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

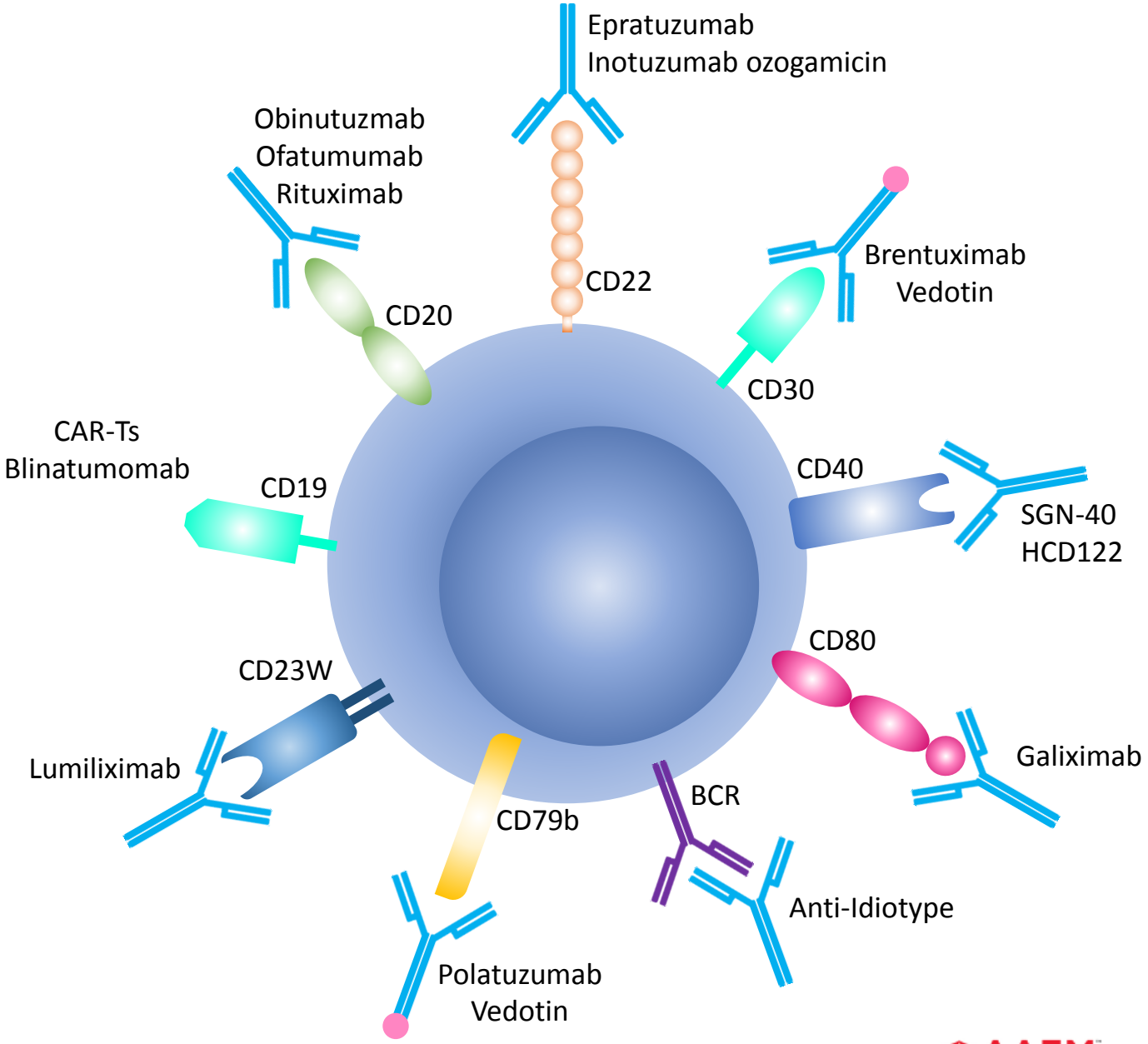
ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- Speakers Bureau: Genentech
- Advisory Role: Celgene
- I will be discussing non-FDA approved indications during my presentation.



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Checkpoint Inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

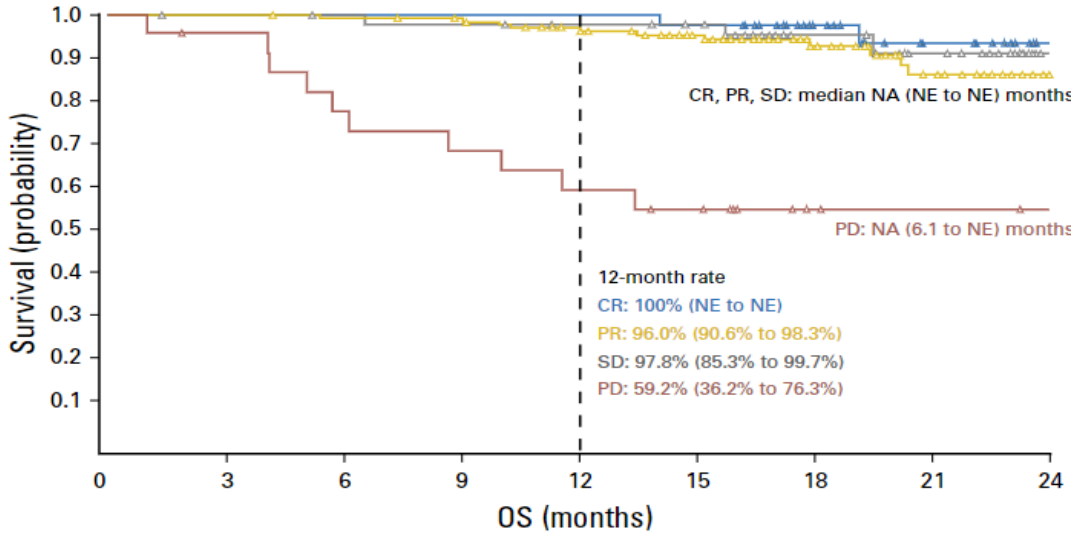
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg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

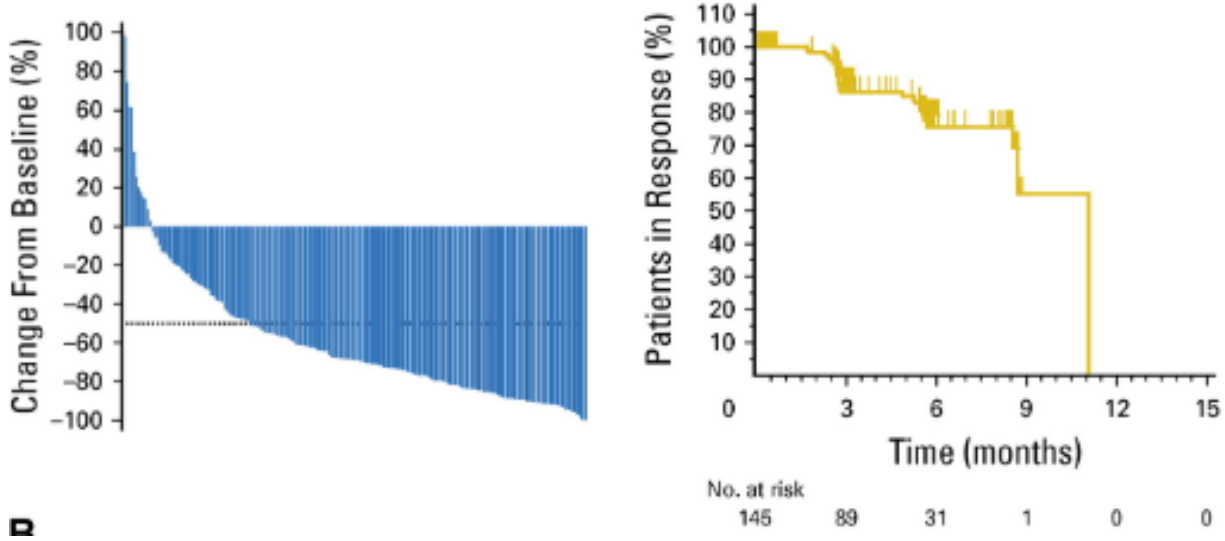
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

