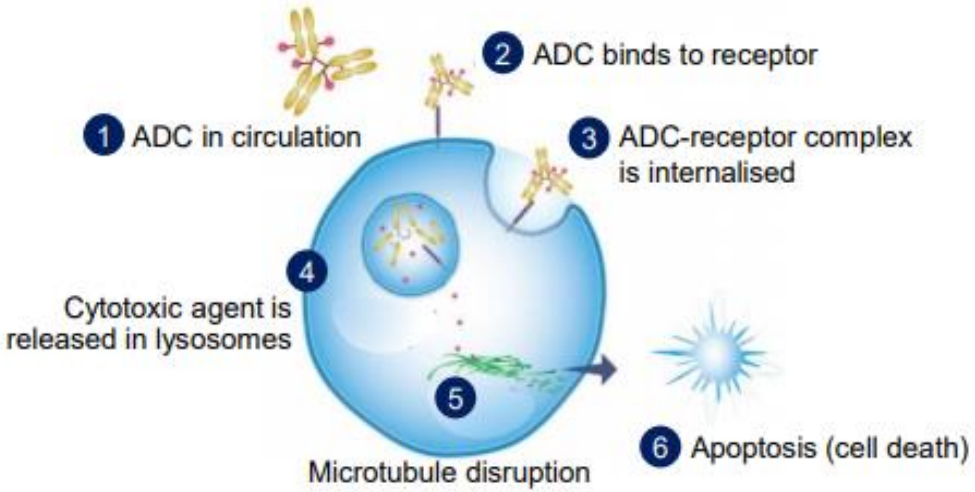
Antibody-drug conjugates (ADC)

FDA-Approved Antibody-Drug Conjugates

Drug	Target antigen	Year of approval	Indication
Brentuximab vedotin	CD30	2011	• Classical Hodgkin lymphoma, relapsed after HSCT or ≥2 previous therapies • Anaplastic large cell lymphoma ≥ 1 previous therapies
		2018	cHL - first line with combination chemo
Inotuzumab ozogamicin	CD22	2017	Relapsed/refractory/MRD+ B-cell ALL
Polatuzumab vedotin (w/ bendamustine & rituximab)	CD79b	2019	DLBCL ≥ 2 previous therapies

Polatuzumab vedotin: DLBCL





Polatuzumab vedotin has demonstrated efficacy in R/R DLBCL in combination with rituximab[1,2] and rituximab-bendamustine[3]

Treatment	Best overall response
Pola +/- rituximab	51–56%[1,2]
Pola + rituximab + bendamustine	68%[3]

ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E

1. Palanca-Wessels A, et al. Lancet Oncol 2015;16:704–15; 2. Morschhauser F, et al. Lancet Hematology 2019;6:e254–65; 3. Sehn H, et al. Blood 2018;132:1683

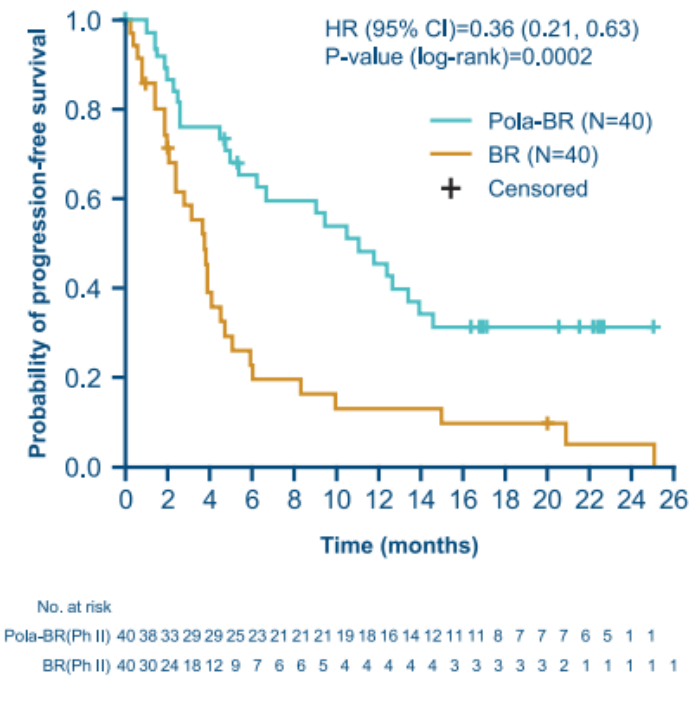
Slide credit: Tilly et al. ICML 2019

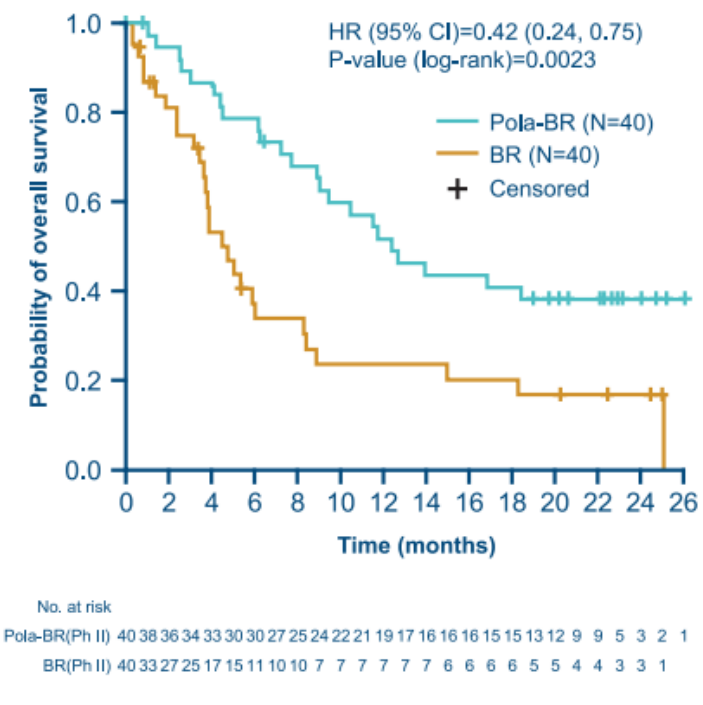
Polatuzumab vedotin: DLBCL

- Randomized phase 2 study
- Pola-BR vs. BR in R/R DLBCL

- Higher CR = 40% vs. 18% (p: 0.03)
- Median PFS = 7.6 m (HR=0.34, p<0.01)
- Median OS = 12.4 m (HR=0.42, p<0.01)

