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

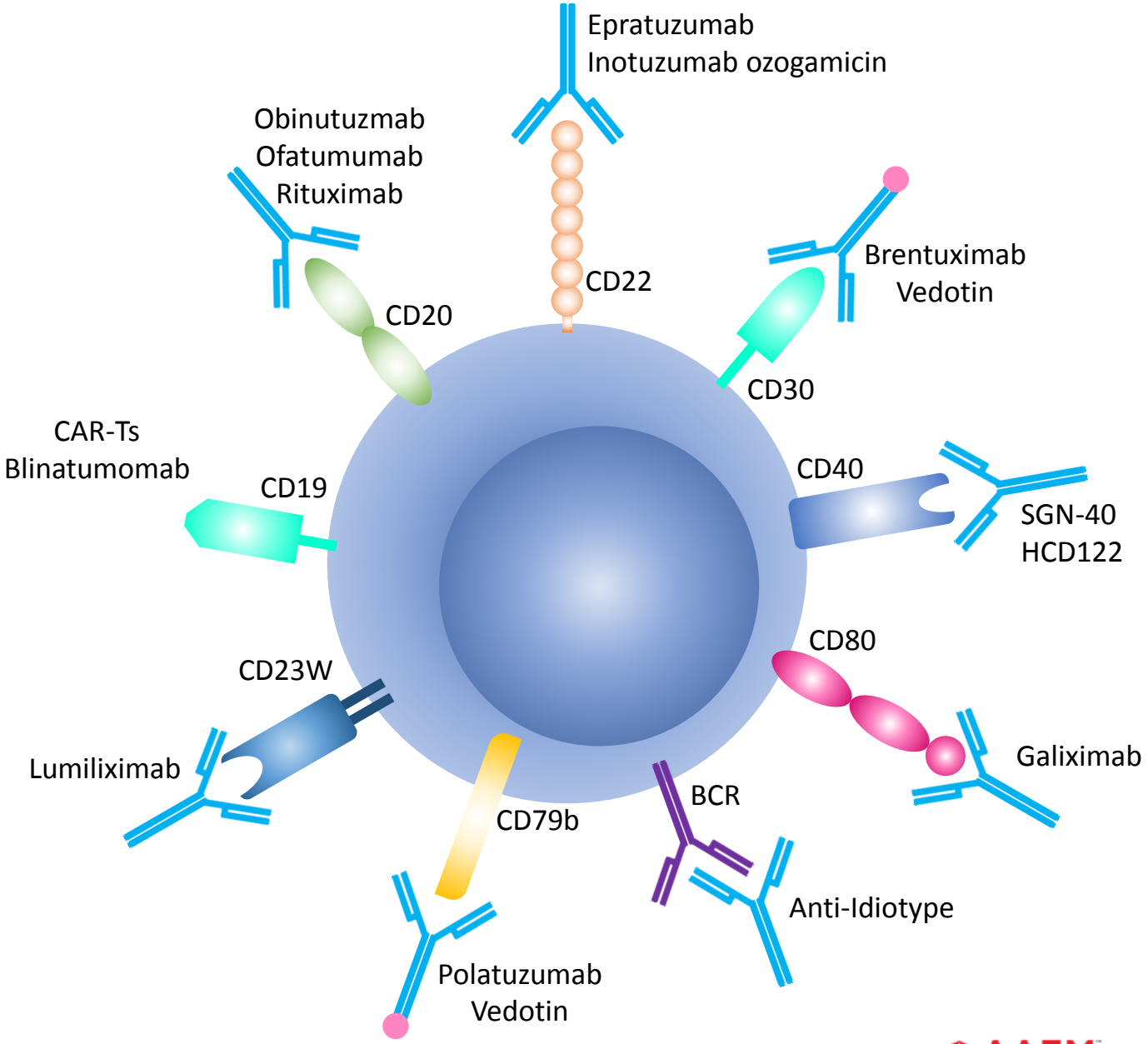
ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- Spouse – Janssen Research & Development, LLC
- Research funding from Merck, Bayer, Takeda, Seattle Genetics, and Celgene
- I will be discussing non-FDA approved indications during my presentation.



Checkpoint inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

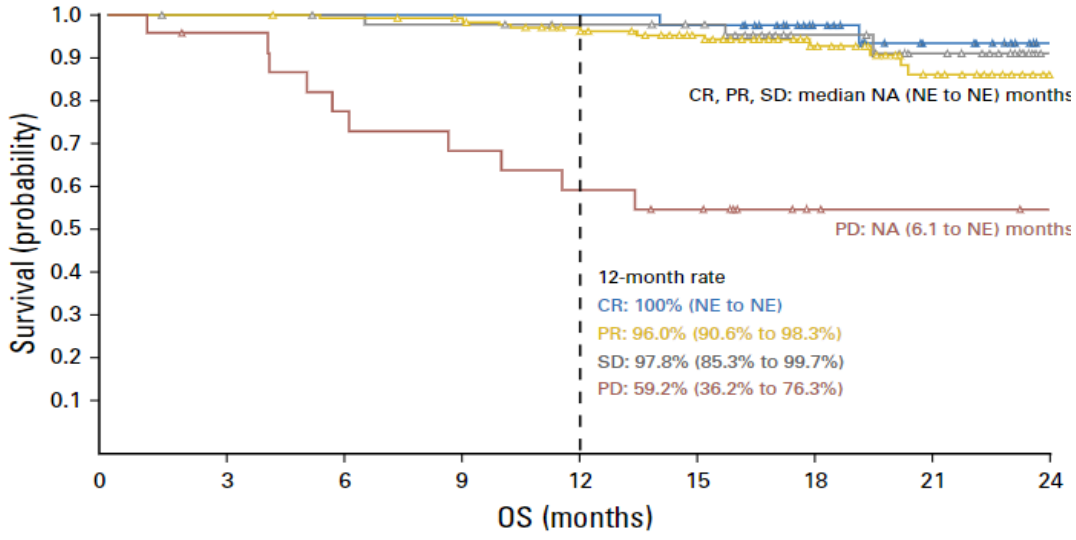
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg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

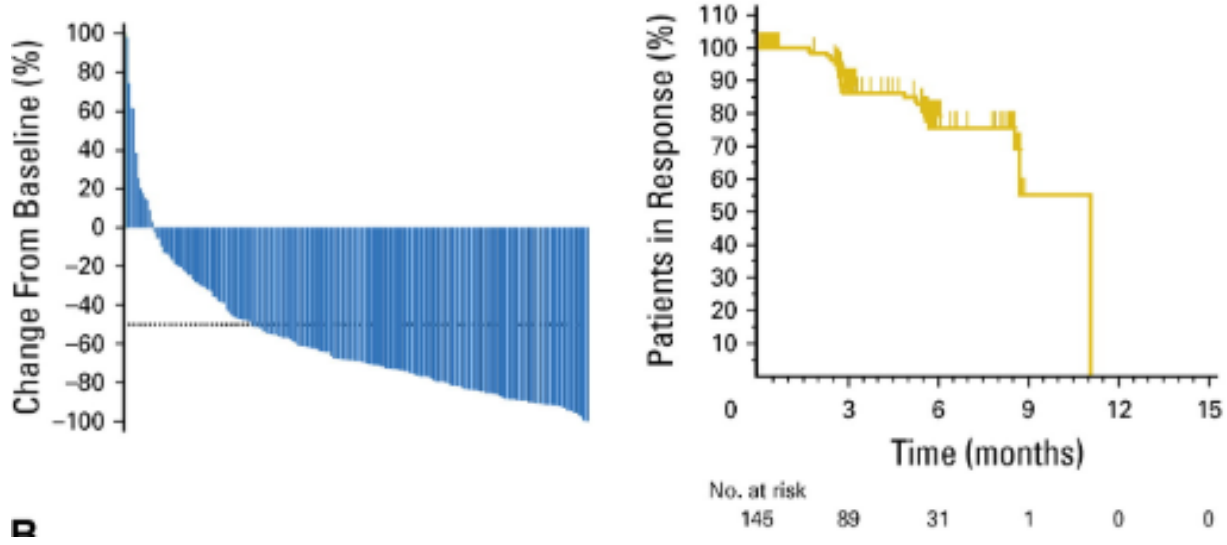
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

