sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hematologic Malignancies

Brian Hill, MD, PhD

Director, Lymphoid Malignancies Program

Cleveland Clinic Cancer Center

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

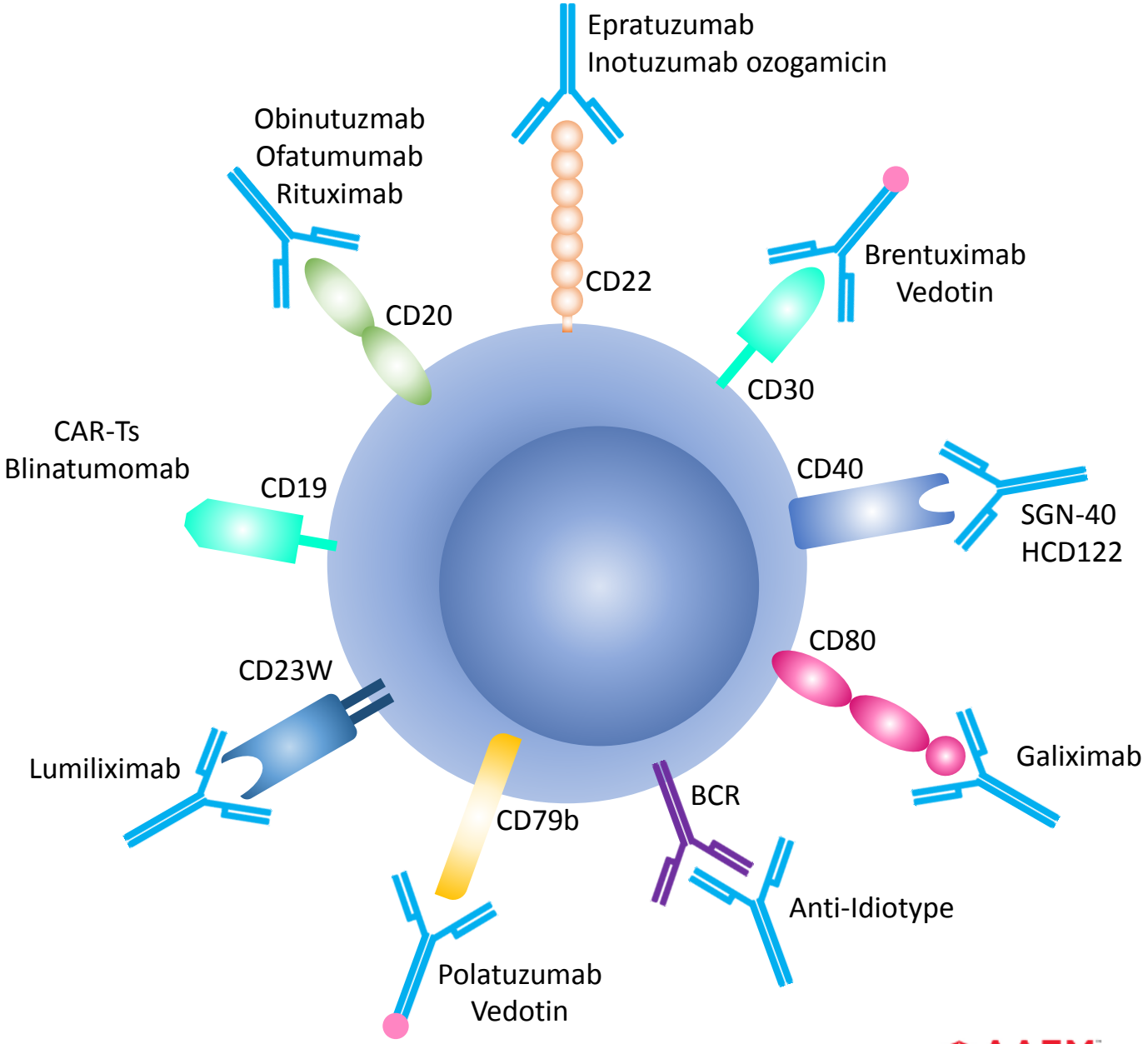
ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer

Disclosures

- Consulting Fees:
  - Kite (Gilead), Novartis, Juno (Celgene)
- Contracted Research:
  - Kite (Gilead)
- I will be discussing non-FDA approved indications during my presentation.



Checkpoint inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

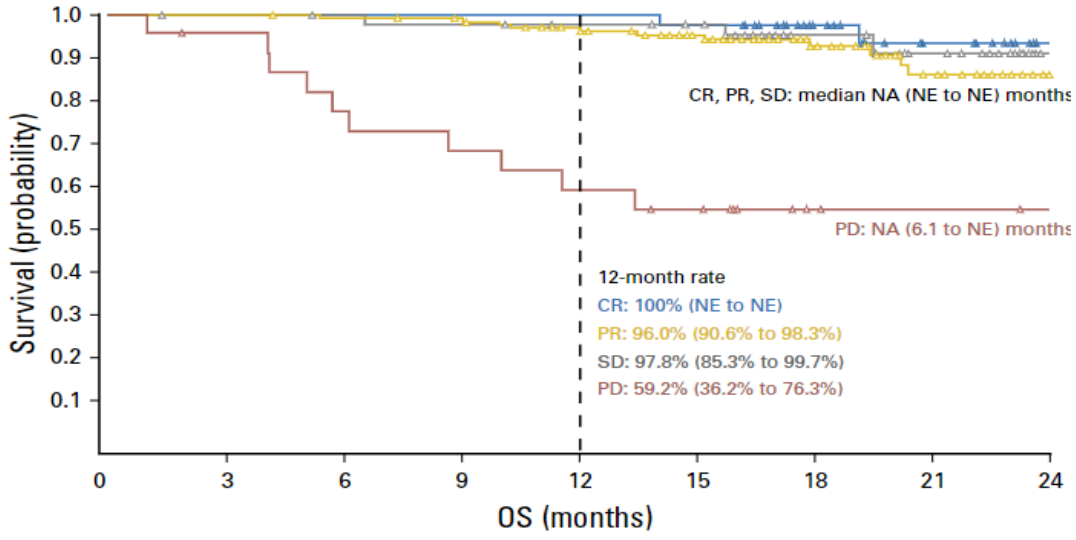
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg (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:

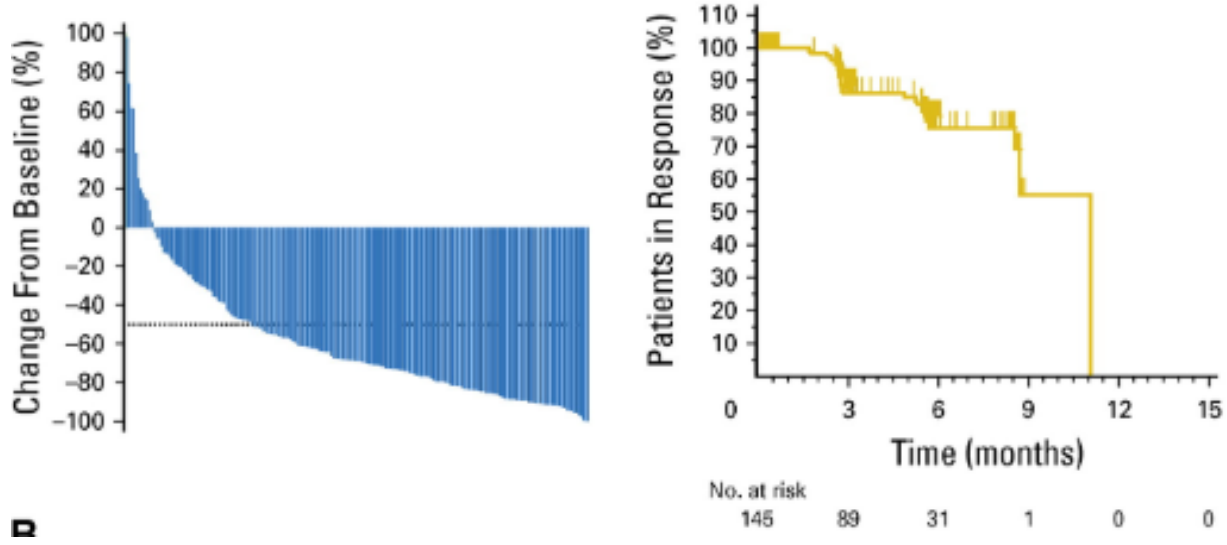
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

