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

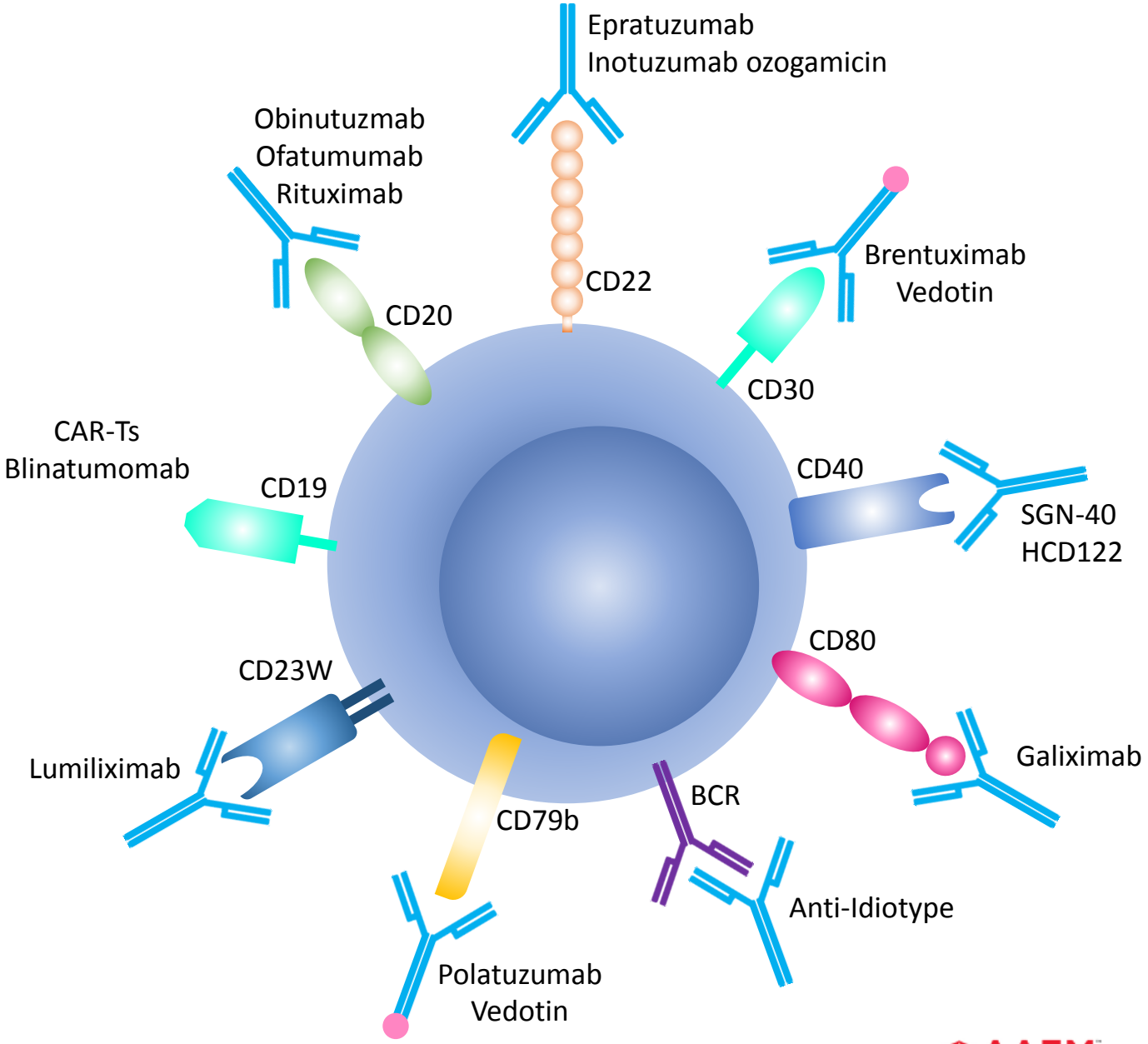
ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- No relevant disclosures.
- I will be discussing non-FDA approved indications during my presentation.



Checkpoint inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

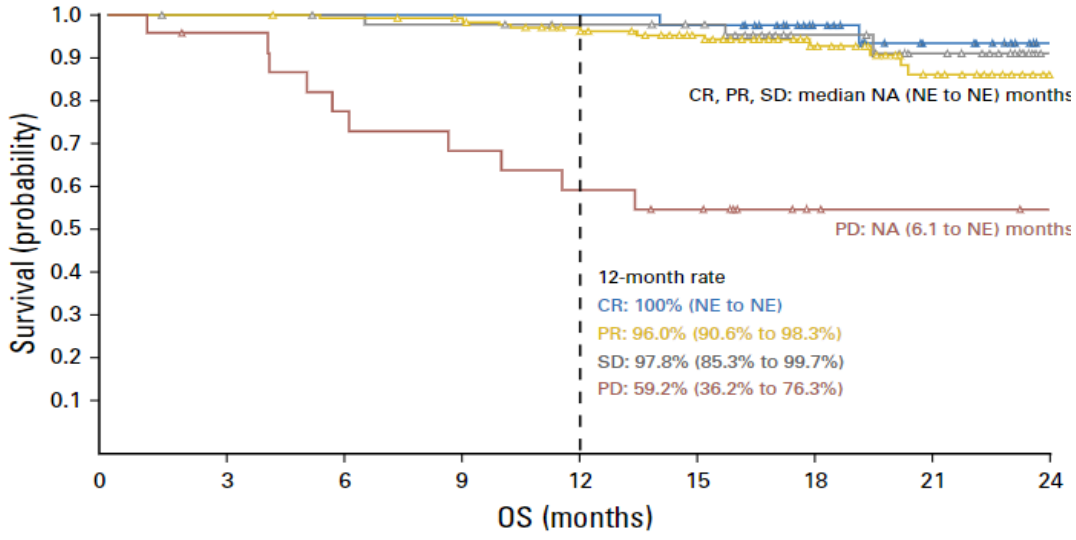
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg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

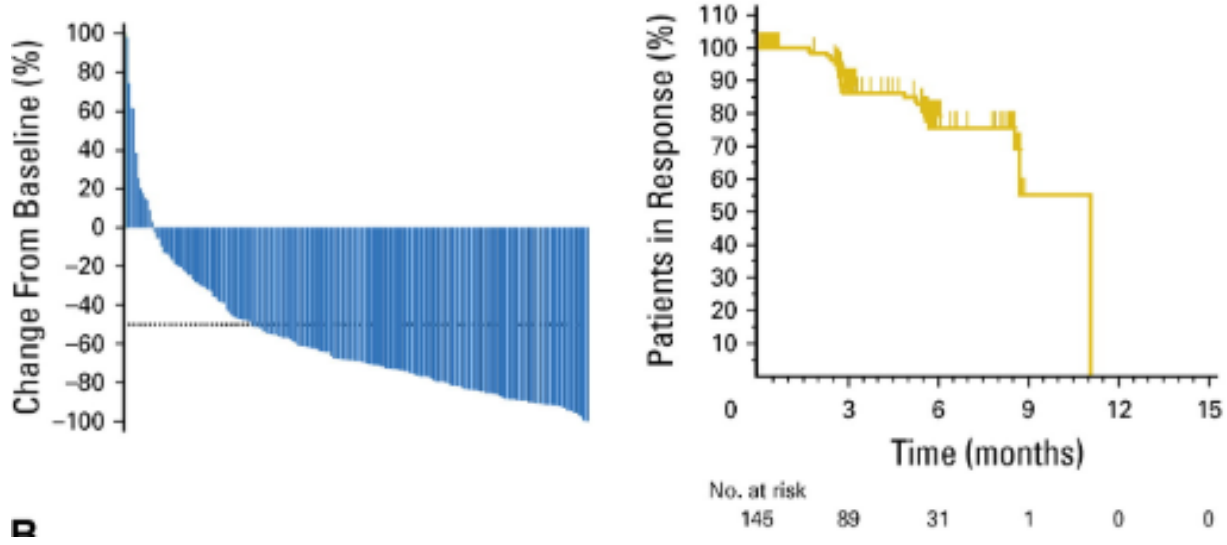
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

