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

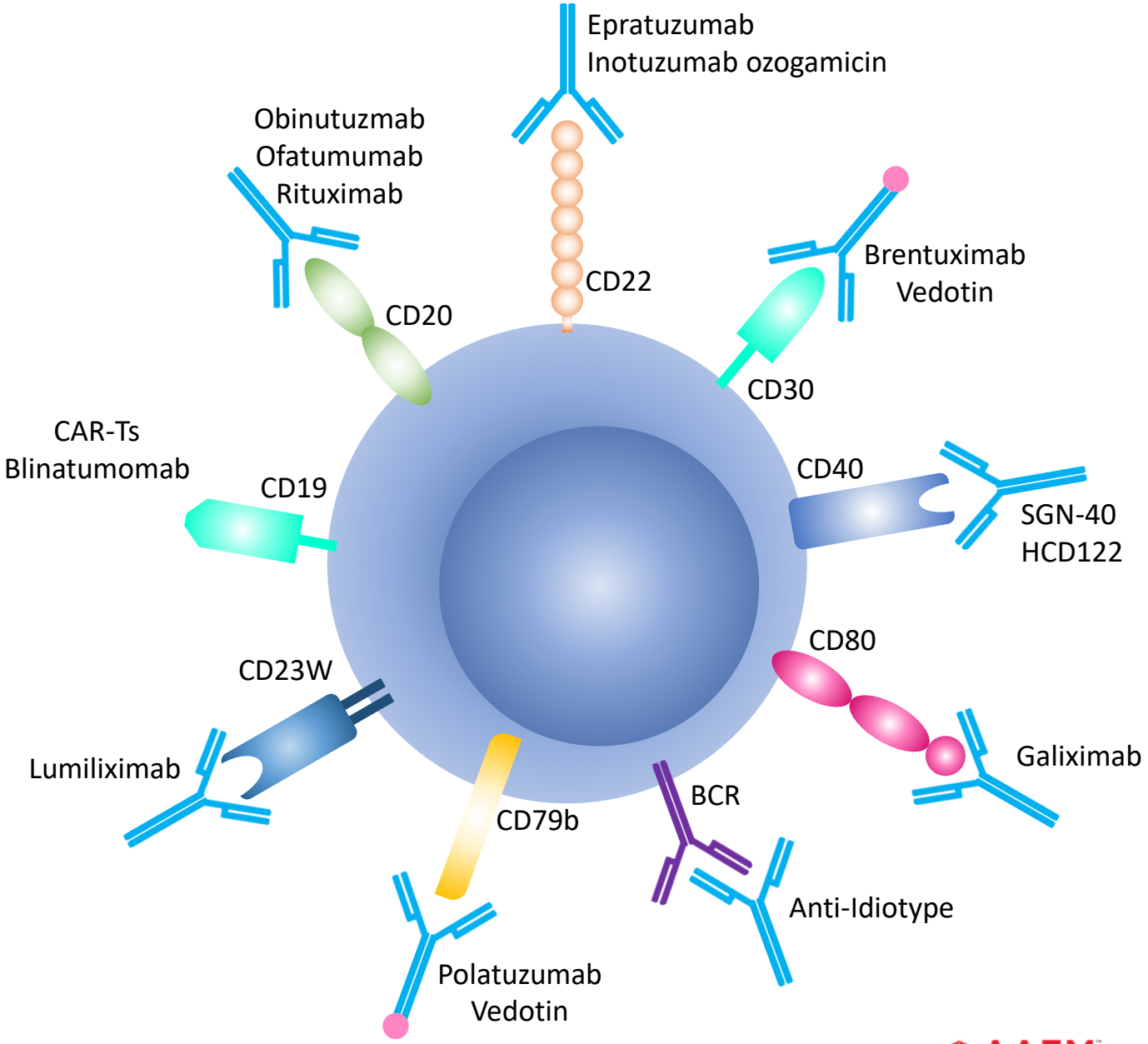
ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- Partner Consulting Fees: Morphosys
- Partner Contracted Research: Juno therapeutics, Rhizen, Takeda, TG Therapeutics, Bayer, Cyteir, Incyte, Genentech
- I will NOT be discussing non-FDA approved indications during my presentation.



Checkpoint inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

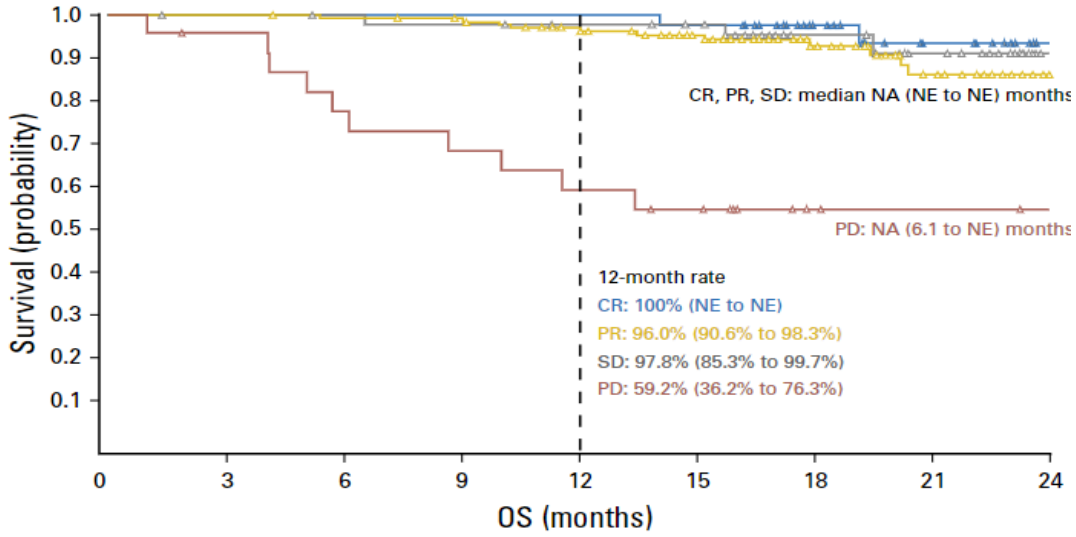
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies (any relapse/refractory adult)	200 mg q3W adults or 400 mg q6w 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 or 400 mg q6w 2 mg/kg (up to 200 mg) q3w (pediatric)

Checkpoint inhibitors: Hodgkin Lymphoma

Checkmate-205

ORR = 69%

CR = 16%



No. at risk:

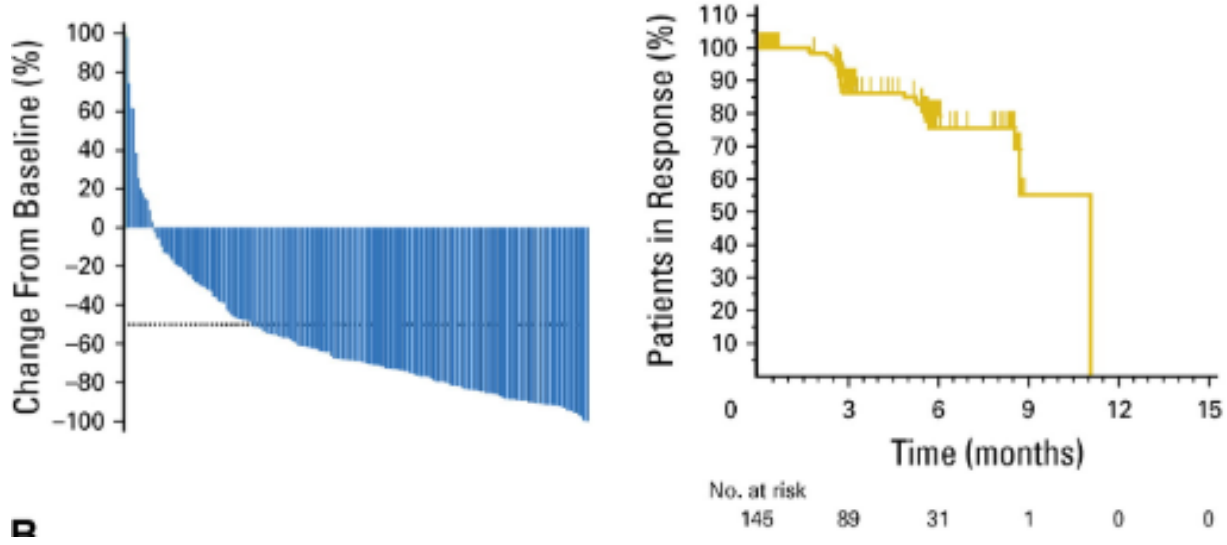
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