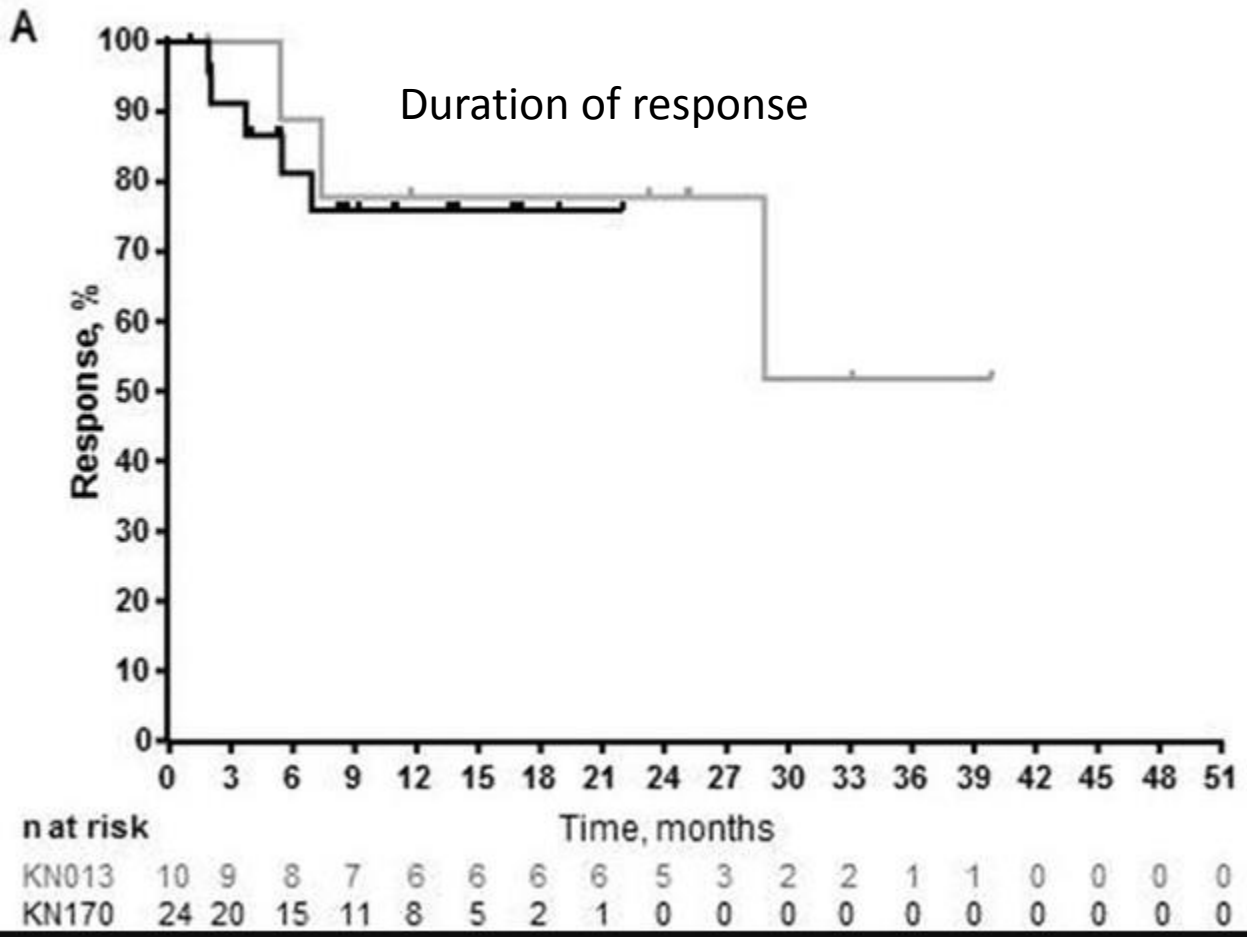
CR = 22.4%

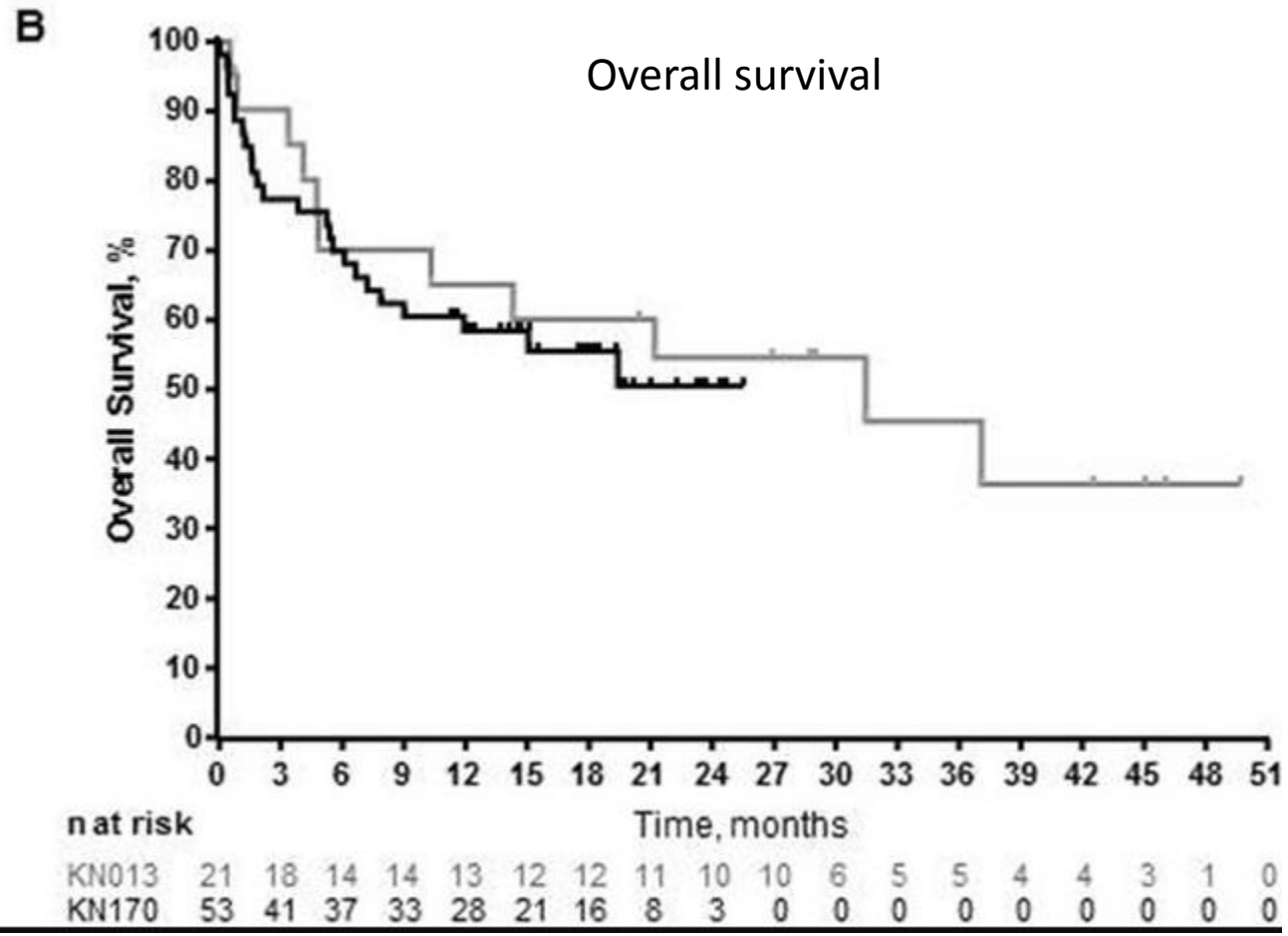
Activity seen regardless of PD-L1 expression



Armand, J Clin Oncol 2018.
Chen, J Clin Oncol 2017.

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

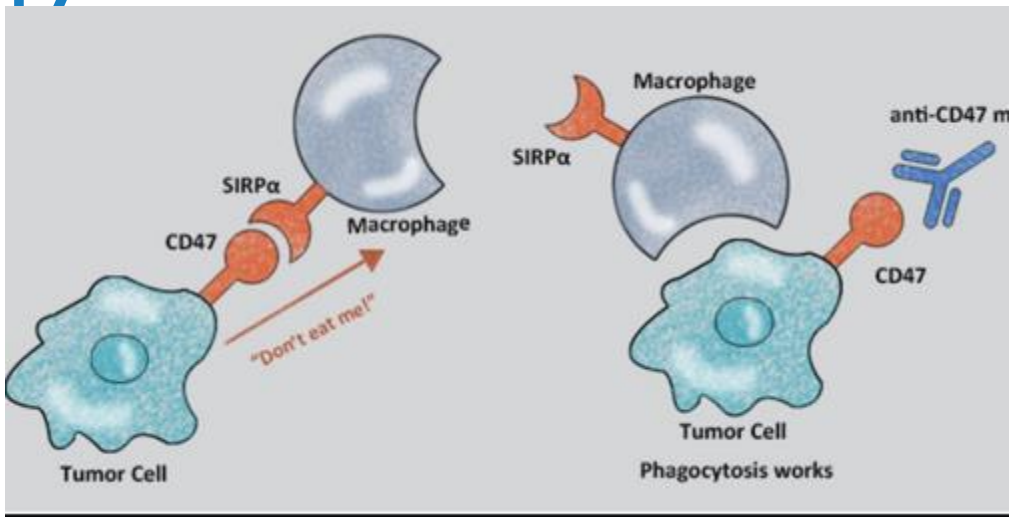


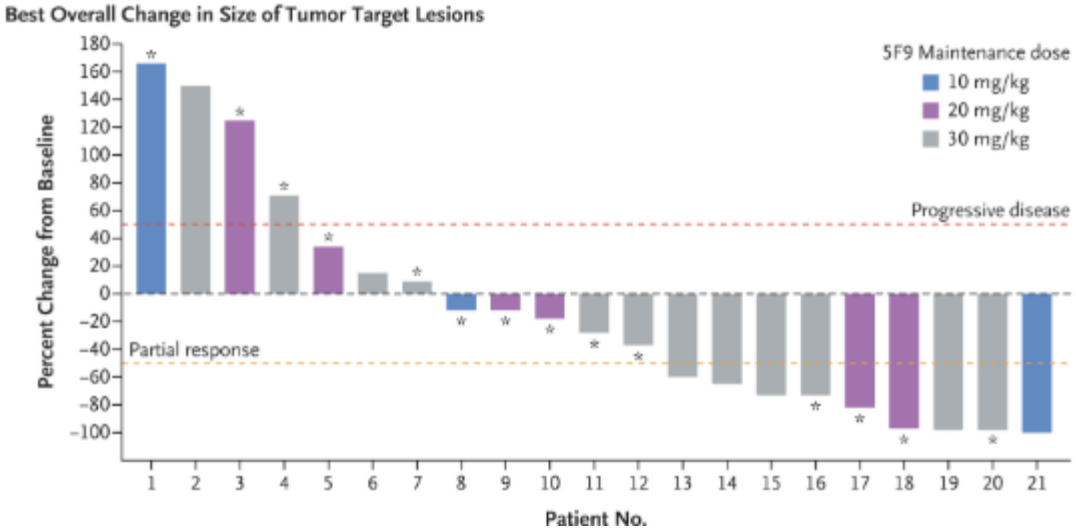


Armand, Blood 2018.