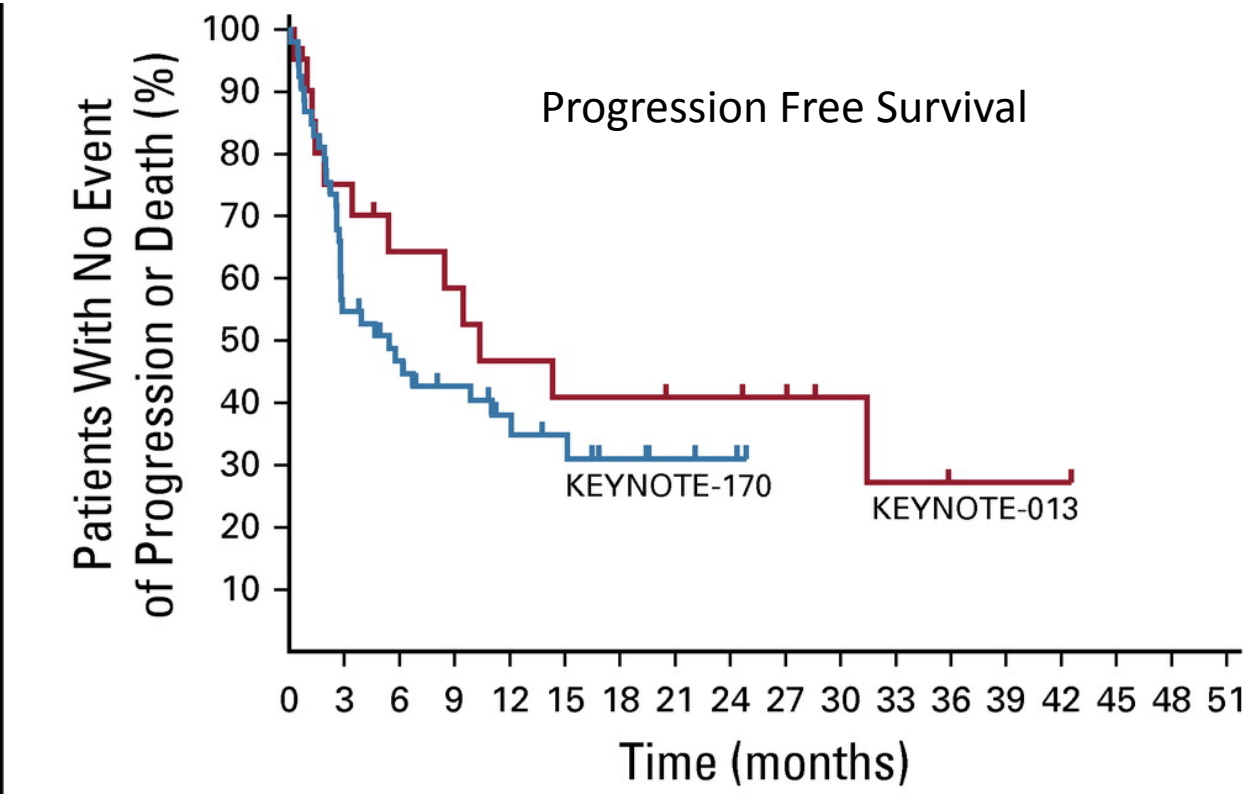
CR = 22.4%

Activity seen regardless of PD-L1 expression



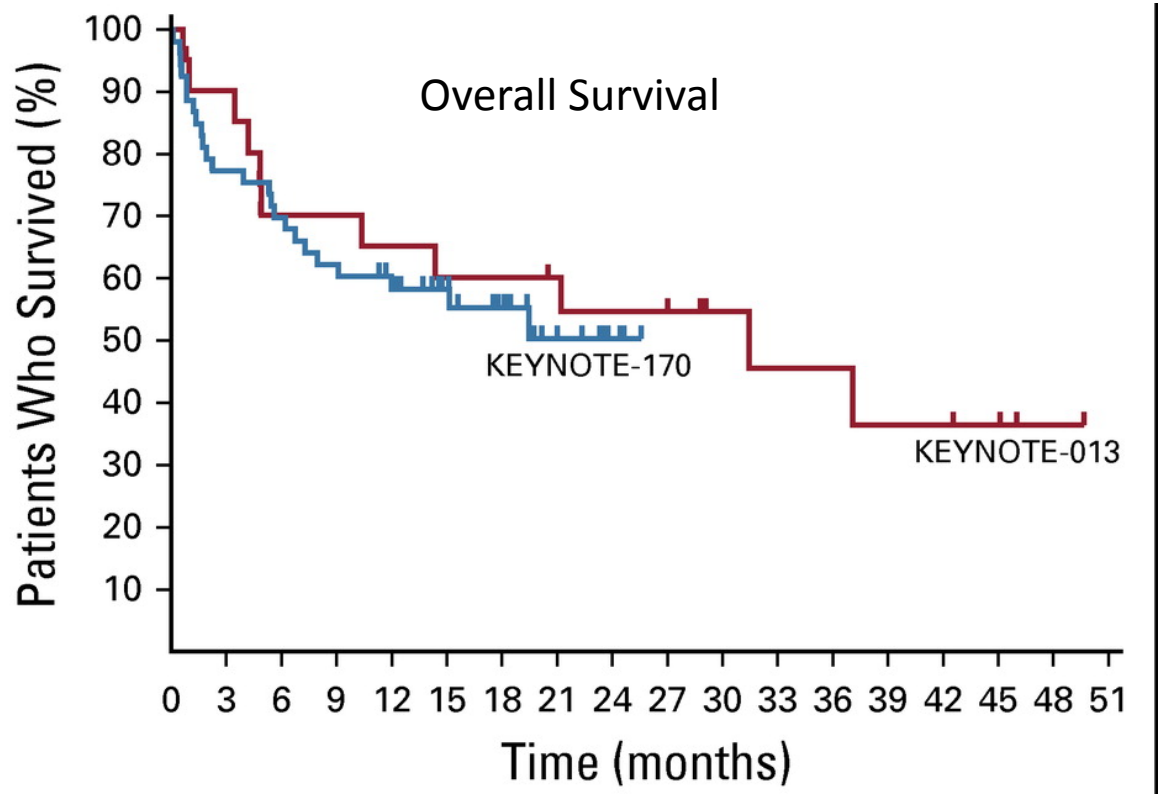
Armand, J Clin Oncol 2018.
Chen, J Clin Oncol 2017.

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



No. at risk:

KEYNOTE-013	21	15	11	10	8	7	7	6	6	5	3	2	1	1	1	0	0	0
KEYNOTE-170	53	29	23	19	12	9	6	3	2	0	0	0	0	0	0	0	0	0



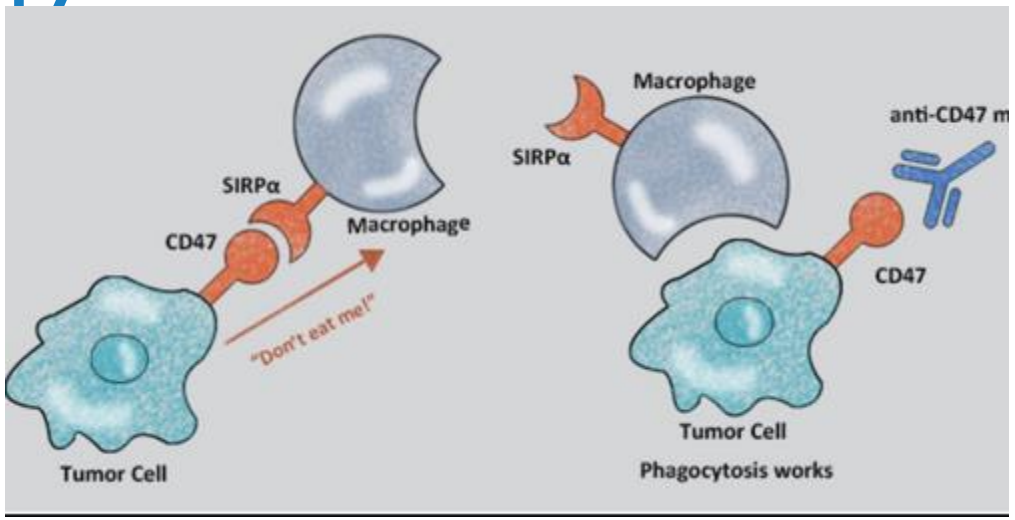
No. at risk:

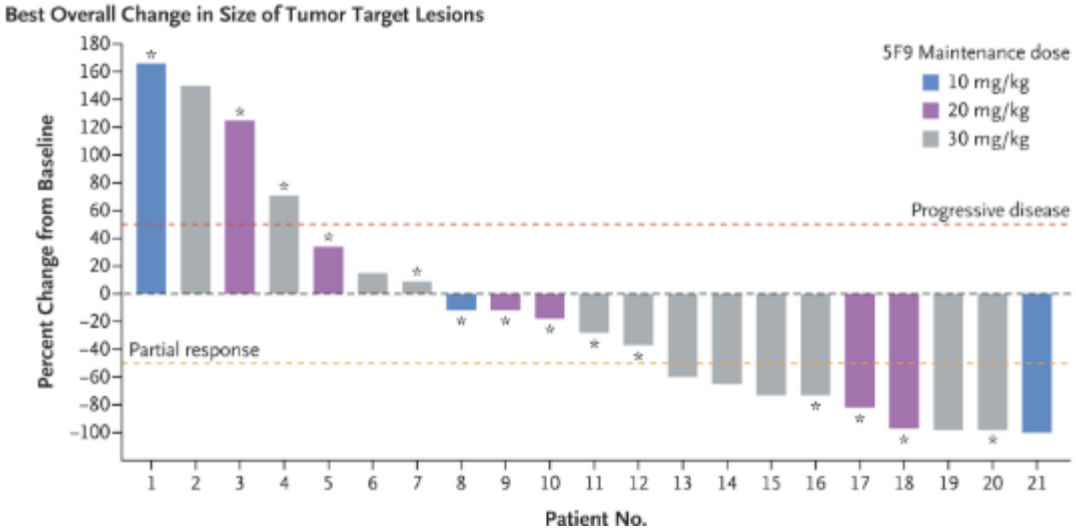
KEYNOTE-013	21	18	14	14	13	12	12	11	10	10	6	5	5	4	4	3	1	0
KEYNOTE-170	53	41	37	33	28	21	16	8	3	0	0	0	0	0	0	0	0	0

Armand, J Clin Oncol 2019.