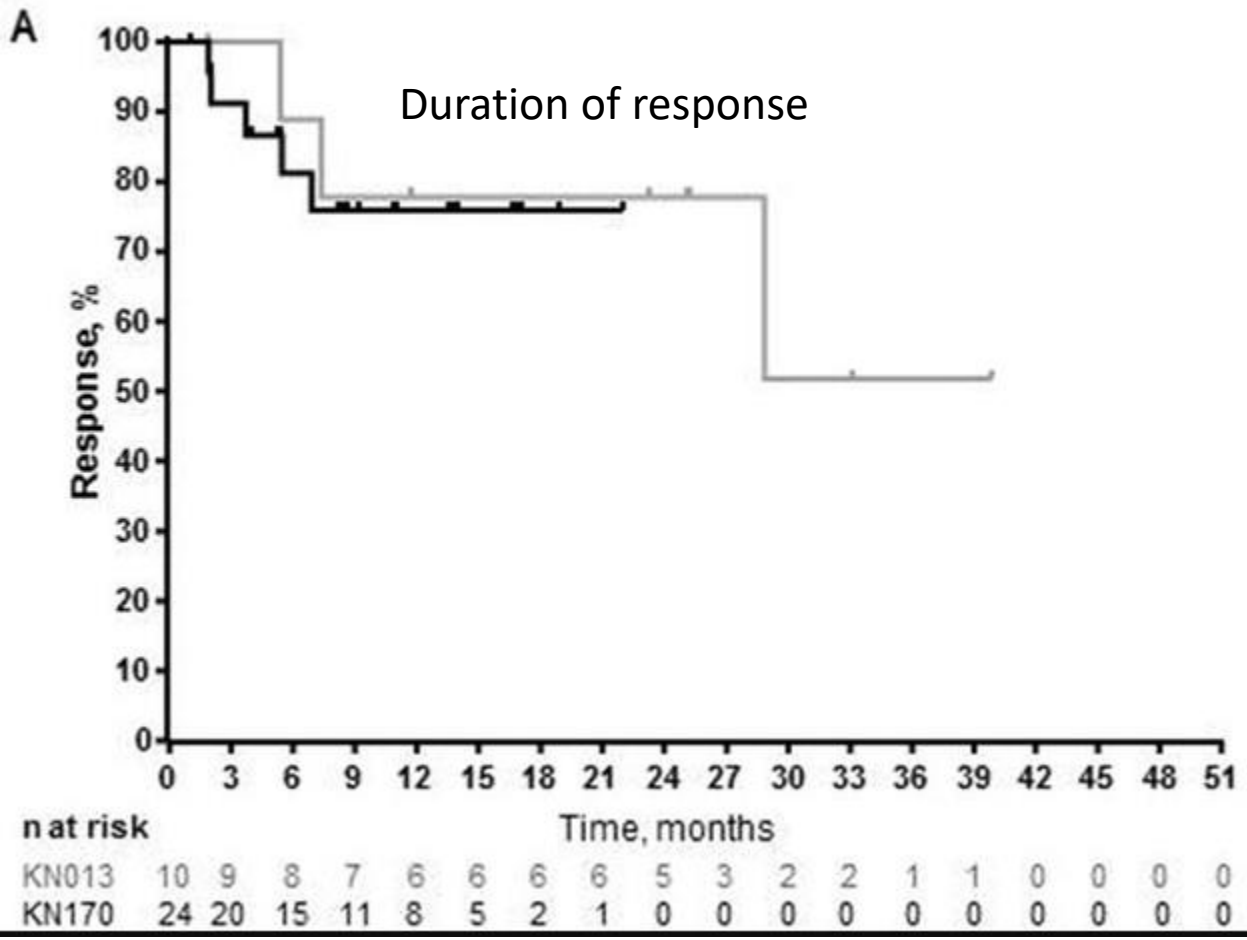
CR = 22.4%

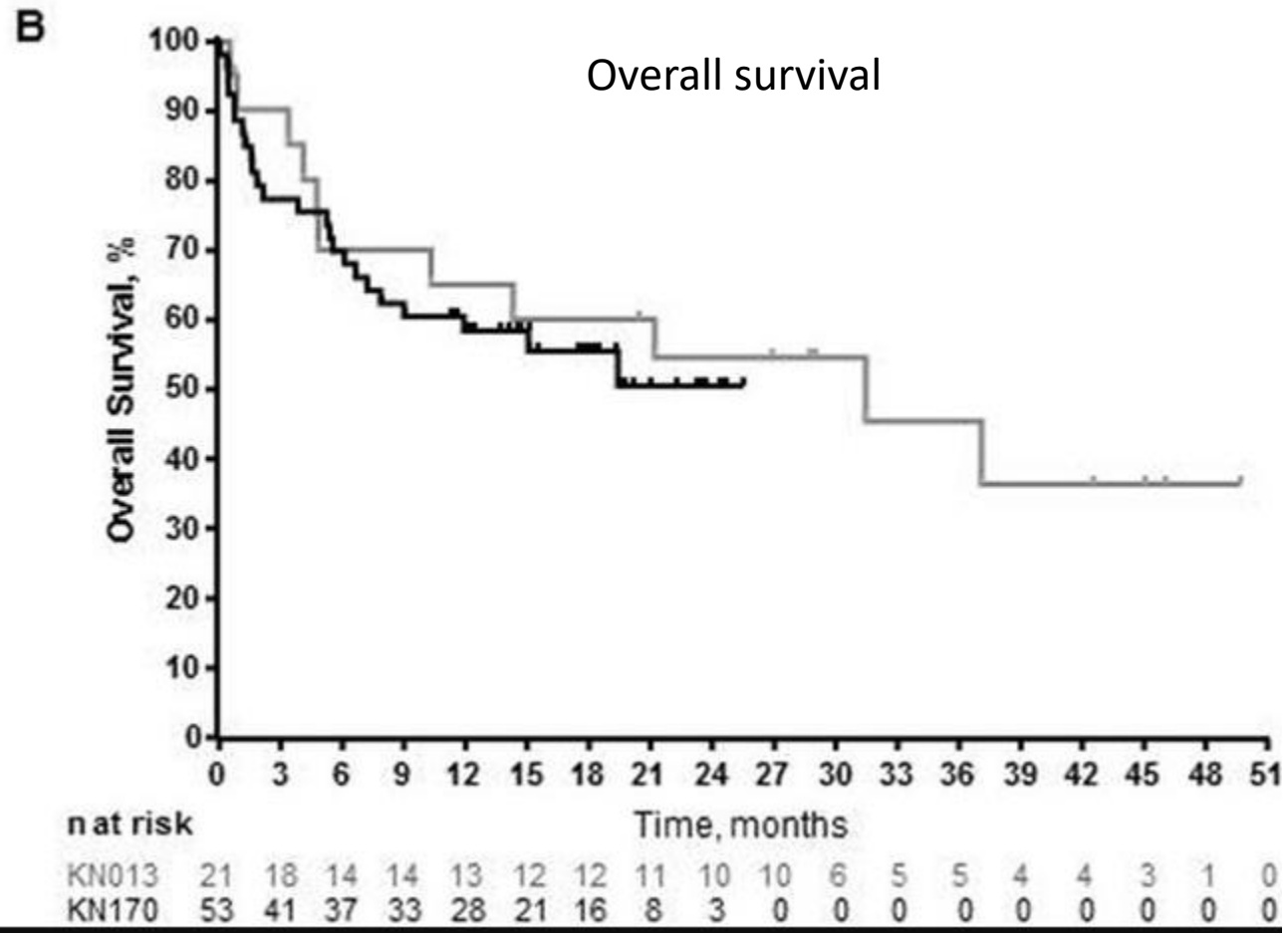
Activity seen regardless of PD-L1 expression



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

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

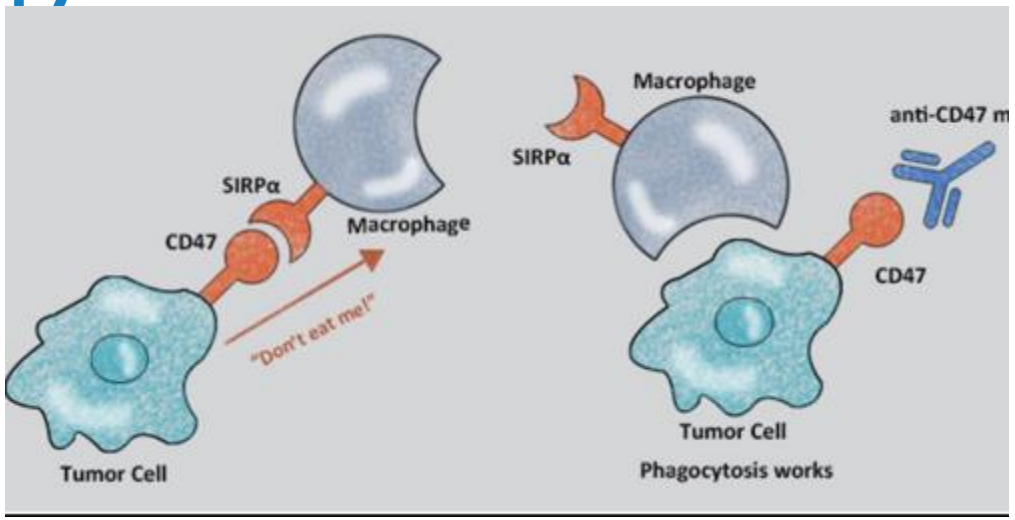


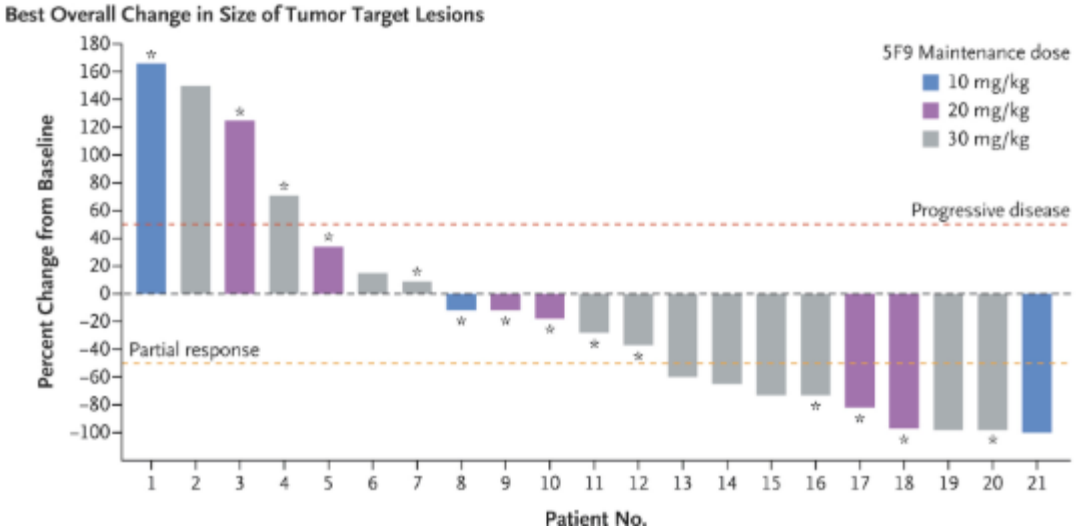


Armand, Blood 2018.