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%



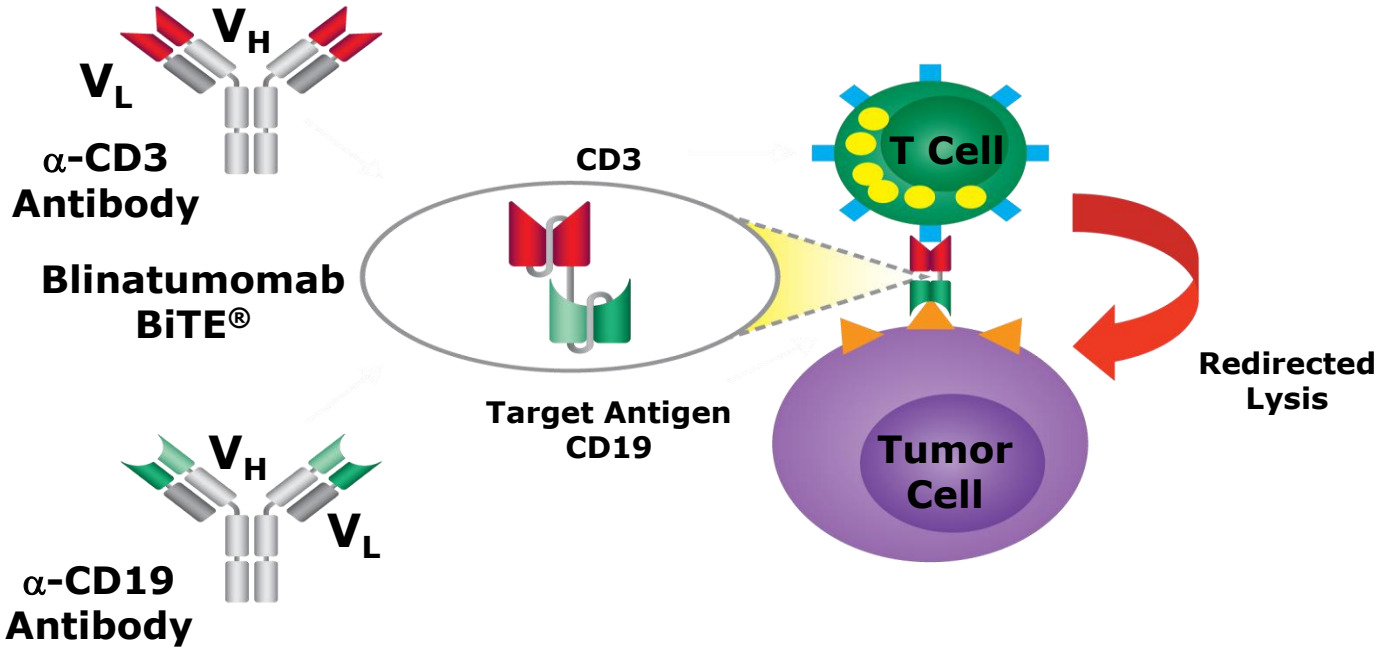


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

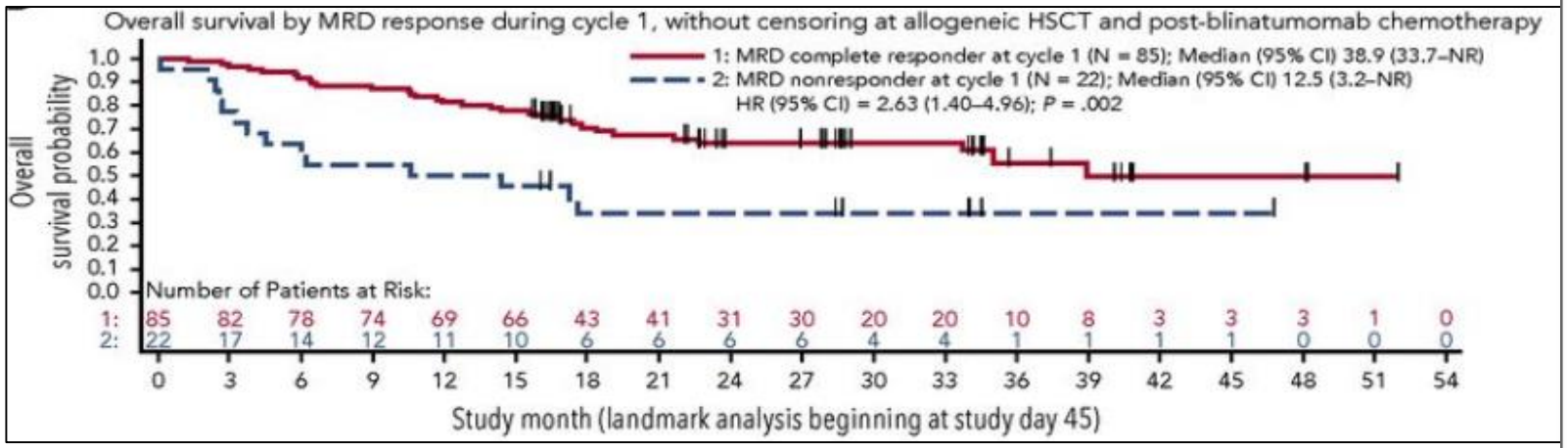
BiTE (Blinatumomab) Therapy

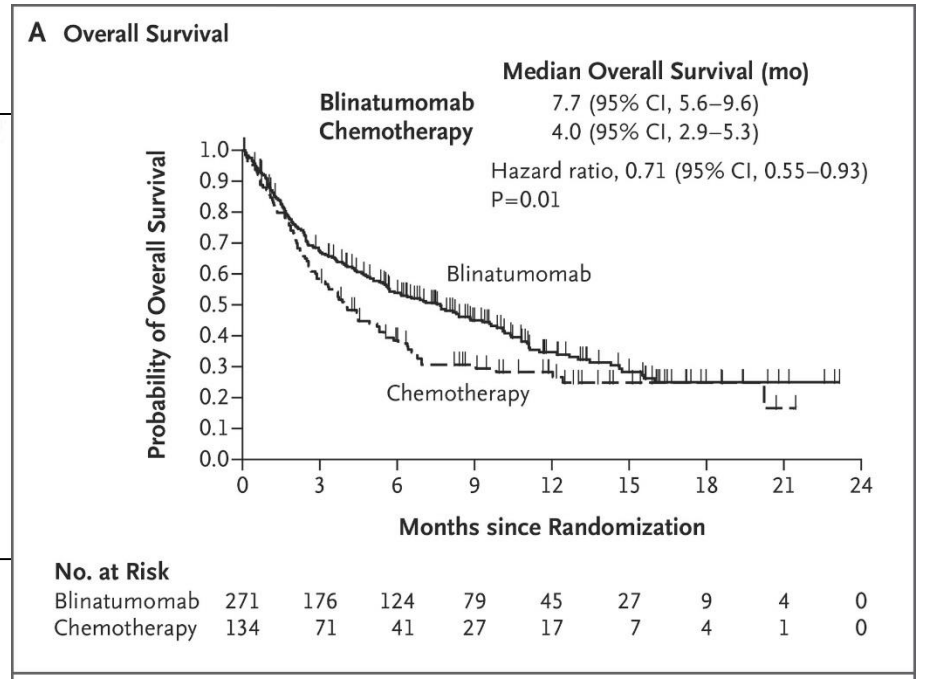
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





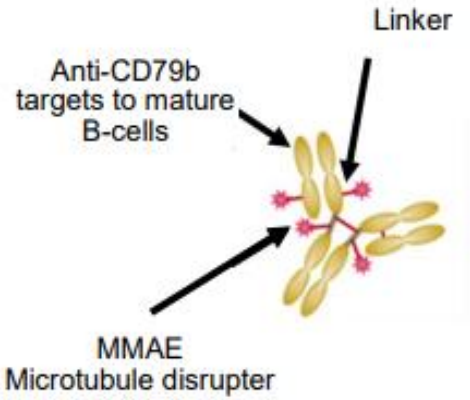
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

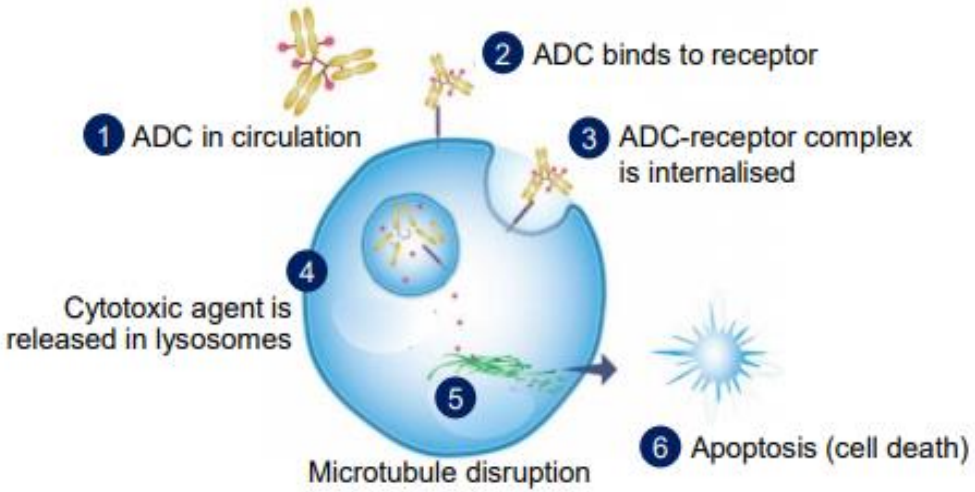
Antibody-drug conjugates (ADC)