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%



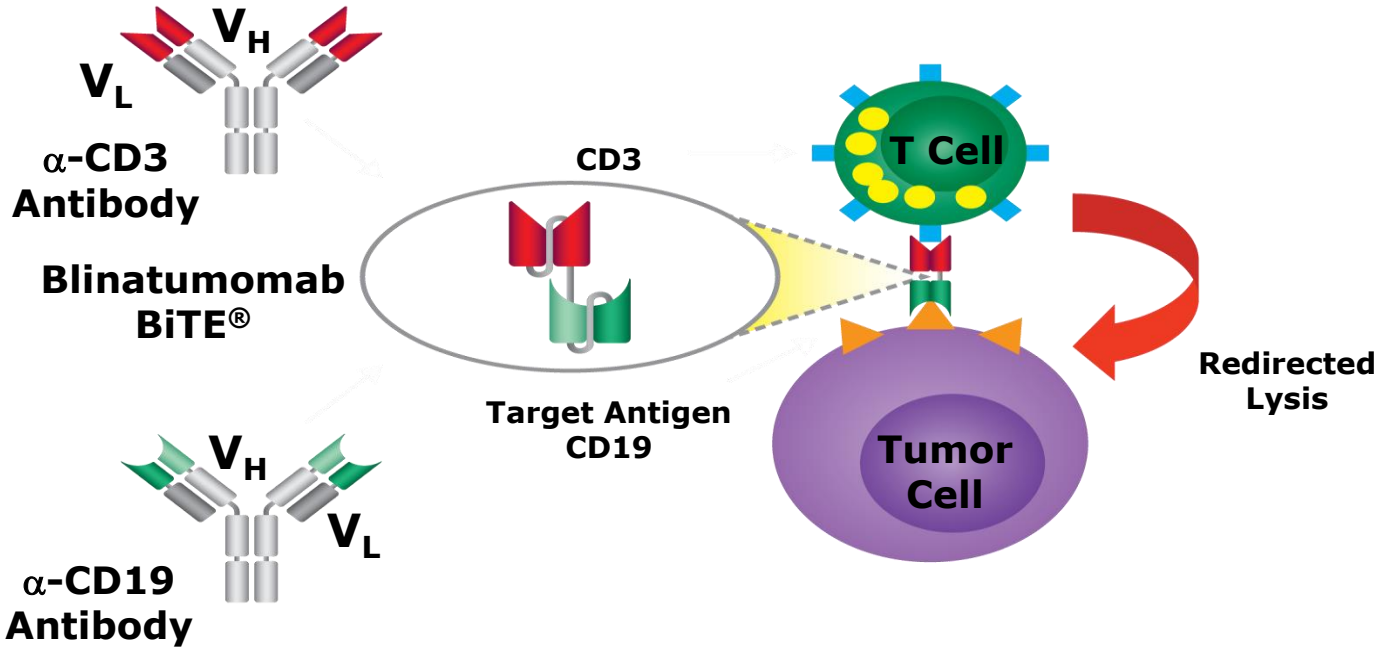


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

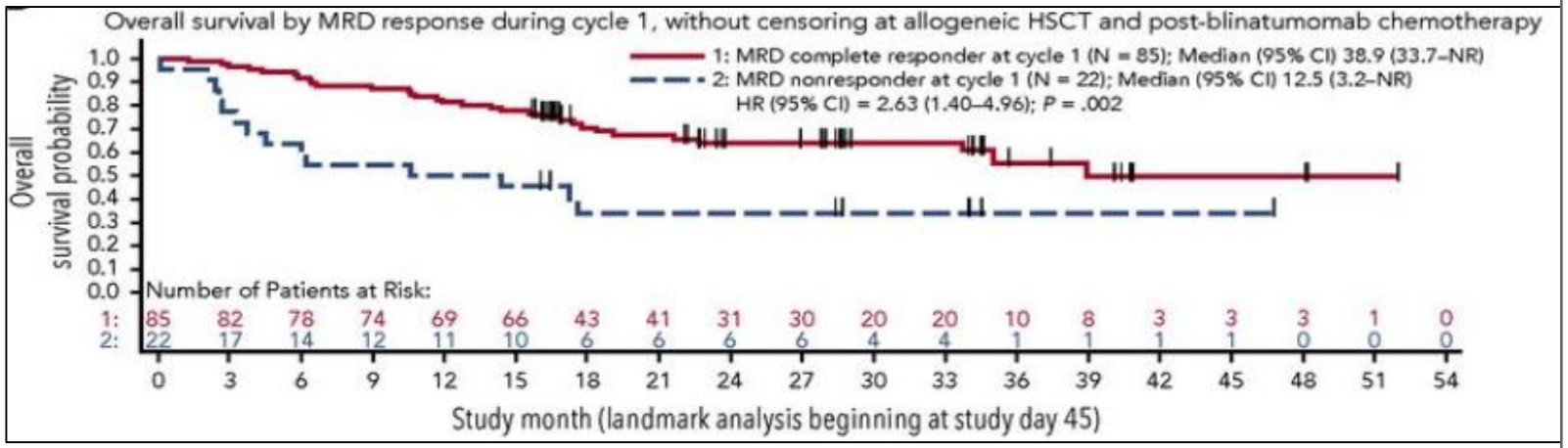
BiTE (Blinatumomab) Therapy

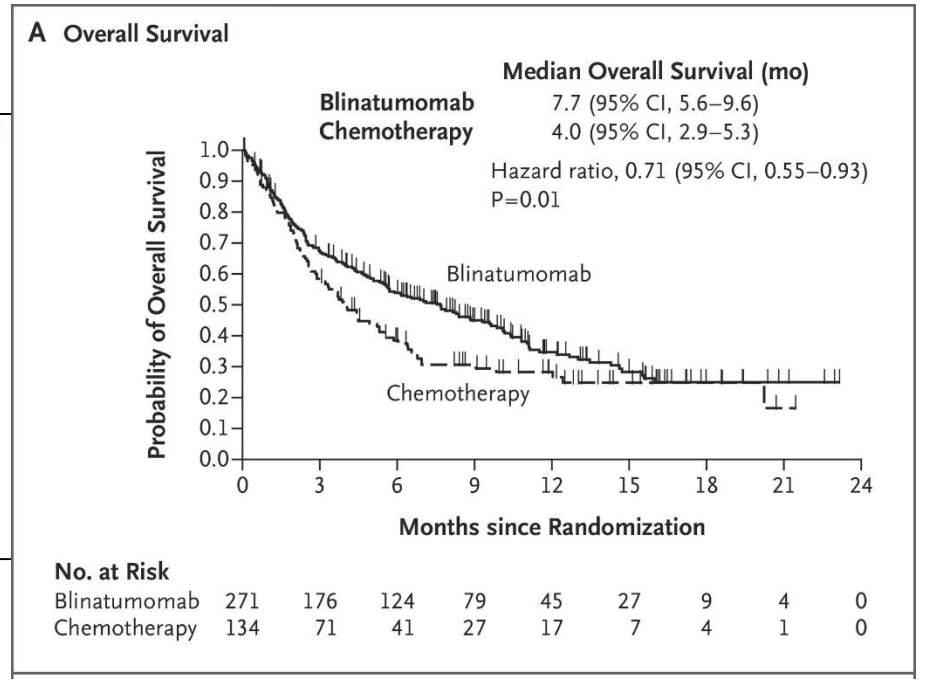
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





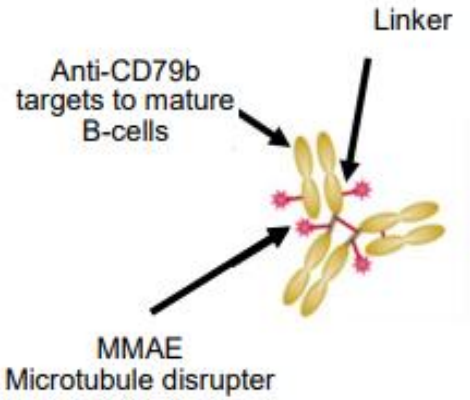
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

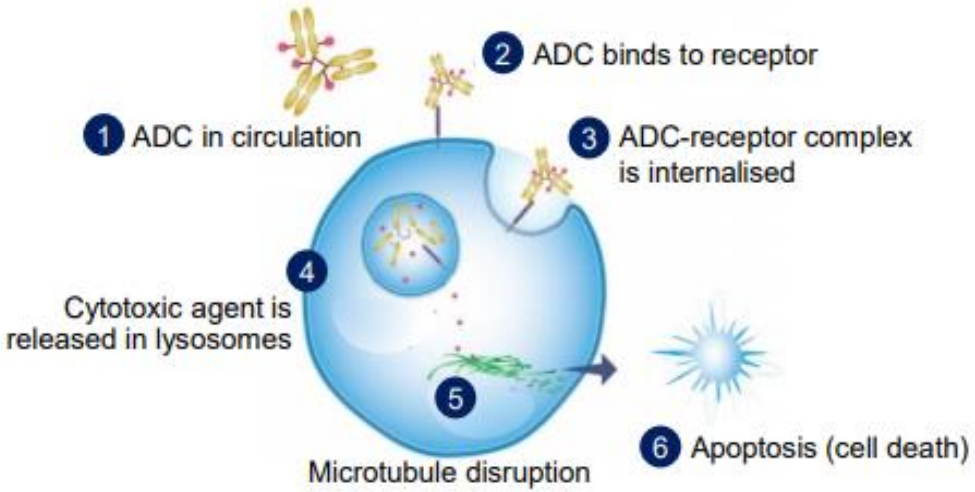
Antibody-drug conjugates (ADC)