CR = 22.4%

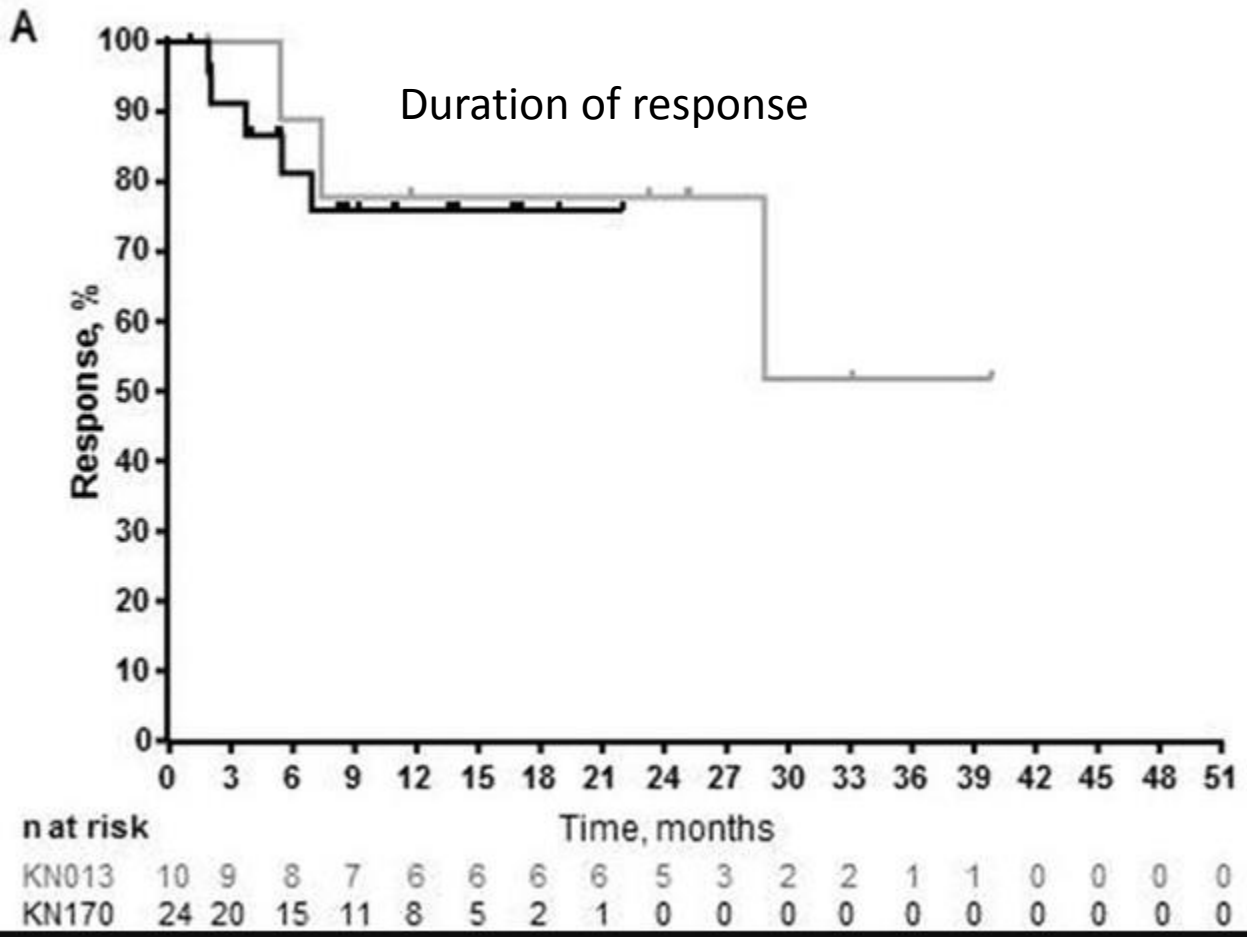
Activity seen regardless of PD-L1 expression

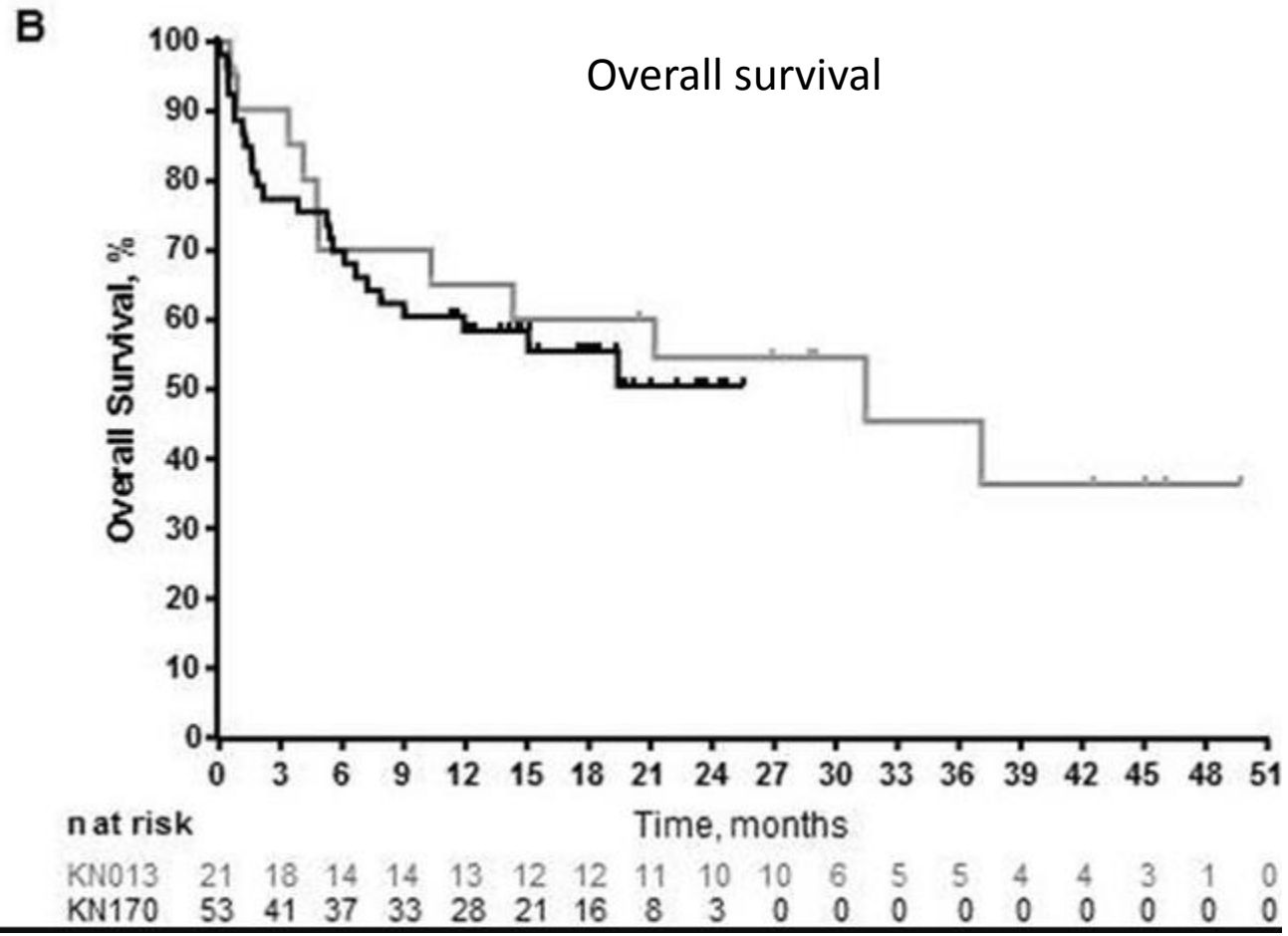


Armand, J Clin Oncol 2018.

Chen, J Clin Oncol 2017.

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

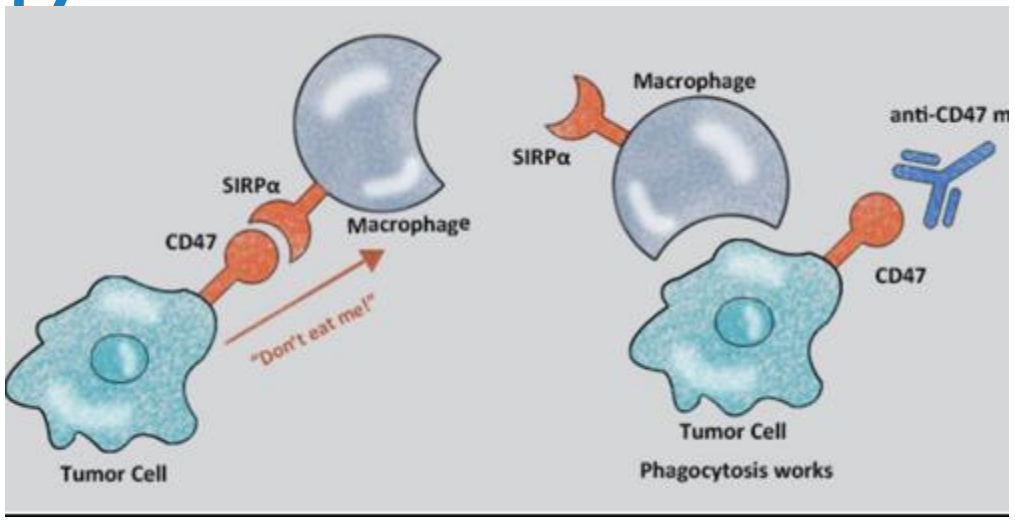


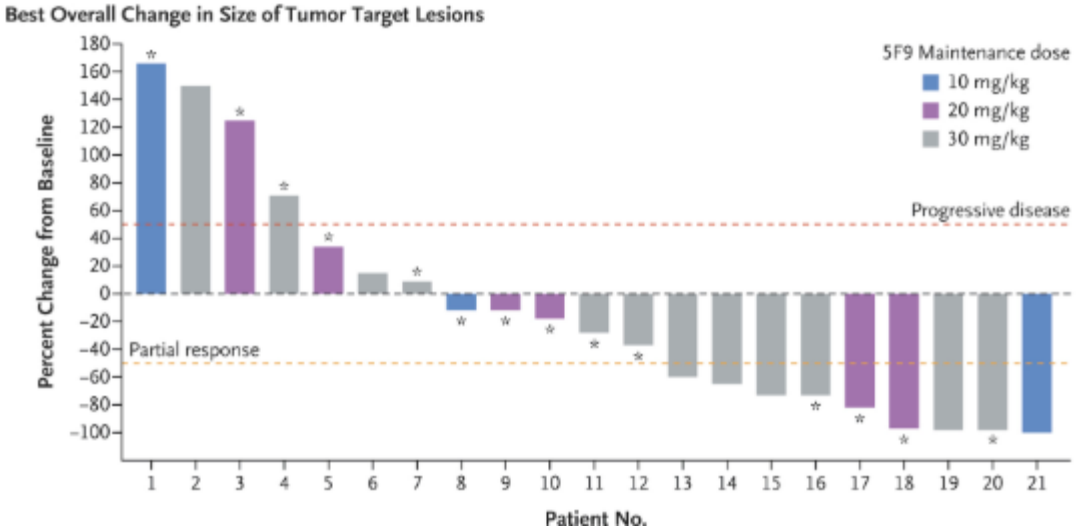


Armand, Blood 2018.