- Ongoing phase 3 (POLARIX)
- Frontline DLBCL- R-CHOP vs R-CHP+Pola

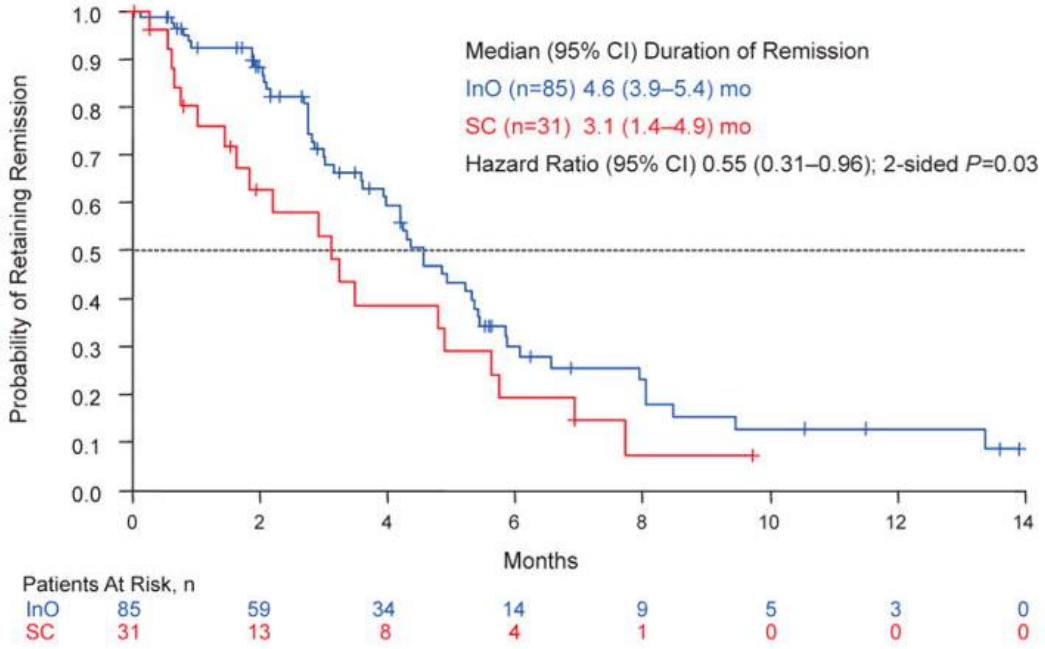


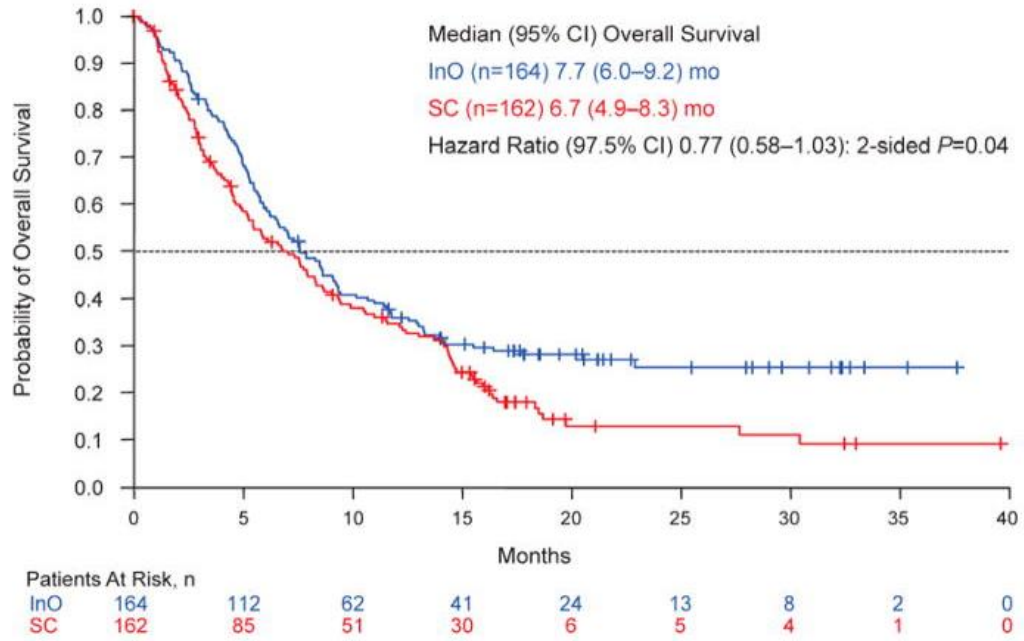


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

- Anti-CD22 antibody conjugated to calicheamicin
- Higher response, MRD-negativity, PFS, and OS than standard-of-care