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

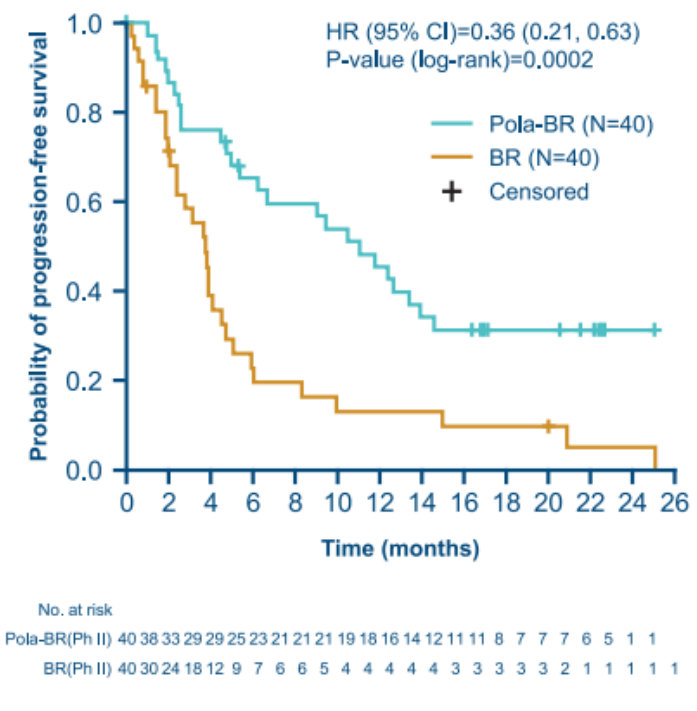
Slide credit: Tilly et al. ICML 2019

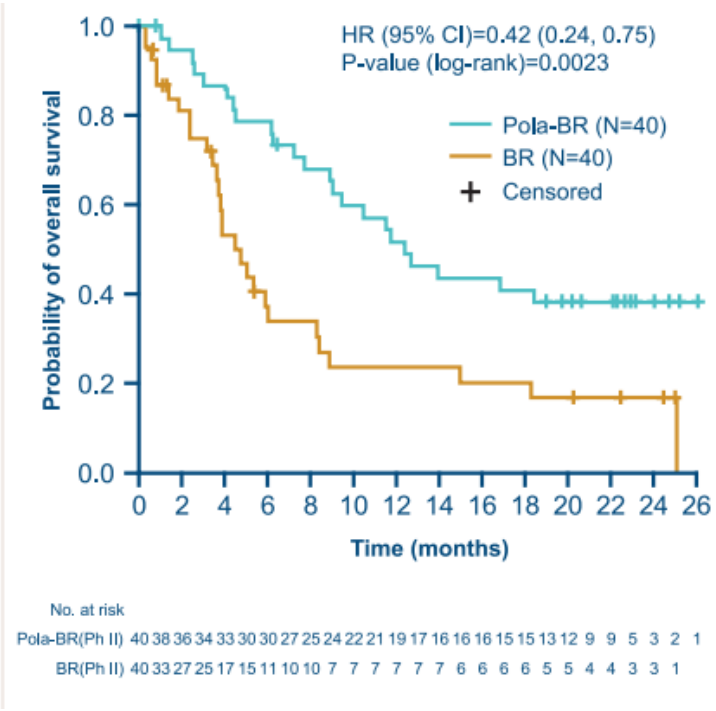
Polatuzumab vedotin: DLBCL

- 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

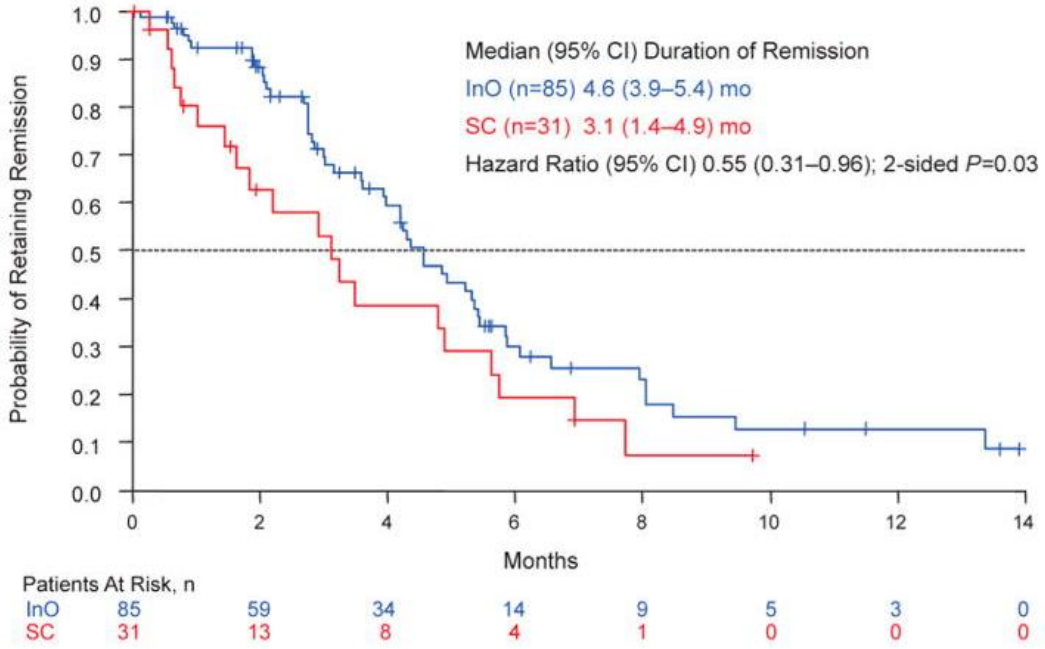


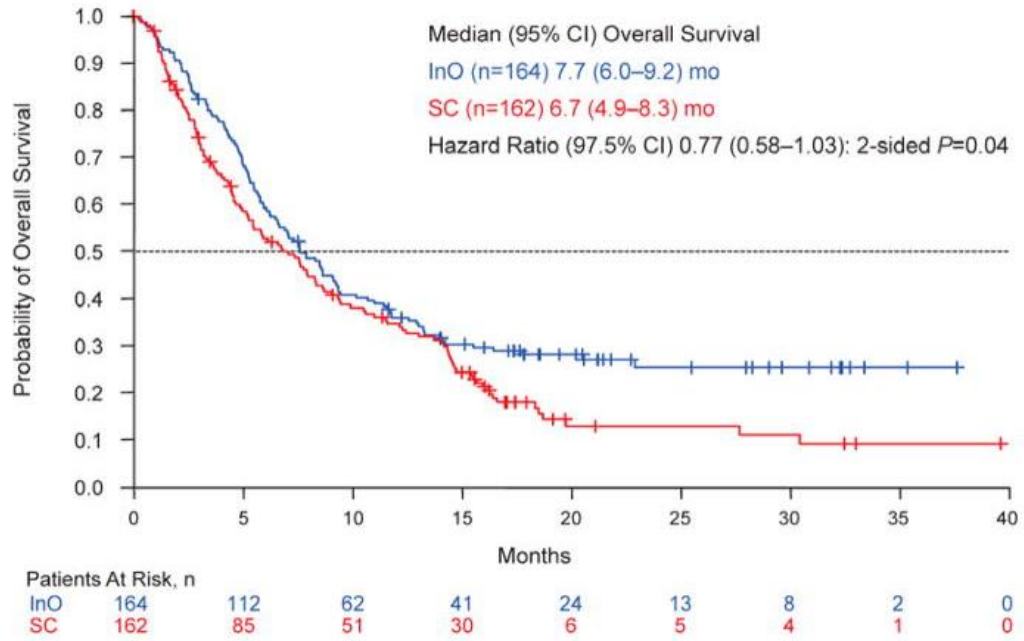


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



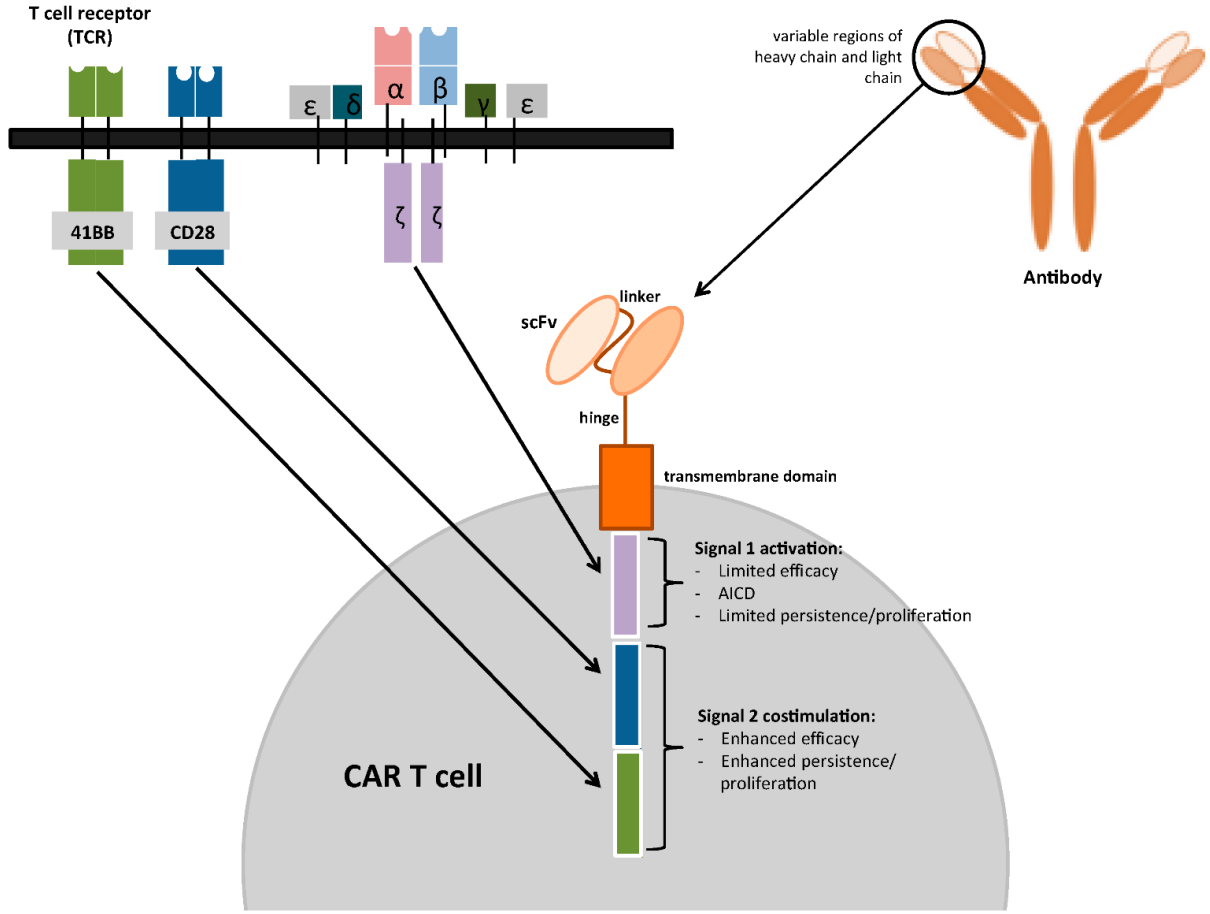


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