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%



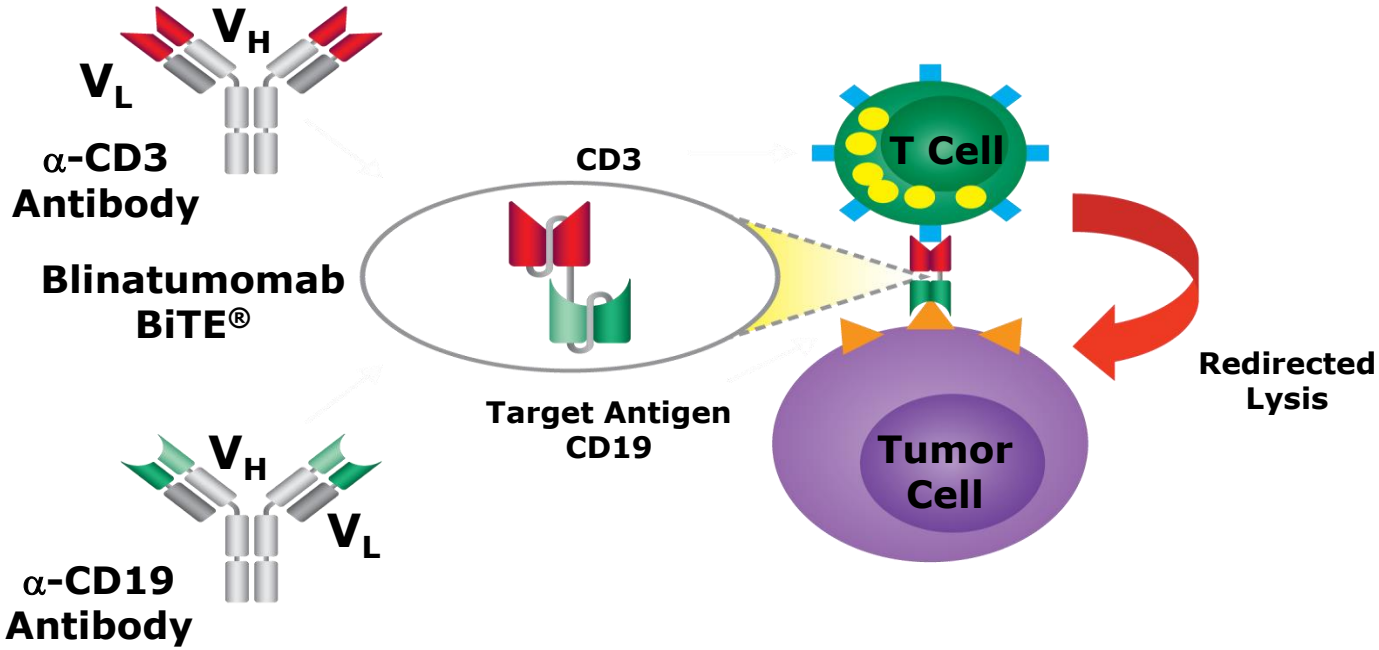


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

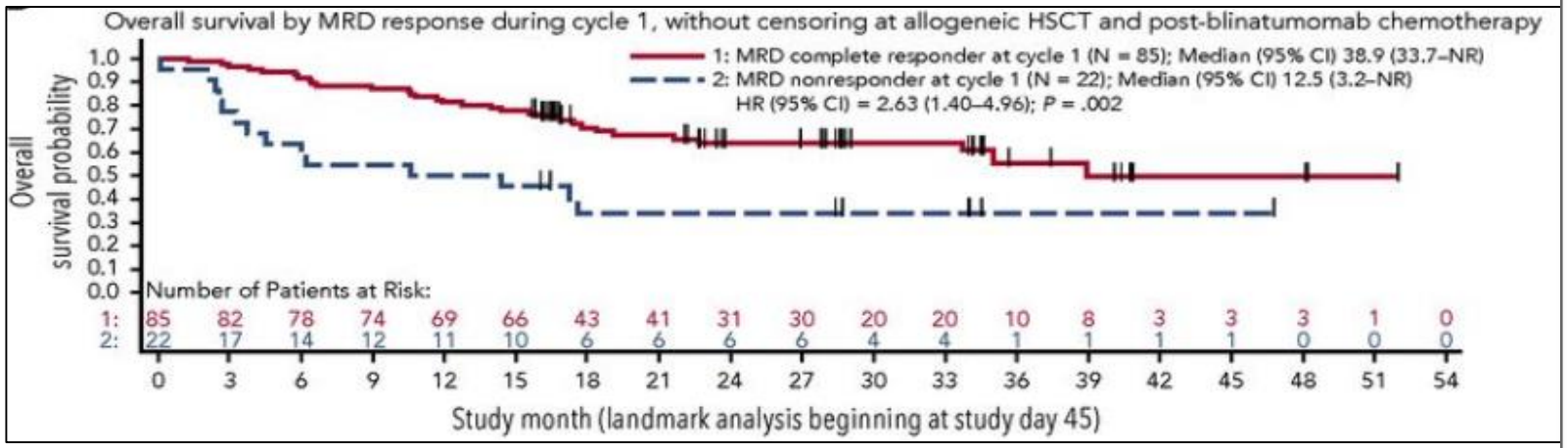
BiTE (Blinatumomab) Therapy

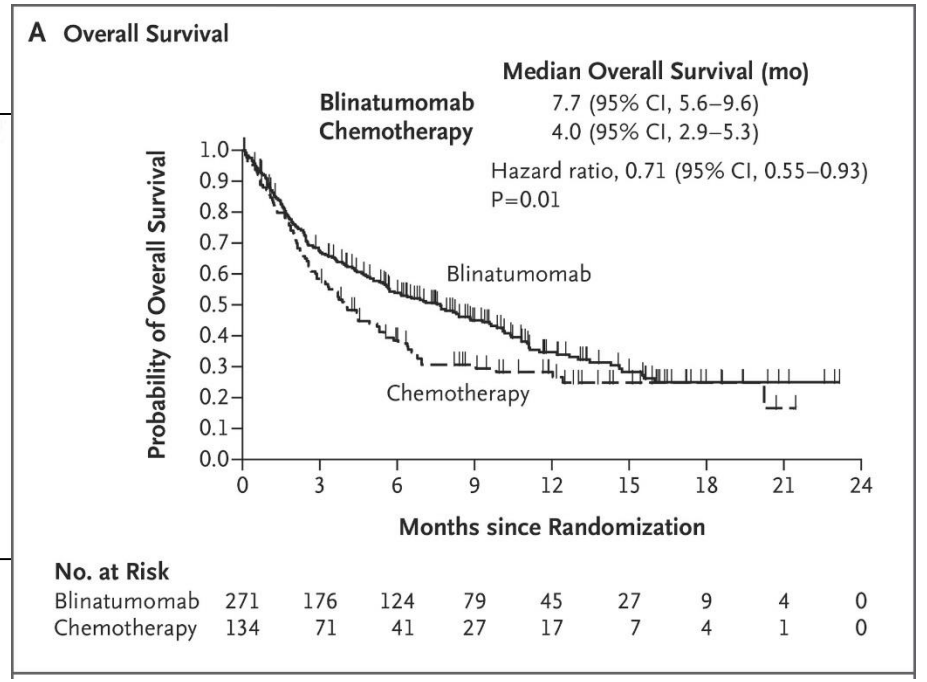
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





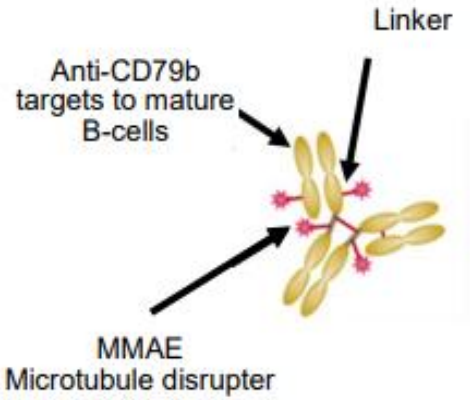
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

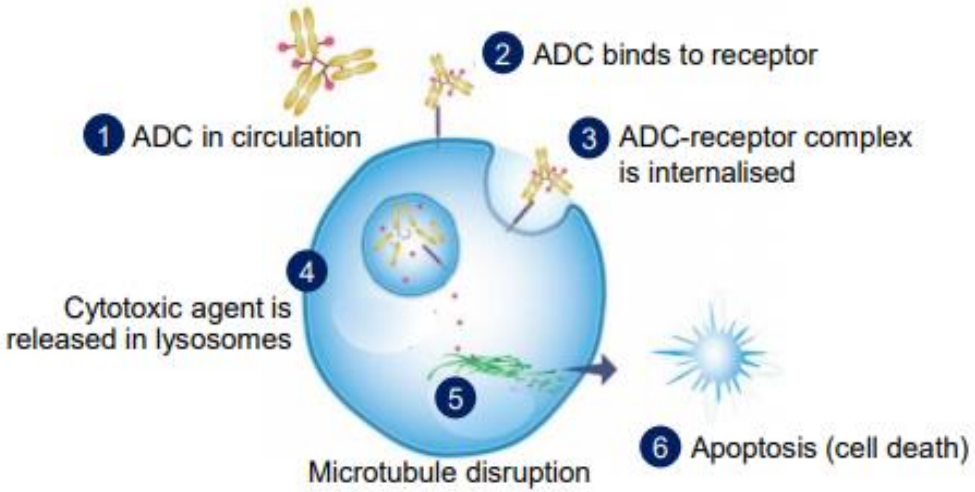
Antibody-drug conjugates (ADC)