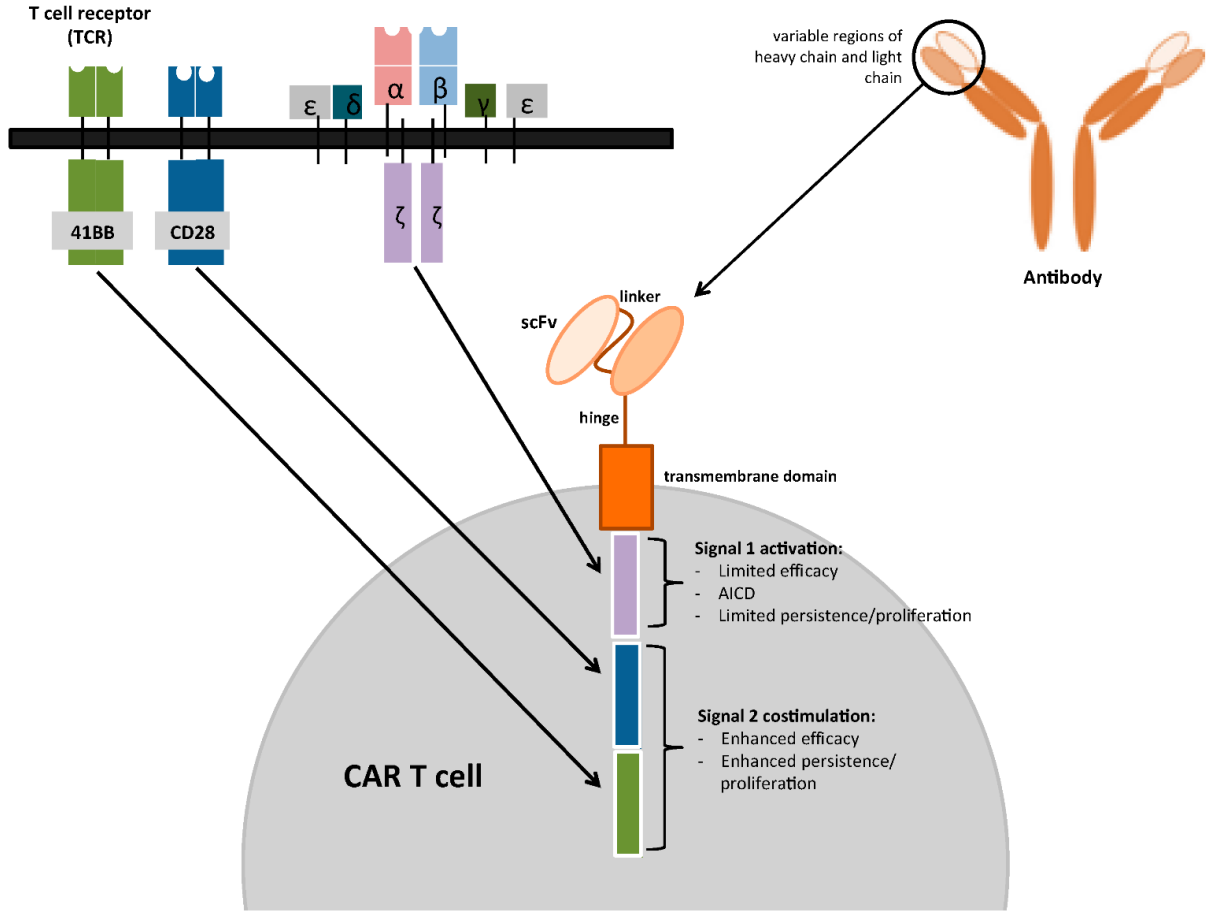


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

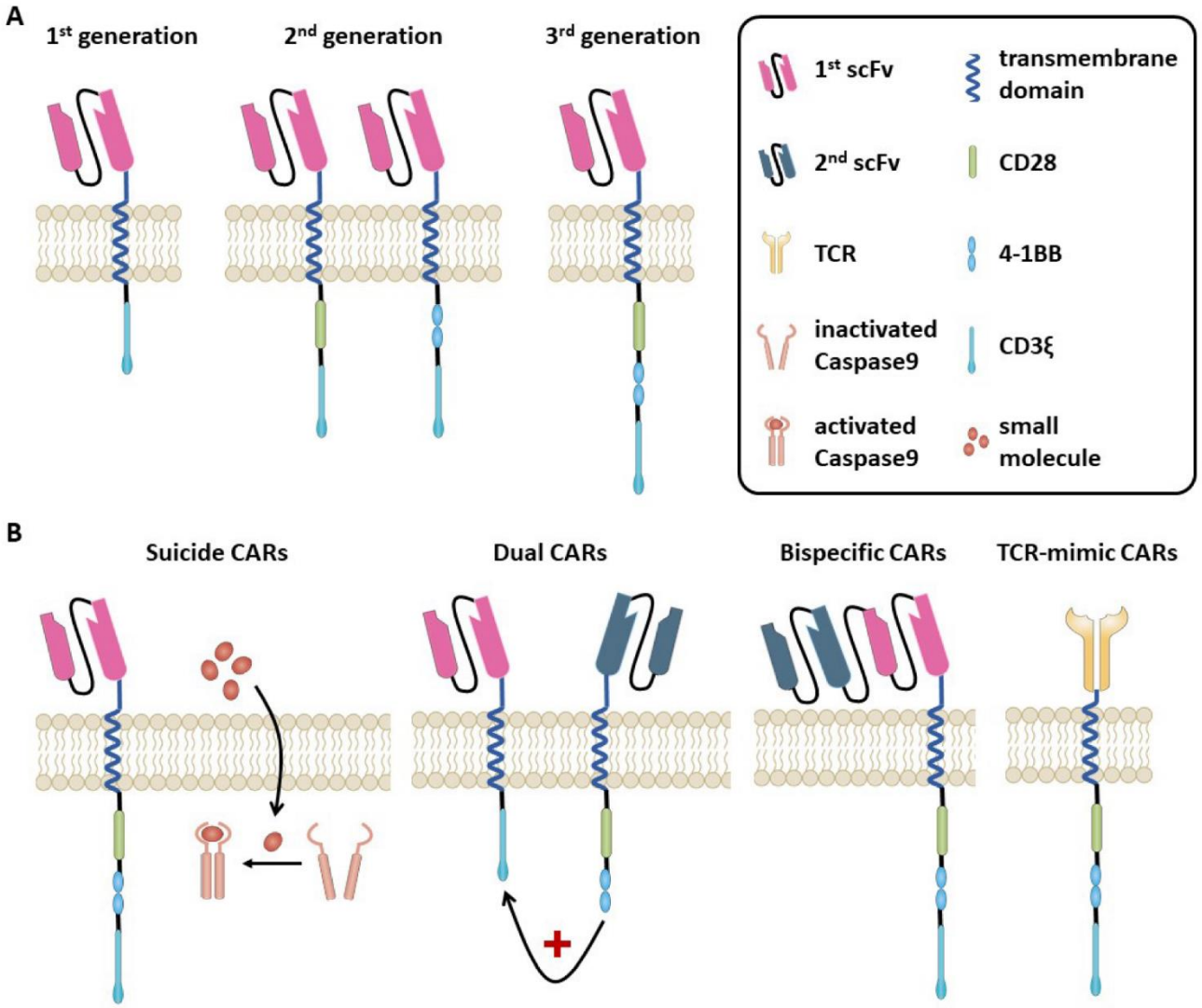
Chimeric antigen receptors

- Specific and potent: B - specific, T - toxic
- Overcome immune tolerance
- Targets surface molecules in native conformation
- Independent of antigen presenting cell and MHC complex



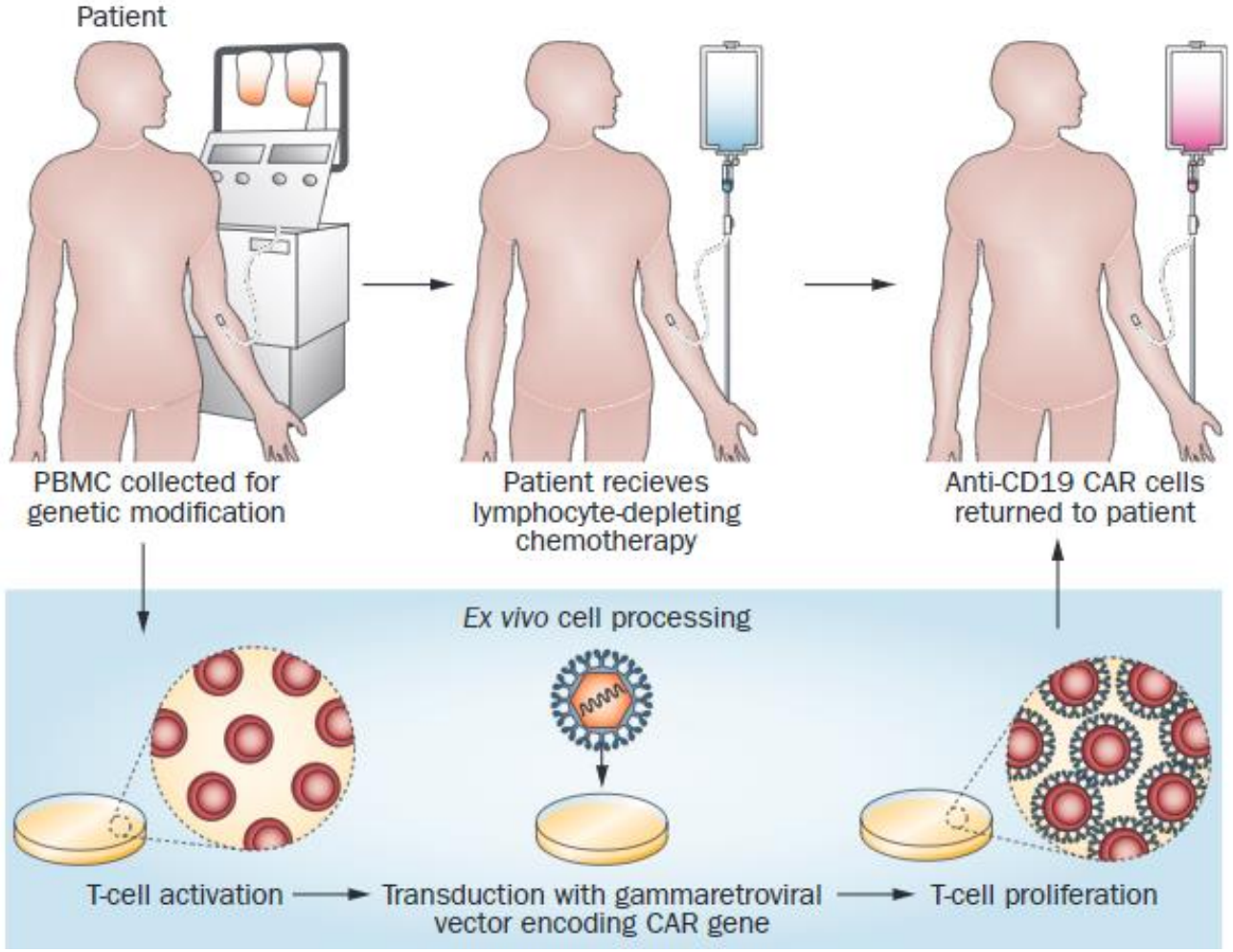
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