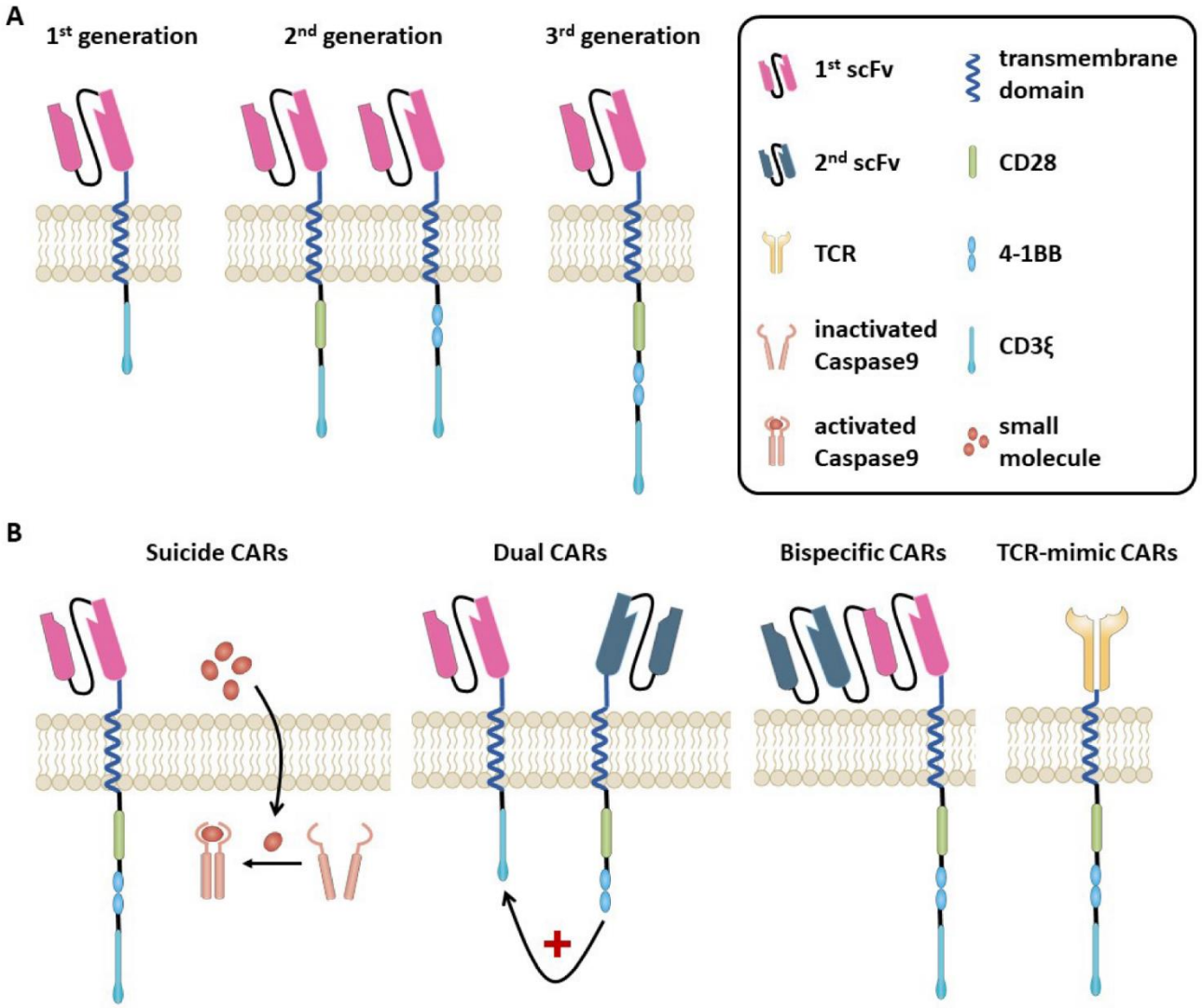
Chimeric antigen receptors

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



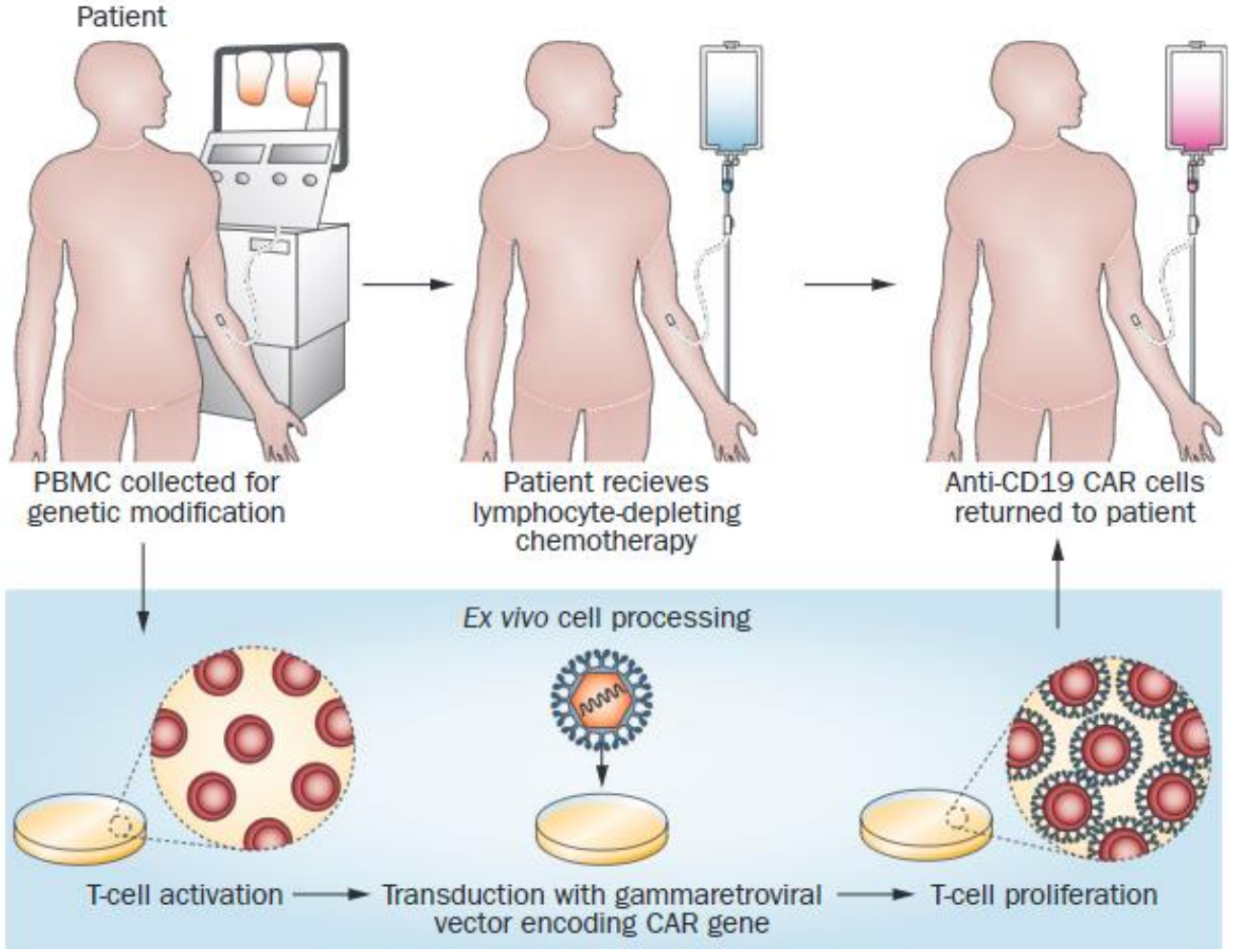
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

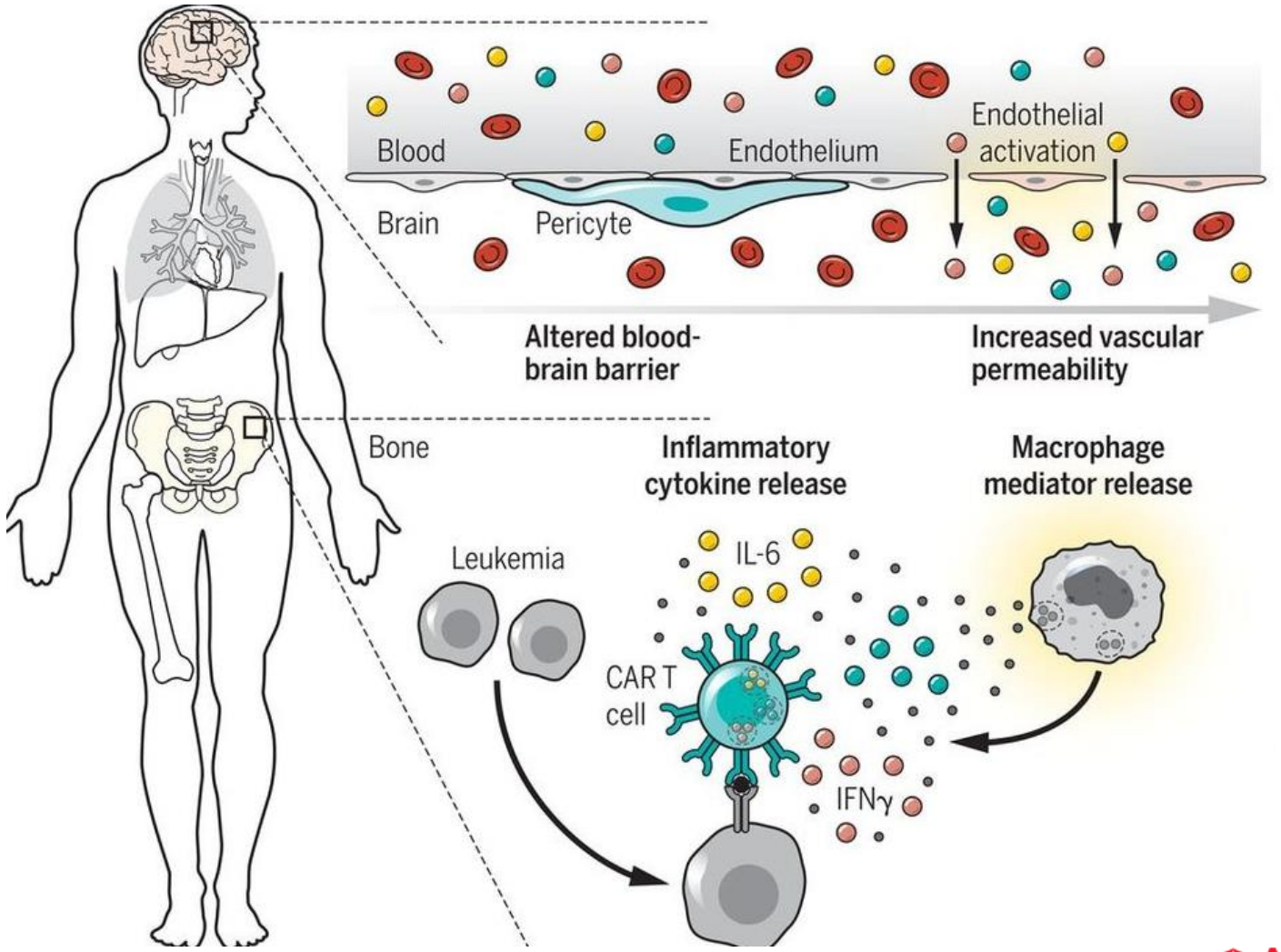


Kochenderfer, Nat Rev Clin Oncol 2013.

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

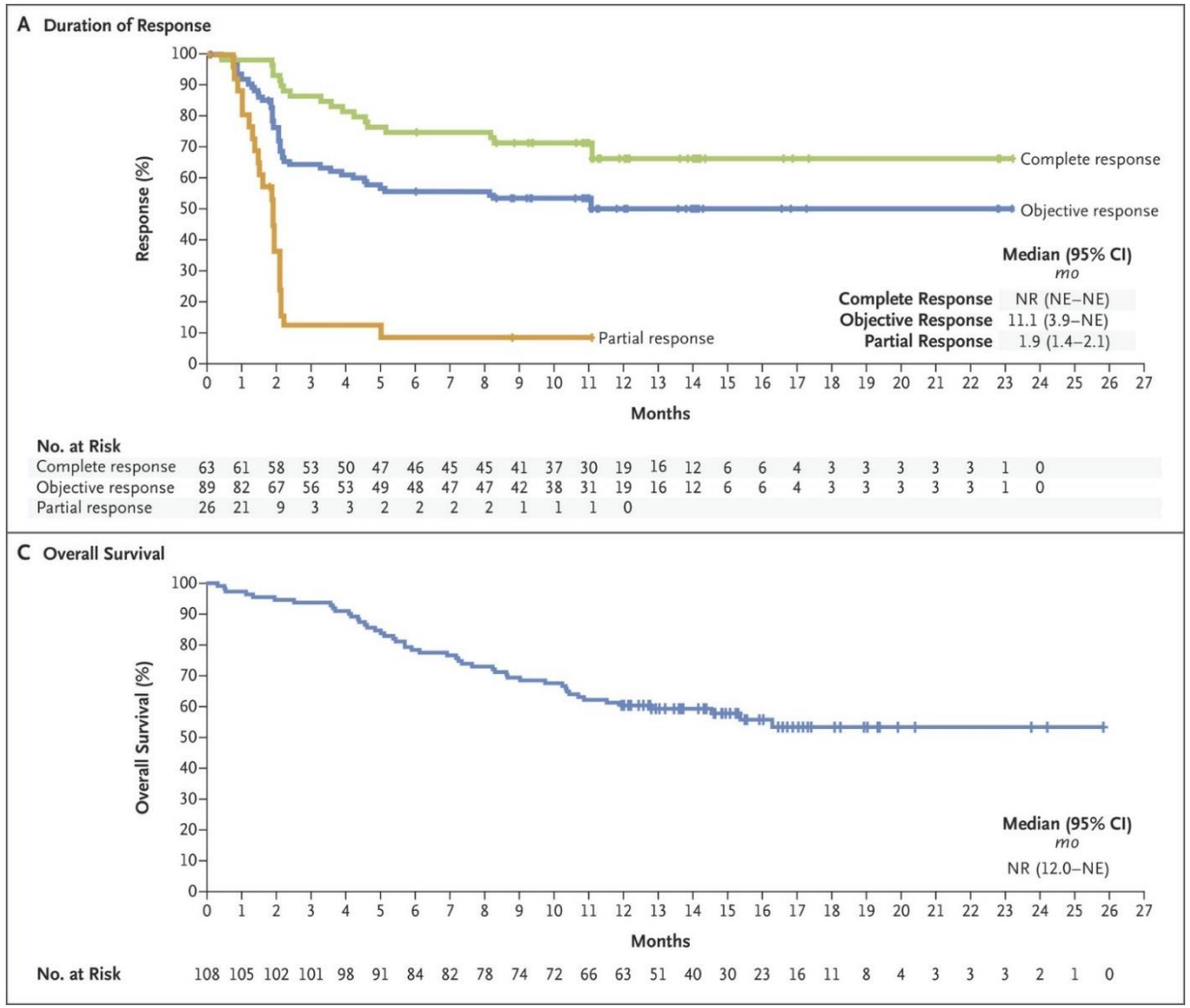
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight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