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

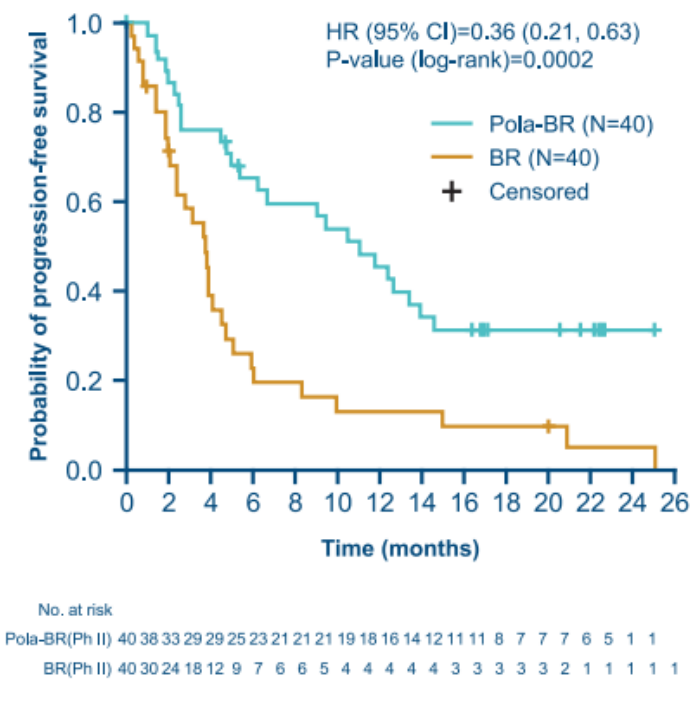
Slide credit: Tilly et al. ICML 2019

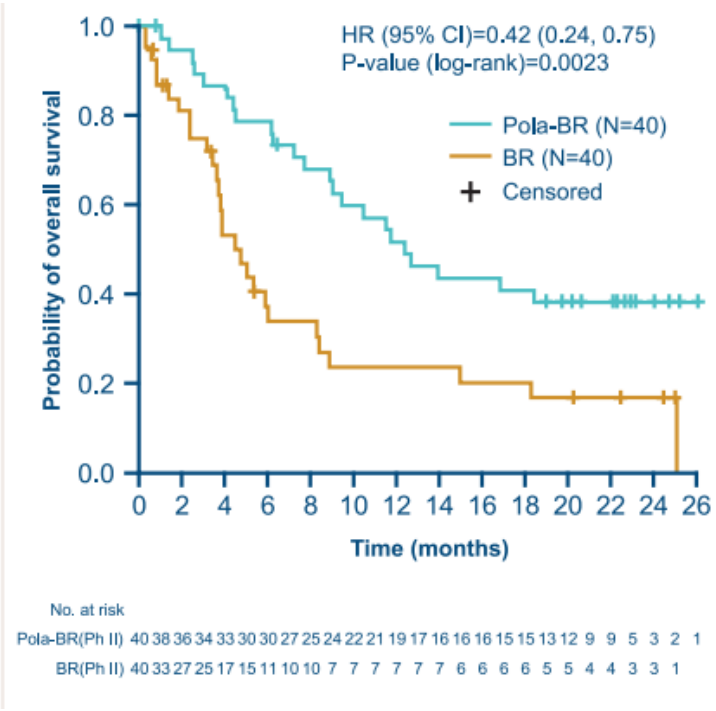
Polatuzumab vedotin: DLBCL

- 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

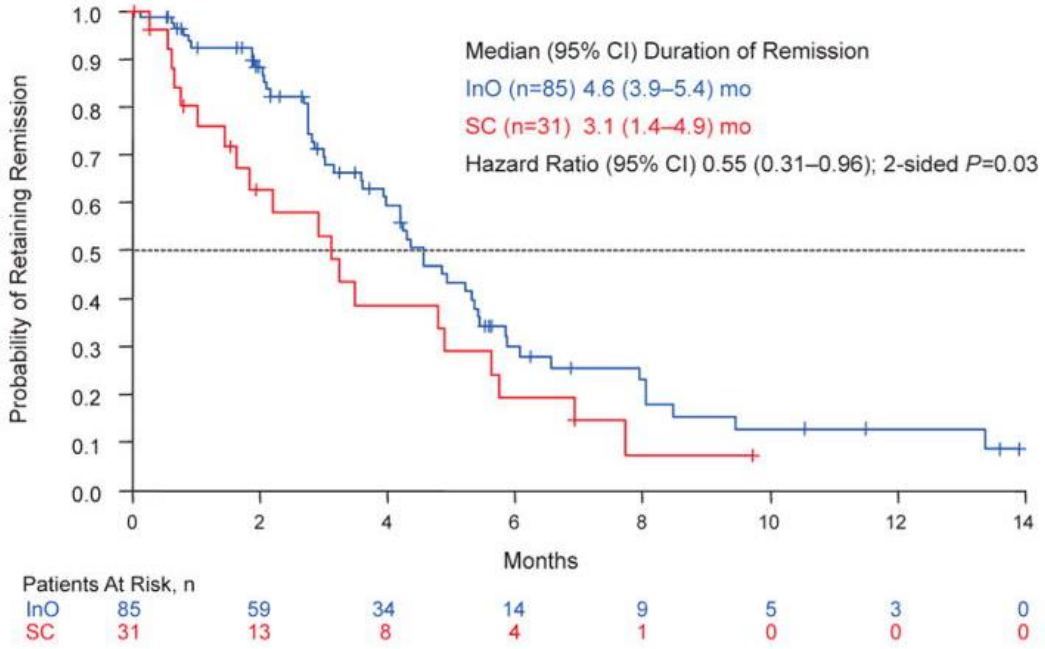


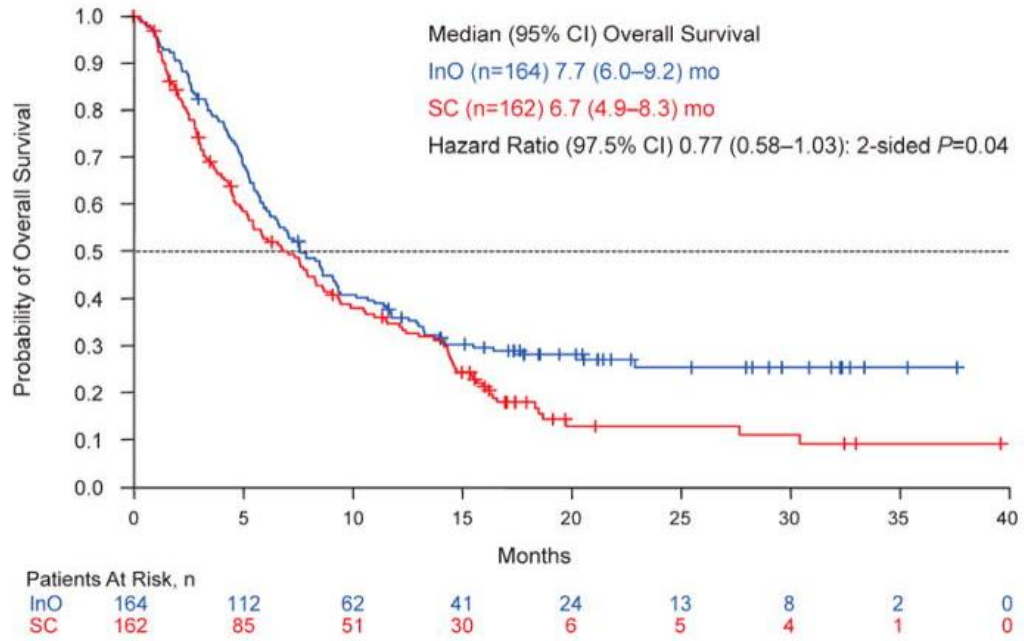