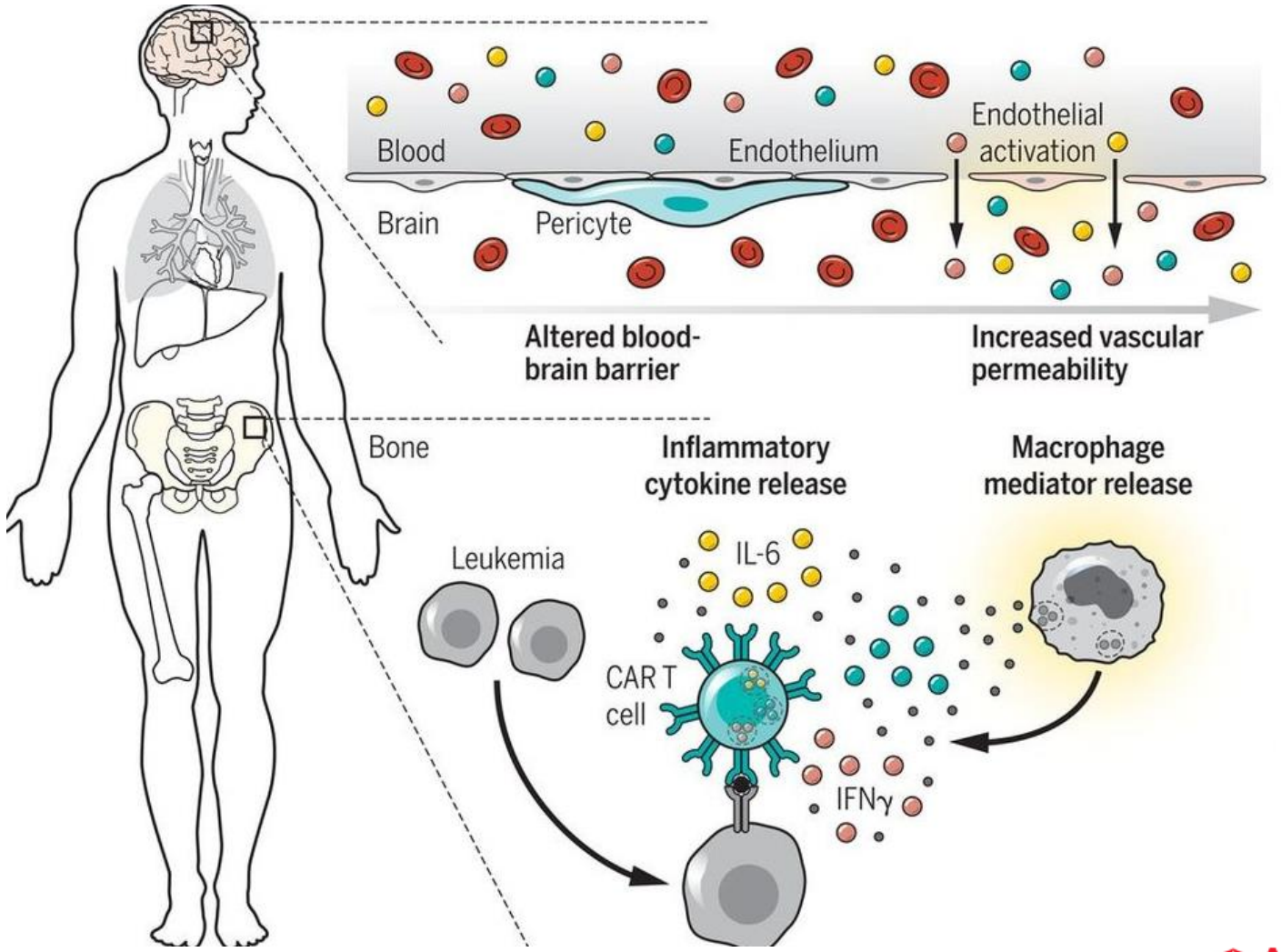


Kochenderfer, Nat Rev Clin Oncol 2013.

CAR T Side Effects

- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- B Cell aplasia
- Macrophage Activation Syndrome (MAS)/HLH

CAR T Side Effects



Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

Treatment

Steroids
Anti-epileptics

Tocilizumab
Steroids

June et al. Science 2018

FDA-Approved CAR T cell therapies

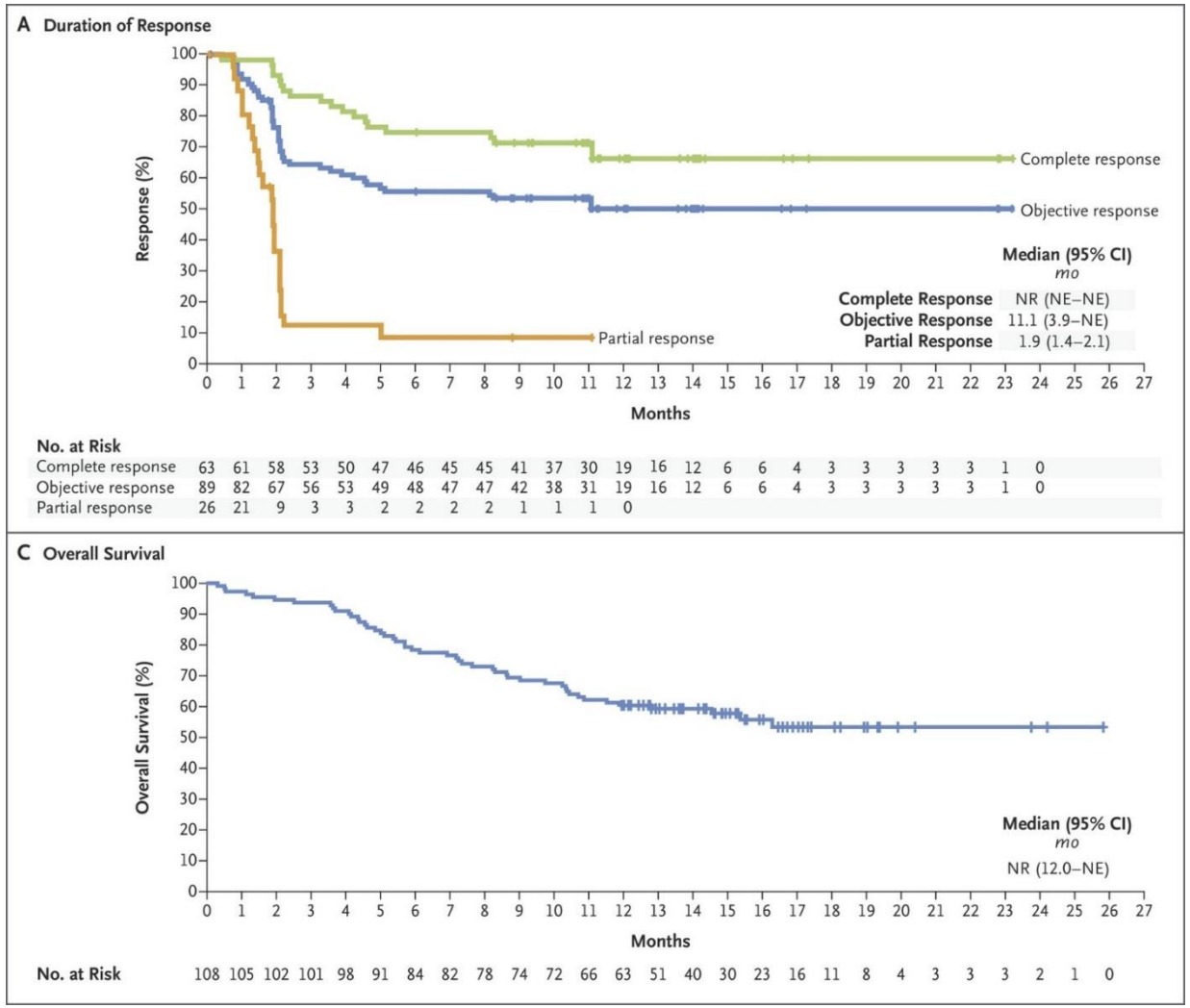
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight (up to 2x10^8)
Tisagenlecleucel	2017	Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse	0.2-0.5x10^6 CAR-positive, viable T-cells per kg if under 50 kg 0.1-2.5x10^8 CAR-positive, viable T-cells if over 50 kg
Tisagenlecleucel	2018	Adults with r/r large B-cell lymphoma after 2+ therapies Including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma	0.6-6.0 x 10^8 CAR-positive, viable T-cells