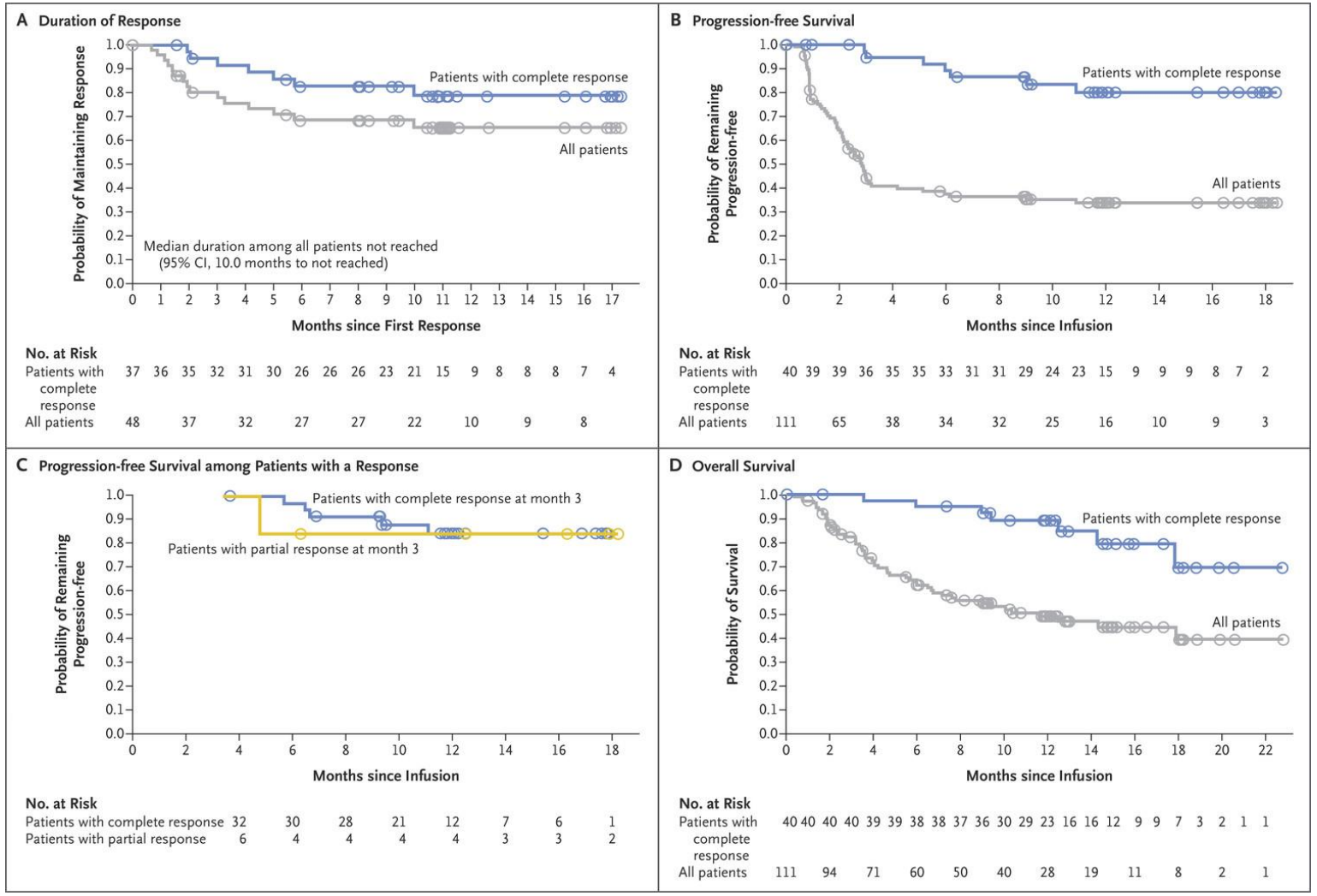
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

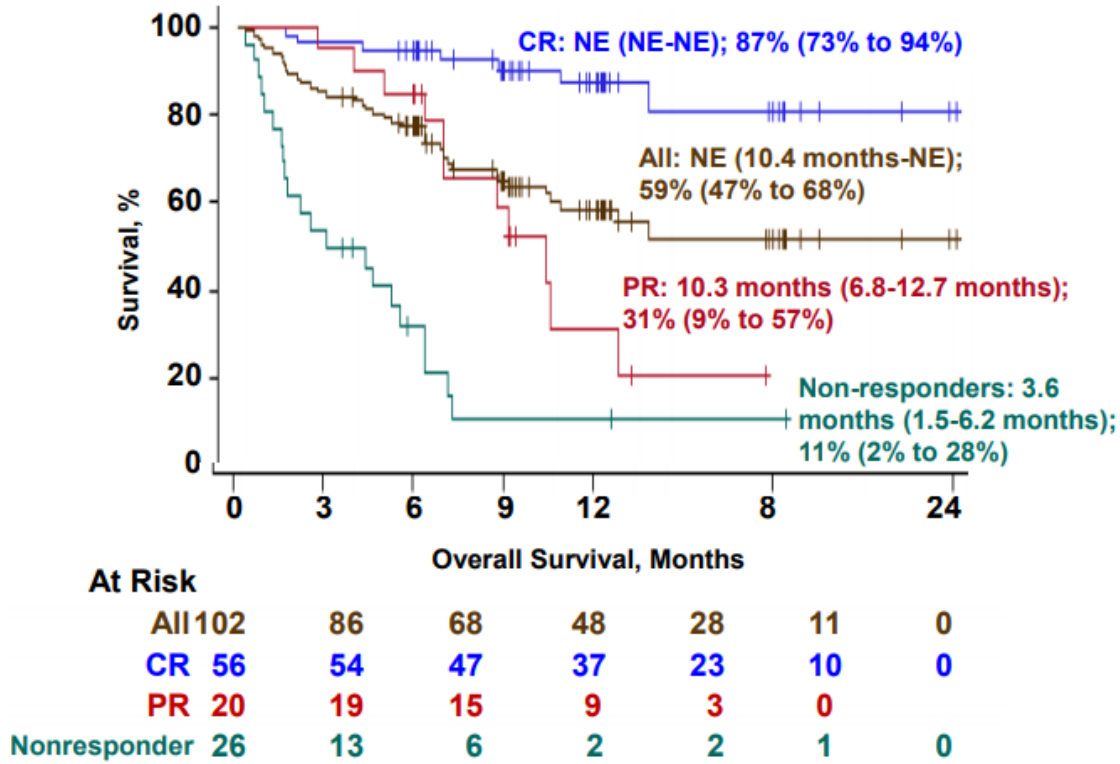
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

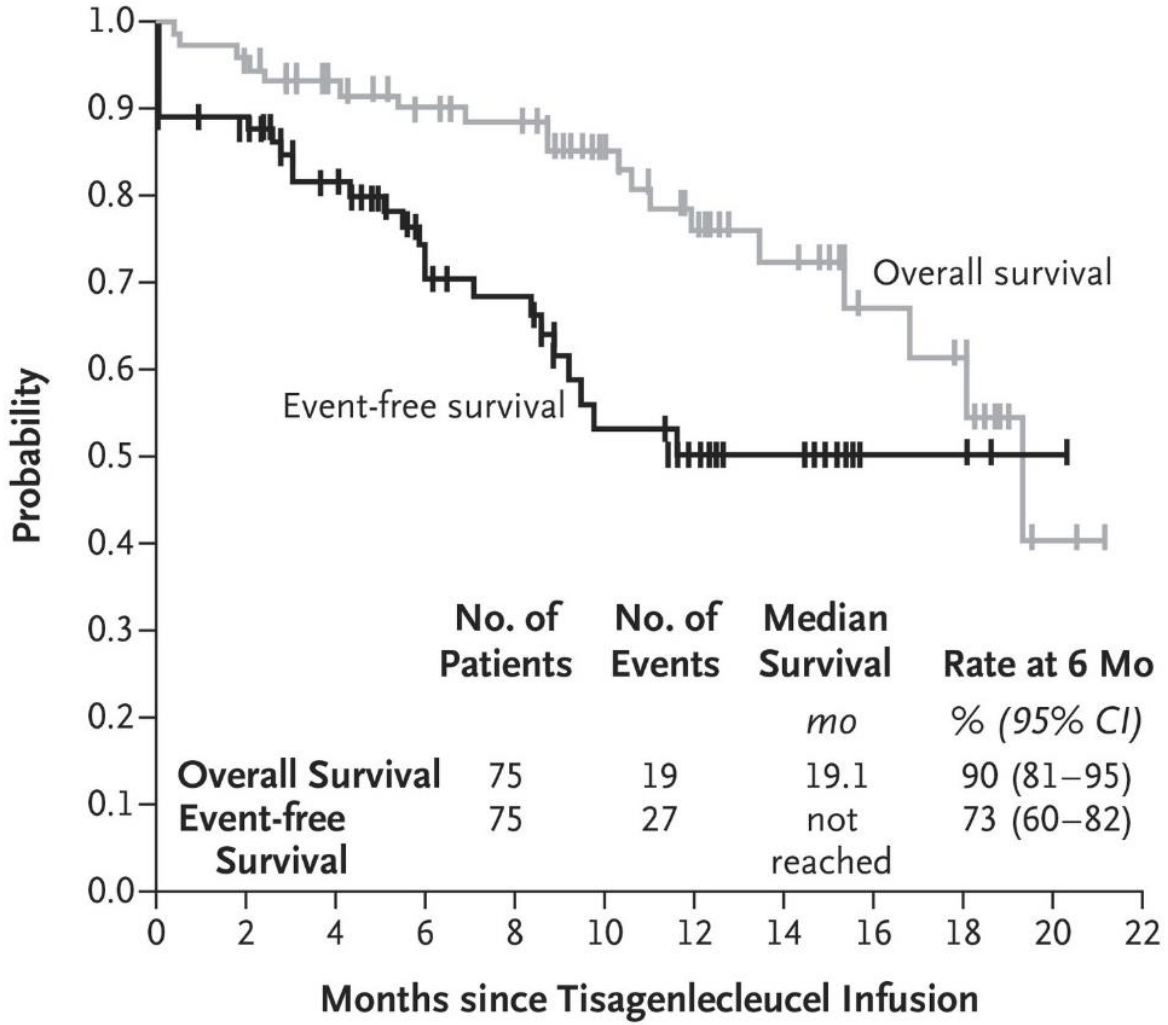
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