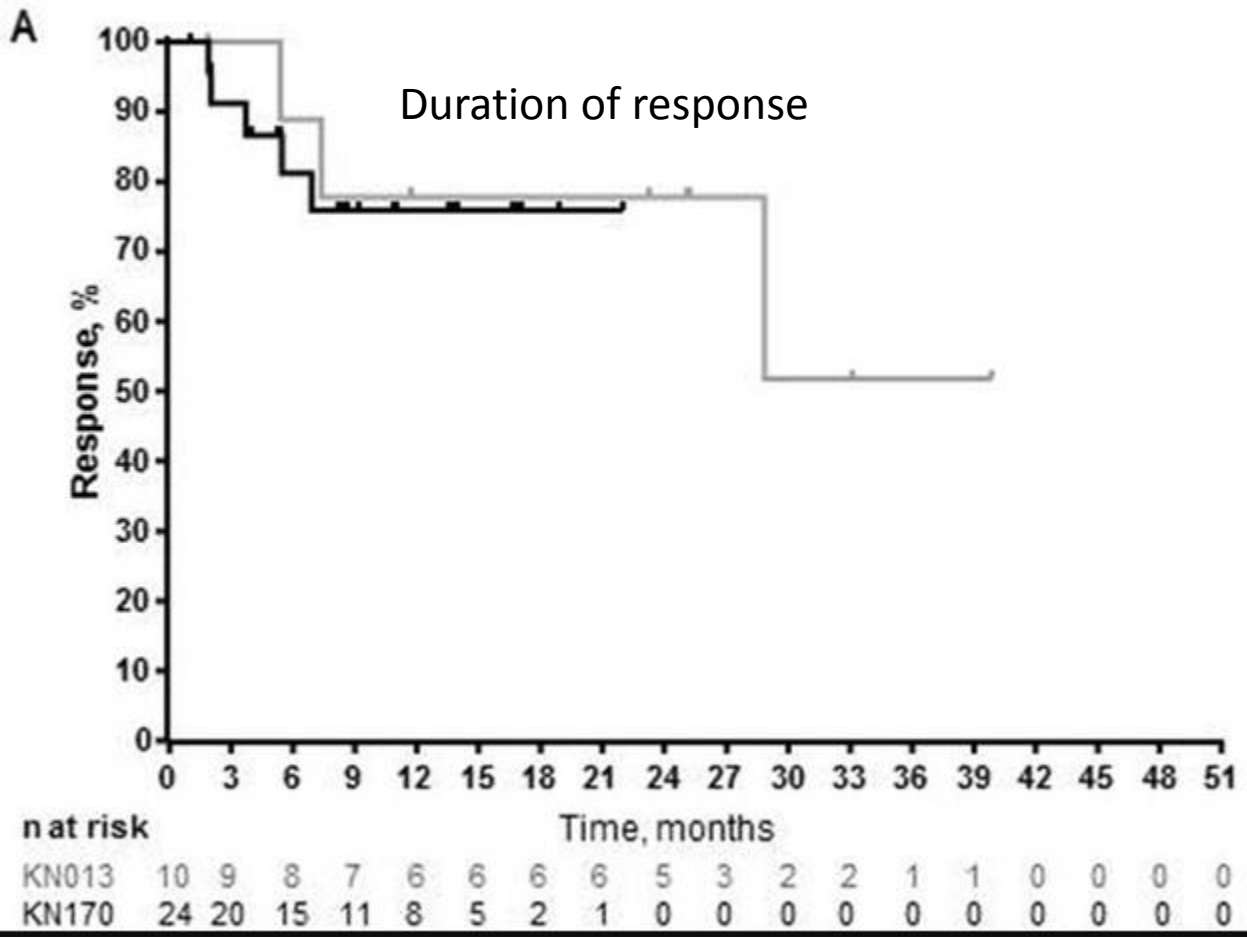
CR = 22.4%

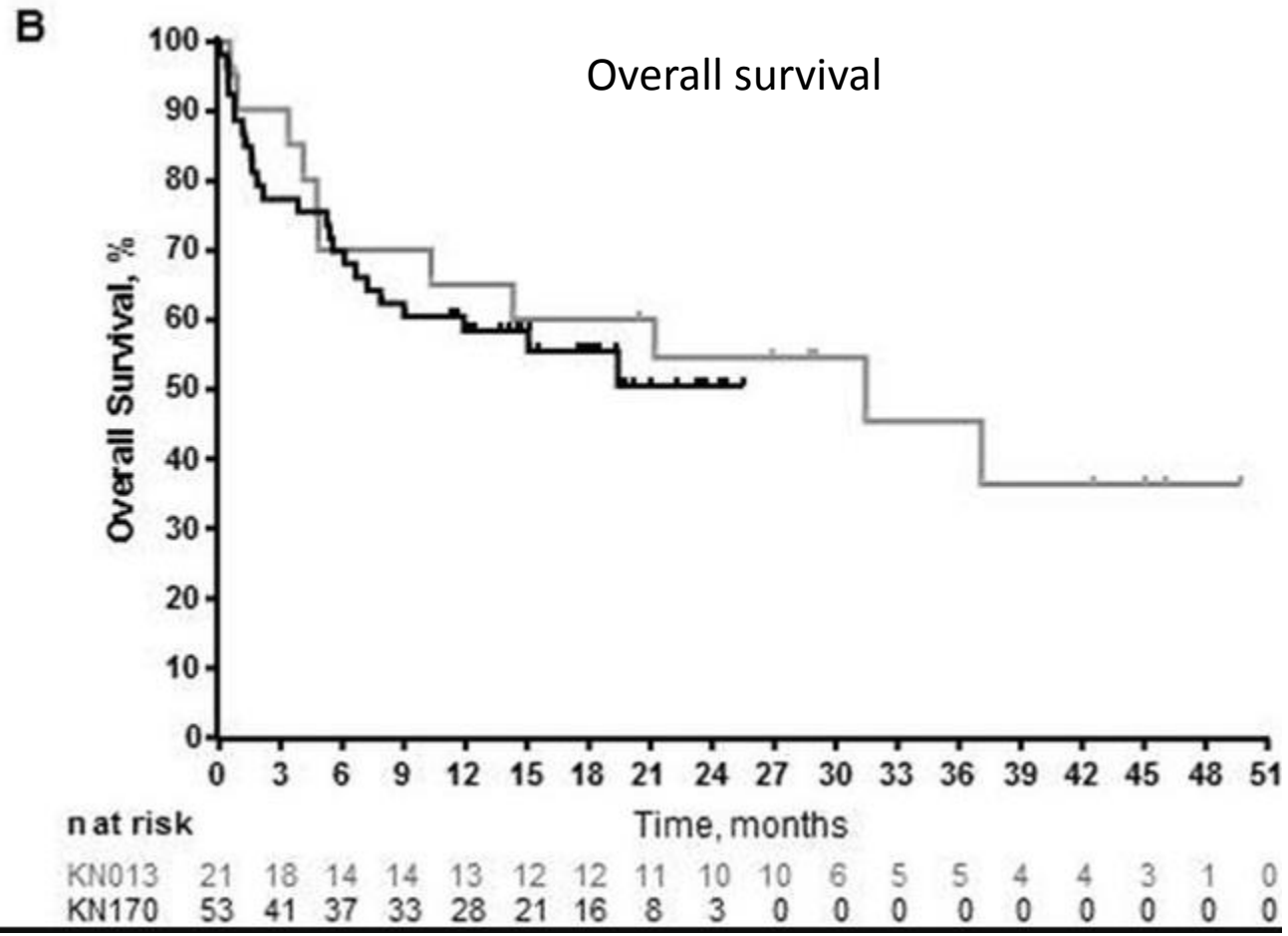
Activity seen regardless of PD-L1 expression



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

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

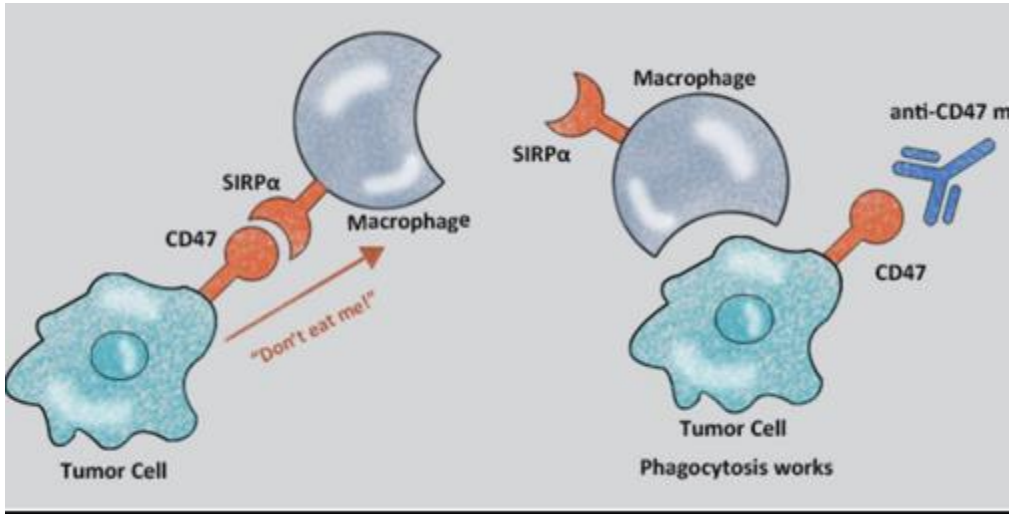


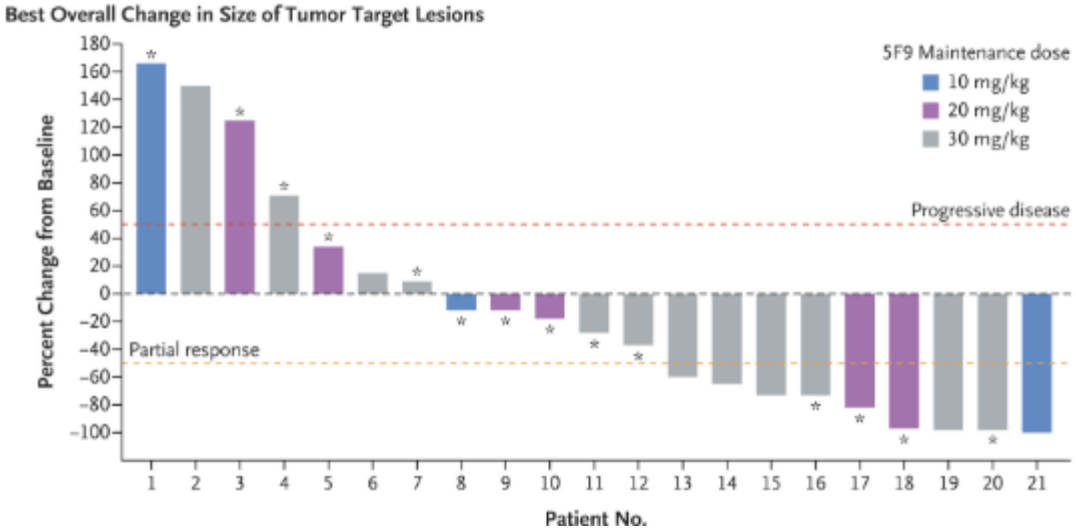


Armand, Blood 2018.