Eligibility considerations for CAR

- Disease
  - Relative stability during CAR T manufacturing (~2-6 weeks)
  - Bridging therapy (chemo, RT, steroids, lenalidomide, ibrutinib)
  - CNS control
- Patient
  - Adequate cell counts
  - DVT, bleeding, infection, neuro disorders
  - Functional status: at screen vs. day of CAR T infusion
- Other
  - Social support, reimbursement

CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

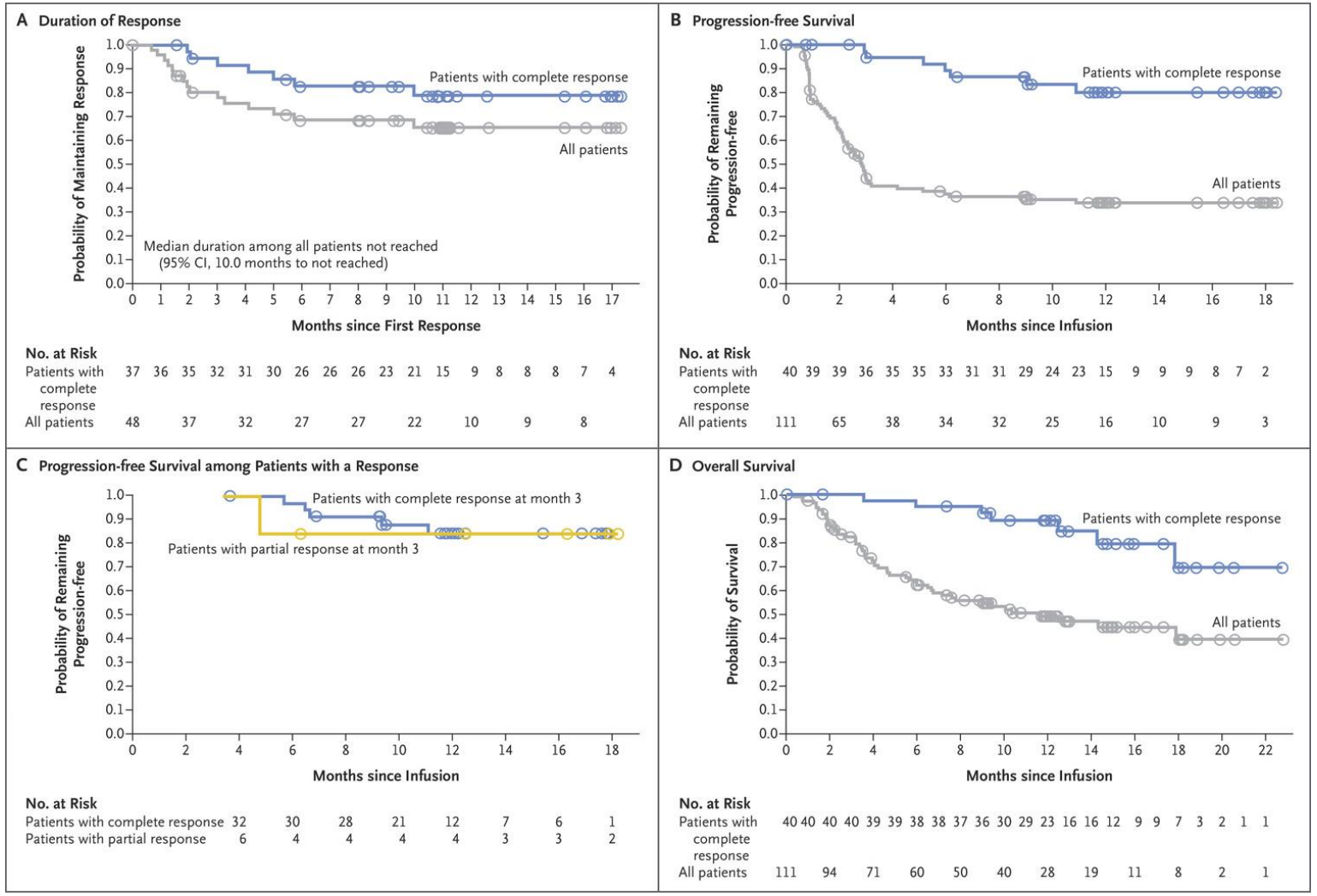
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

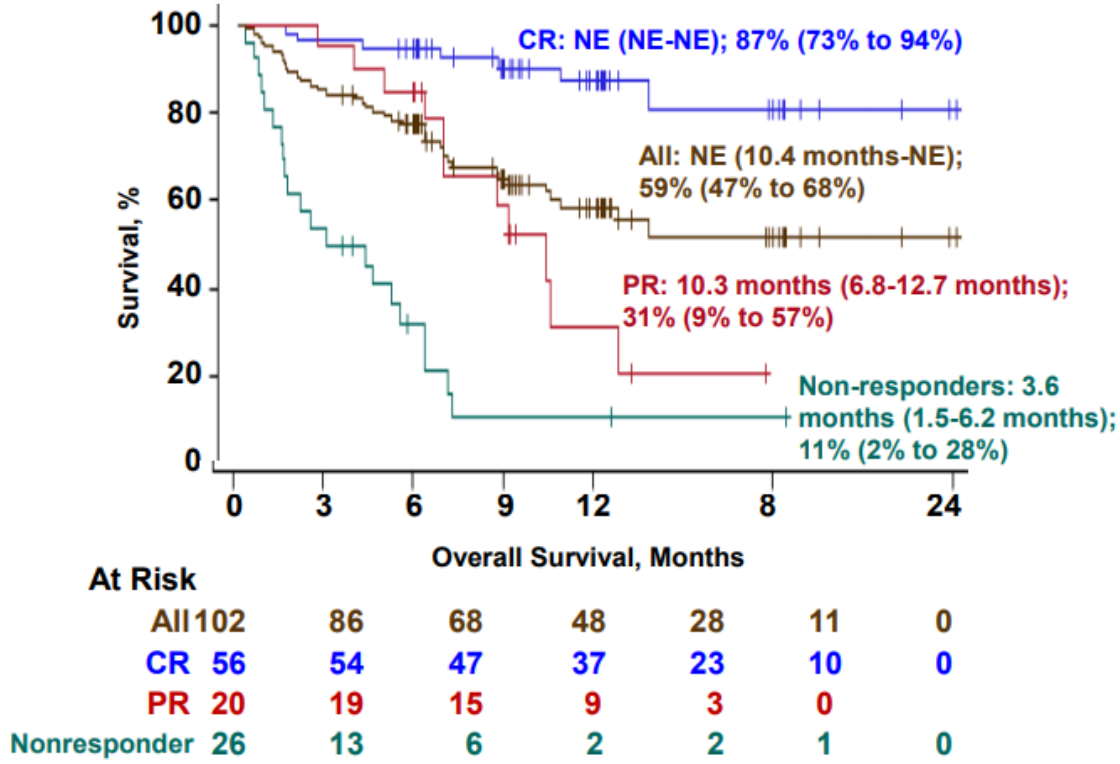
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