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%



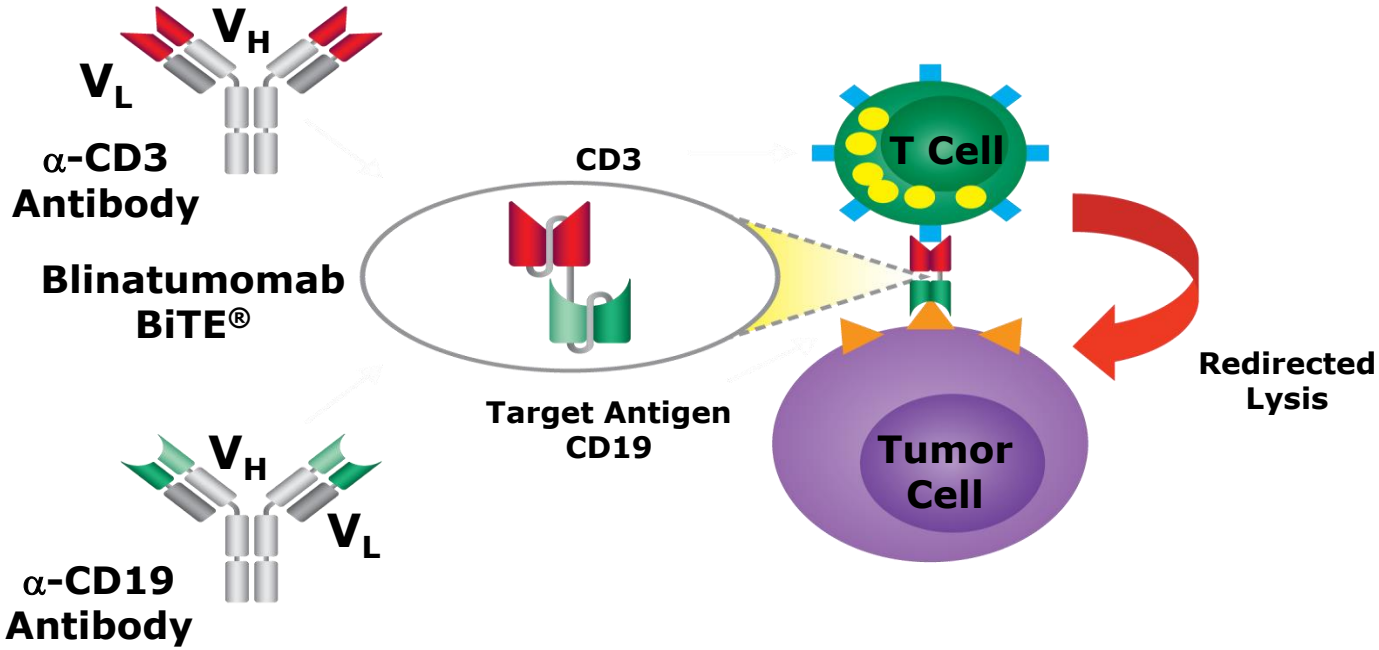


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

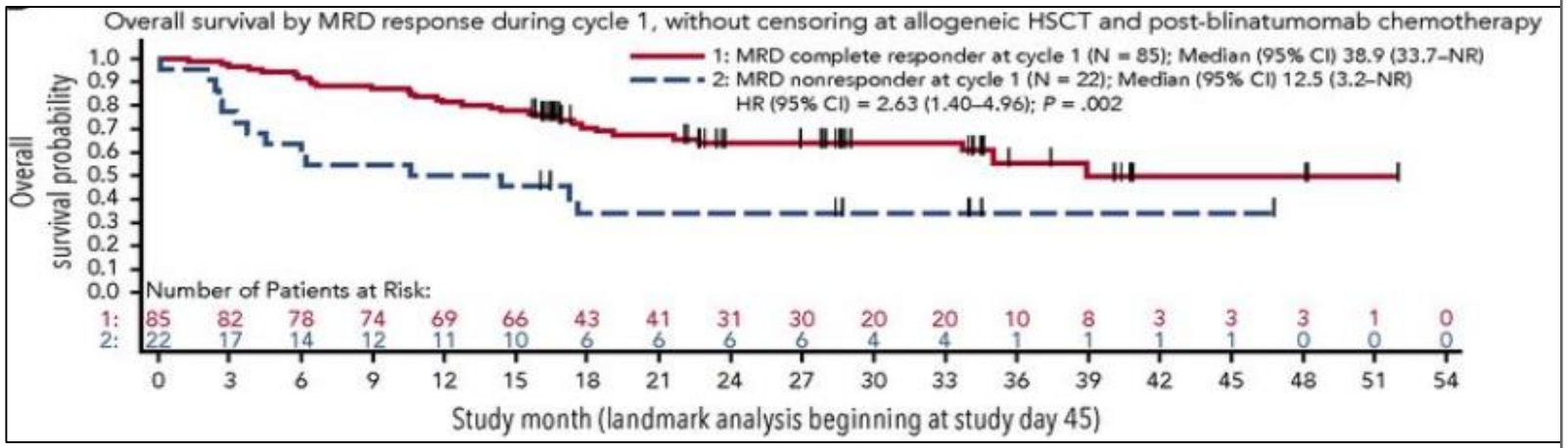
BiTE (Blinatumomab) Therapy

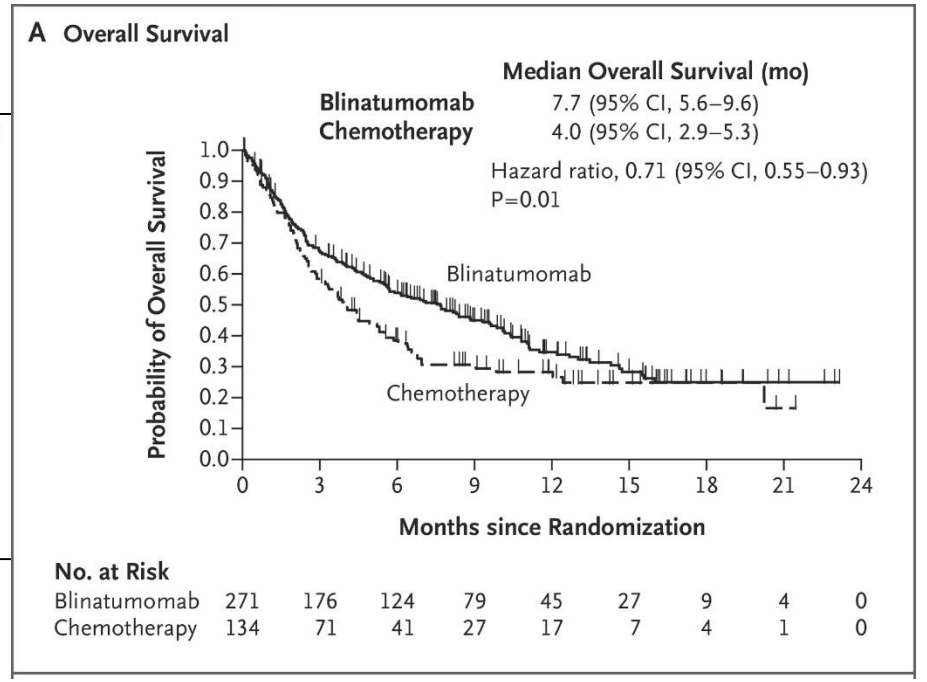
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





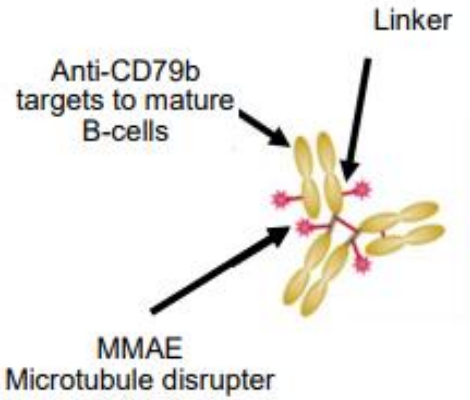
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

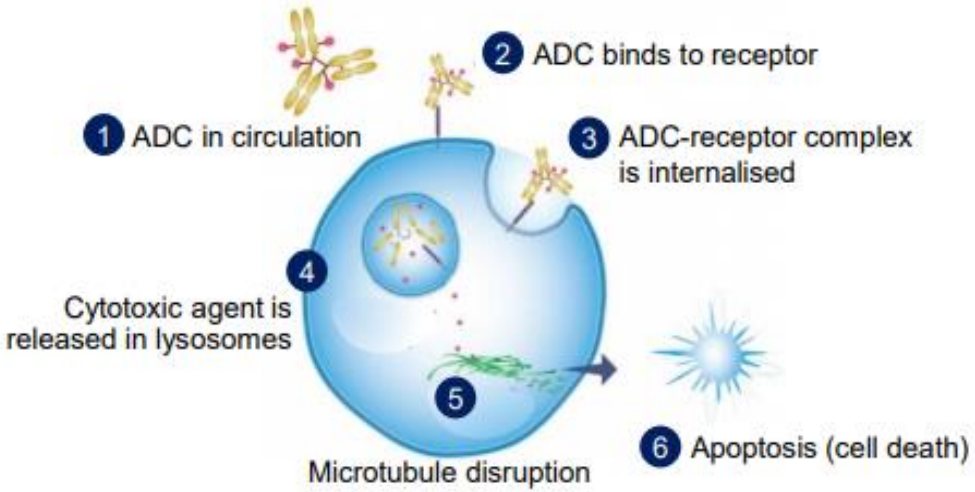
Antibody-drug conjugates (ADC)