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%



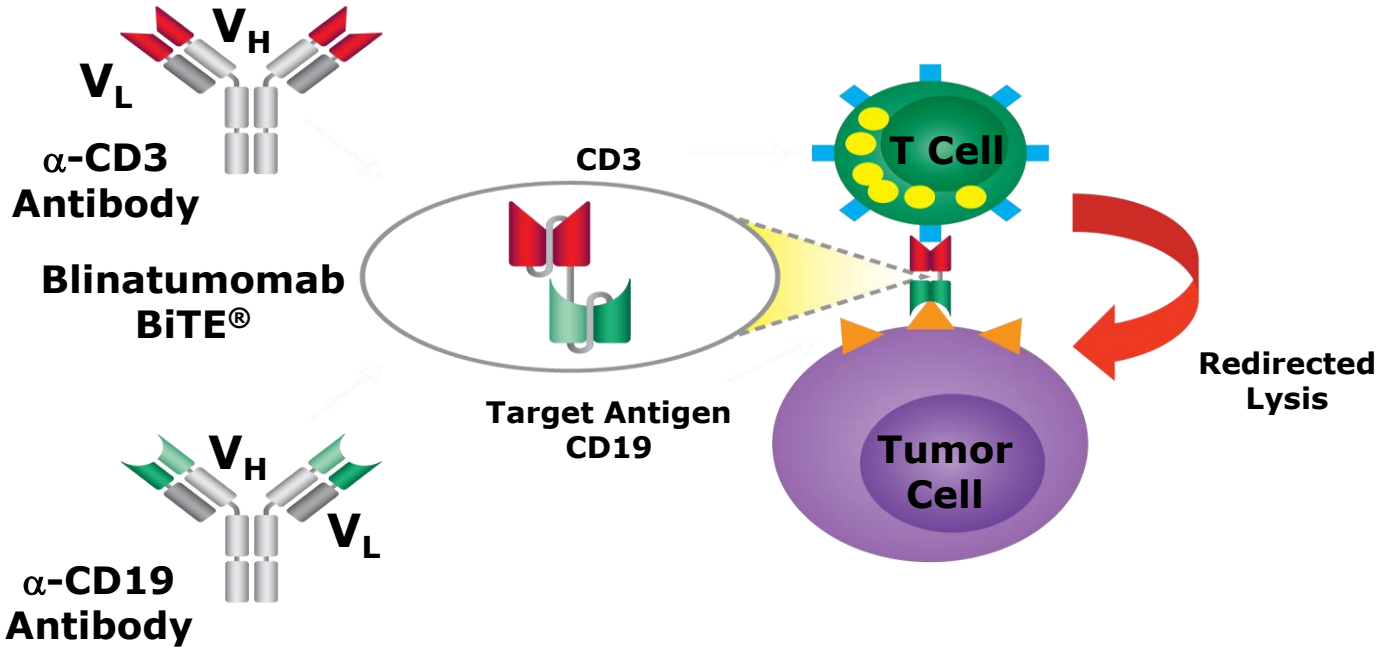


Advani, NEJM 2018.

Bi-specific T-cell Engagers (BiTEs)

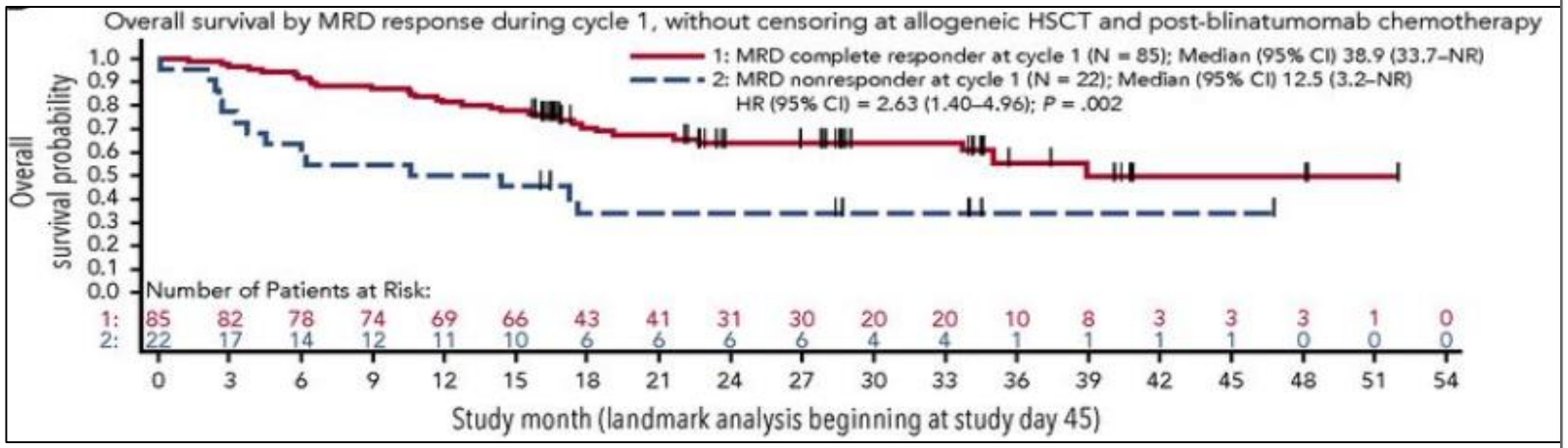
BiTE (Blinatumomab) Therapy

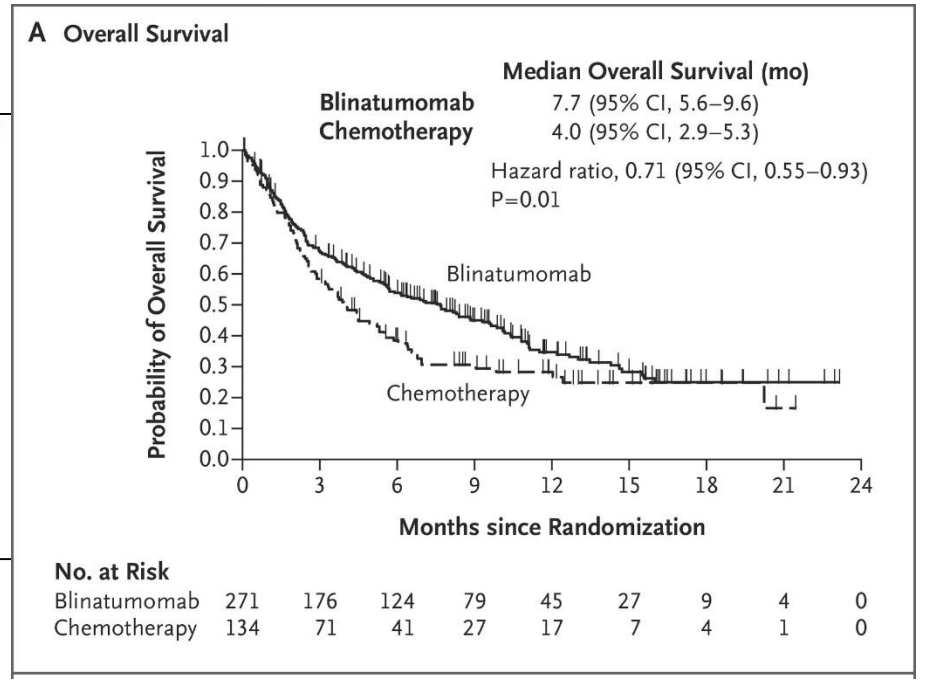
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





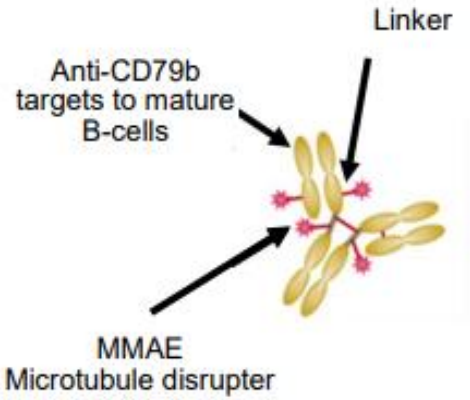
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

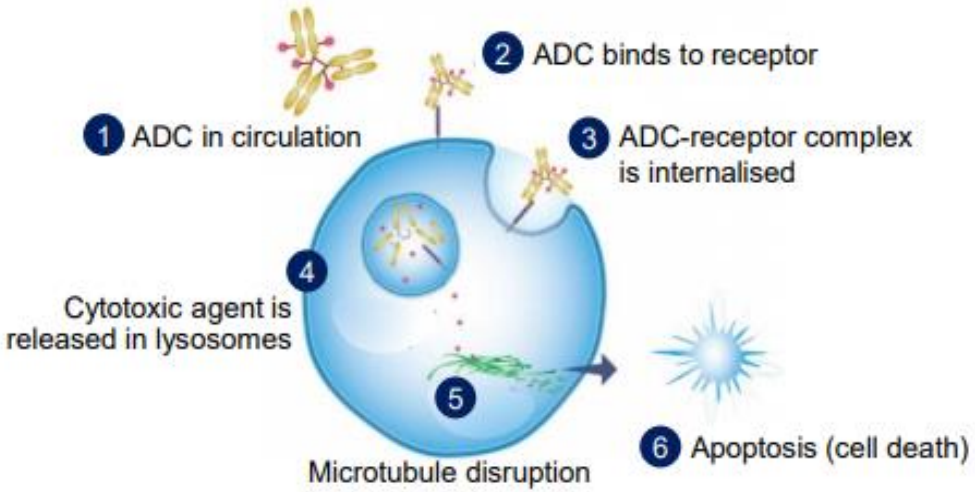
Antibody-Drug Conjugates (ADC)