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



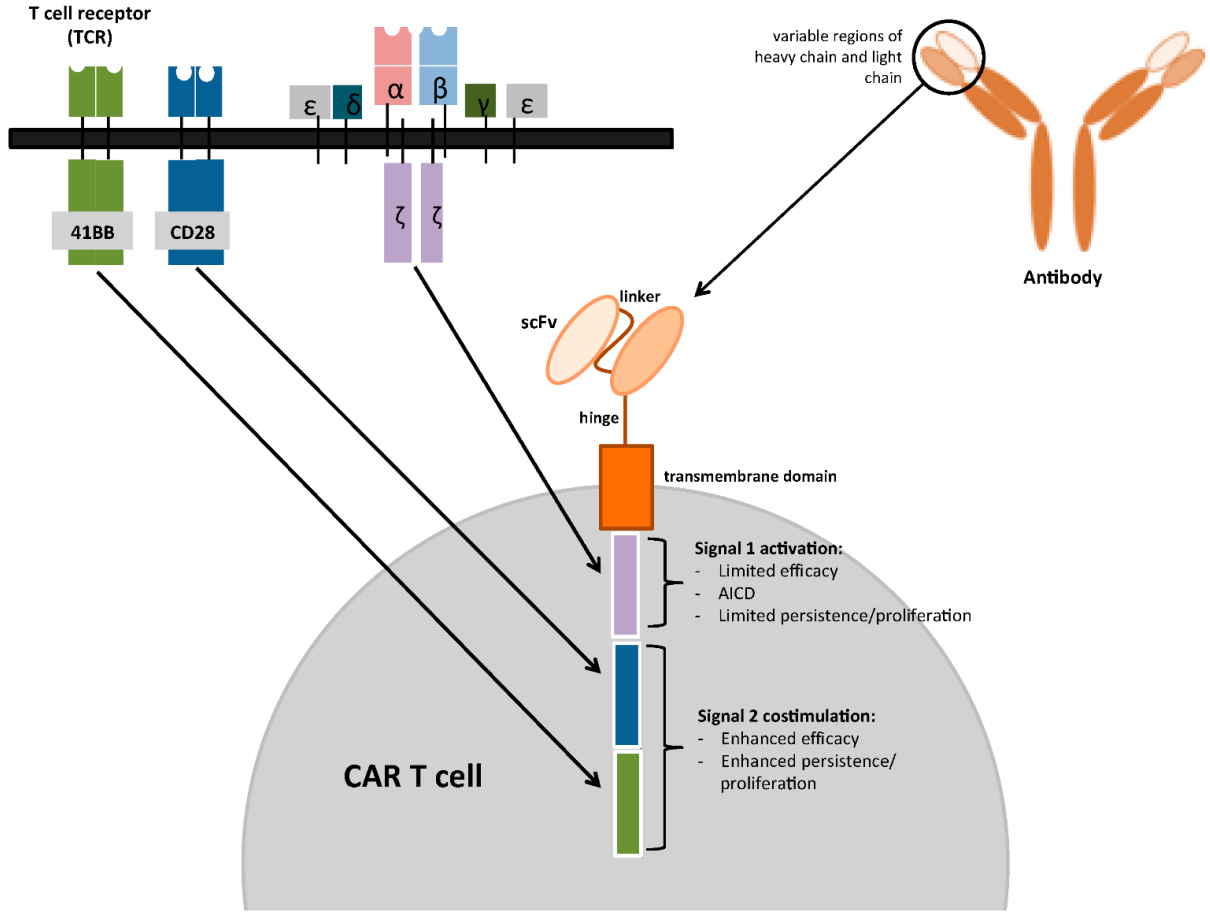


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

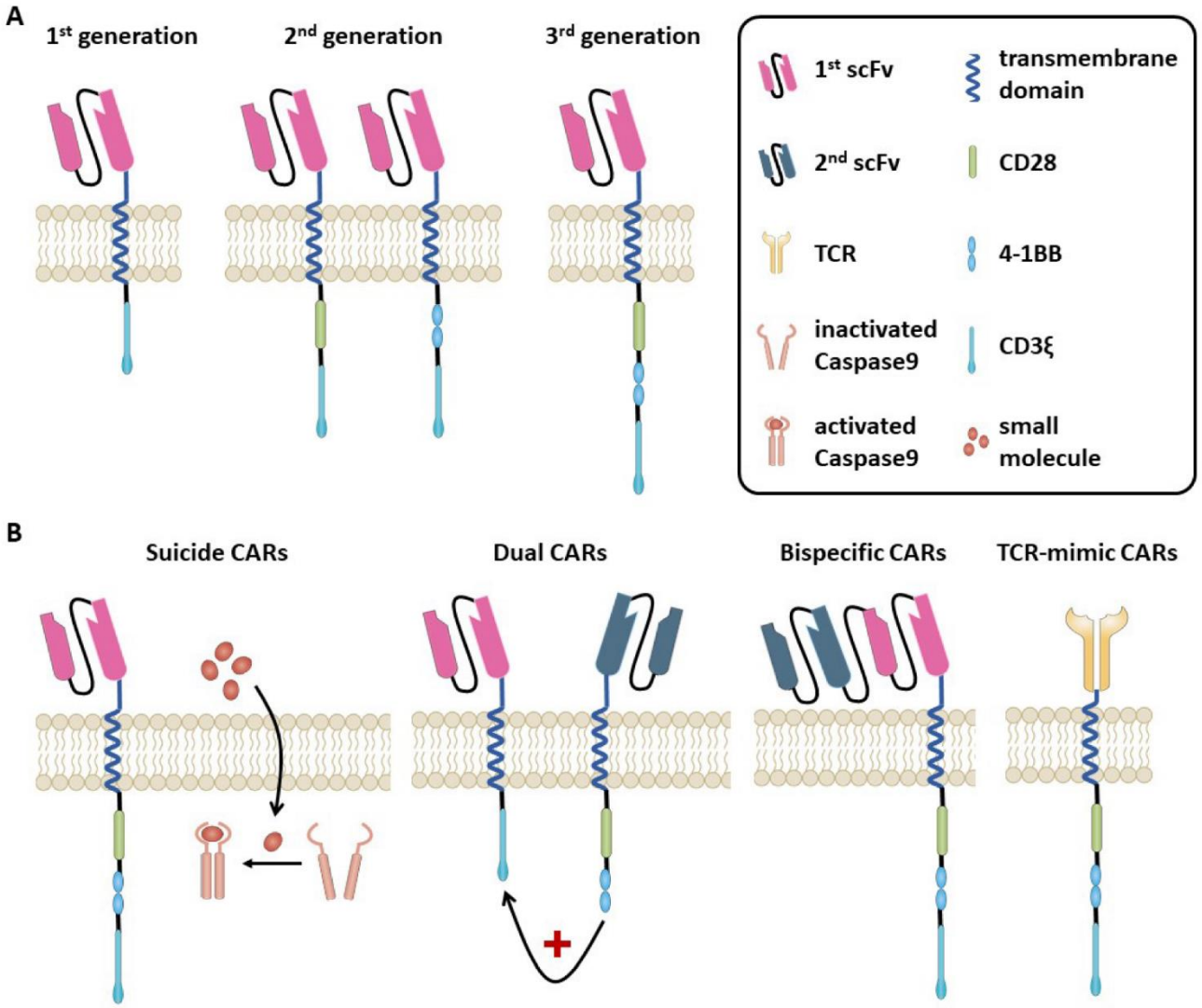
Chimeric antigen receptors

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



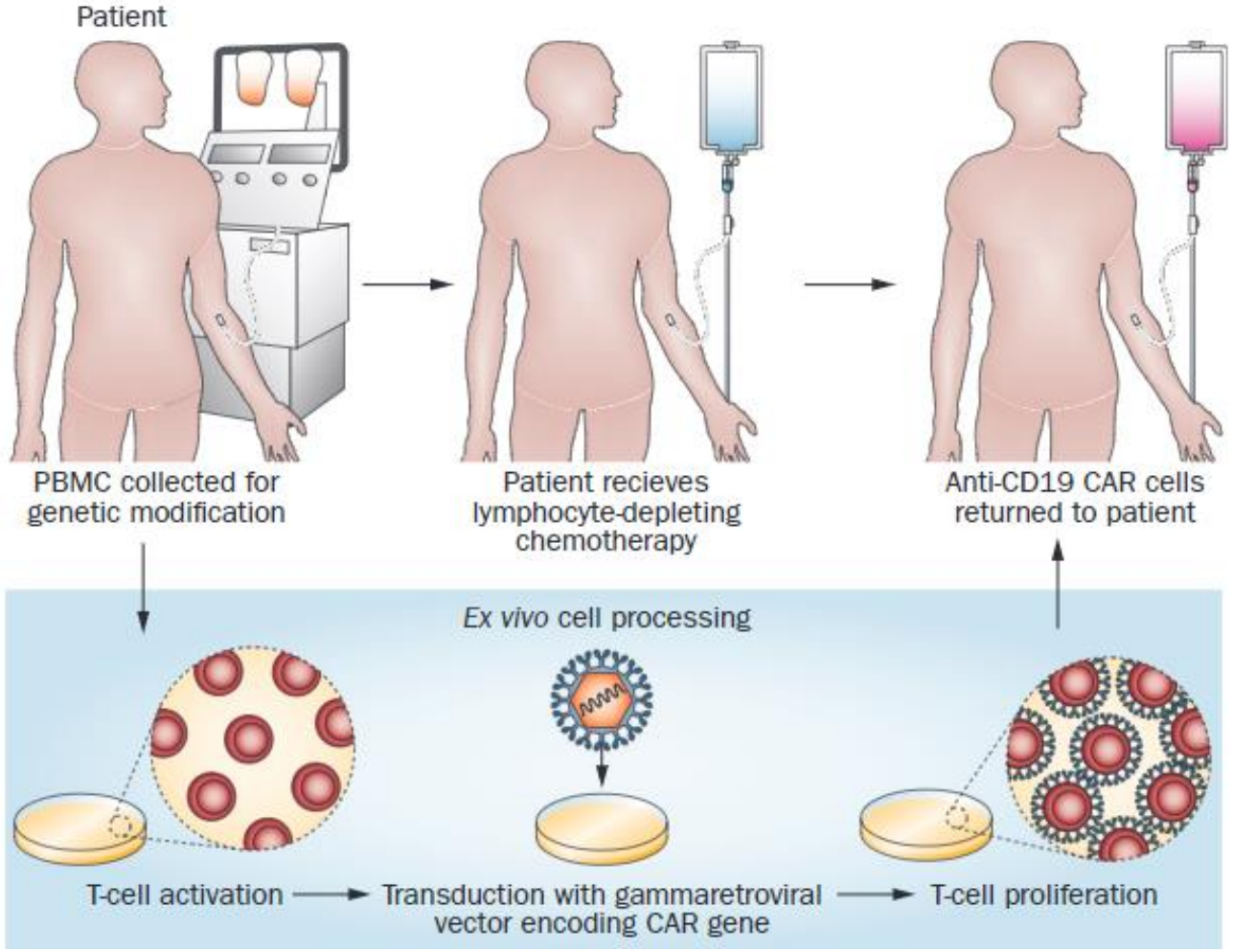
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