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

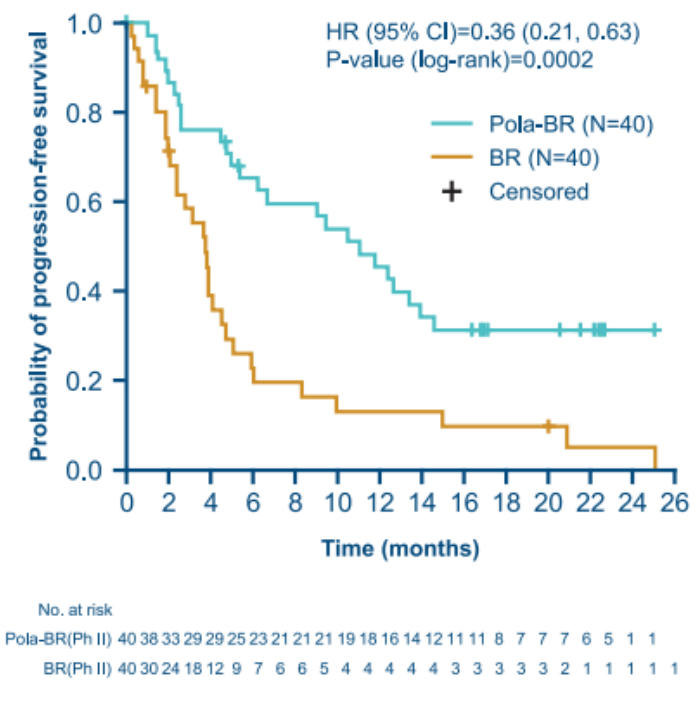
Slide credit: Tilly et al. ICML 2019

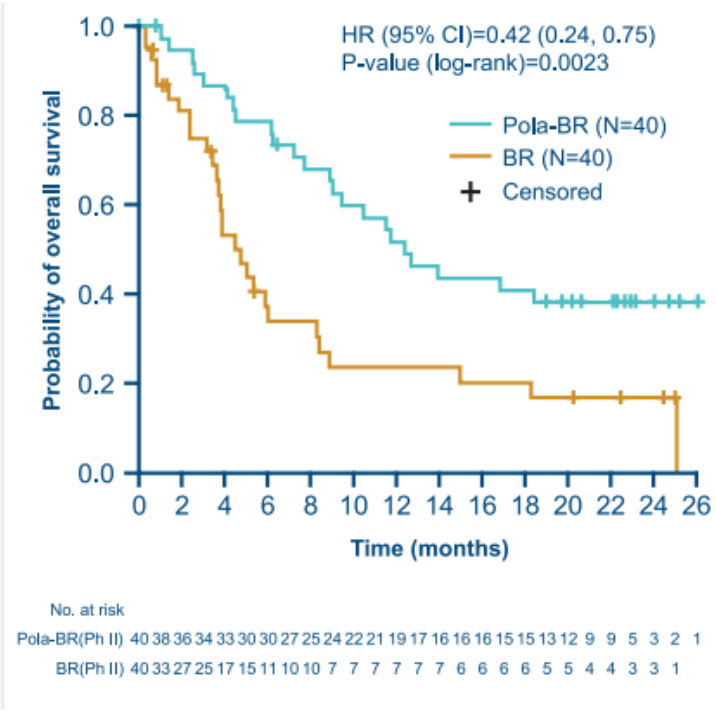
Polatuzumab vedotin: DLBCL

- 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

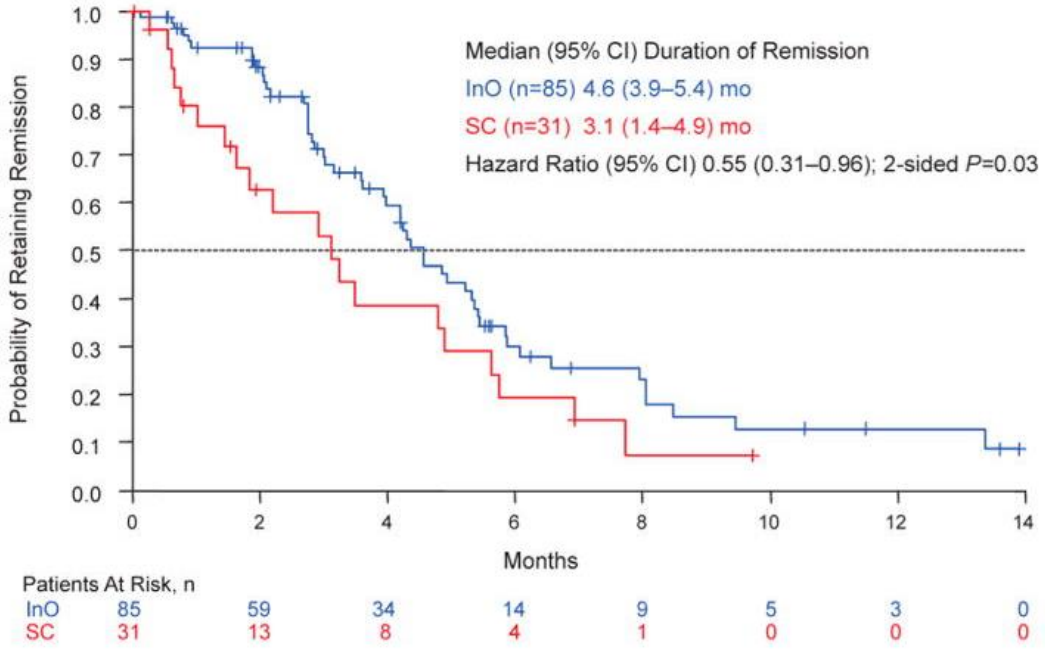


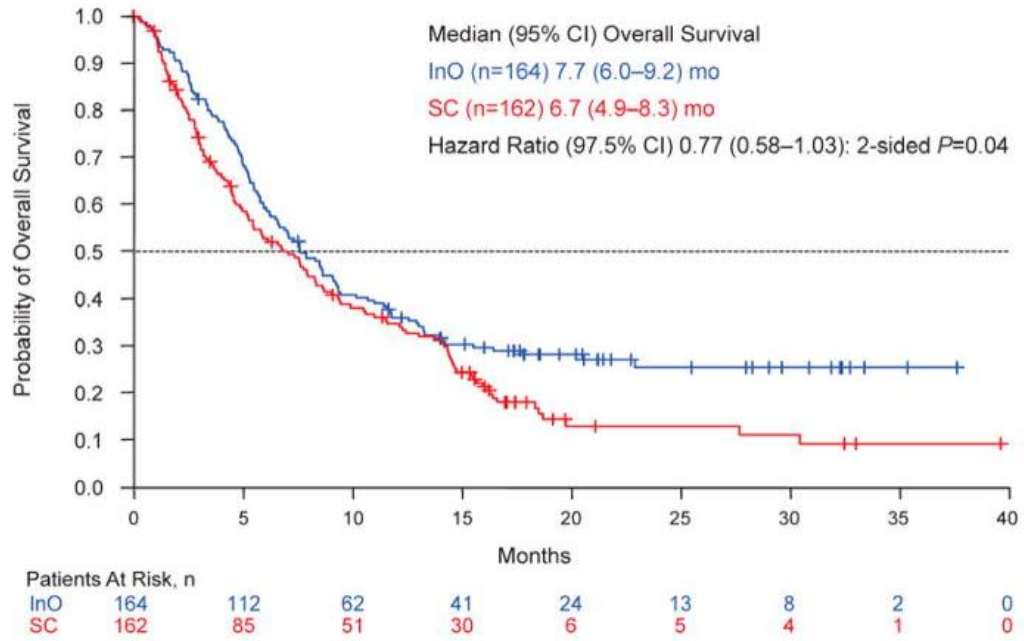


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



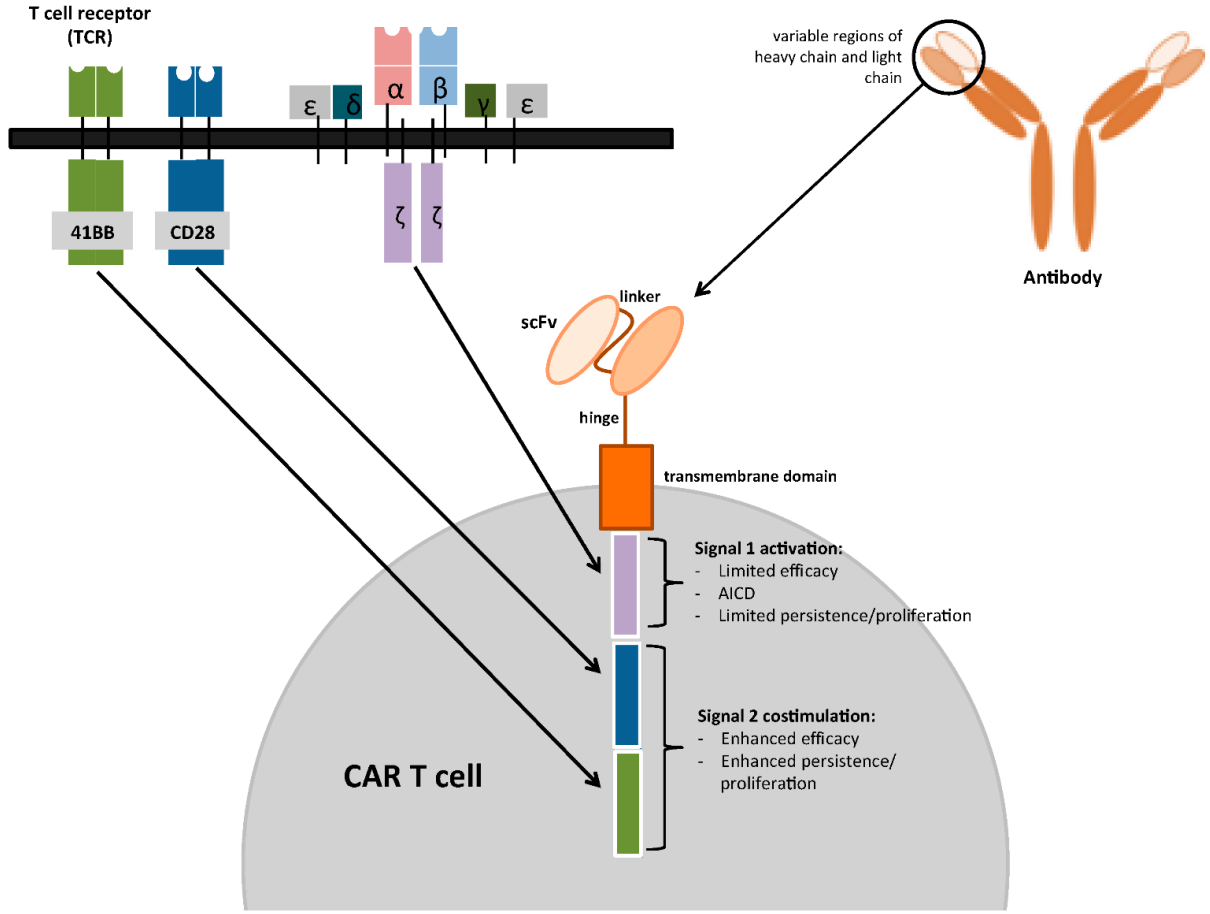


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

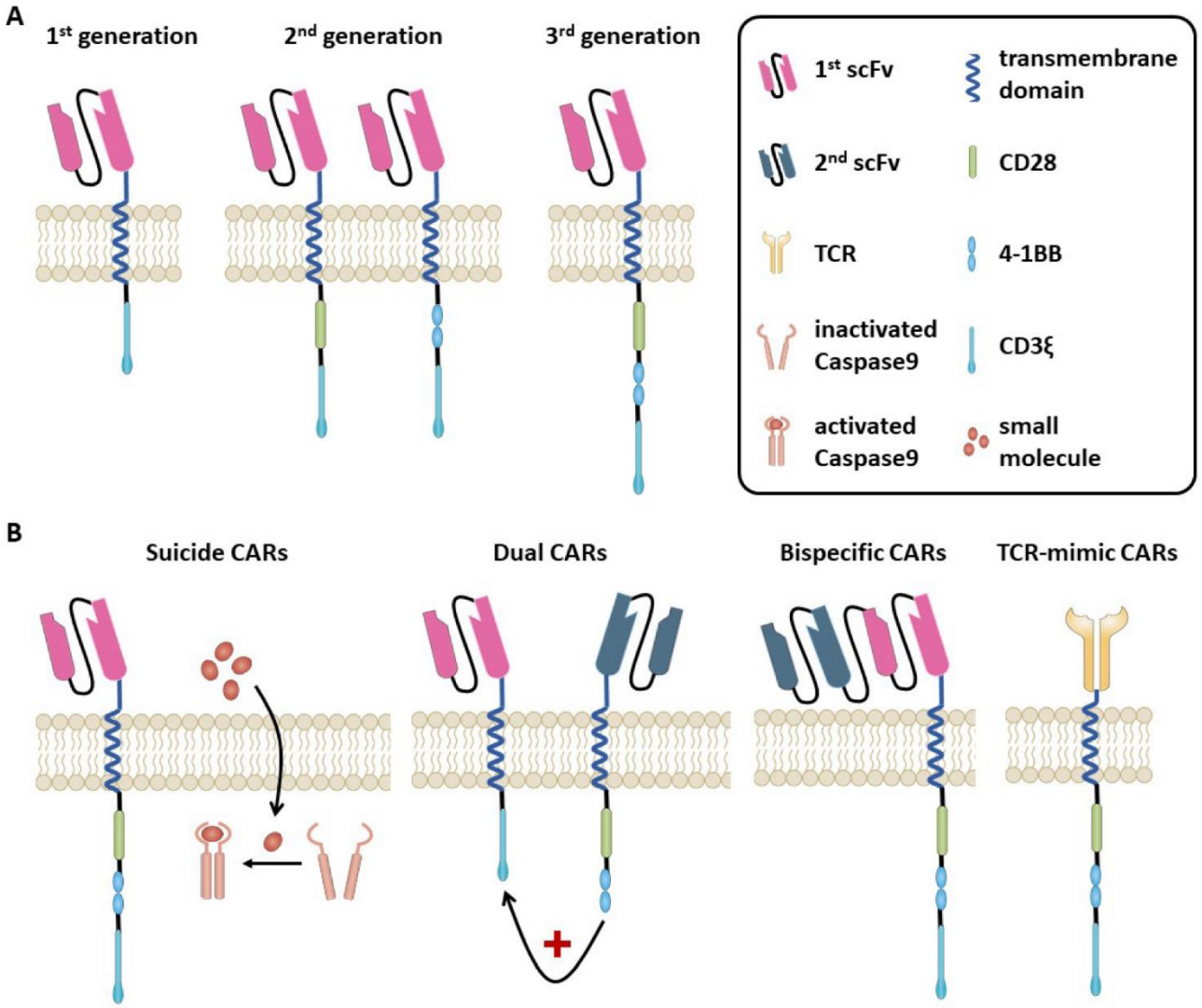
Chimeric antigen receptors