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

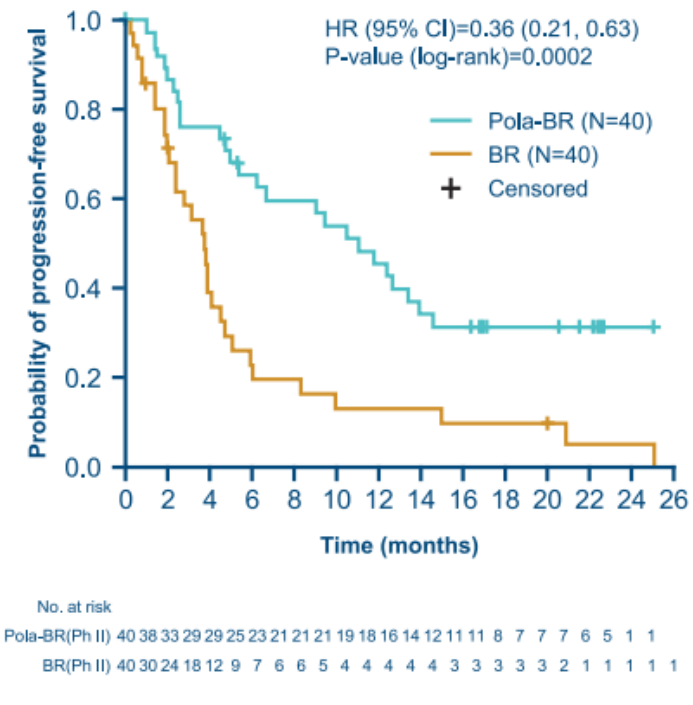
Slide credit: Tilly et al. ICML 2019

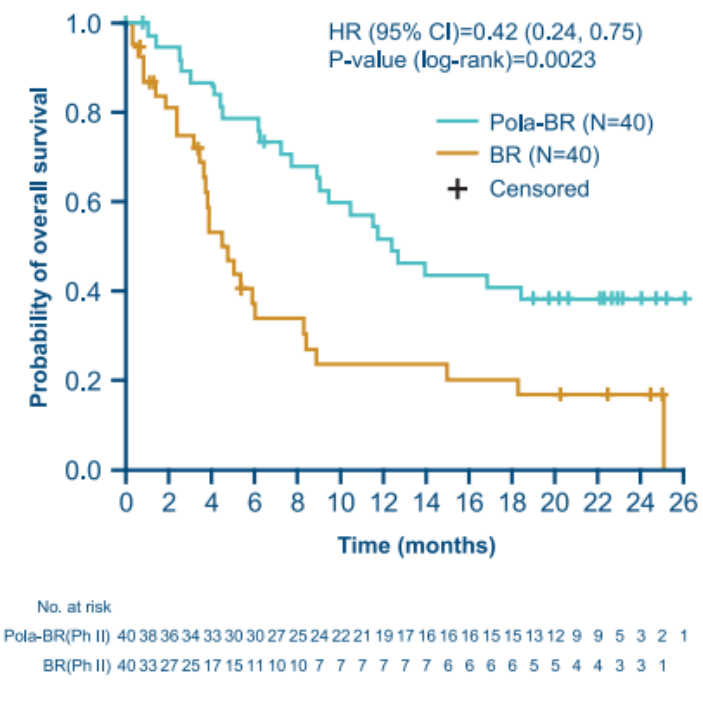
Polatuzumab vedotin: DLBCL

- 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

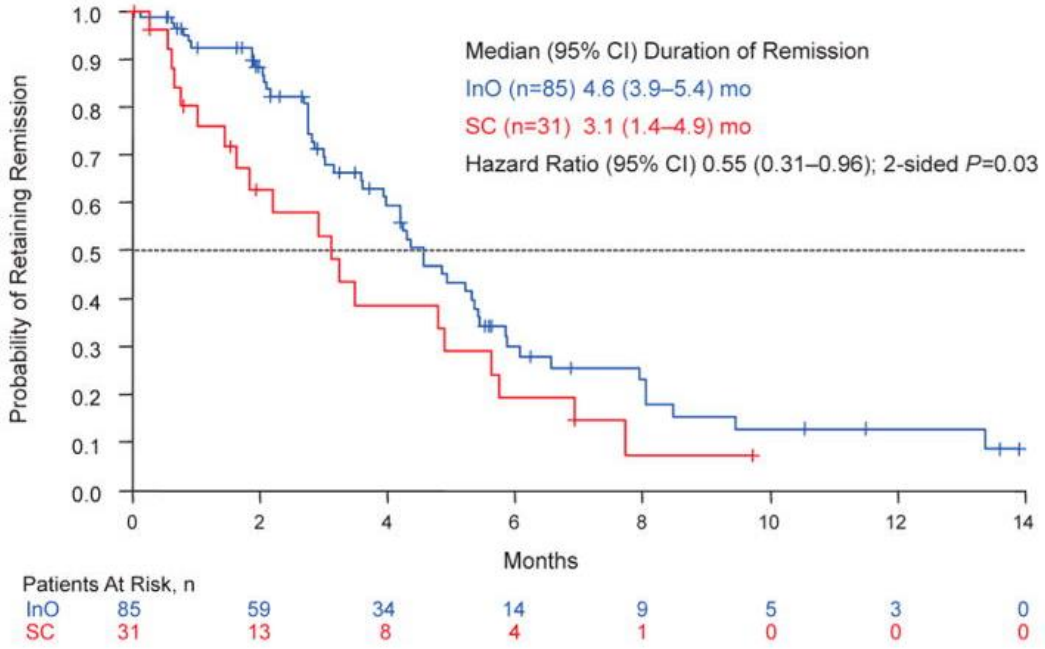


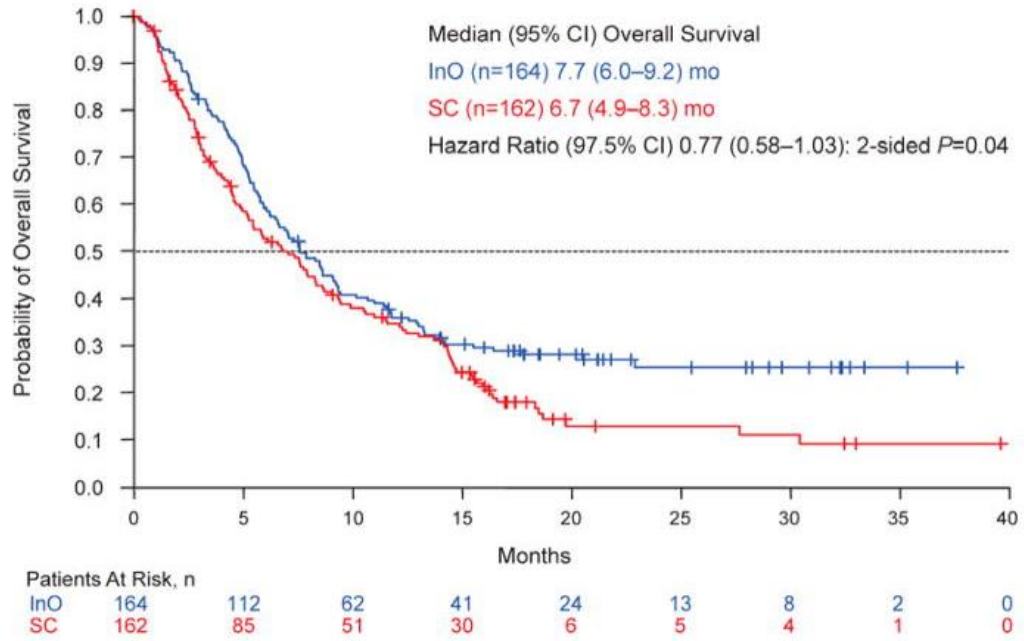