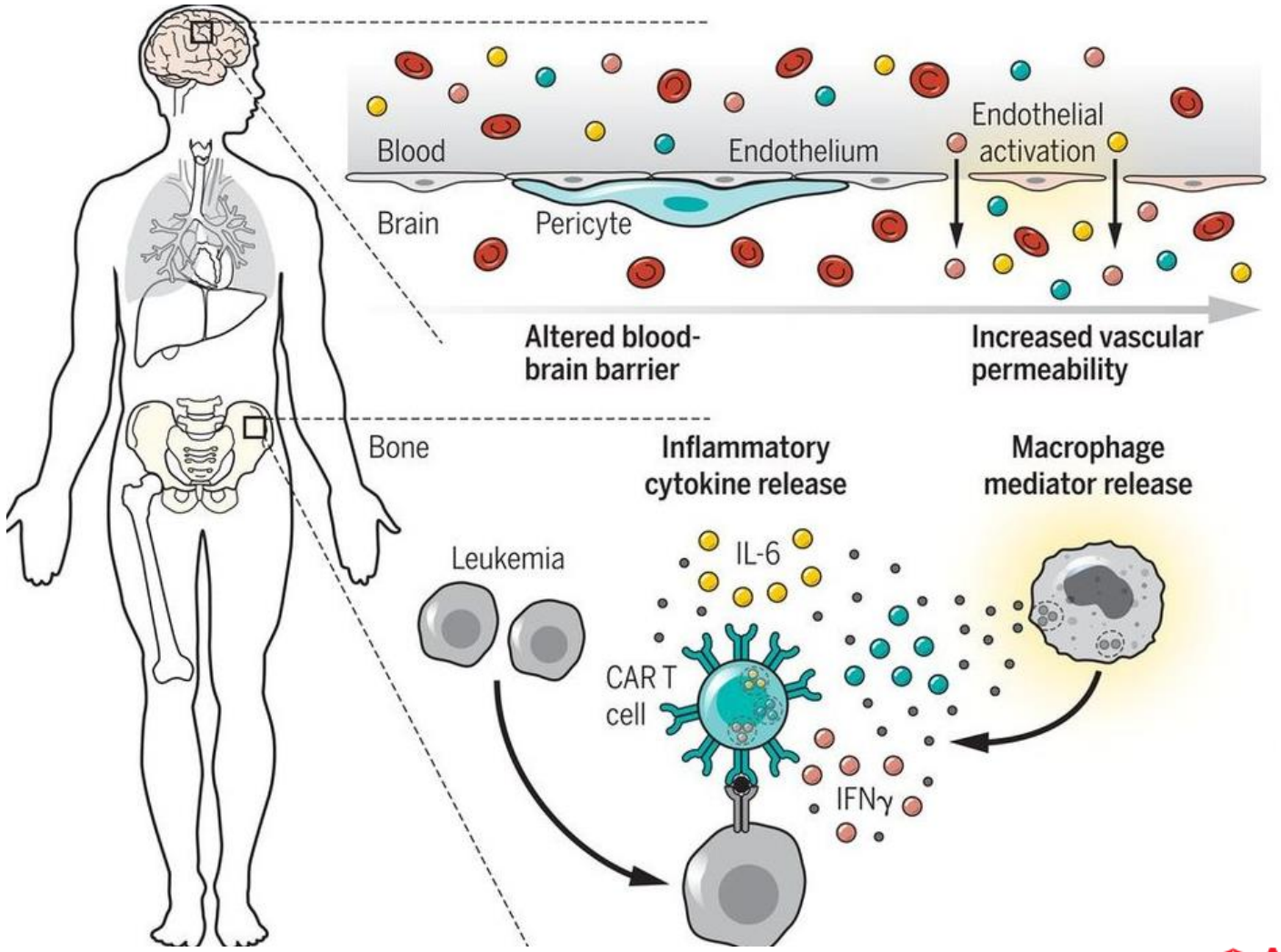


Kochenderfer, Nat Rev Clin Oncol 2013.

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

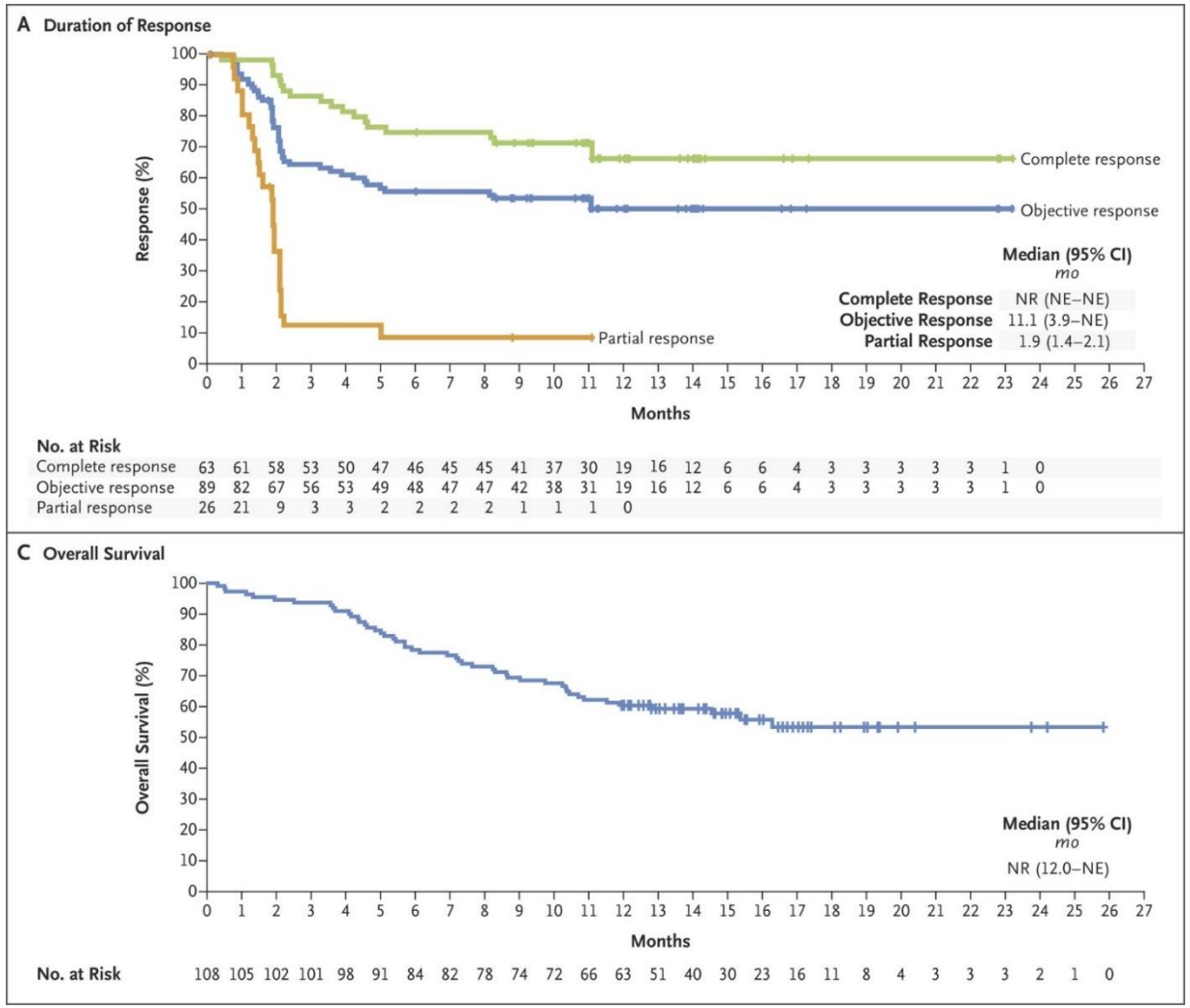
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight (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)

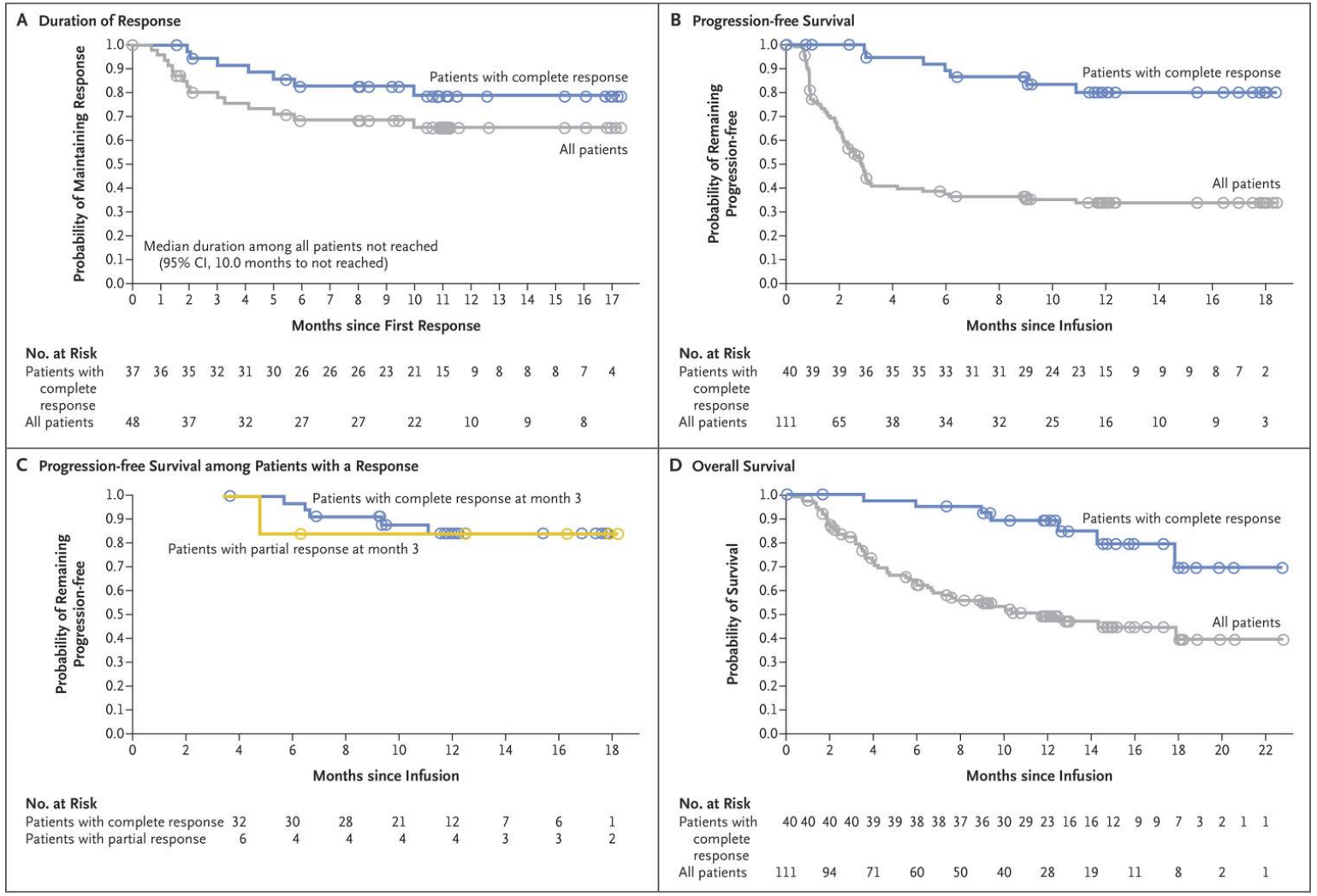
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