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



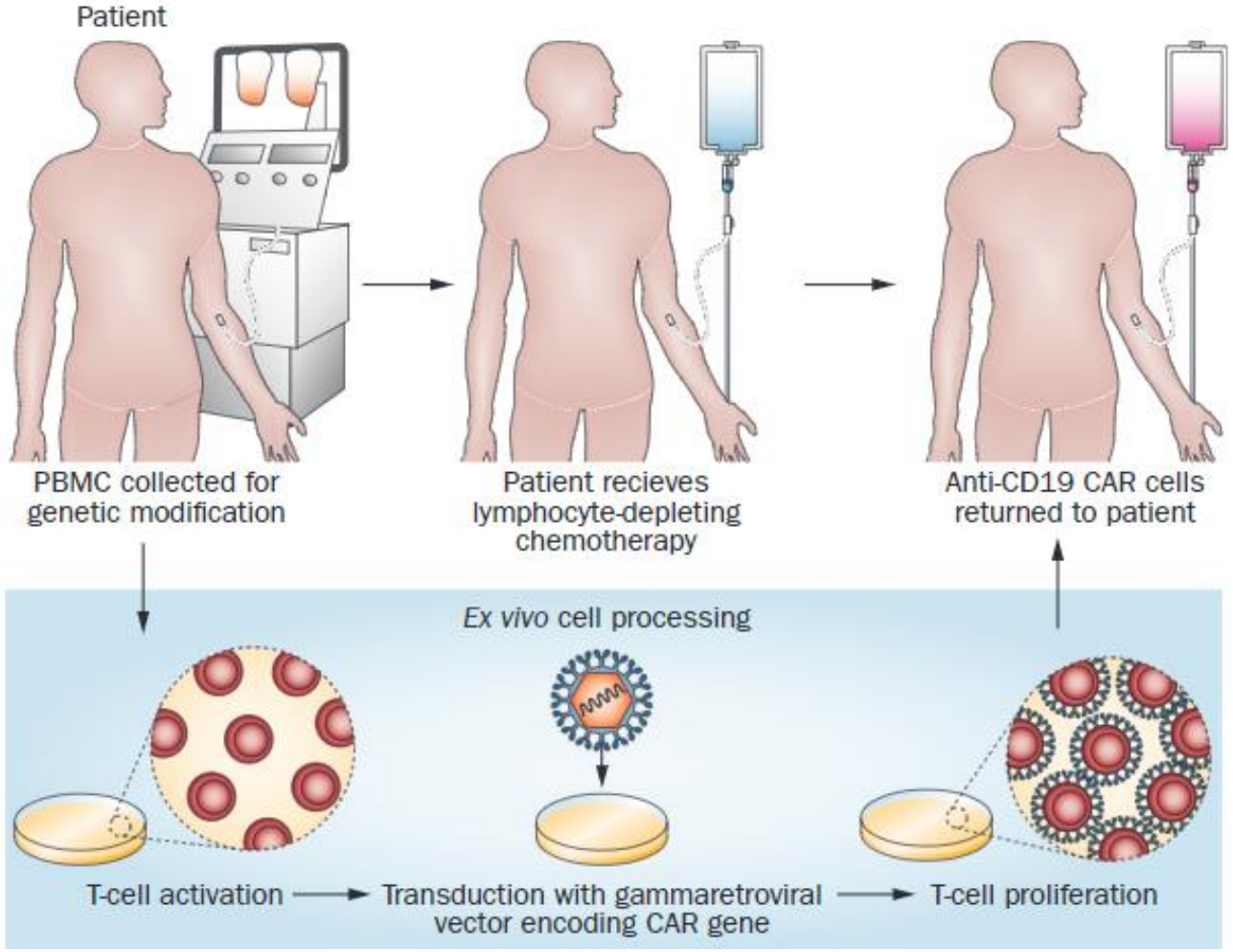
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

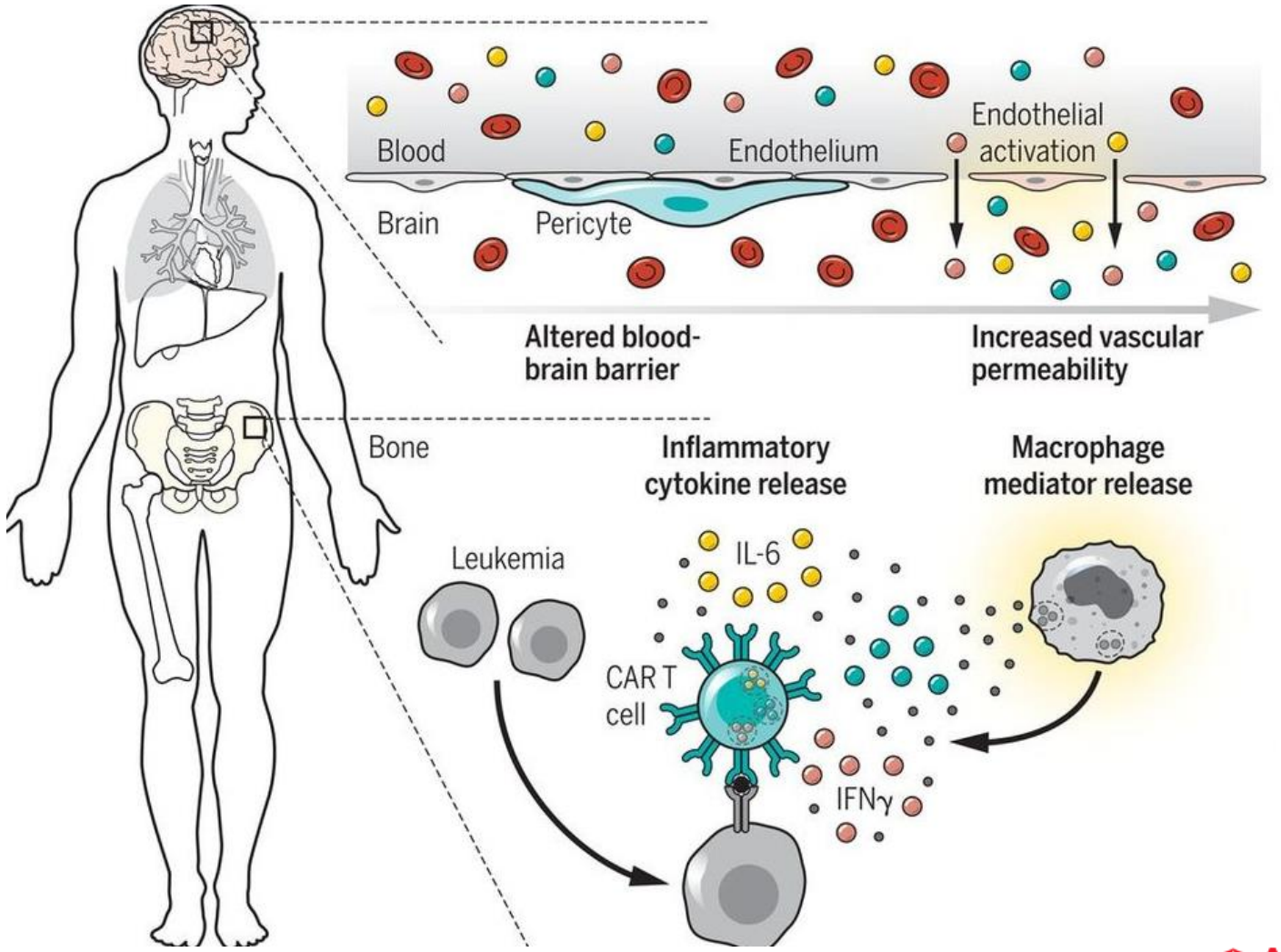


Kochenderfer, Nat Rev Clin Oncol 2013.

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

FDA-Approved CAR T cell therapies

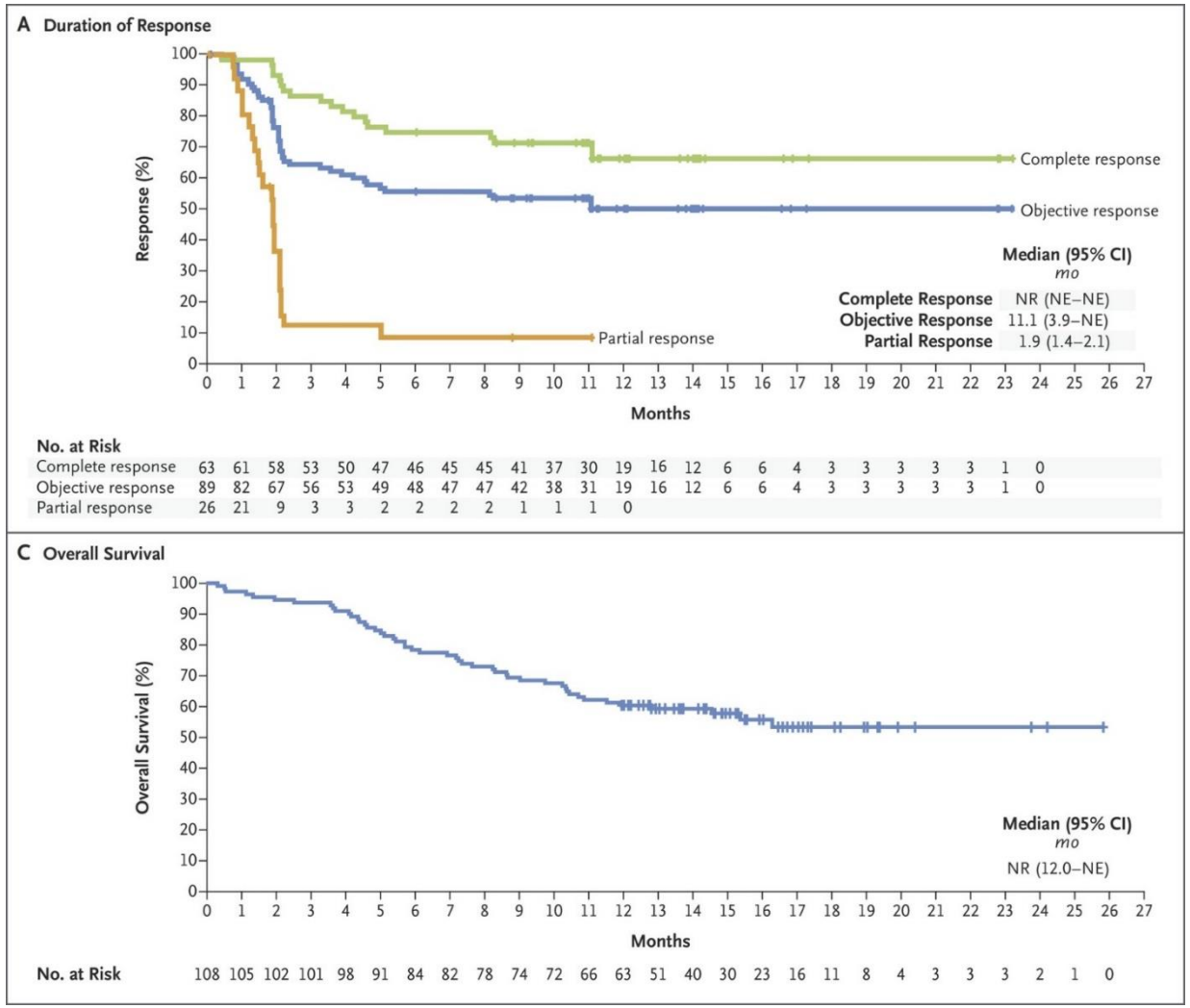
DRUG	APPROVED	INDICATION	DOSE
Brexucabtagene autoleucel	2020	Adult patients with relapsed/refractory mantle cell lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight (up to $2x10^8$)