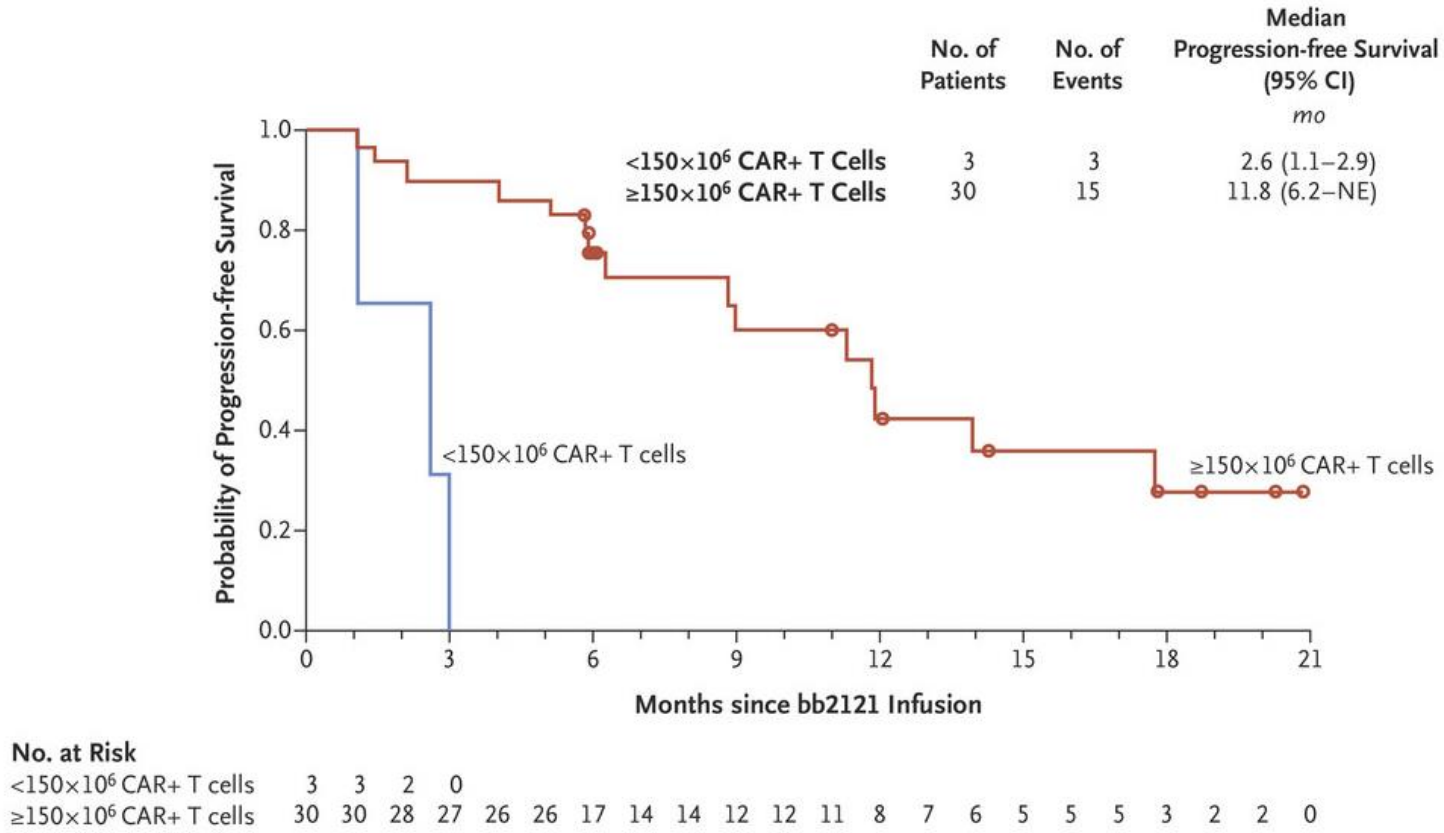


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

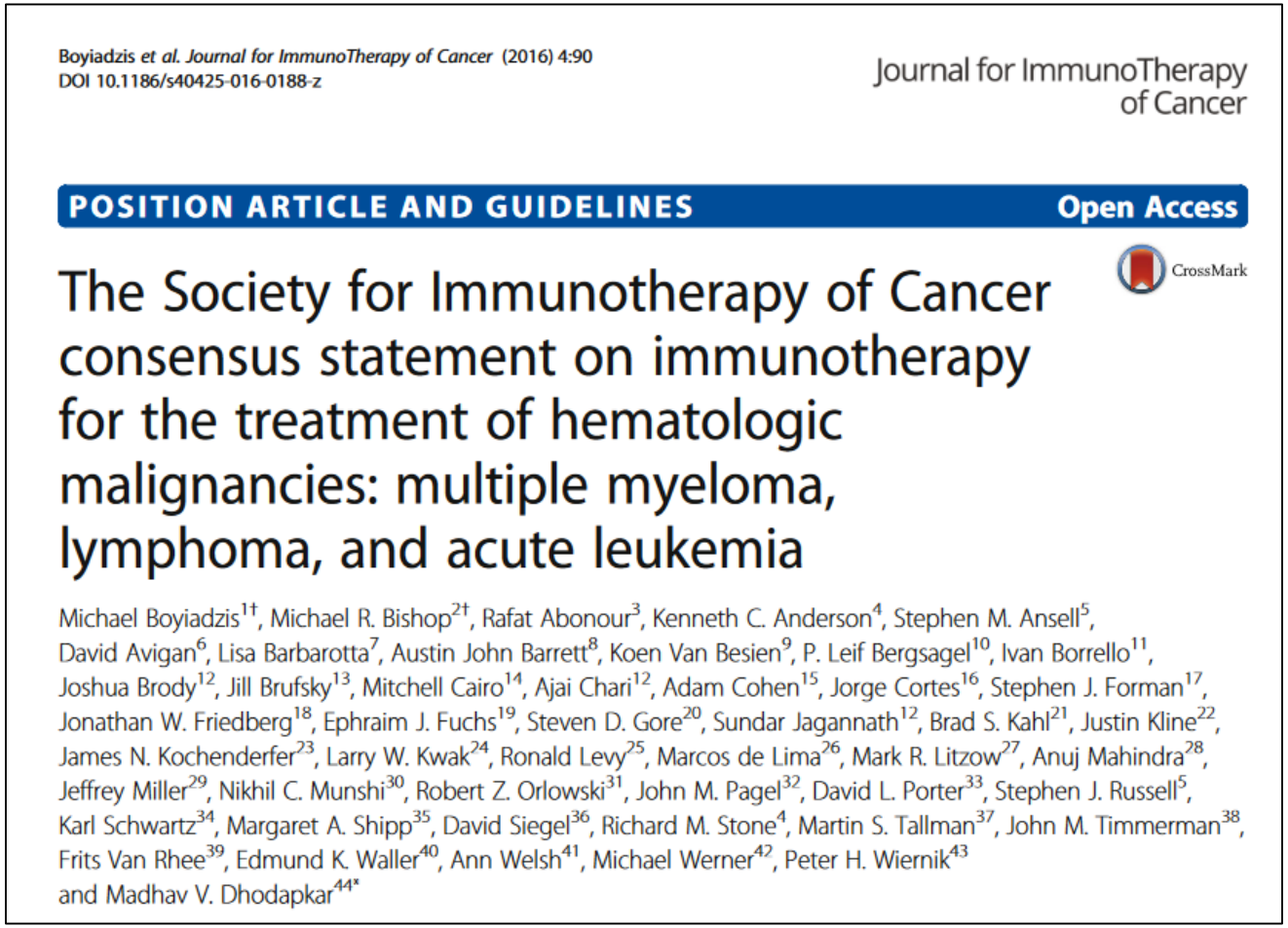


Raje, NEJM 2019.

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

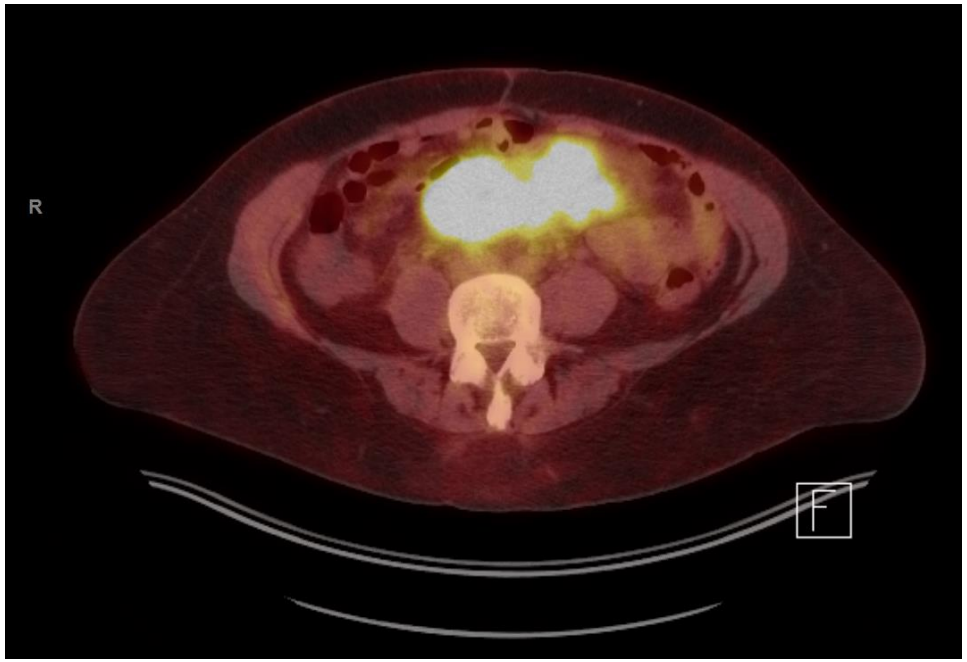
Case Study 1

- 44 year old female with a history of Stage IV follicular lymphoma s/p R-CHOP x 6 cycles with a partial response, followed by maintenance rituximab, now with evidence of transformed large B-cell lymphoma
- She initially presented with a 19 cm mesenteric mass with hepatosplenomegaly. Biopsy was consistent with follicular lymphoma, grade 1. She had bone marrow involvement. She tolerated 6 cycles of R-CHOP with a very good partial response. She was then started on maintenance rituximab.
- Three months after starting rituximab, she developed worsening abdominal pain. PET/CT showed extensive disease above and below the diaphragm with increasing size and activity of mesenteric adenopathy.
- She underwent laparoscopic biopsy of the mesenteric mass which was consistent with diffuse large B-cell lymphoma, germinal center type with high grade features. FISH was positive for t(14;18) but negative for MYC and BCL2 rearrangement.

Case Study 1

- She received 2 cycles of R-ICE. PET/CT after 2 cycles of R-ICE showed persistent FDG-avid mesenteric mass.
- PS: ECOG 1
- What would be your next step?