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



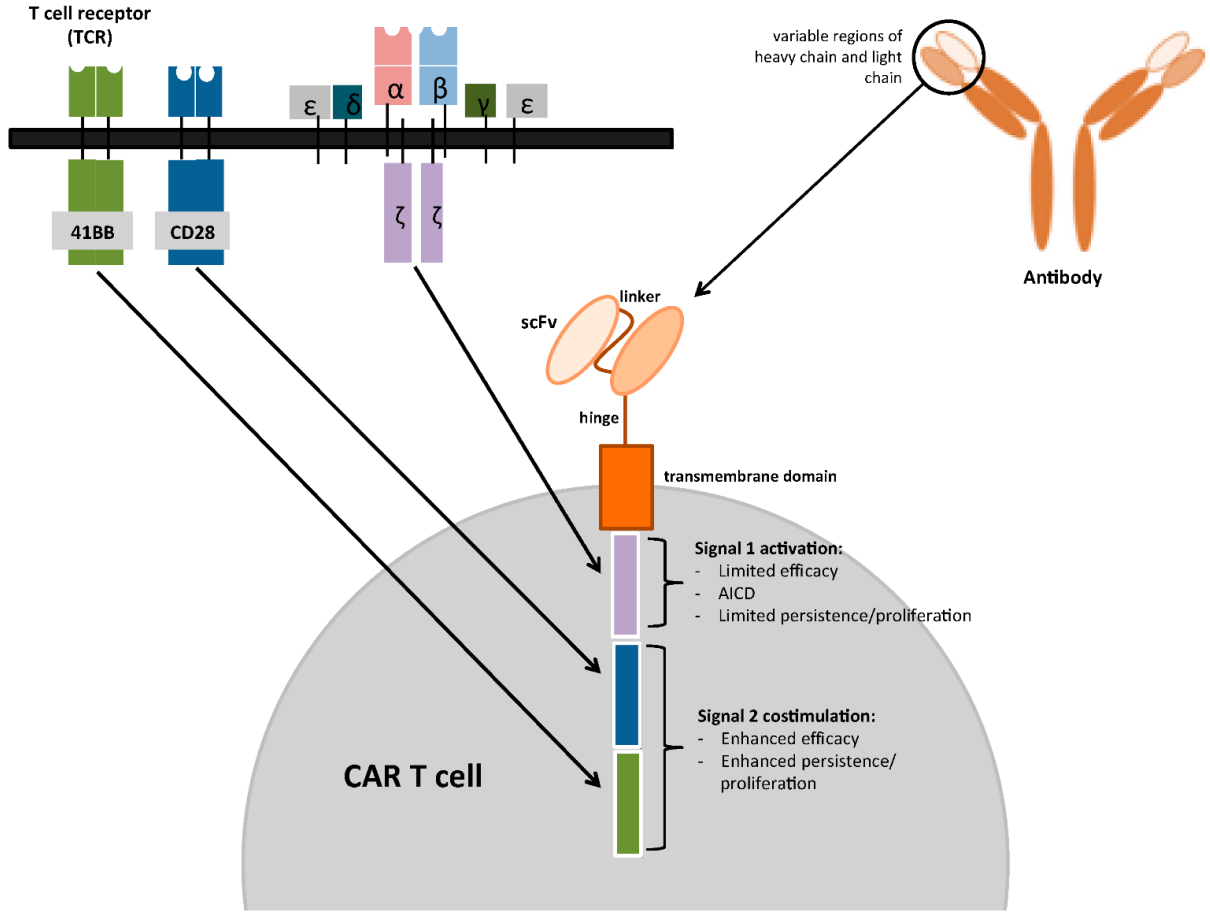


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

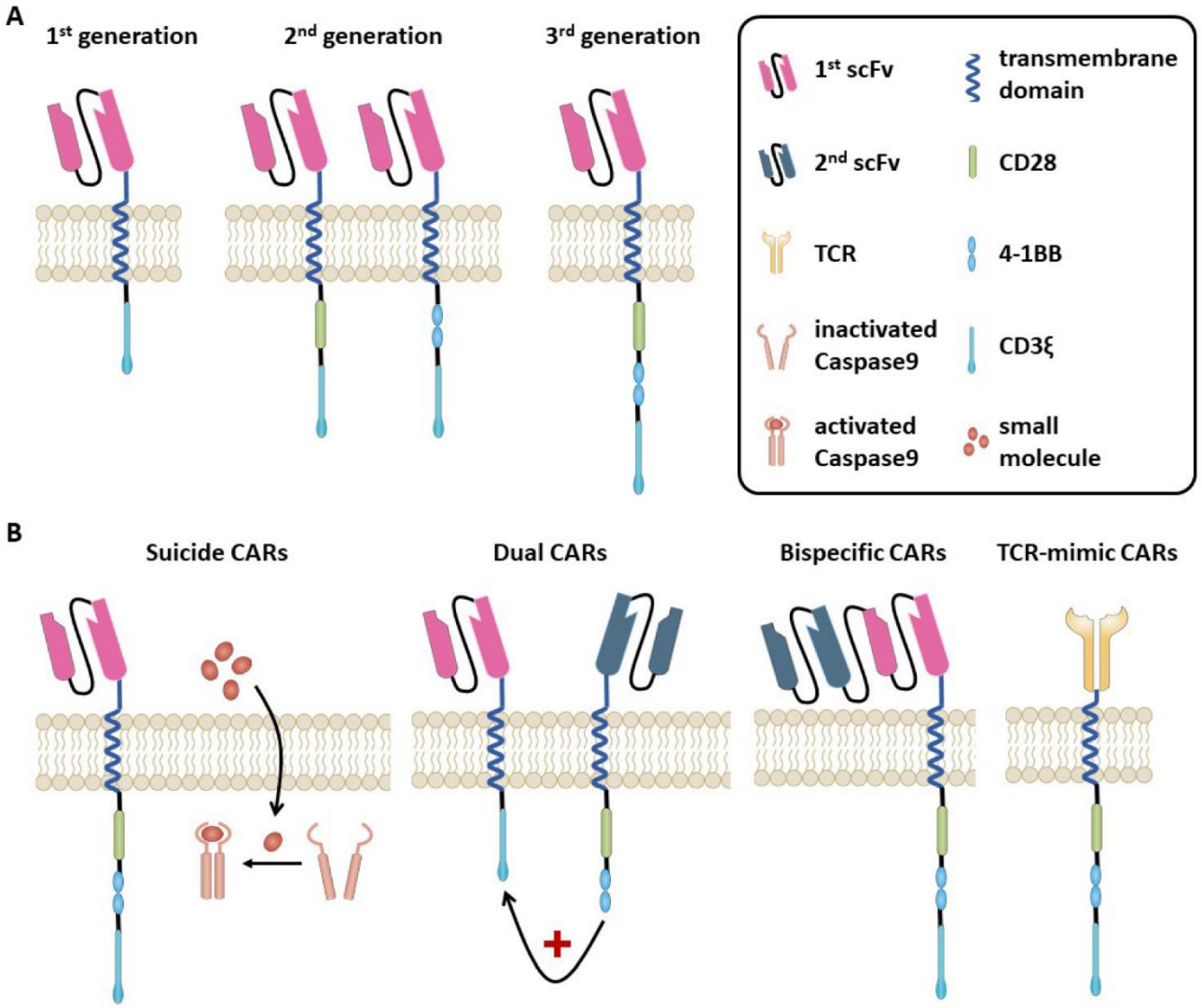
Chimeric antigen receptors

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



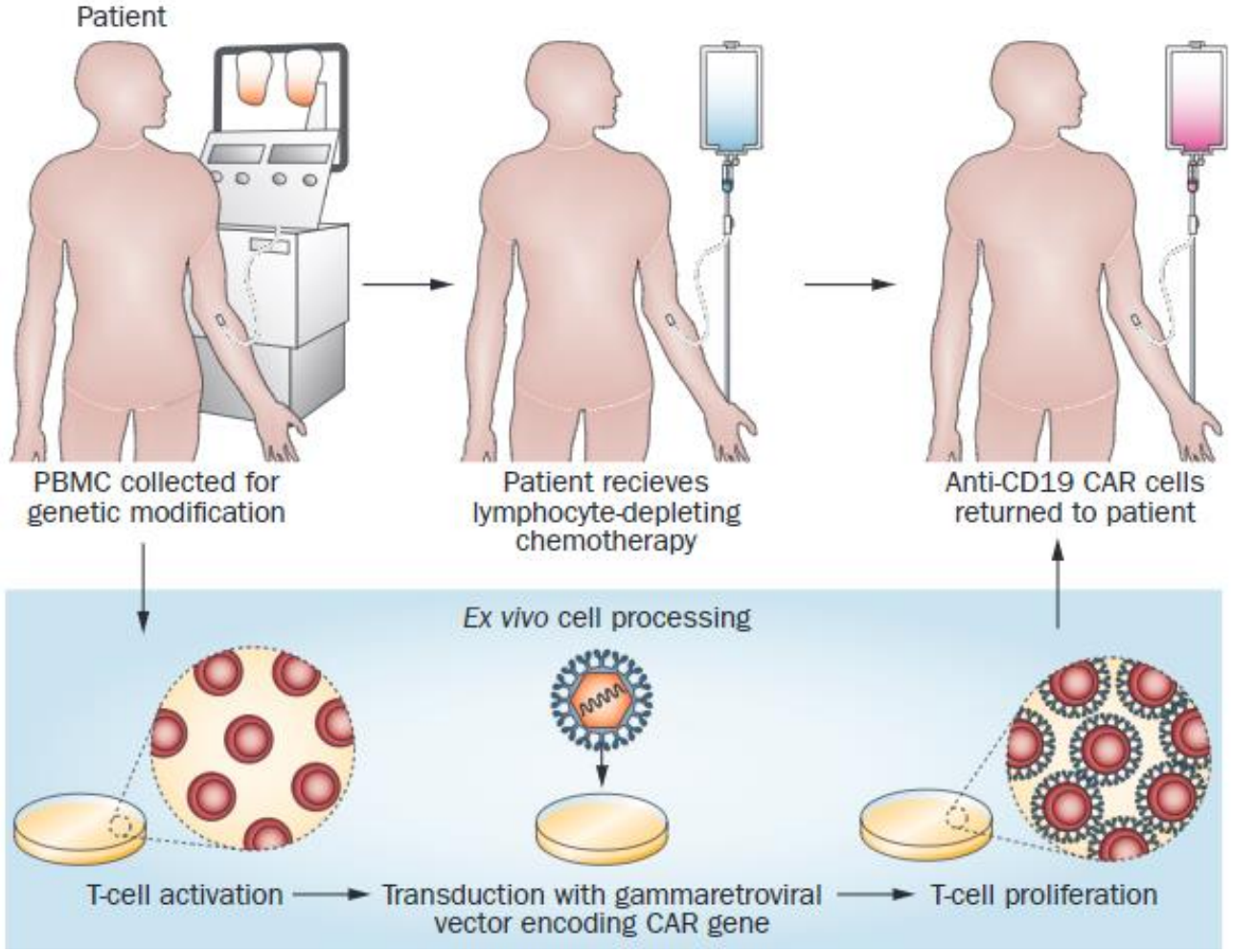
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