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)

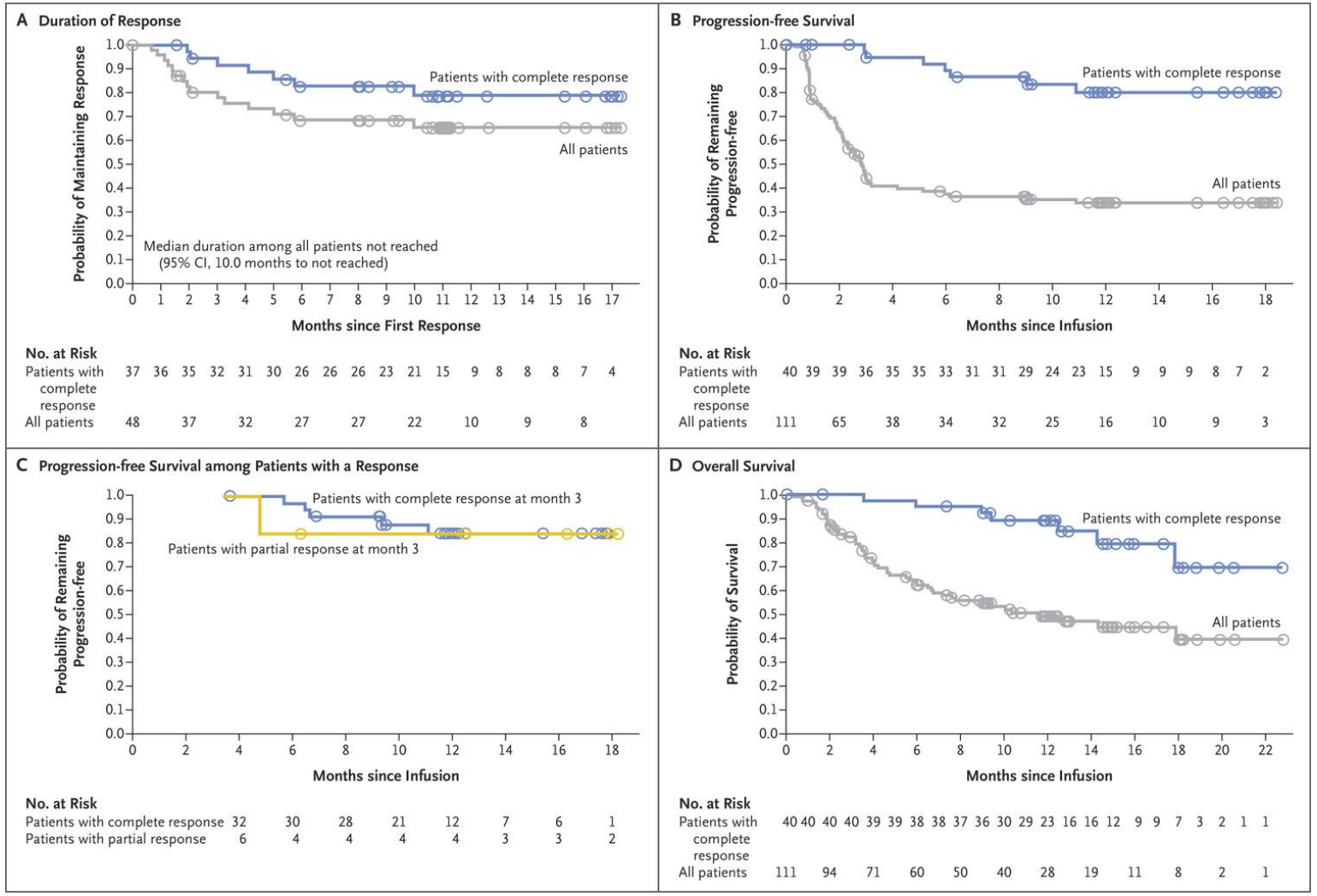
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

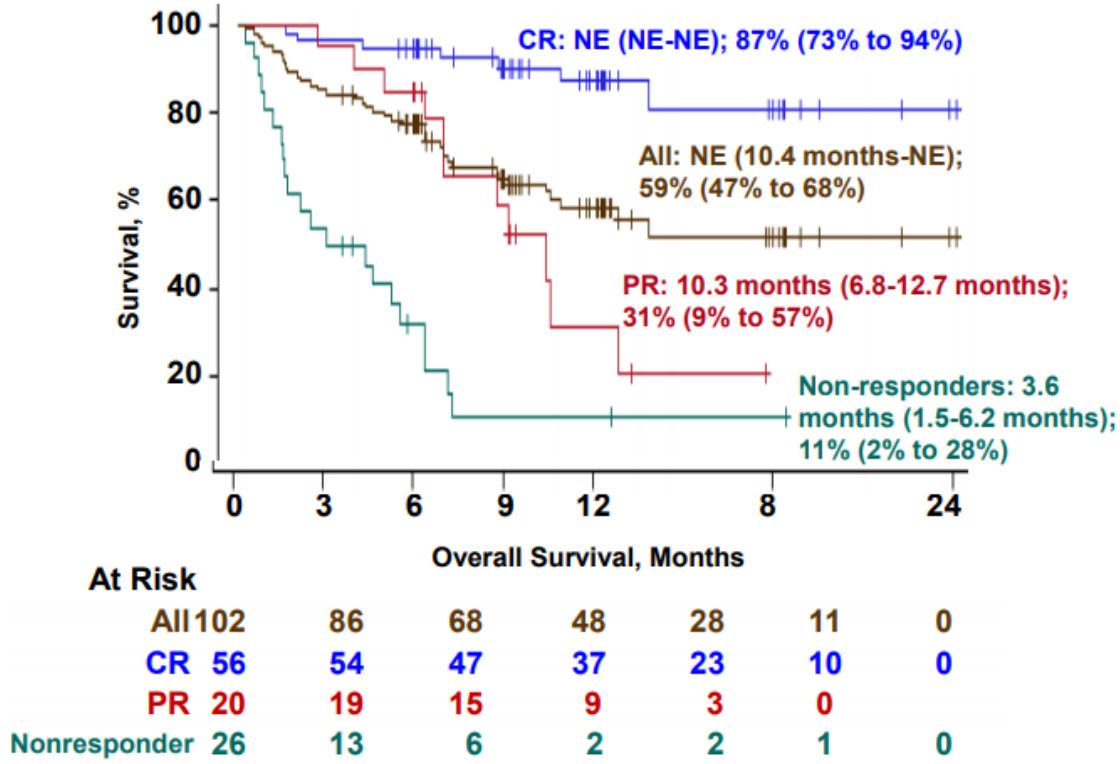
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

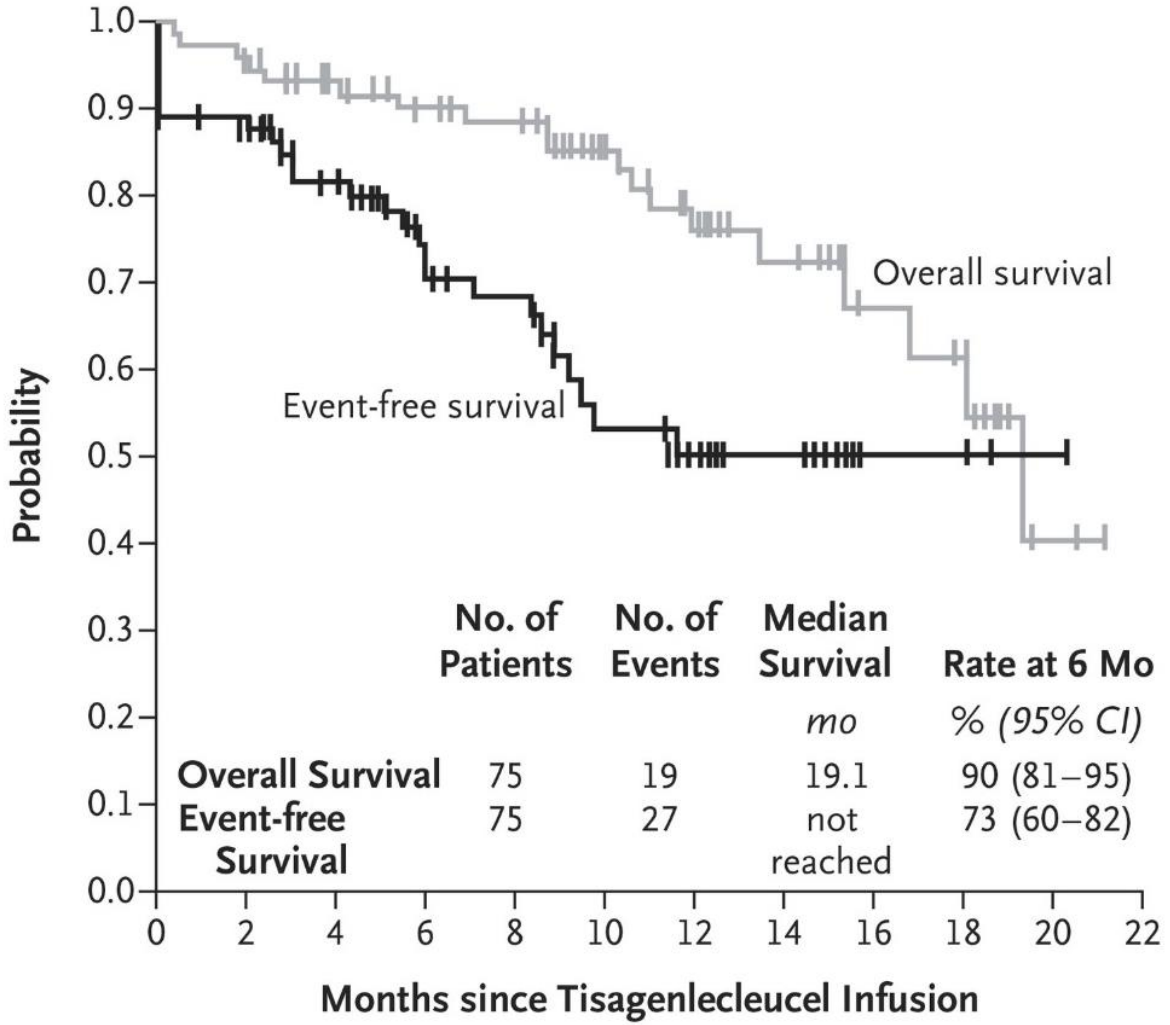
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