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

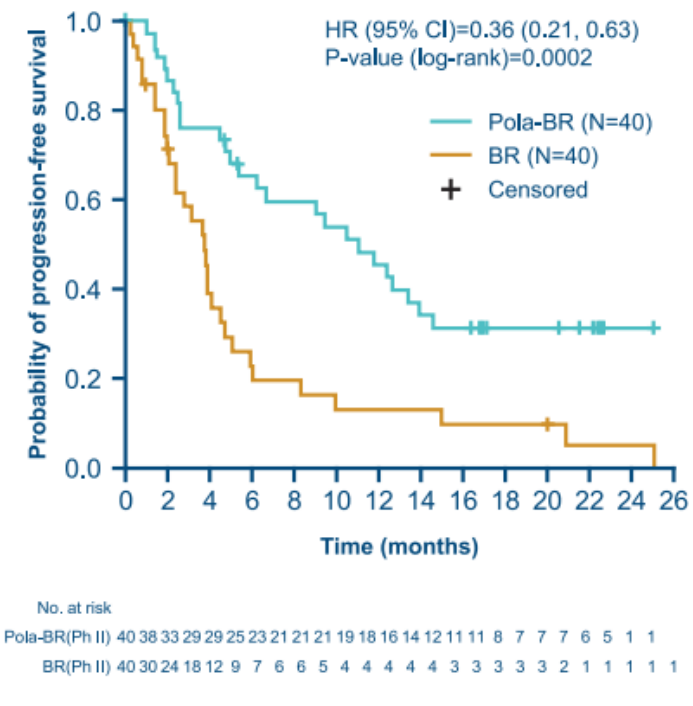
Slide credit: Tilly et al. ICML 2019

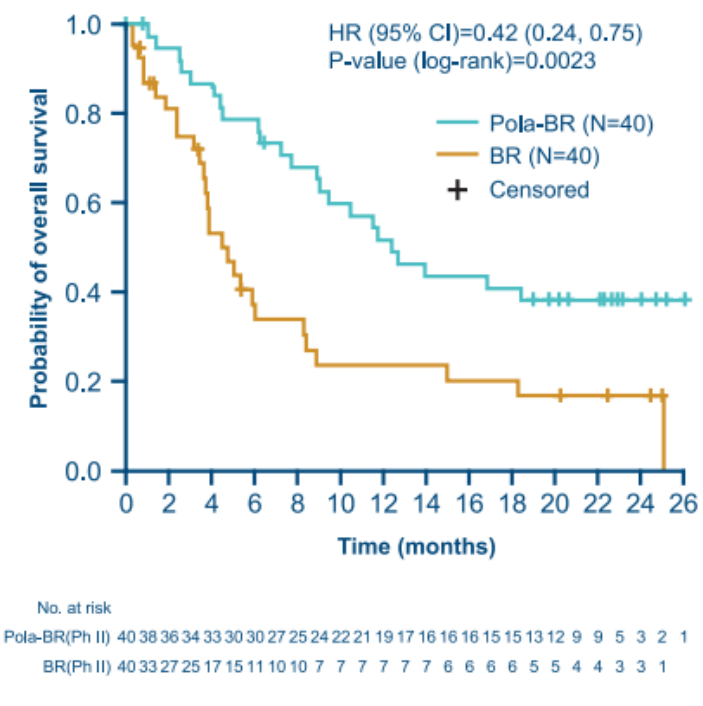
Polatuzumab vedotin: DLBCL

- 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

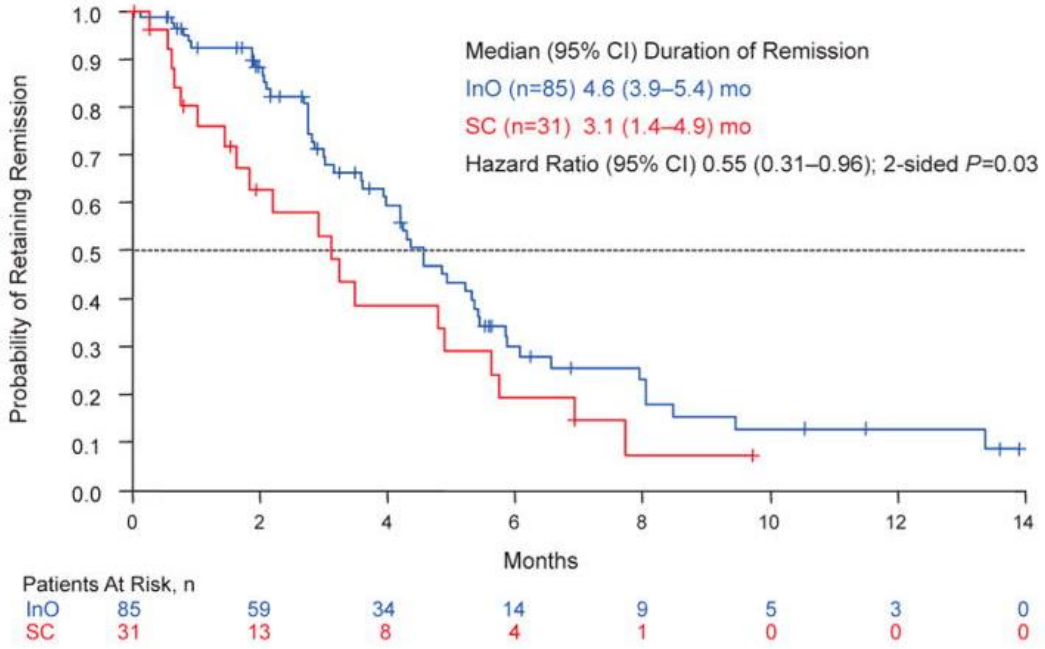


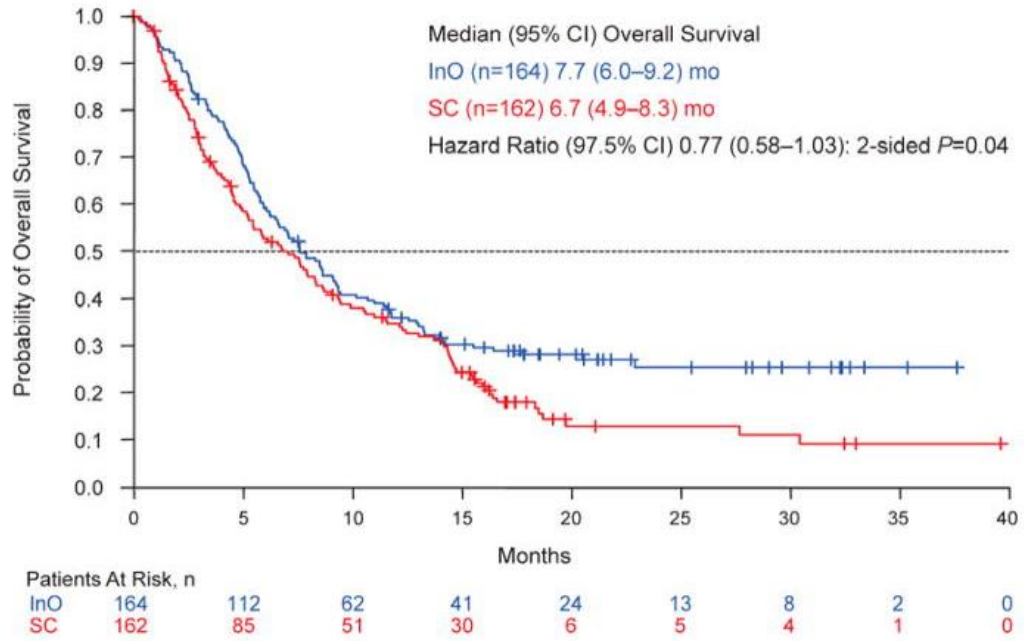


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