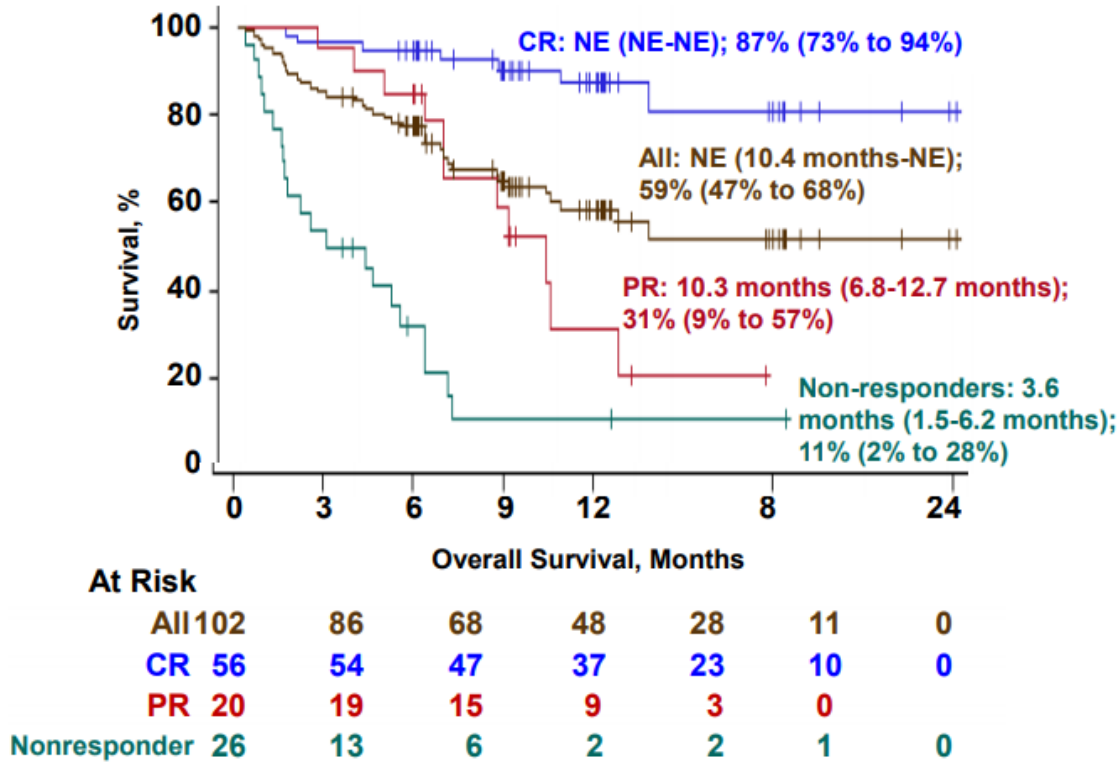
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

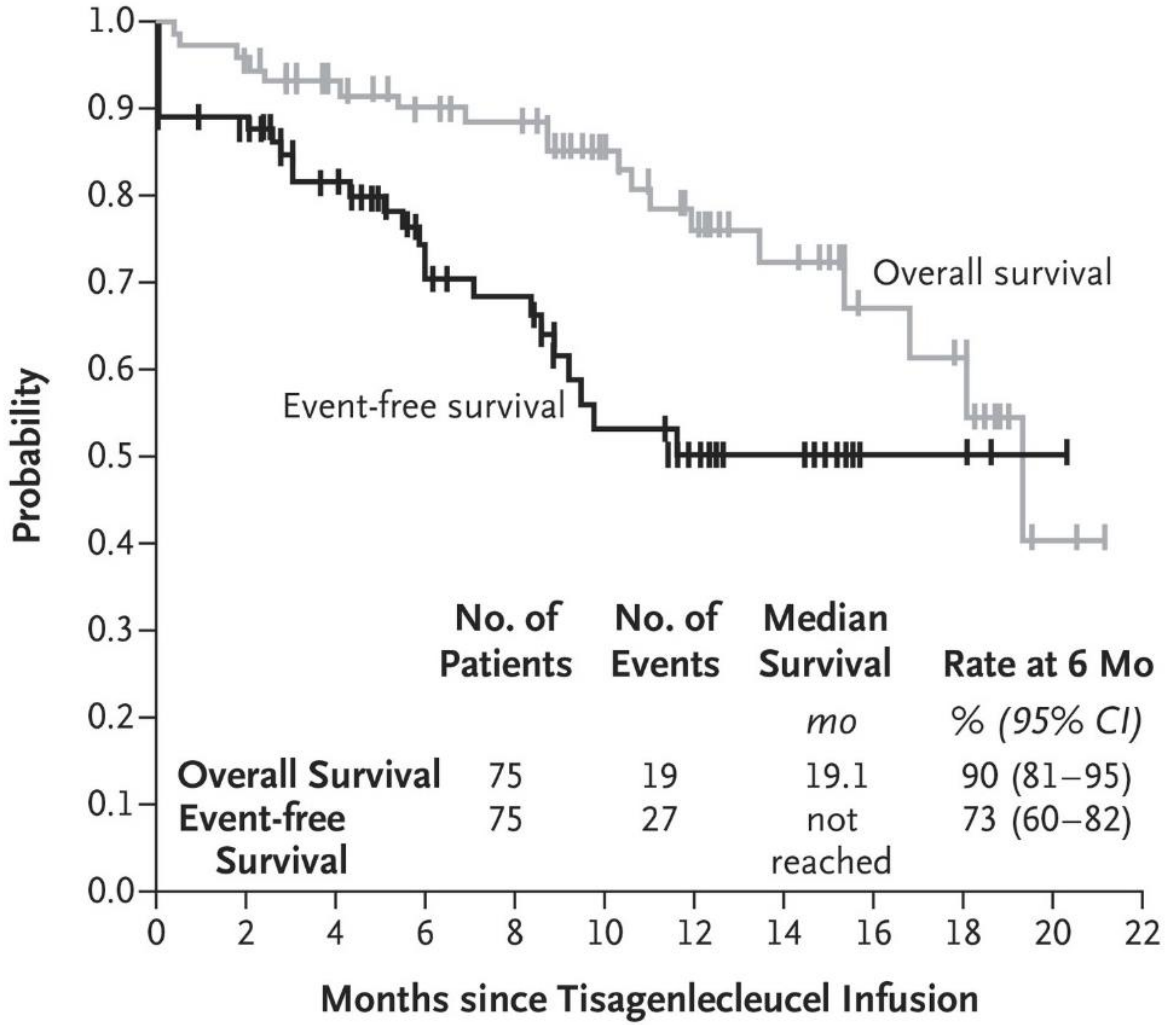
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