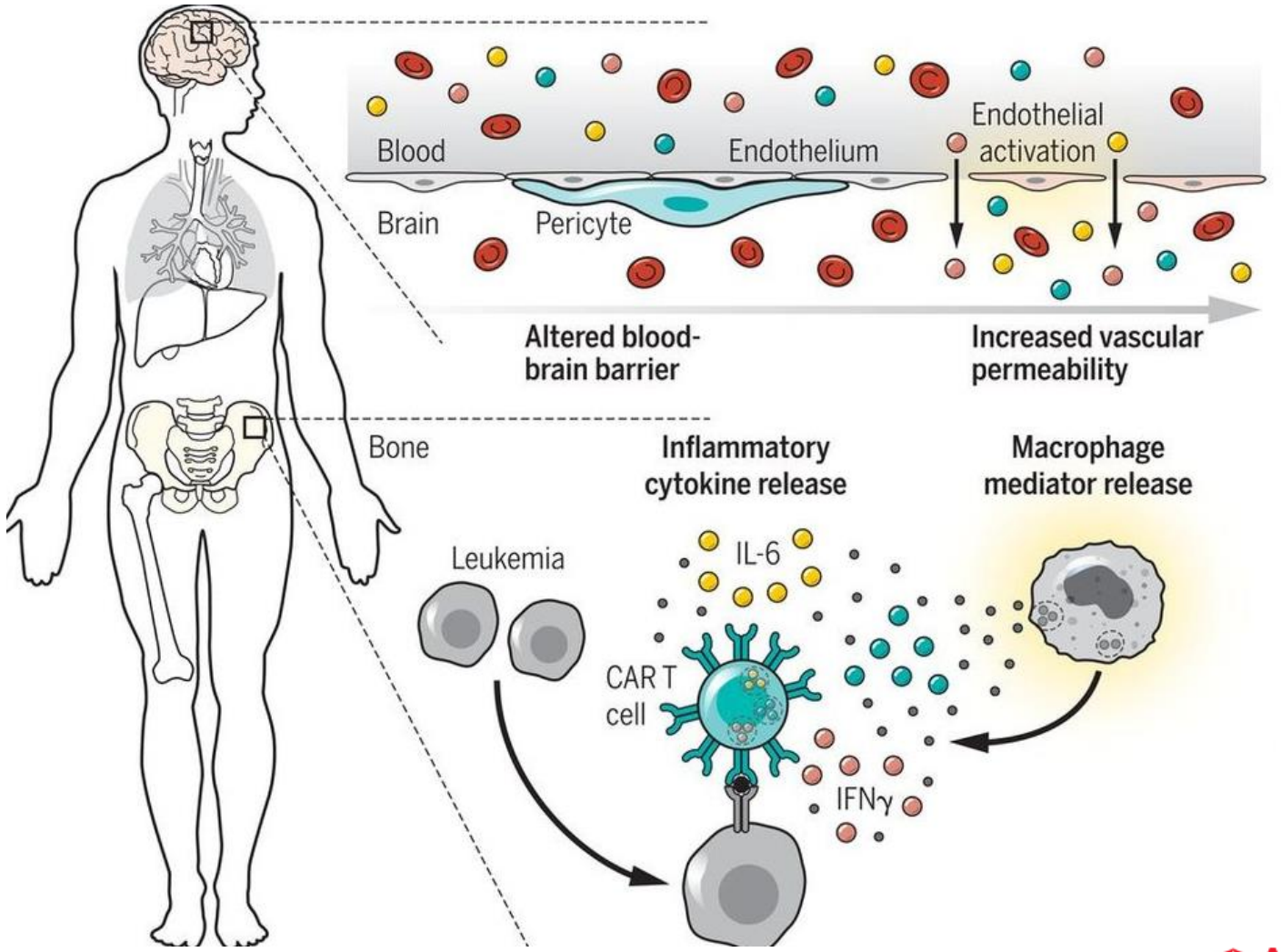


Kochenderfer, Nat Rev Clin Oncol 2013.

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

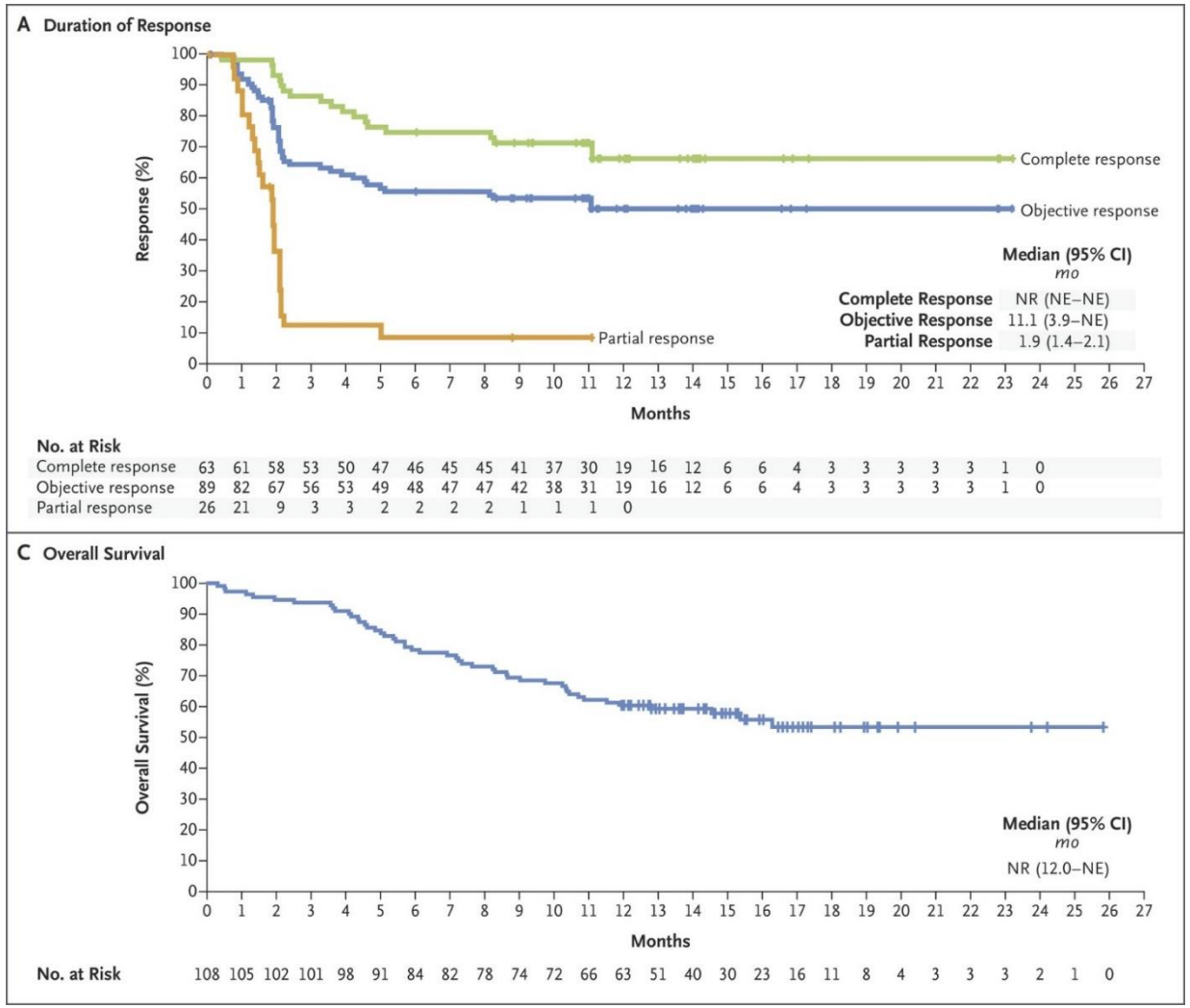
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight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