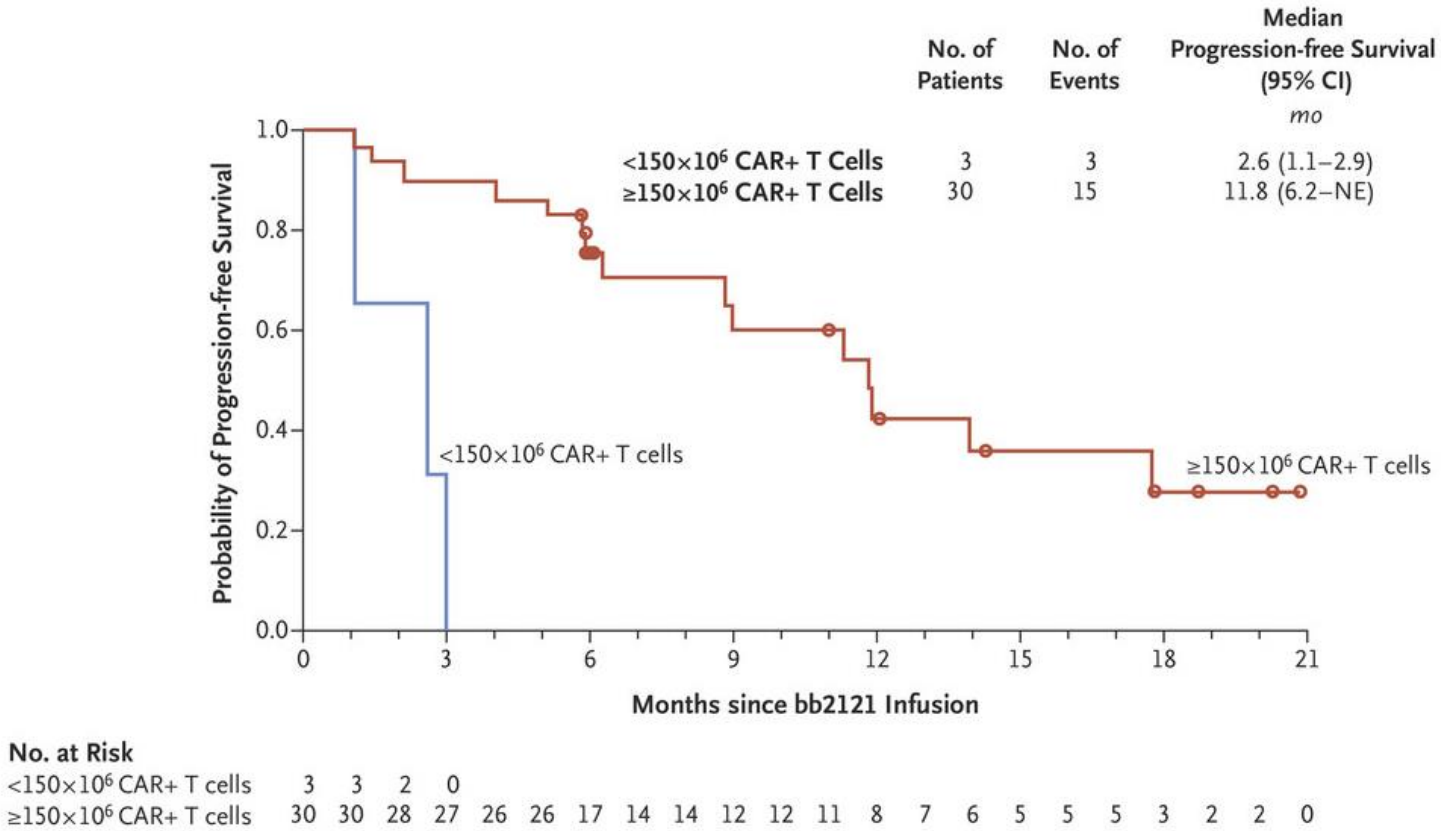


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

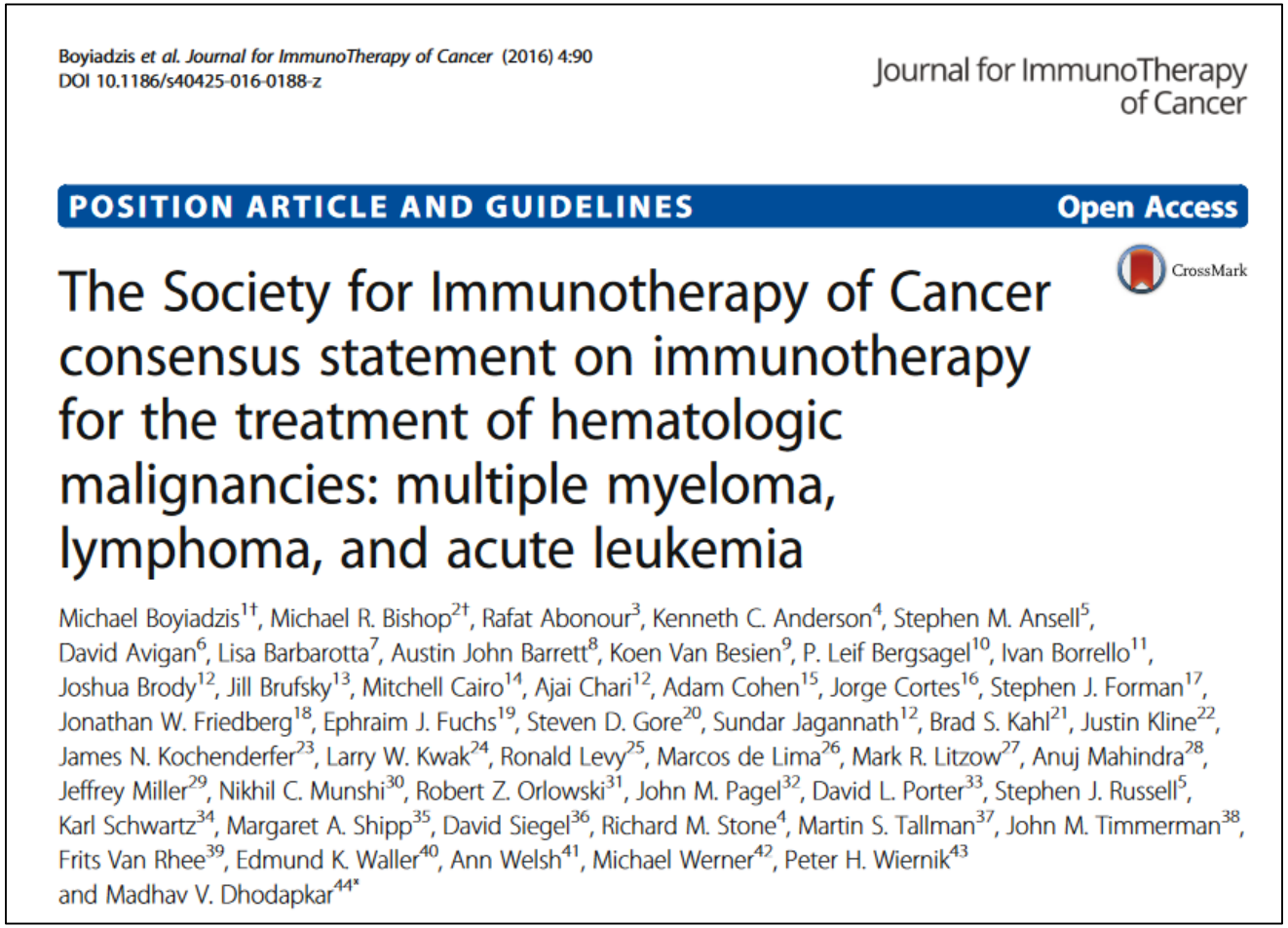


Raje, NEJM 2019.

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*]

Case Studies

Case Study 1

- A 65 yo female with a history of relapsed/refractory Hodgkin lymphoma is currently on pembrolizumab monotherapy. Prior therapies include ABVD x 6, ICE x 2 followed by high dose chemo/autologous transplant, brentuximab vedotin x 4, and now pembrolizumab. Prior to starting pembrolizumab, she had significant bone pain and B symptoms, which resolved with one week of starting treatment. She sees you about 2 months into therapy due to a new maculopapular rash on her arms and back that covers about 30% of her body surface area.
- What is your next step in management?

  A. Continue pembrolizimab, add topical corticosteroid

  B. Hold pembrolizumab, add topical corticosteroid

  C. Continue pembrolizumab, start oral prednisone

  D. Hold pembrolizumab, start oral prednisone

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  D. **Hold pembrolizumab, start oral prednisone**

Case Study 1

Grading	Management
Grade 1 - Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic; covers < 10% BSA	Continue immunotherapy, treat with topical corticosteroids
Grade 2 - Inflammatory reaction that affects quality of life and requires intervention based on diagnosis, Covers 10%-30% BSA	Consider holding immunotherapy, Administer prednisone 0.5-1 mg/kg daily, tapering over at least 4 weeks
Grade 3 - As G2 but with failure to respond to indicated interventions for a G 2 dermatitis; Covers > 30% BSA	Hold immunotherapy, Administer IV methylprednisolone 1-2 mg/kg daily, tapering over at least 4 weeks
Grade 4 - All severe rashes unmanageable with prior interventions and intolerable	Hold immunotherapy, Administer IV methylprednisolone 1-2 mg/kg daily, tapering over at least 4 weeks, urgent hospitalization

***Strongly consider dermatologic evaluation at any point, mandatory for grade 3+**

****Only resume immunotherapy IF rash resolves and prednisone no more than 10 mg**

Brahmer et al JCO 2018

Case Study 1

- This patient completes a prednisone taper over 4 weeks while holding pembrolizumab. After the prednisone is tapered, the pembrolizumab is resumed. 3 months after reinitiating pembrolizumab, a PET/CT is performed that demonstrates significant reduction in the initial extent of disease, but is notable for several new 2-3 cm R axillary lymph nodes. The patient is asymptomatic

- What is the next step in management?