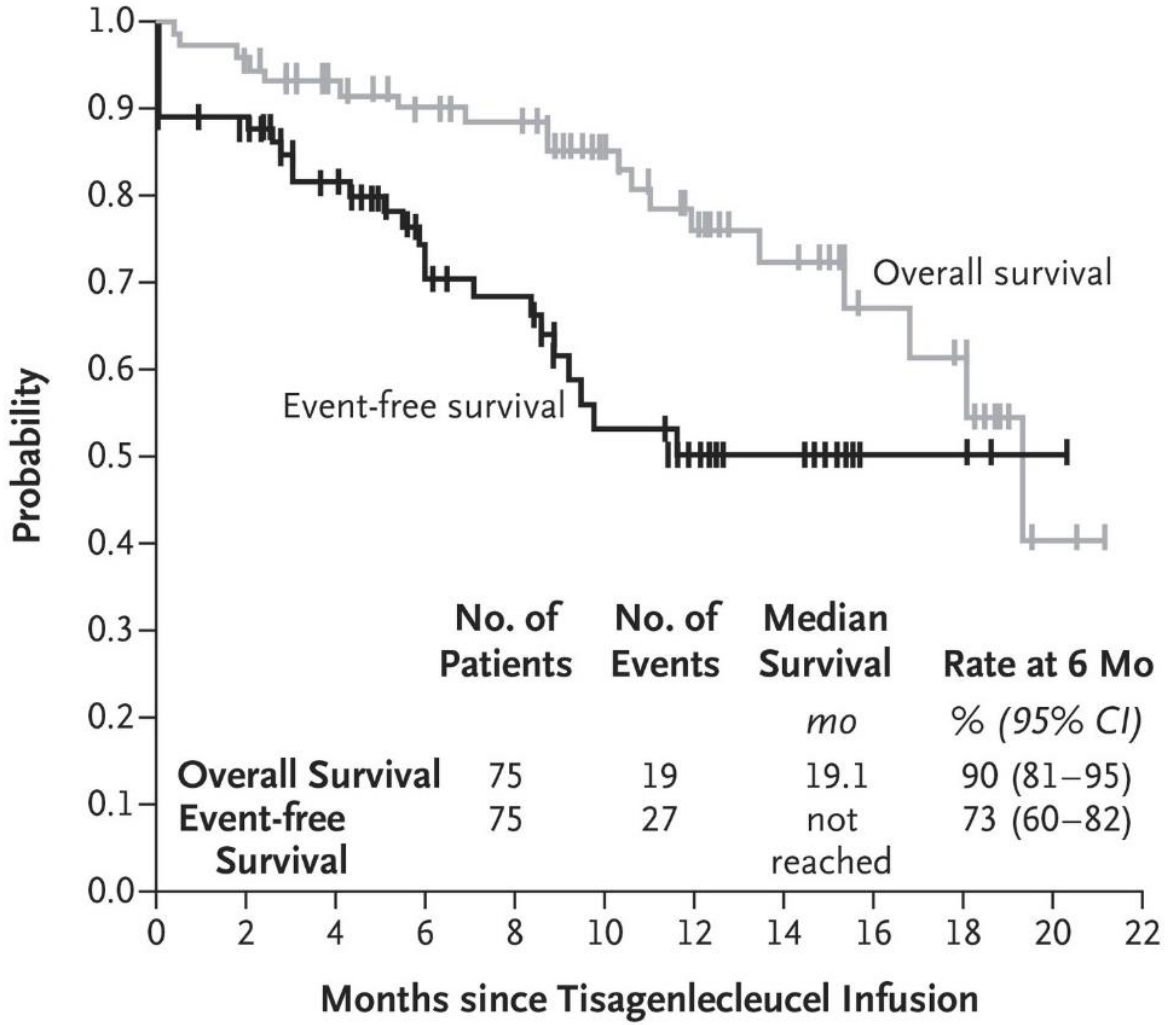
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



Abramson JS, et al. HemaSphere. 2018;2(S1): Abstract S800.

CD19 CAR in B-ALL: ELIANA (Tisa-cel)

- CD19/4-1-BB
- ORR = 81%
- CR = 60%, CRi = 21%
- CRS grade ≥3 = 47%
- Neurotox grade ≥3 = 13%