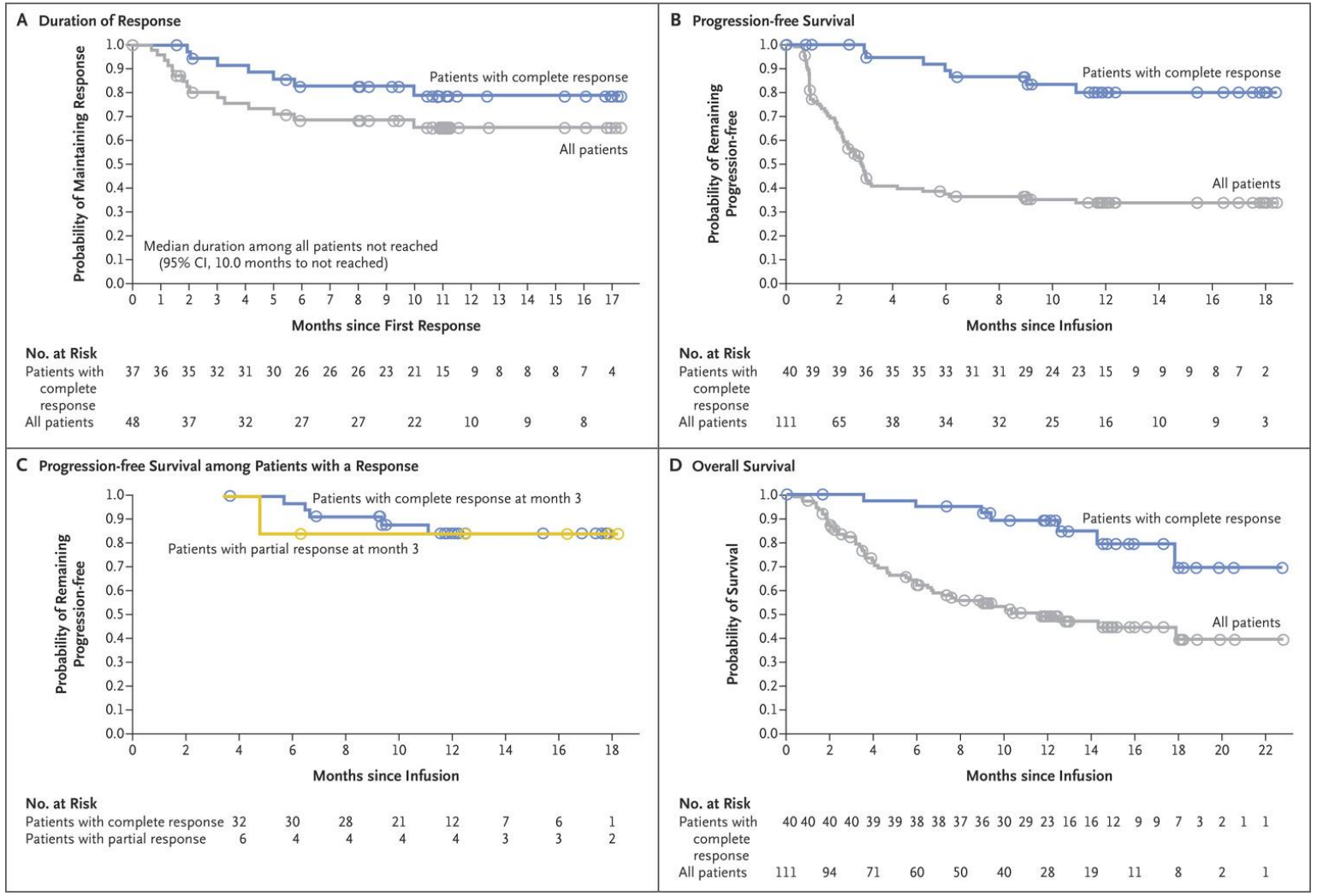
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

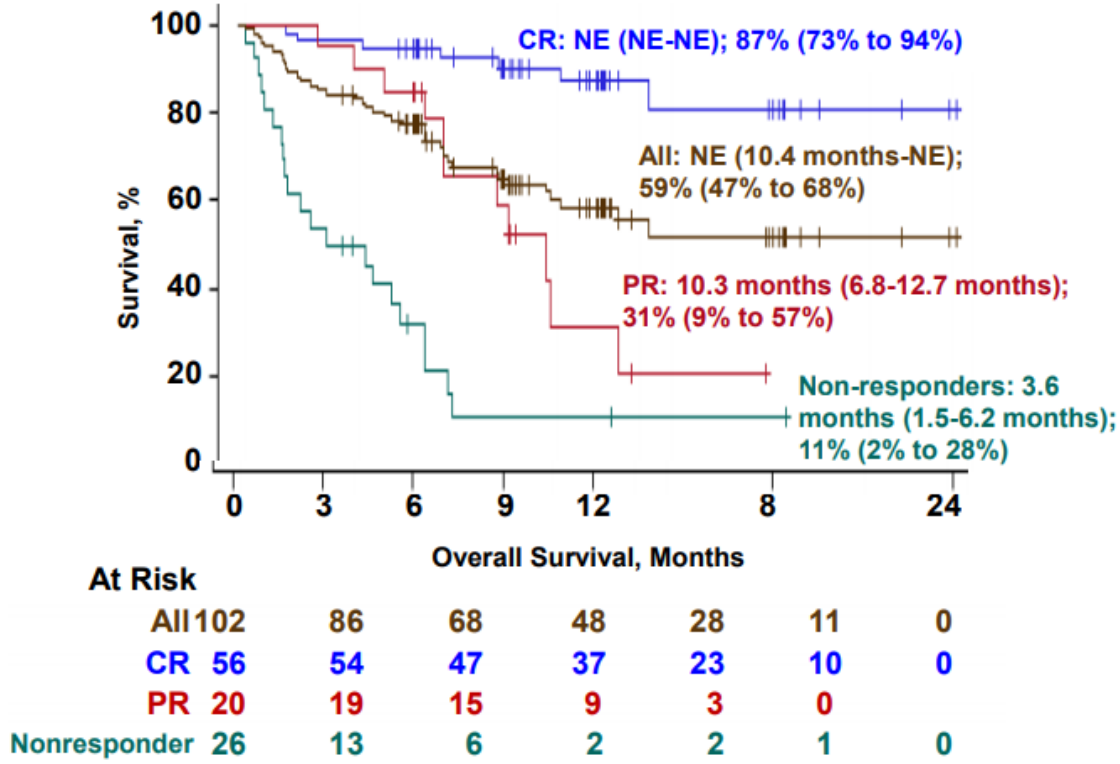
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

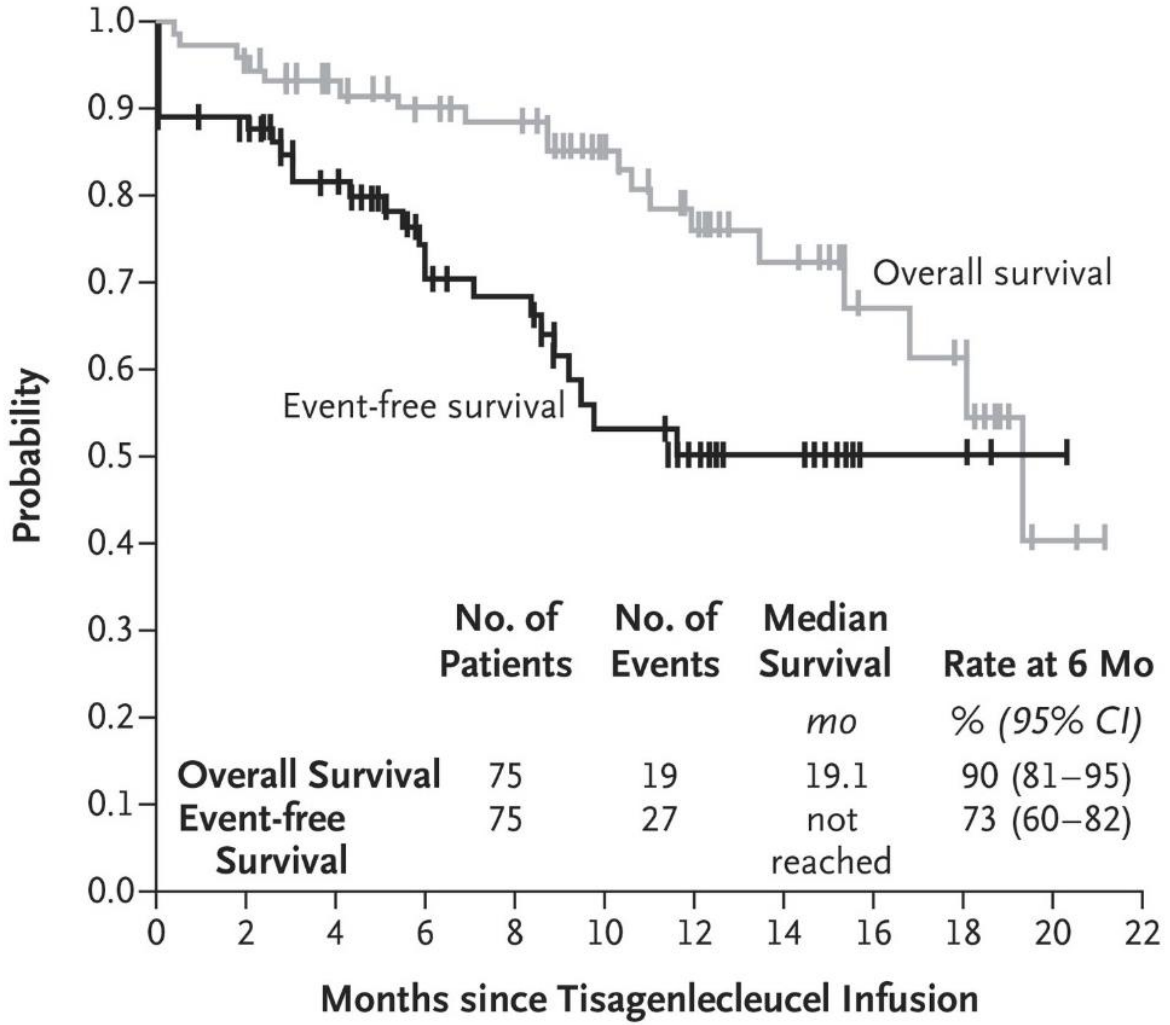
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