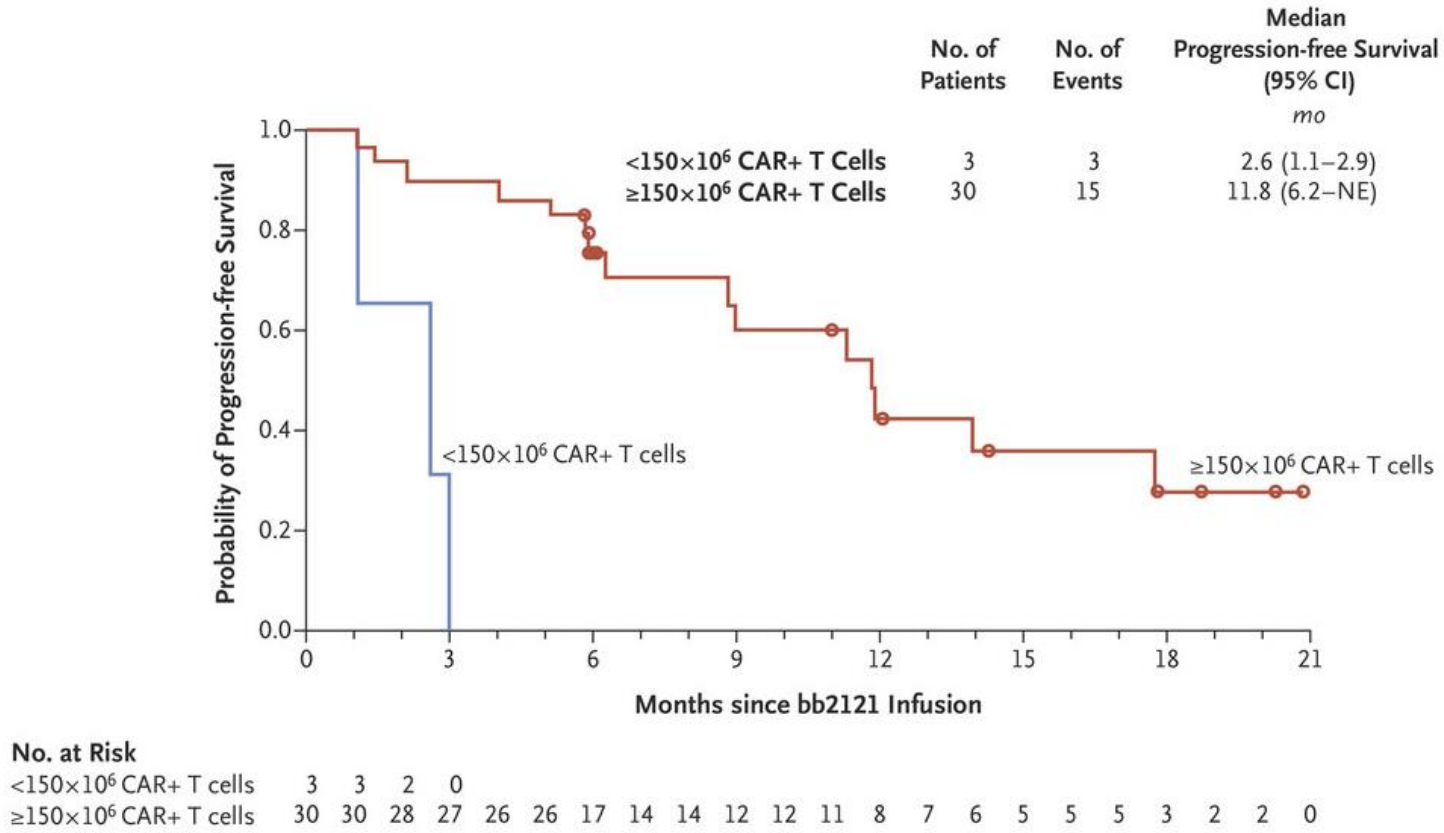


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

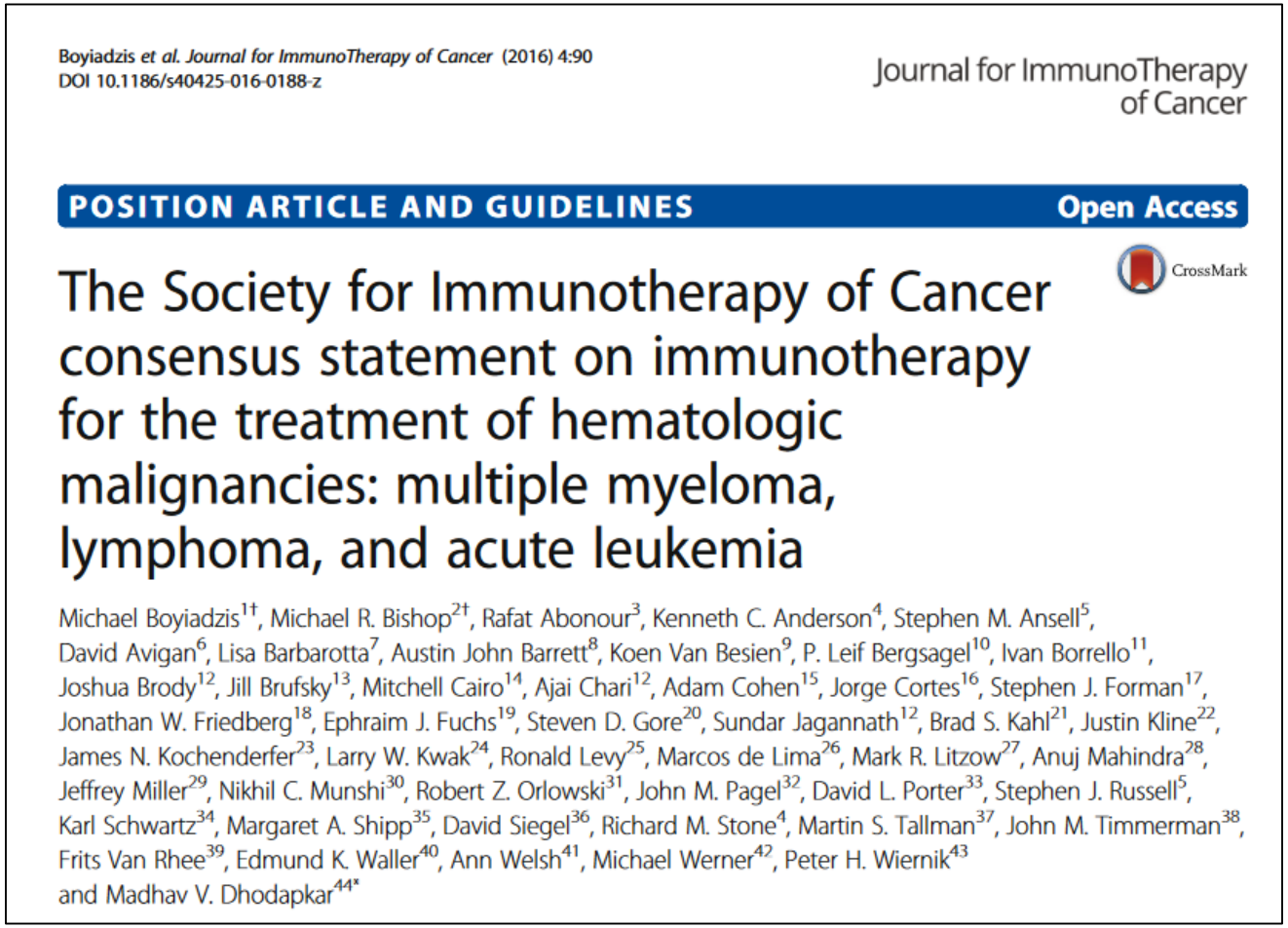


Raje, NEJM 2019.

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*]

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

Case Study 1

- 24 year old male with advanced-staged Hodgkin lymphoma is treated with in combination with ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) x 6 cycles. After achieving complete remission, he subsequently relapses and undergoes “salvage” chemotherapy followed by high dose chemotherapy and autologous stem cell transplantation (“auto transplant”) followed by ongoing/maintenance treatment with brentuximab vedotin. Unfortunately, he now has progressive disease.
- FDA approved treatment options for this patient include:
  A. Allogeneic Transplant
  B. Pembrolizumab
  C. Nivolumab
  D. CAR T-Cell
  E. B and D

Case Study 1

- 24 year old male with advanced-staged Hodgkin lymphoma is treated with in combination with ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) x 6 cycles. After achieving complete remission, he subsequently relapses and undergoes “salvage” chemotherapy followed by high dose chemotherapy and autologous stem cell transplantation (“auto transplant”) followed by ongoing/maintenance treatment with brentuximab vedotin. Unfortunately, he now has progressive disease.
- FDA approved treatment options for this patient include:
  A. Allogeneic Transplant
  B. Pembrolizumab
  C. Nivolumab
  D. CAR T-Cell
  E. B and D

Case Study 1

- 24 year old male with advanced-staged Hodgkin lymphoma is treated with in combination with ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) x 6 cycles. After achieving complete remission, he subsequently relapses and undergoes "salvage" chemotherapy followed by high dose chemotherapy and autologous stem cell transplantation ("auto transplant") followed by ongoing/maintenance treatment with brentuximab vedotin. Unfortunately, he now has progressive disease.
- FDA approved treatment options for this patient include:
  A. Allogeneic Transplant
  B. Pembrolizumab
  C. Nivolumab
  D. CAR T-Cell
  E. B and D
- Both Pembrolizumab and Nivolumab are FDA-approved agents for relapsed/refractory Hodgkin lymphoma after ≥3 therapies. These checkpoint inhibitors have high response rates in this patient population.

Case Study 2

- A previously fit 64 year old female with stage IIIA diffuse large B-cell lymphoma (DLBLC) was treated with 6 cycles of R-CHOP but subsequently relapsed and underwent salvage chemotherapy followed by high dose chemotherapy and autologous stem cell transplant ("auto transplant"). She has been following with you for the past year, has recovered from toxicities of prior therapy and is back to work with an excellent performance status. She develops new lymphadenopathy. Biopsy shows recurrent DLBCL.
- Which of the following is most likely to provide long-term disease control for this patient:

A. Bendamustine + Rituximab (BR)

B. Bendamustine + Rituximab (BR) in combination with Polatuzumab Vedotin

C. Ibrutinib

D. Anti-CD19 Chimeric Antigen Receptor (CAR) T- cell therapy (i.e. axicabtagene ciloleucel or tisagenlecleucel)

Case Study 2

- A previously fit 64 year old female with stage IIIA diffuse large B-cell lymphoma (DLBLC) was treated with 6 cycles of R-CHOP but subsequently relapsed and underwent salvage chemotherapy followed by high dose chemotherapy and autologous stem cell transplant ("auto transplant"). She has been following with you for the past year, has recovered from toxicities of prior therapy and is back to work with an excellent performance status. She develops new lymphadenopathy. Biopsy shows recurrent DLBCL.
- Which of the following is most likely to provide long-term disease control for this patient:

A. Bendamustine + Rituximab (BR)

B. Bendamustine + Rituximab (BR) in combination with Polatuzumab Vedotin

C. Ibrutinib

D. Anti-CD19 Chimeric Antigen Receptor (CAR) T- cell therapy (i.e. axicabtagene ciloleucel or tisagenlecleucel)

Case Study 2

- A previously fit 64 year old female with stage IIIA diffuse large B-cell lymphoma (DLBLC) was treated with 6 cycles of R-CHOP but subsequently relapsed and underwent salvage chemotherapy followed by high dose chemotherapy and autologous stem cell transplant ("auto transplant"). She has been following with you for the past year, has recovered from toxicities of prior therapy and is back to work with an excellent performance status. She develops new lymphadenopathy. Biopsy shows recurrent DLBCL.
- Which of the following is most likely to provide long-term disease control for this patient:
  - A. Bendamustine + Rituximab (BR)
  - B. Bendamustine + Rituximab (BR) in combination with Polatuzumab Vedotin
  - C. Ibrutinib
  - **D. Anti-CD19 Chimeric Antigen Receptor (CAR) T- cell therapy (i.e. axicabtagene ciloleucel or tisagenlecleucel)**
- CAR-T cell therapy has a reasonable likelihood of leading to prolonged disease control. Both currently available therapies - axicabtagene ciloleucel or tisagenlecleucel – are approved for patients with relapsed/refractory DLBCL after auto transplant or who are ineligible for transplant.