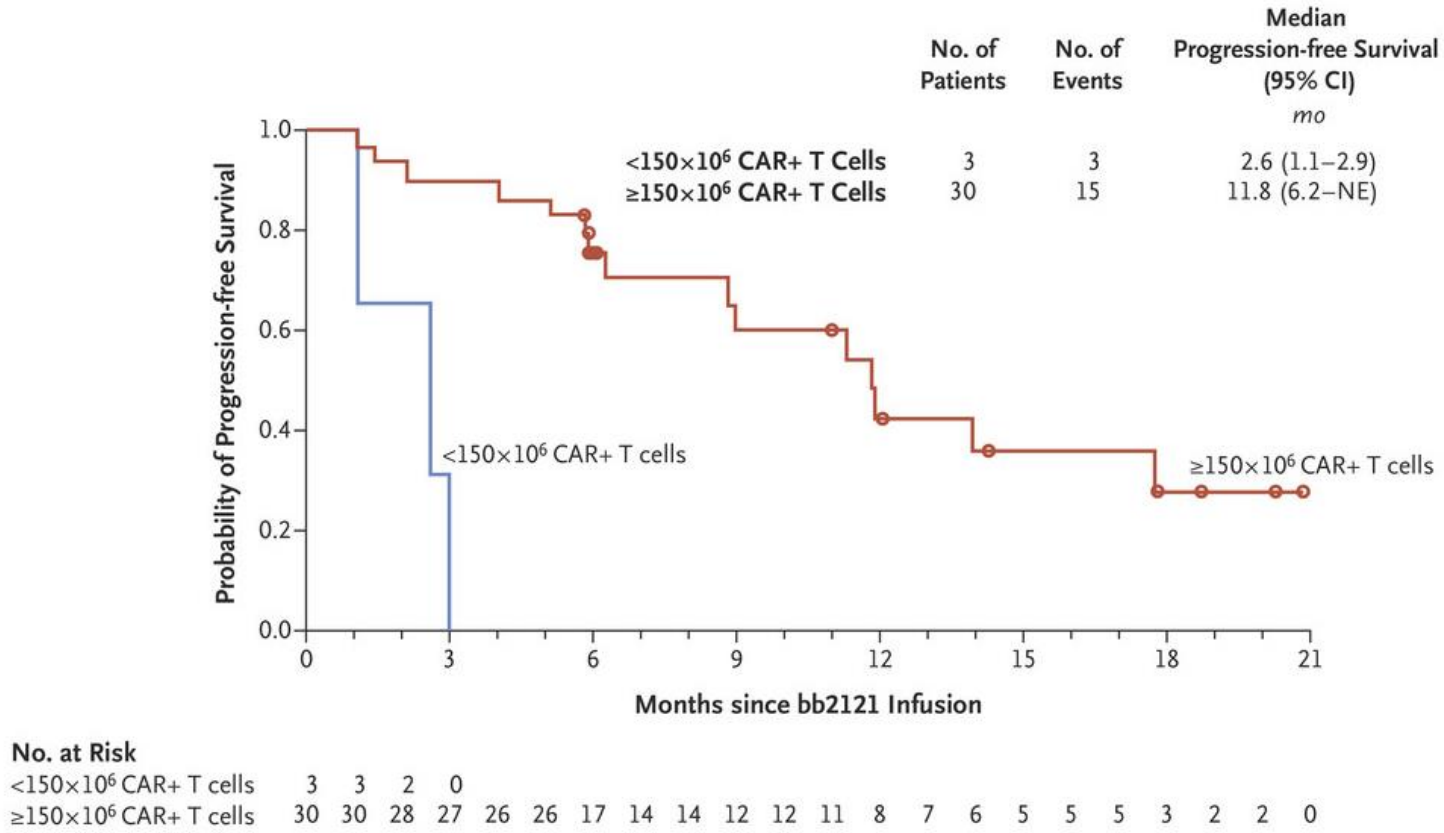


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

Maude et al. NEJM 2018

In Development: BCMA+ CAR T Therapy for Myeloma

- bb2121
  - B cell maturation antigen (BCMA)
  - Phase I CRB-401 study
  - Previously treated patients with relapsed/refractory multiple myeloma
  - ORR: 85%, CR: 45%

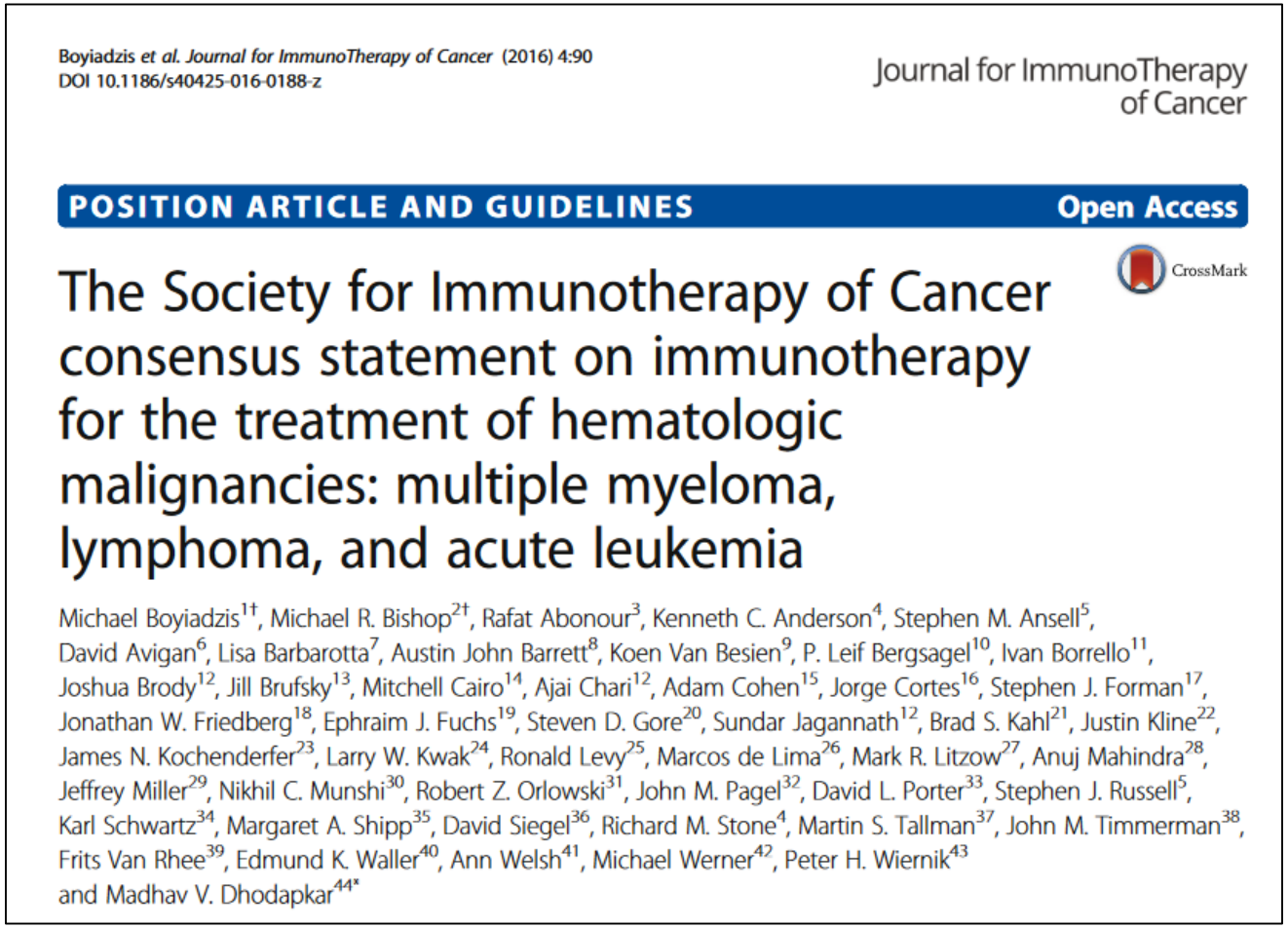


Raje, NEJM 2019.

Conclusions

- Many immunotherapy options for hematological malignancies
- Checkpoint inhibitors for Hodgkin lymphoma and PMBCL – high response rate, excellent tolerance, durable responses if CR
- Blinatumomab and inotuzumab for ALL – effective salvage, deeper remissions
- Polatuzumab vedotin for DLBCL – effective salvage, potential to become frontline
- CAR T therapy – ever-increasing indications; patient selection and toxicity management still concerns

Additional 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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Case Studies

Case Study 1

- 72 year-old active, healthy female (ECOG 0) with no significant PMH diagnosed with bulky ABC subtype, p53 deleted *aggressive* DLBCL

- <u>TREATMENT SUMMARY:</u>
  - 6 cycles DA-EPOCH-R (Feb - Jun 2016)→ Complete Response (CR)
  - Relapse 3 months later
  - 3 cycles Rituximab, Gemcitabine, and Cisplatin→ Progressive Disease (PD)
  - Enrolled on CAR T cell clinical trial

Timeline of CAR T Cell Therapy

T cell Apheresis

December

March (3 days)