  A. Chimeric antigen receptor T-cell therapy
  B. Allogeneic stem cell transplant
  C. High-dose chemotherapy with autologous stem cell transplant
  D. Clinical trial



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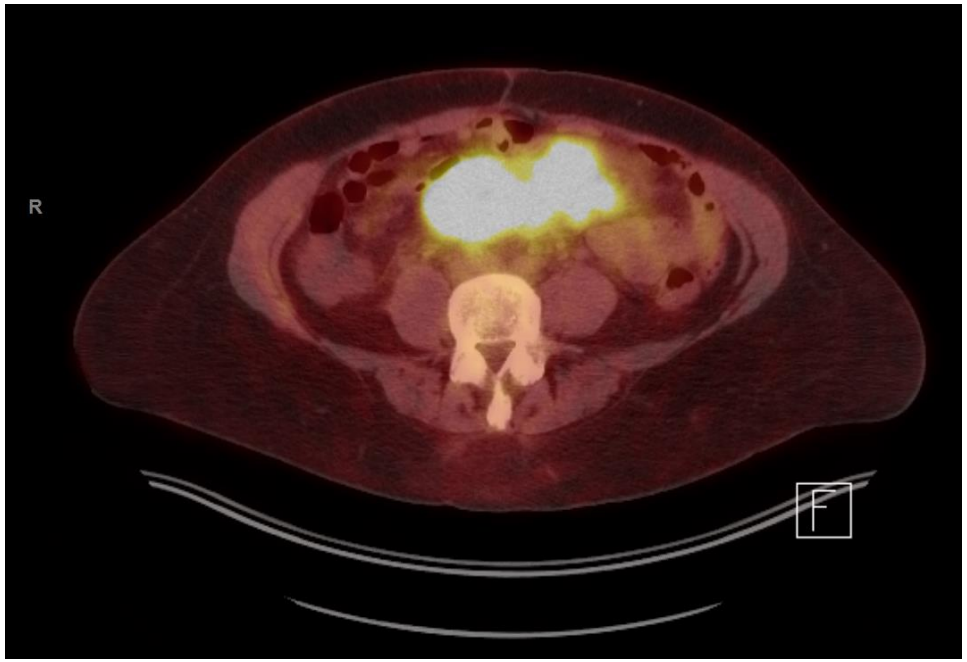
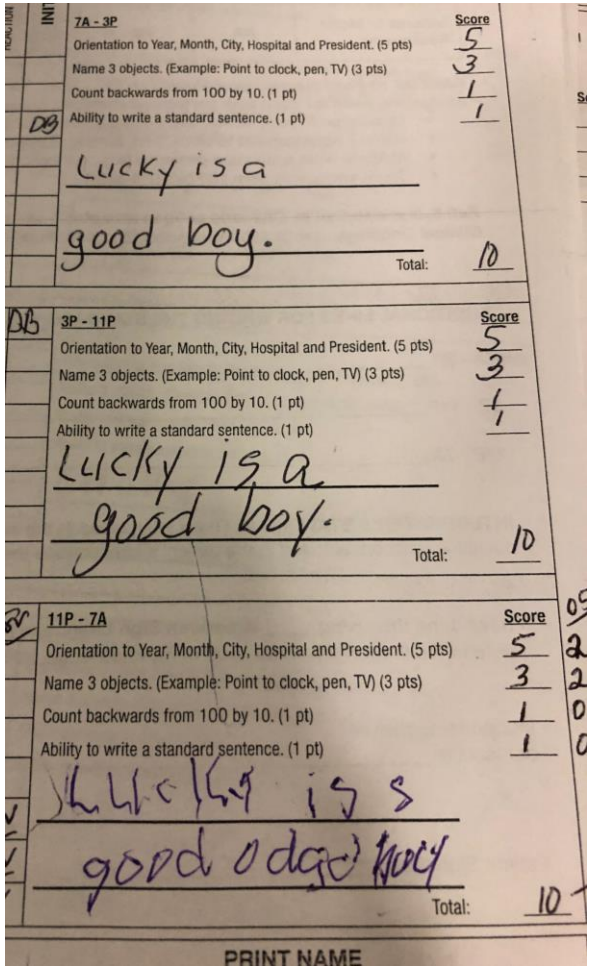


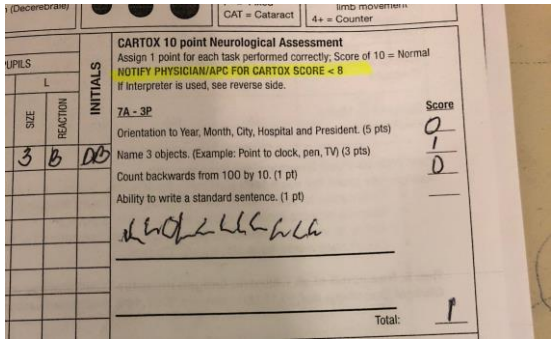
Case Study 1

- Received 1 cycle of R-DHAP as bridging therapy prior to CAR-T therapy (Axi-cel).
- Received fludarabine/cyclophosphamide conditioning chemotherapy followed by Axi-cel infusion.
- On day +3, the patient developed fevers (39 C) with hypotension (BP 90/55) but not requiring vasopressor support.
  - Grade 2 CRS based on the ASBMT consensus group grading system
  - Supportive care with acetaminophen, IV fluid bolus, antibiotics (ANC <500)
- Day +4: Persistent fevers, hypotension requiring vasopressor support, hypoxia requiring O2 by NRB mask
  - Grade 3 CRS
  - Transferred to ICU
  - Given tocilizumab with improvement of symptoms

Case Study 1

- Day +6, the patient developed aphasia, confusion, dysgraphia. Awakens only to tactile stimulus. No concurrent CRS.
- CARTOX 10 score was 1
- MRI brain: unremarkable. LP opening pressure: 15 cm H2O (normal).
- No seizure activity. Patient was on levetiracetam prophylaxis.
- What would you give this patient?
  - A. Tocilizumab
  - B. Corticosteroids
  - C. IV antibiotics
  - D. Antithymocyte globulin





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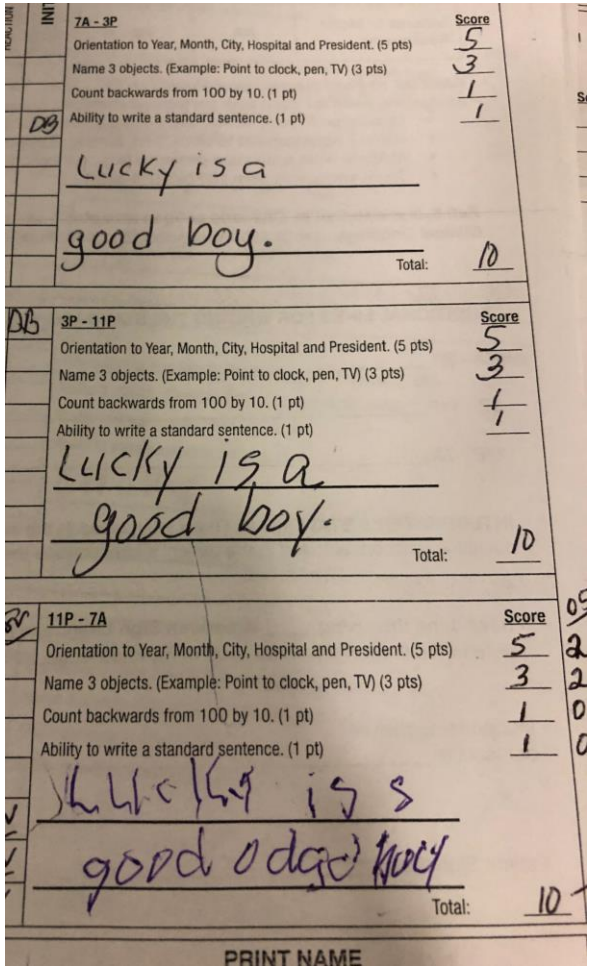
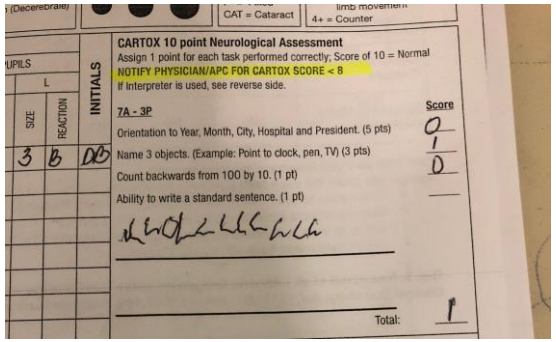
C. IV antibiotics
D. Antithymocyte globulin





Case Study 1

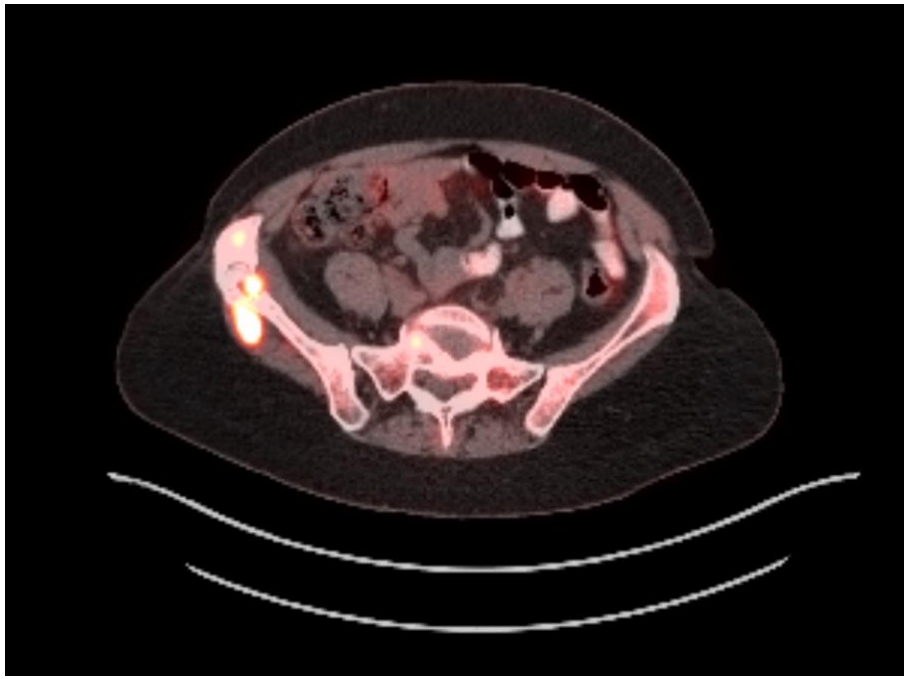
- Patient had resolution of her CNS symptoms. She was transferred out of the ICU and discharged a few days later.
- Repeat PET/CT on day +30 showed a partial response (smaller mesenteric mass with lower SUV) with Deauville score of 4.
- Patient went on to receive radiation therapy to the mesenteric mass and systemic pembrolizumab.
- Repeat PET/CT showed no FDG avid lesions/complete metabolic response

Case Study 2

- 42 year old female with history of sarcoidosis with non-ischemic cardiomyopathy (LVEF 25-30%) presenting with relapsed/refractory Stage IV DLBCL, non-GCB subtype (BM involvement).
- Initially presented with right sided hip pain and was found to a right hip mass, which was biopsied and was consistent with DLBCL, non-GCB subtype.
- Received R-CVP x 4 cycles with progressive disease
- R-GemOx x 6 cycles with complete metabolic response . Patient was not considered a transplant candidate due to her NICM/HFrEF.
- 3 months after completing R-GemOx, the patient developed worsening right hip pain. PET/CT showed increased FDG avid right iliac mass and abdominopelvic lymphadenopathy.

Case Study 2

- Biopsy of the right iliac mass was consistent with DLBCL, non-germinal center subtype. CD30 negative.
- FISH negative for BCL2, BCL2, and MYC rearrangements.
- What would you use to treated her relapsed/refractory DLBCL?
    A. Polatuzumab vedotin-piiq, bendamustine, rituximab
    B. Chimeric antigen receptor T-cell therapy
    C. Allogeneic stem cell transplant
    D. Brentuximab vedotin



Case Study 2

- Patient started on polatuzumab vedotin-piiq with bendamsutine and rituximab
- Fatal and/or serious infections have occurred in patients treated with polatuzumab vedotin
  - Package insert recommends prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus through treatment with polatuzumab vedotin.
- The patient was started on acyclovir and trimethoprim-sulfamethoxazole prophylaxis
- She has tolerated 3 cycles and will be getting an interim scan to assess her response.