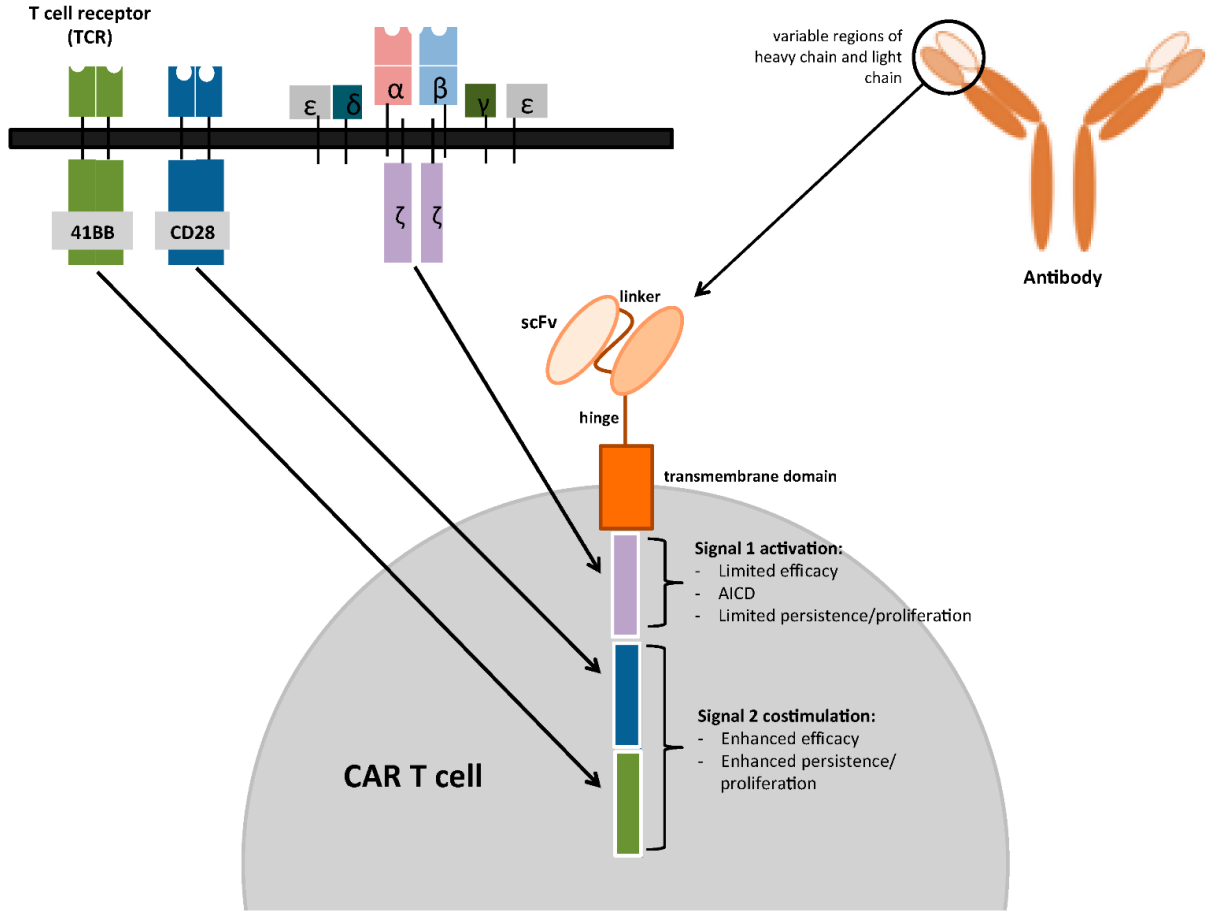


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

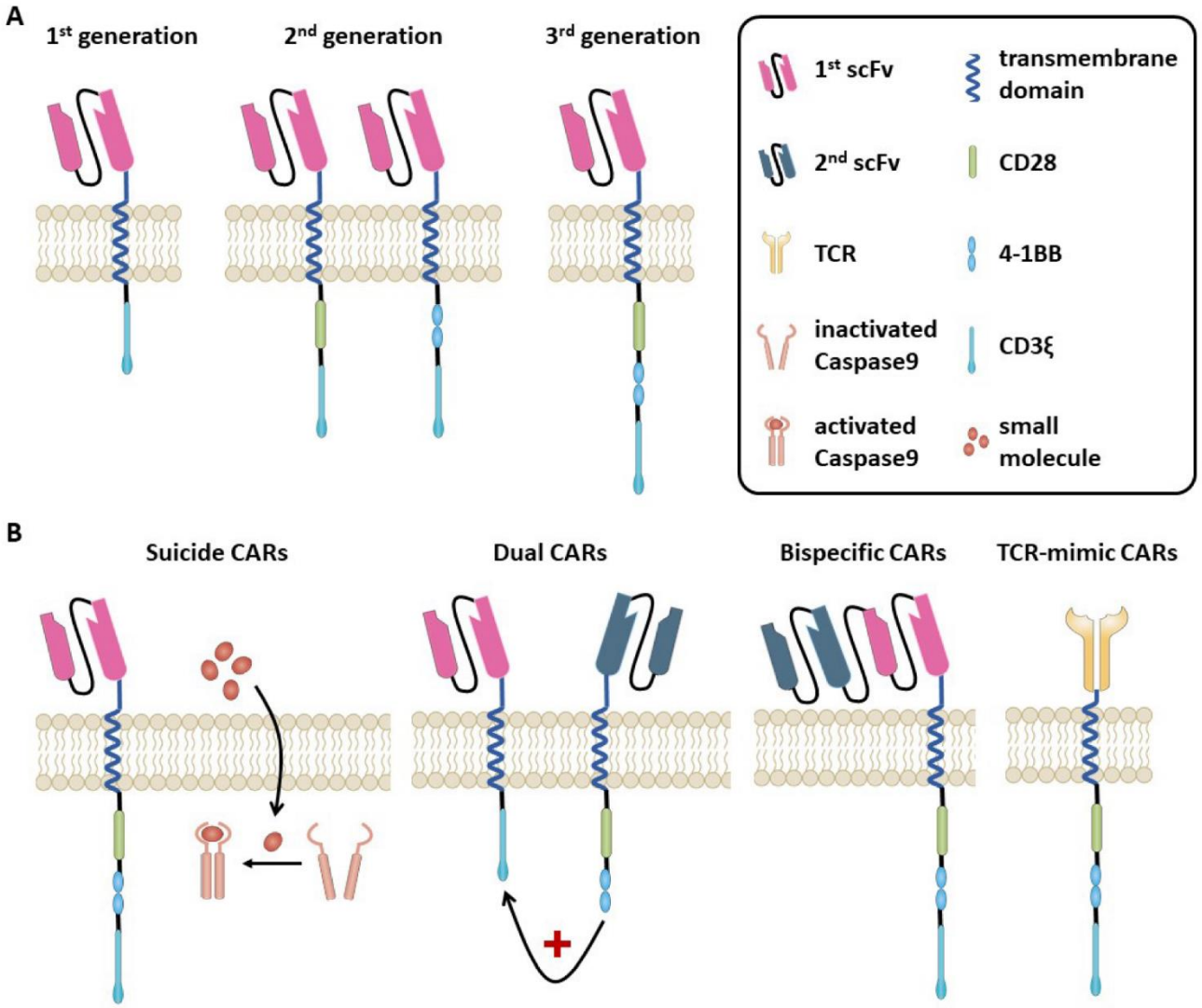
Chimeric Antigen Receptors

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



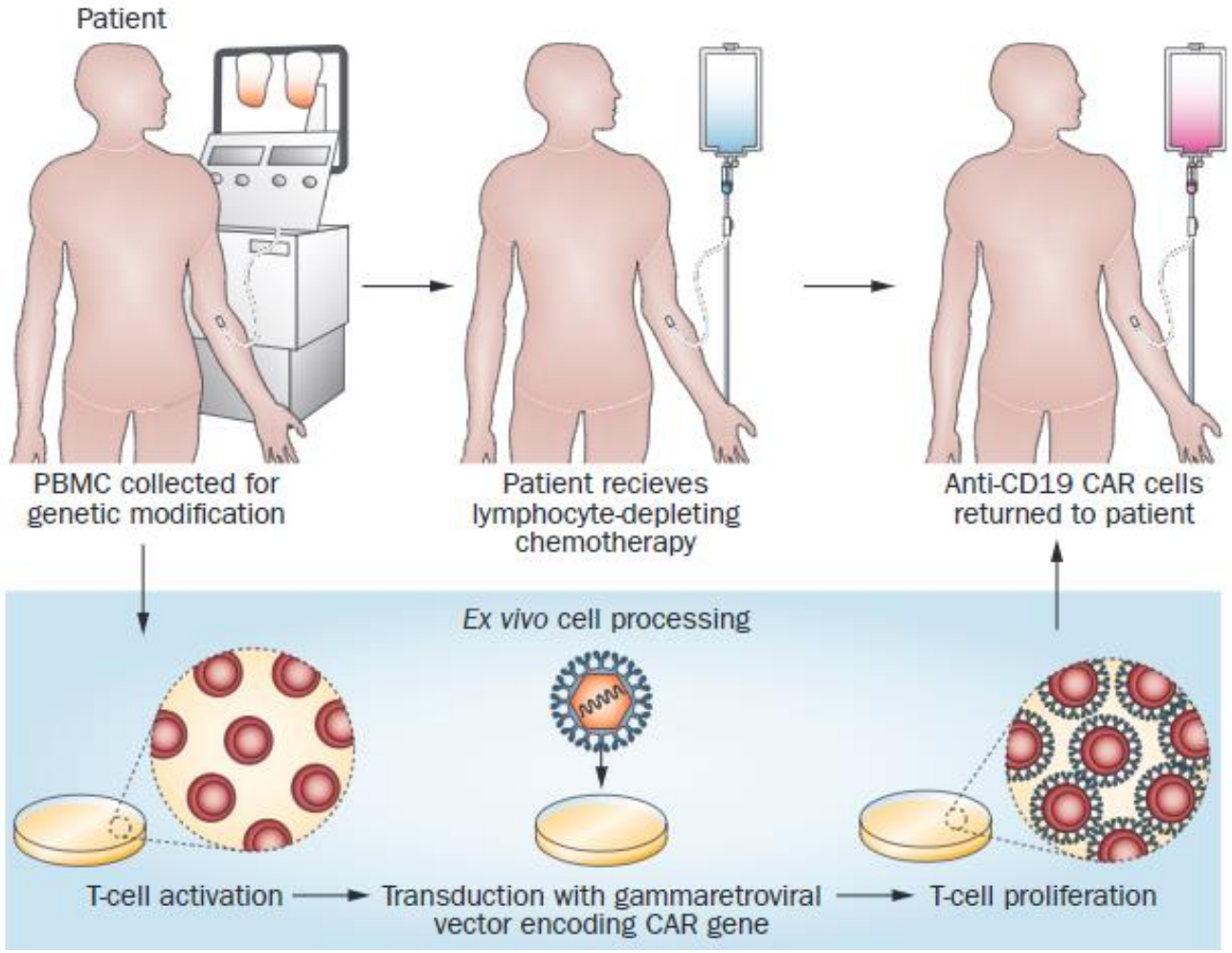
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

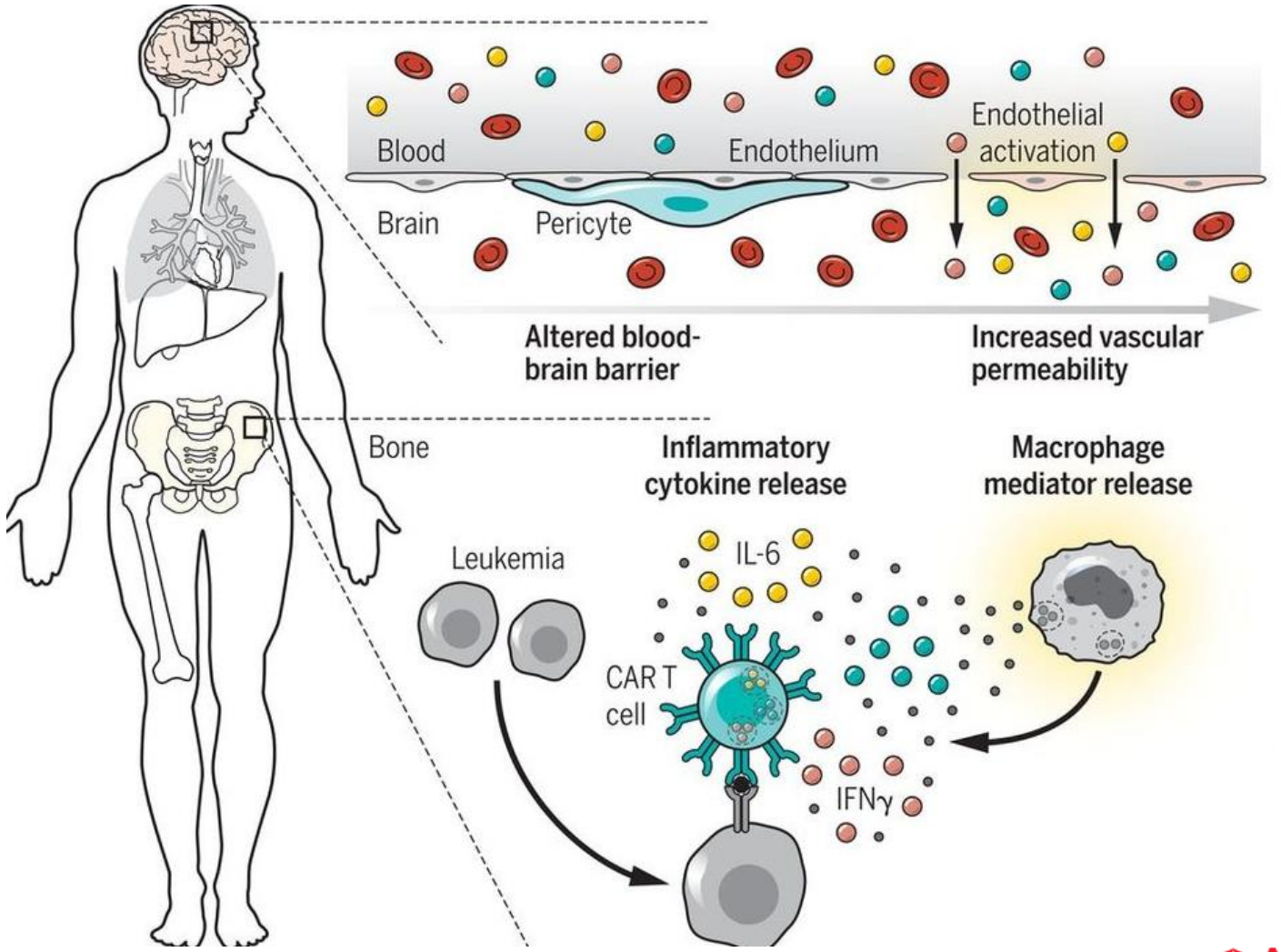


Kochenderfer, Nat Rev Clin Oncol 2013.