Fludarabine/ Cyclophosphamide lymphodepletion chemotherapy

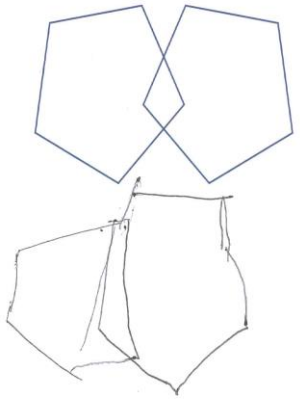
1 x 10^8 CAR T cell Infusion

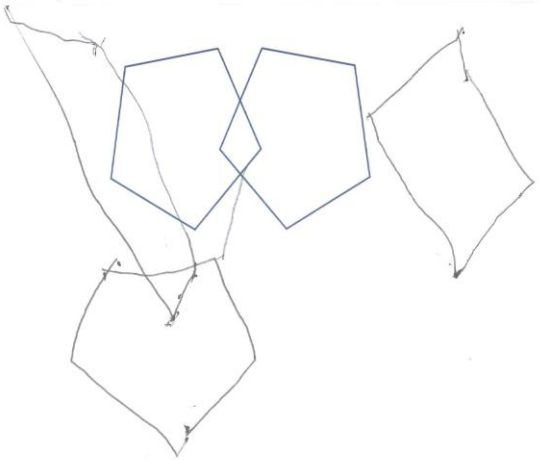
Day 0

Day 4

- Fatigue
- Gr 1 CRS
- CRP mildly elevated
- Changes in MMSE

Pre-Treatment





Timeline of CAR T Cell Therapy

Day 6 → **Day 10**

- New headache with facial droop
- Grade 3 CRS (hypotension requiring 2 pressors and fever 101F)
- Ongoing difficulty with MMSE

- Neurology Consult
  - Non-contrast head CT normal
  - MRI brain
  - LP unrevealing
  - EEG: no seizure activity

- Tocilizumab
- Steroids
- Anti-seizure

Complete resolution of symptoms

Neurotoxicity

- 133 patients (ALL, NHL, CLL) treated with CD-19 CAR T cell with 4-1BB costimulatory domain
- 53 of 133 (40%) with neurotoxicity
- 48 of these 53 (91%) also had CRS
- The 5 without CRS had only grade 1 neurotoxicity
- All patients with grade 3 or higher neurotoxicity had an antecedent fever
- **Median 4.5 days (range 2-17 days) after CRS**
- Median time from onset of neurotoxicity to highest grade 1 day (range 0-19)
- Median duration of reversible neurotoxicity was 5 days (range 1-70 days)

Gust et al. Cancer Discovery. 2017

Neurotoxicity CTCAE grade		Grade 0[a]	Grade 1–2[a]	Grade 3–5[a]	Total	Univariate[b]	Multivariable[c]
Overall, *n* (%)		80 (60)	25 (19)	28 (21)	133 (100)		
Age, *n* (%)	<40 years	11 (41)	10 (37)	6 (22)	27	0.094	
	40–60 years	42 (66)	8 (13)	14 (22)	64		
	>60 years	27 (64)	7 (17)	8 (19)	42		
Sex, *n* (%)	Male	59 (63)	17 (18)	17 (18)	93	0.4	
	Female	21 (53)	8 (20)	11 (28)	40		
Diagnosis, *n* (%)	ALL	22 (47)	11 (23)	14 (30)	47	0.084	
	CLL	16 (67)	2 (8)	6 (25)	24		
	NHL	42 (68)	12 (19)	8 (13)	62		
Race, *n* (%)	White	62 (56)	22 (20)	26 (24)	110	0.17[d]	
	Not white	18 (78)	3 (13)	2 (9)	23		
Prior therapies	Median (range)	4 (1–11)	4 (1–10)	4 (1–11)	4 (1–11)	0.5	
Transplant history, *n* (%)	Auto	17 (68)	5 (20)	3 (12)	25	0.5	
	Allo	14 (50)	8 (29)	6 (21)	28		
Karnofsky score[e], *n* (%)	60–70	7 (50)	3 (21)	4 (29)	14	0.5	
	80–90	65 (61)	18 (17)	23 (22)	106		
	100	8 (62)	4 (31)	1 (8)	13		
Preexisting neurologic comorbidities, *n* (%)	Any	26 (45)	16 (28)	16 (28)	58	0.0059[g]	0.0023[g]
	PN[f]	14 (47)	7 (23)	9 (30)	30	0.2	
	CNS involvement	6 (43)	5 (36)	3 (21)	14	0.2	
	Headache disorder	6 (43)	5 (36)	3 (21)	14	0.2	
	Other	5 (50)	2 (20)	3 (30)	10	0.7	
	ICH[h]	4 (67)	1 (17)	1 (17)	6	1	
	Seizures	2 (33)	2 (33)	2 (33)	6	0.3	
	Cog impairment[i]	1 (25)	2 (50)	1 (25)	4	0.1	
	MTX CNS toxicity[j]	1 (50)	1 (50)	0	2	0.4	
Marrow disease, %	Median (range)	0.6 (0–97)	0.4 (0–93)	25.8 (0–97)	1.3 (0–97)	0.072	0.0165
Total CD19$^+$ cells in marrow, %	Median (range)	5.3 (0–99)	12.4 (0–93)	29.1 (0–97)	8.8 (0–99)	0.062	
CD8$^+$ central memory enriched CAR-T cells[k], *n* (%)	Selected	48 (67)	11 (15)	13 (18)	72 (54)	0.242	
Lymphodepletion regimen[l], *n* (%)	Cy/Flu	58 (56)	23 (22)	23 (22)	104	0.11	0.0259
	Non-Cy/Flu	22 (76)	2 (7)	5 (17)	29		
CAR-T cell dose, *n* (%)	2×10^5 cells/kg	20 (57)	10 (29)	5 (14)	35	<0.0001	0.0009
	2×10^6 cells/kg	55 (64)	15 (17)	16 (19)	86		
	2×10^7 cells/kg	5 (42)	0	7 (58)	12		
Cytokine release syndrome, *n* (%)	None (G 0)	35 (88)	5 (13)	0	40	<0.0001	n/a
	Mild (G 1–2)	44 (57)	19 (25)	14 (18)	77		
	Severe (G 3–5)	1 (6)	1 (6)	14 (88)	16		

Neelapu et al. Nature Review. 2016

Case Study 2

- 30 year-old male with no PMH diagnosed with Stage IV Hodgkin lymphoma

- *TREATMENT HISTORY:*
  - 6 cycles of ABVD → CR
  - Relapsed → ASCT
  - Relapsed → Anti-PD-1 blockade

Patient Develops New Symptoms

- Headache
- Fatigue
- Dizziness with standing

What is the differential?

A. ?

B. ?

C. ?

D. ?

What is the differential?

A. Progressive disease with CNS involvement
B. Hypophysitis
C. Adrenal insufficiency alone
D. Dehydration

What are you next steps?

What are you next steps?

- Vitals: Orthostatic hypotension
- Physical exam: Pale
  - ADMIT PATIENT

Work-Up Shows…

- Low TSH
- Low ACTH
- Low LH

- Brain MRI: a swollen pituitary gland is seen

- <u>Now what should you do?</u>

Management

- STOP immunotherapy
- Endocrine consult:
  - High-dose glucocorticoids, levothyroxine, and sex hormone replacement
- Almost all patients experienced resolution of acute symptoms within a few days

I can rechallenge patient with anti-PD-1 therapy

- True
- False

I can rechallenge patient with anti-PD-1 therapy

- True
- False