  A. Discontinue pembrolizumab, initiate single agent gemcitabine

  B. Discontinue pembrolizumab, discuss hospice

  C. Increase dose of pembrolizumab, re-image in 3 months

  D. Continue same dose of pembrolizumab, re-image in 3 months.

Case Study 1

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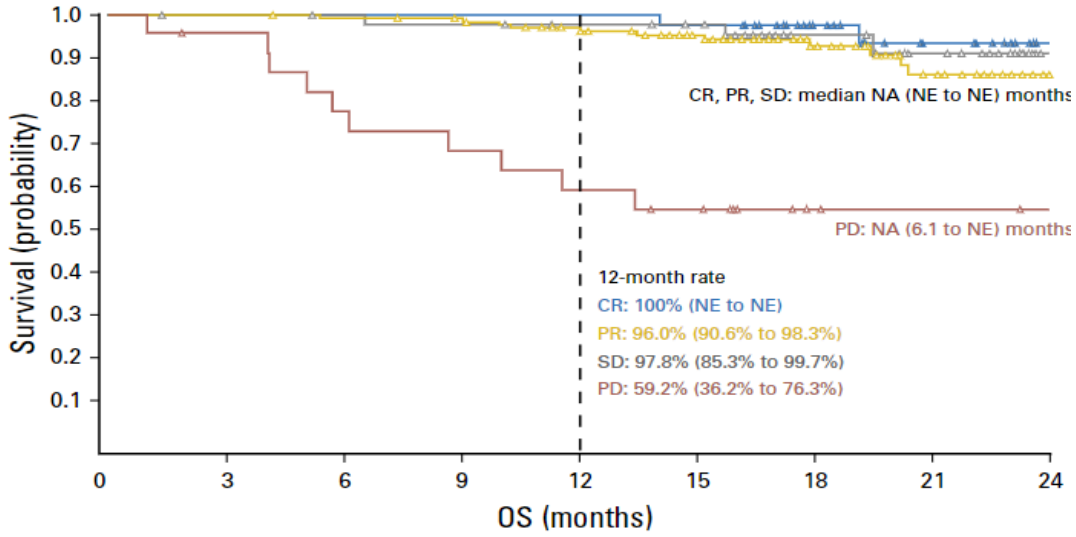

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Keynote-087

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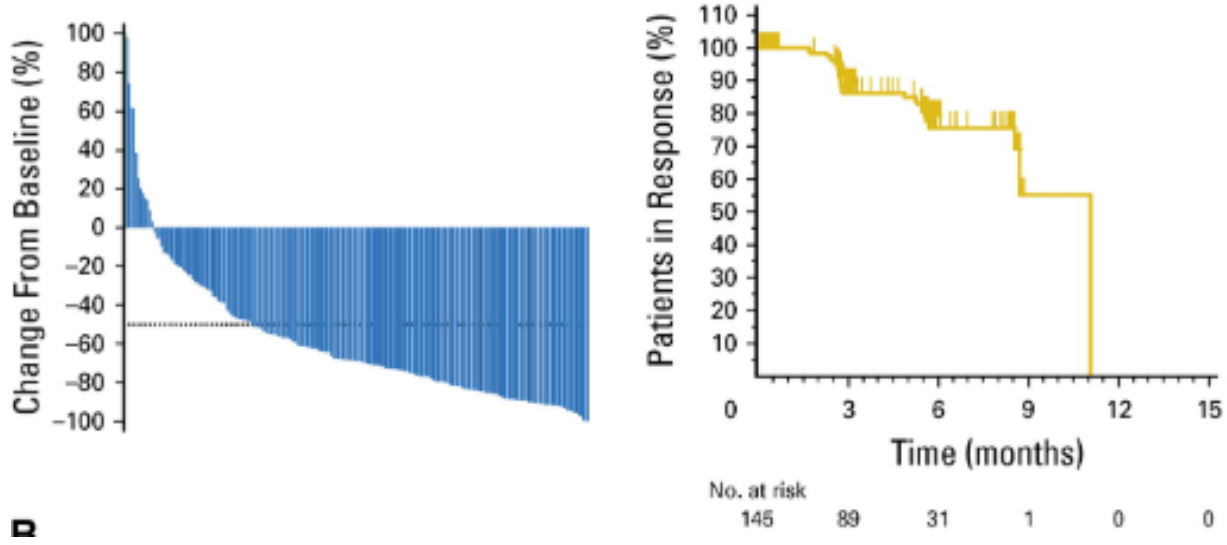

Armand, J Clin Oncol 2018.
Chen, J Clin Oncol 2017.

Case Study 2

- A 56 yo male with a history of relapsed/refractory DLBCL sees you in clinic. He had primary refractory disease after R-CHOP x 6. He did not achieve a response to salvage RICE and was referred for CD19 directed CAR-T cell therapy. He is eventually treated with axicabtagene ciloleucel and does not develop any significant cytokine release syndrome or neurotoxicity. He does have one admission for neutropenic fever within 30 days of infusion. He has a repeat PET/CT about 30 days after completion of therapy which shows a partial response (overall decrease in size and FDG uptake in sites of involvement, but still with mildly FDG avid lymphadenopathy above and below the diaphragm, none of which is easily accessible for biopsy. He also has not completely recovered his blood counts and has an ANC of 350 and platelet count of 15. He currently has no symptoms attributable to his lymphoma
- What is the next step?

  A. Initiate treatment with polatuzumab vedotin/bendamustine/rituximab

  B. Consolidative radiotherapy

  C. Observation with repeat PET/CT in 2 months

  D. Referral for hospice

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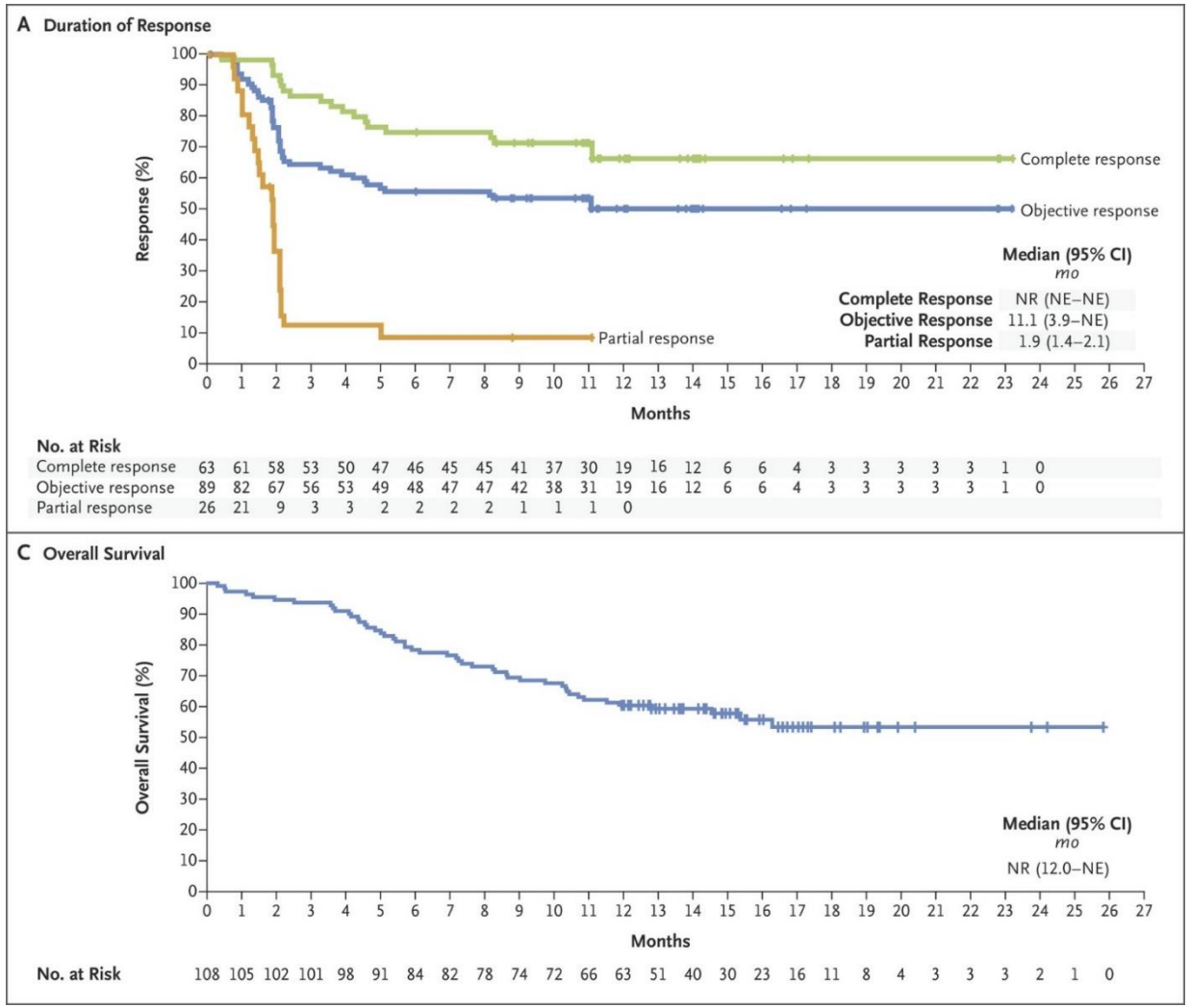
- Cytopenias preclude any treatment at this time. Polatuzumab/bendamustine/rituximab is very myelosuppressive.Biopsy would pose risk without possibility of intervention at the time. If the patient had symptomatic lesions one could consider palliative radiotherapy.
- Some partial responses may convert to complete responses and in a patient who is still recovering from treatment toxicities, observation is most reasonable. However, most partial responses are not durable, so close follow up with short interval PET/CT is warranted.

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.

Case Study 2

- Two months later, the patient undergoes a PET/CT which demonstrates significant progression in existing FDG-avid lesions as well as new bony and soft tissue lesions. The patient has developed worsening fatigue and anorexia. There is still residual hematological toxicity with ANC 150 and platelet count 7. ECOG PS 2
- What is the next step?

  A. Treatment with polatuzumab vedotin/bendamustine/rituximab

  B. Treatment with a cytarabine-based salvage regimen, initiate donor search in anticipation of allogeneic transplant

  C. Referral for second axicabtagene ciloleucel infusion

  D. Discussion of hospice/palliative care

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Case Study 2

- Prognosis after post-CAR progression is very poor, particularly in light of the poor count recovery. Additional therapy would bring significant toxicity without meaningful chance of long term disease control. There is no role at this time outside of a clinical trial of an additional CAR-T infusion. Discussion of hospice/palliative care is appropriate at this time.