CAR T Side Effects

- Cytokine Release Syndrome (CRS)
- IEC-associated Neurotoxicity Syndrome (ICANS)
- 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

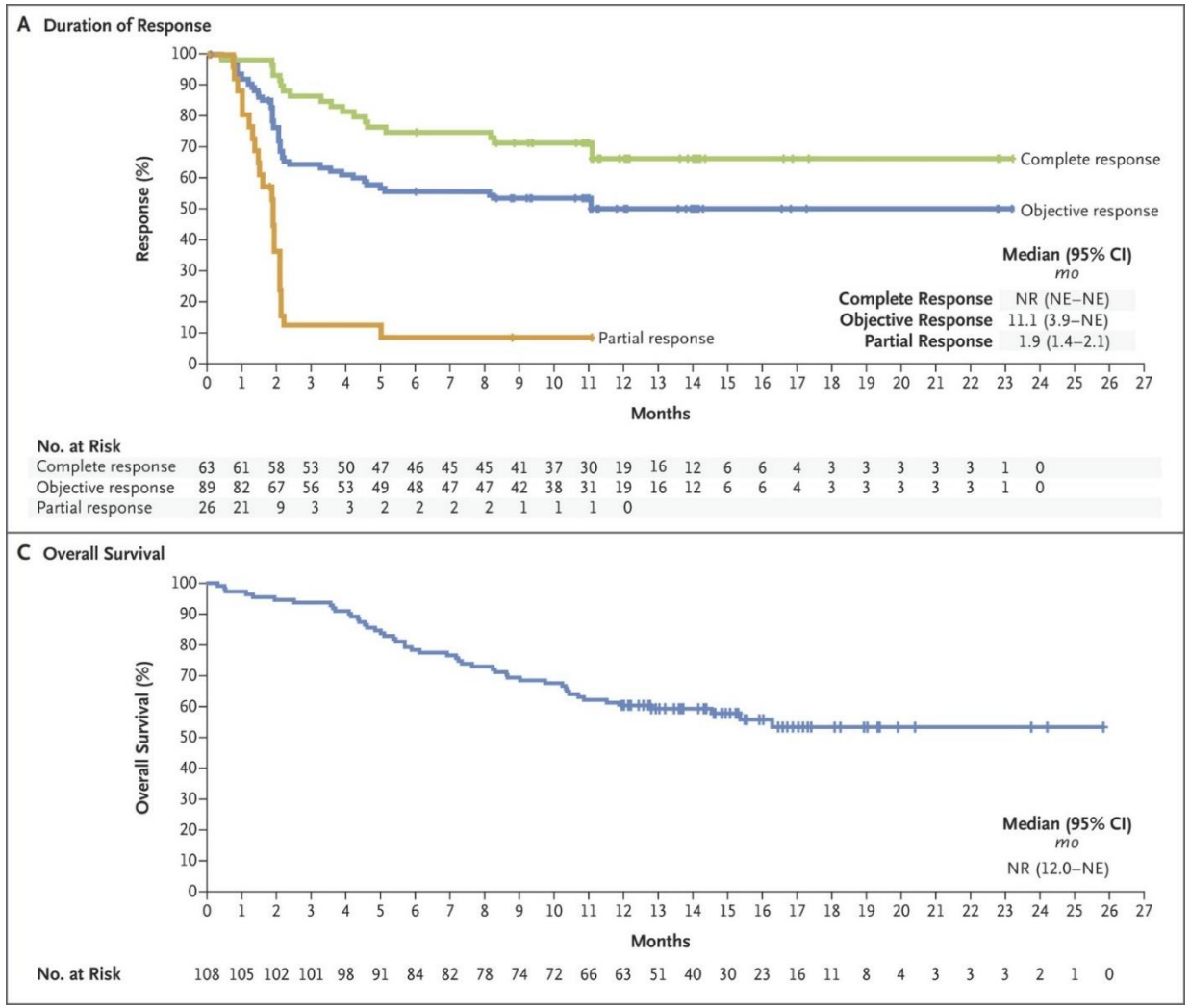
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight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

- 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 screening vs. day of CAR T infusion
- Other
  - Social support, reimbursement

CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

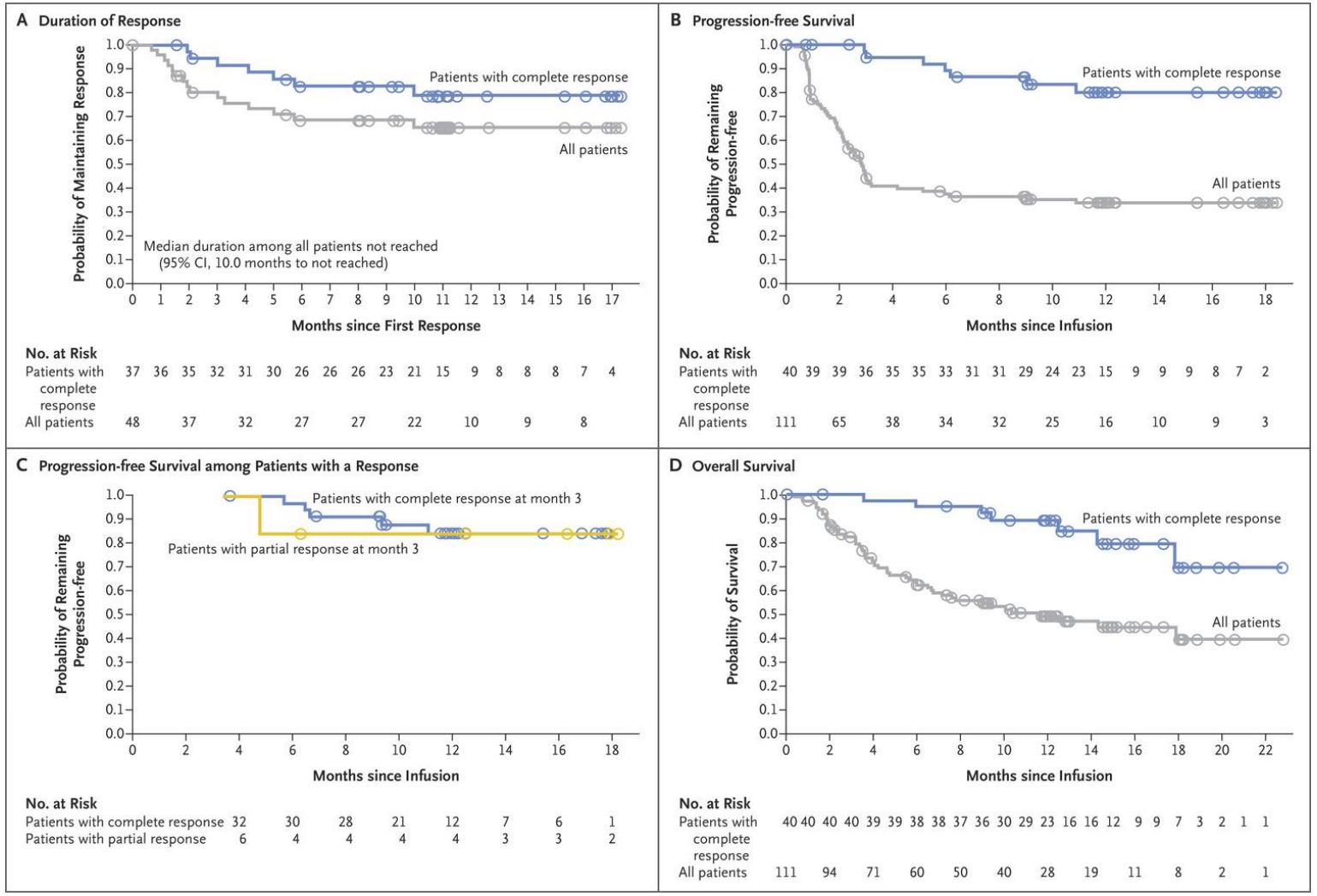
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

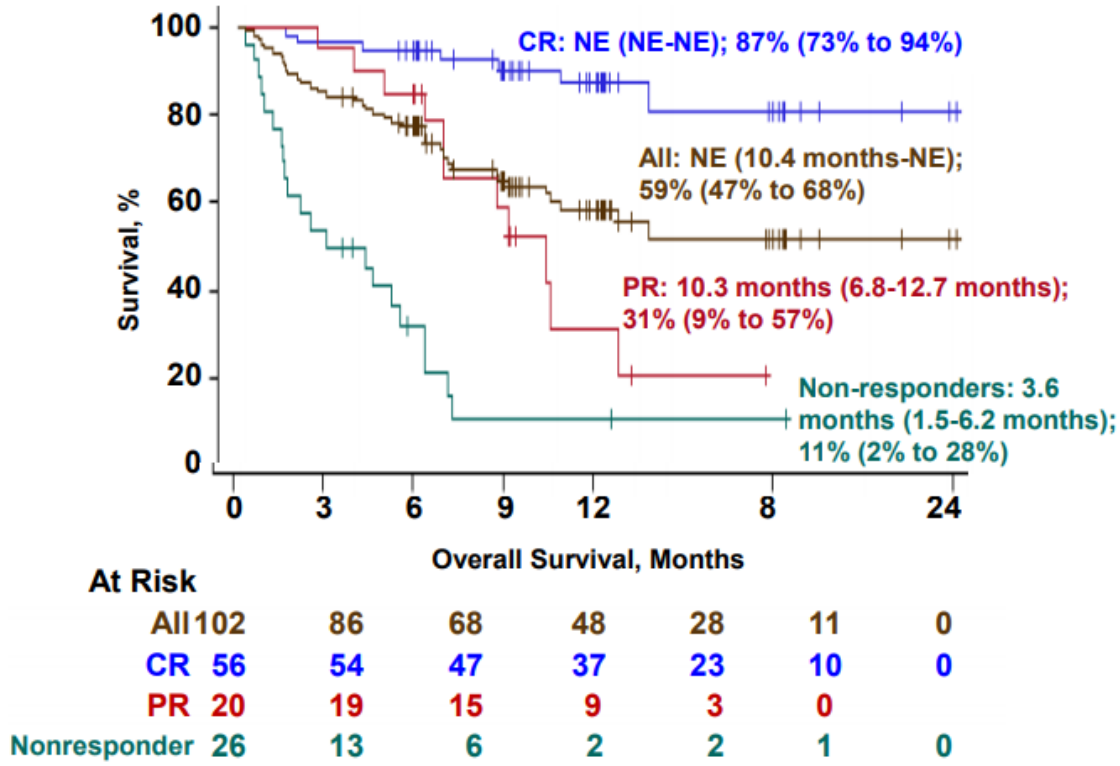
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

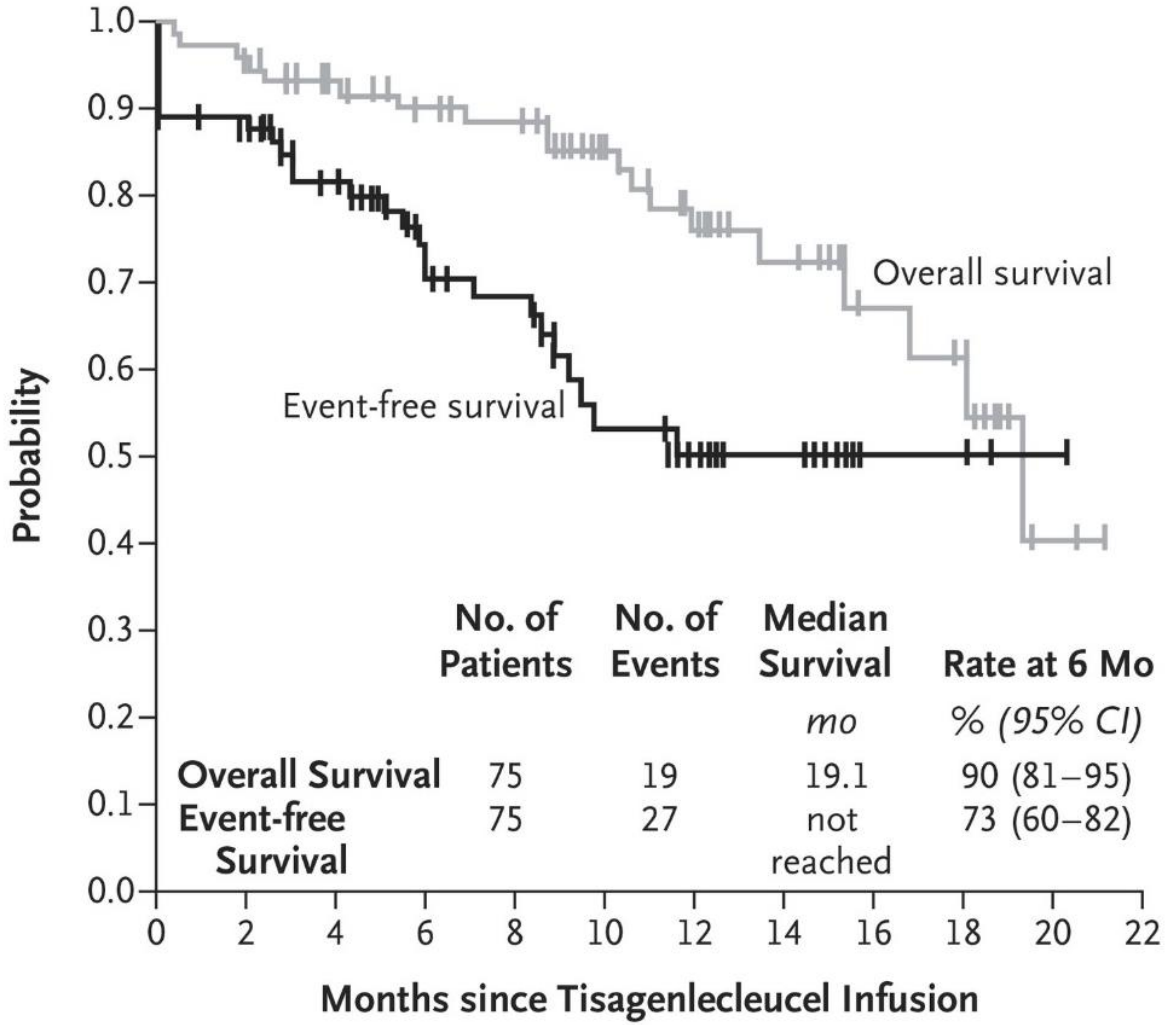
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

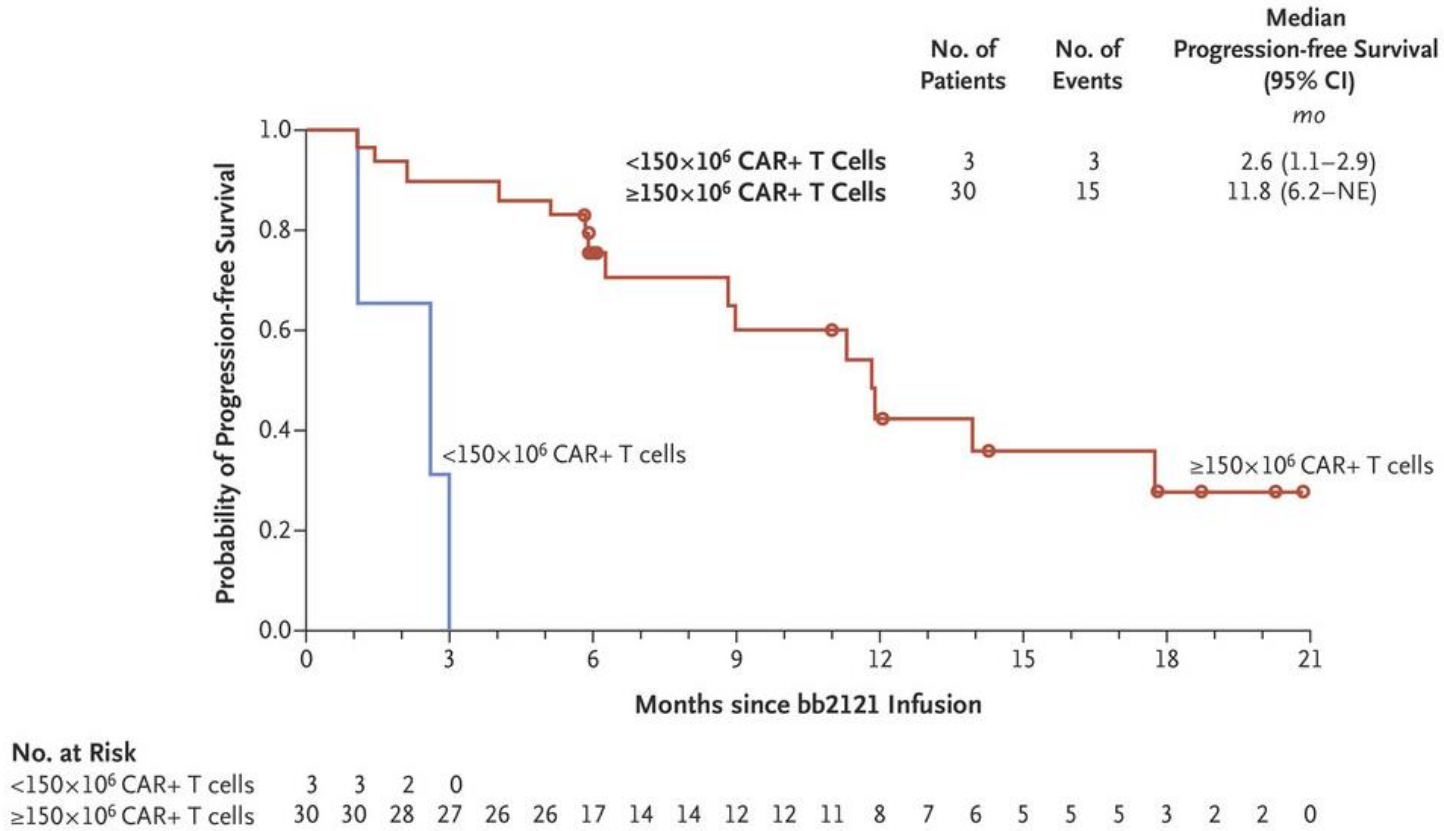


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

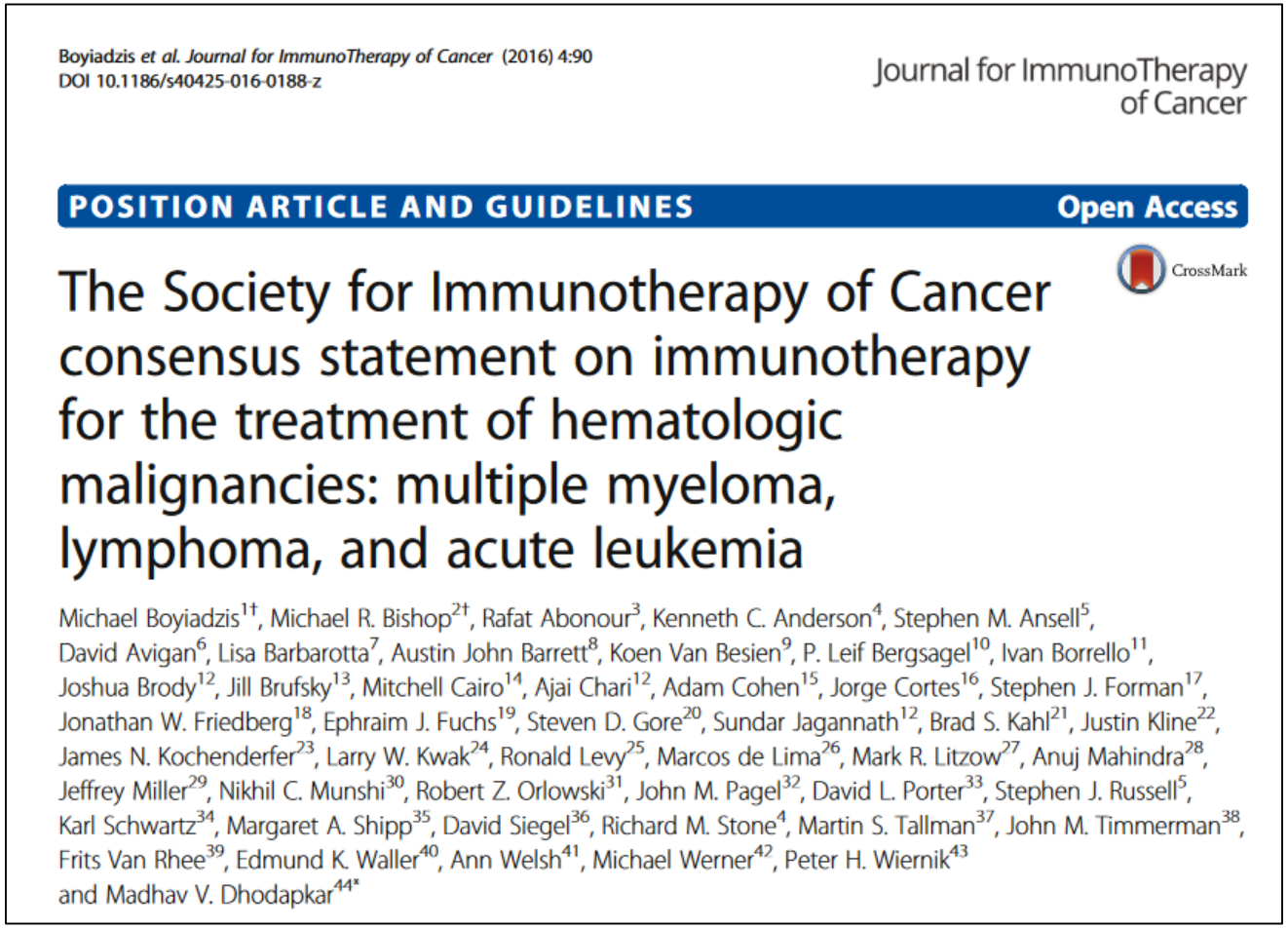


Raje, NEJM 2019.

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

Ms. A is a 36 y/o female with Hodgkin Lymphoma, originally dx'd in 2016, s/p ABVD x 8 cycles with CR, relapsed 1.5 years later, s/p 2 cycles of ICE with progressive disease. Now with secondary refractory HL here for 2nd opinion.

1. Which of the following regimens would you consider the best approach for this patient? More than one answer may be correct.

   A. Brentuximab +/- Bendamustine
   B. Pembrolizumab
   C. More salvage chemotherapy or autologous stem cell transplant
   D. Participation in a clinical trial

Case Study 1

1. Which of the following regimens would you consider the best approach for this patient? More than one answer may be correct.

   A. Brentuximab +/- Bendamustine – Correct. FDA approved in 2011 for Classical Hodgkin Lymphoma relapsed after HSCT or ≥2 previous therapies.
   B. Pembrolizumab – Incorrect. Must have relapsed after 3 lines of therapy (including autologous SCT or Brentuximab) or be refractory.
   C. More salvage chemotherapy or autologous stem cell transplant – Incorrect. Does not have chemotherapy-sensitive disease.
   D. Participation in a clinical trial – Correct. Must consider at every treatment decision; however, Brentuximab has 61% ORR and is also effective when combined with chemotherapy, so would have to be confident that response to treatment on clinical trial would be similar.

ANSWER: Ms. A had a PR to 2 cycles of Brentuximab and Bendamustine.

Case Study 1

She subsequently proceeded to BEAM autologous stem cell transplant followed by post-transplantation Brentuximab. Unfortunately, she relapsed 8 months after transplant.

1. Which of the following regimens would you consider the best approach for this patient at this time?

   A. Further salvage chemotherapy
   B. Anti-PD1 Blockade (Pembrolizumab)
   C. Reduced intensity allogeneic HCT
   D. Participation in a clinical trial

Case Study 1

Ms. A had a PR to 2 cycles of Brentuximab and Bendamustine and subsequently proceeded to BEAM autologous stem cell transplant followed by post-transplantation Brentuximab. Unfortunately, she relapsed 8 months after transplant.

1. Which of the following regimens would you consider the best approach for this patient at this time?
   A. Further salvage chemotherapy – Incorrect – Patient's disease is not chemo-sensitive.
   B. Anti-PD1 Blockade (Pembrolizumab) – Correct – FDA approved for relapse after 3 lines of therapy.
   C. Reduced intensity allogeneic HCT – Correct –Because she was young with good medical fitness and no toxicities from prior treatments, however, current practice is to give Pembrolizumab and then consider allogeneic HCT at relapse.
   D. Participation in a clinical trial – Correct – Must consider at every treatment decision.

ANSWER: She initiated Pembrolizumab and remains in remission at 6 months.

Case Study 2

Mr. B is a 70 y/o male with R/R multiple myeloma, originally dx'd in 2013, now slowly progressing on Daratumuamb/Pomalidemide and interested in CAR T-cell therapy.

- ECOG 1, LBP and walks with cane, CrCl 64ml/min, supportive partner, lives in Chico, CA

1. Is this patient a good candidate for CAR-T?

   A. YES
   B. NO

Case Study 2

Mr. B is a 70 y/o male with R/R multiple myeloma, originally dx'd in 2013, now slowly progressing on Daratumuamb/Pomalidemide and interested in CAR T-cell therapy.

- ECOG 1, LBP and walks with cane, CrCl 64ml/min, supportive partner, lives in Chico, CA

1. Is this patient a good candidate for CAR-T?

   A. YES – Correct. >3 prior lines of therapy, slow progression, good PFS, adequate kidney function, and family support.
   B. NO – Incorrect. Would need to relocate, but trials offer housing/travel reimbursement.

Case Study 2

Mr. B enrolls in a CAR T-cell clinical trial and undergoes apheresis. While his T-cells are being manufactured, he receives bridging chemotherapy with cyclophosphamide/Dex x 3 days. He is given pegfilgrastim and ppx levofloxacin, but 2 days prior to starting lymphodepleting (LD) chemotherapy he develops a fever. He is admitted for w/u, found to +rhinovirus positive and CXR c/f PNA. He is started on empiric IV abx.

1. How should you proceed with CAR-T treatment for this patient?

   A. Start LD chemo as planned
   B. Start LD chemo as planned but delay CAR T infusion
   C. Delay LD chemo and CAR T infusion
   D. No longer a candidate for CAR T-cell therapy

Case Study 2

Mr. B enrolls in a CAR T-cell clinical trial and undergoes apheresis. While his T-cells are being manufactured, he receives bridging chemotherapy with cyclophosphamide/Dex x 3 days. He is given pegfilgrastim and ppx levofloxacin, but 2 days prior to starting lymphodepleting (LD) chemotherapy he develops a fever. He is admitted for w/u, found to +rhinovirus positive and CXR c/f PNA. He is started on empiric IV abx.

1. How should you proceed with CAR-T treatment for this patient?
   A. Start LD chemo as planned. Incorrect. Patient must be without s/sx of acute infection PRIOR to starting LD chemo and PRIOR to administering CAR T infusion.
   B. Start LD chemo as planned but delay CAR T infusion. Incorrect. Patient must be without s/sx of acute infection PRIOR to starting LD chemo and PRIOR to administering CAR T infusion.
   C. Delay LD chemo and CAR T infusion. Correct. Infection must be controlled and in some protocols patient must be off IV or systemic antibiotics.
   D. No longer a candidate for CAR T-cell therapy. Incorrect. Once the infection is controlled, the patient can proceed with treatment.

Case Study 2

Mr. B receives his CAR T-cell infusion and 24 hours later develops fever and hypotension.

1. What is the most likely etiology of the patient's symptoms? More than one answer may be correct.

   A. Infection
   B. Neurotoxicity
   C. Cytokine Release Syndrome
   D. Infusion Related Reaction

Case Study 2

Mr. B receives his CAR T-cell infusion and 24 hours later develops fever and hypotension.

1. What is the most likely etiology of the patient's symptoms? More than one answer may be correct.
   A. Infection. Correct. An infectious etiology must always be considered. Patient may also be neutropenic 2/2 chemotherapy. Perform work-up and start empiric antibiotics.
   B. Neurotoxicity. Incorrect. Fever and hypotension are not symptoms of neurotoxicity.
   C. Cytokine Release Syndrome. Correct. CRS is a clinical syndrome and fever is the sentinel symptom. Hypotension is associated with more severe CRS.
   D. Infusion Related Reaction. Incorrect. IRRs are rare with CAR T-cell therapy and typically occur during the infusions.

ANSWER: Mr. B underwent an infectious workup and was started on empiric antibiotics. He was also started on treatment for Grade 2 CRS.

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1. What is the most appropriate initial treatment be for his Grade 2 CRS? More than one answer may be correct.

   A. Symptom Management.
   B. Tocilizumab.
   C. Steroids.

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1. What is the most appropriate initial treatment be for his Grade 2 CRS? More than one answer may be correct.
   A. Symptom Management. Correct. Symptom management is indicated for any grade CRS.
   B. Tocilizumab. Correct. Tocilizumab is the first-line of treatment for Grade 2 CRS.
   C. Steroids. Incorrect. Steroids are typically reserved for more severe CRS, rapid onset CRS, or CRS unresponsive to Tocilizumab.

ANSWER: Mr. B received Tylenol for his fever and IV fluids for hypotension. He also received a dose of tocilizumab and his vital signs normalized within a few hours.