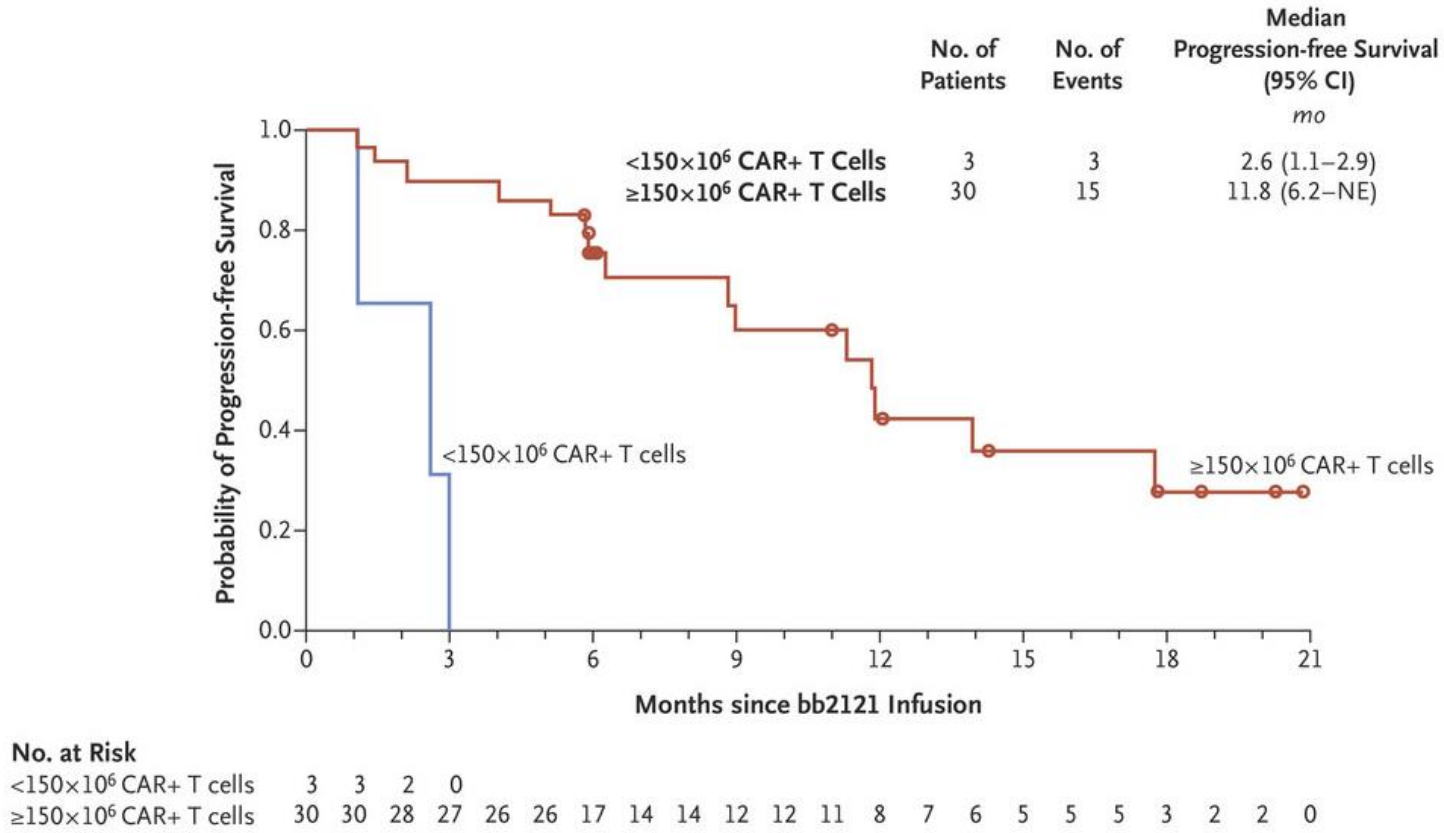


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

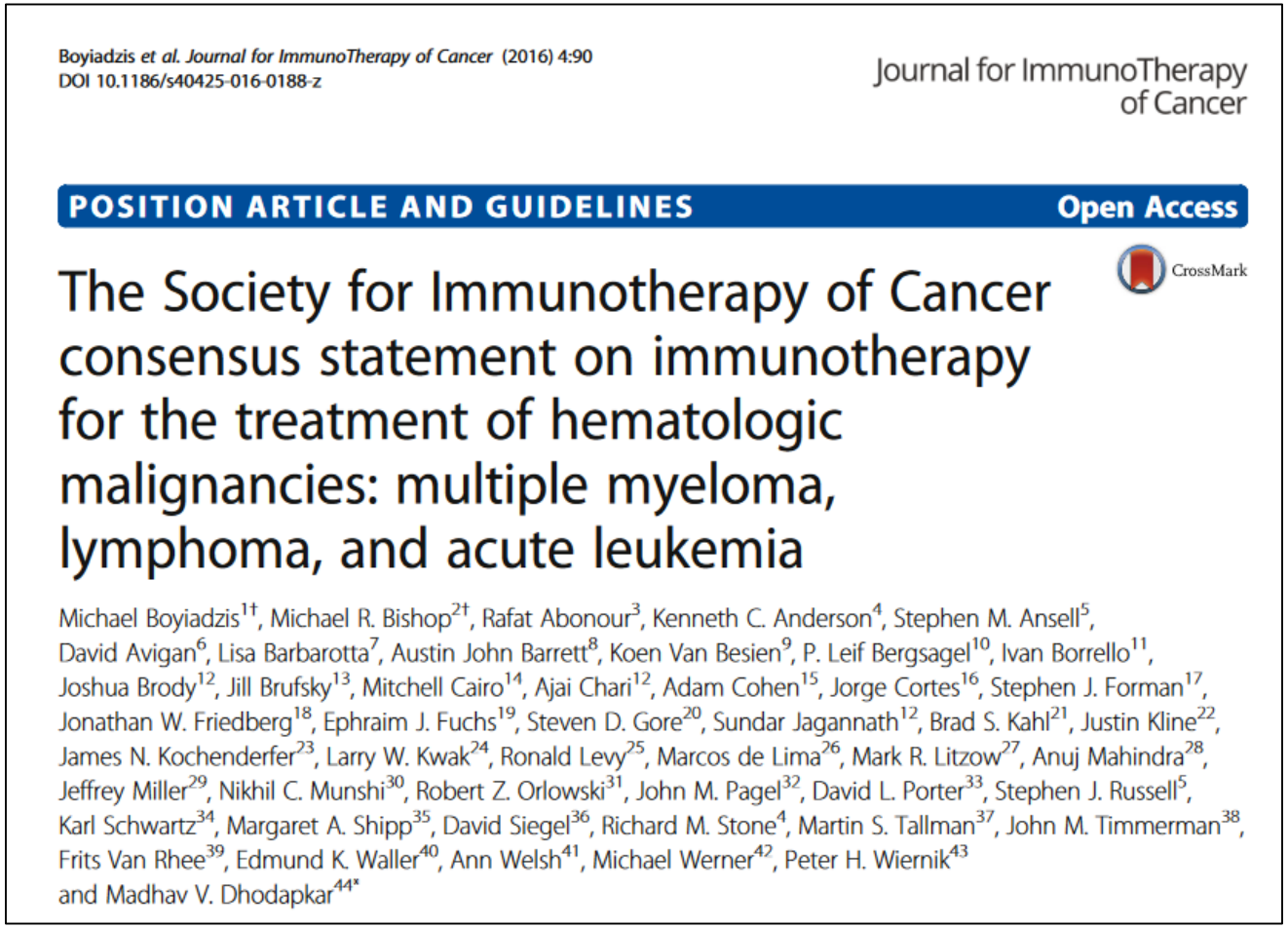


Raje, NEJM 2019.

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
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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

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Case Studies

Case Study 1

- Patient is an 18 yr old female who presented with WBC of 70K, circulating blasts, and thrombocytopenia. She was diagnosed with ALL, CNS-1 and started a 4 drug induction. Cytogenetics were notable for monosomy 7 and t 9;22. Imatinib was added but required switch to dasatinib due to severe myositis. End of induction marrow has 11% blasts by flow. She received extended induction therapy with marrow showing 2.2% blasts. Additional consolidation therapy including HD MTX, HD ara c, PEG-asp, VCR with dasatinib with end of consolidation testing demonstrating + MRD 0.038%. TKI resistance testing was negative.
- **Question 1: What would you do next?**

A. Referral for CAR-T immunotherapy

B. Continue with cytotoxic chemotherapy

C. Initiate blinatumomab therapy and BMT referral

D. Initiate blinatumomoab therapy with dasatinib and BMT referral

Case Study 1

- **Question 1: What would you do next?**

A. Referral for CAR-T immunotherapy

Potential option- however given significant recent cytotoxic therapy, concerns for adequate lymphocyte numbers for collection. Kymriah requires ALC > 500 for collection. Additionally, up to 10% manufacturing failure in published studies.Also unclear currently if CAR-T is best used as stand alone definitive therapy or followed by transplant.

B. Continue with cytotoxic chemotherapy

Unlikely to eradicate remaining MRD and need plans for definitive therapy.

C. Initiate blinatumomab therapy and BMT referral

Excellent choice for bridging therapy and BMT referral as early as possible helps expand options for the patient.

D. Initiate blinatumomoab therapy with dasatinib and BMT referral

Excellent choice for bridging therapy and BMT referral as early as possible helps expand options for the patient.

Case Study 1

- Multiple published accounts of adult experiences with combining blinatumomab and TKI
- King AC et al Leukemia Research 2019, Martinelli G 2017 JCO, Assi R 2017 Clinical Lymphoma, Myeloma, and Leukemia
- Additional notes- combo of monosomy 7 and Ph+ has LFS ~ 40% post BMT (Aldoss BBMT2015)
- After cycle 1 blinatumomab/dasatinib, marrow evaluation was MRD negative, FISH Ph+ 2%, FISH monosomy 7 negative, CNS negative. Improving performance status and weight gain. 10/10 male, matched unrelated donor available.

Case Study 1

- **Question 2: What is the next step?**

A. Referral for CAR-T immunotherapy

B. Continue with blinatumomab/dasatinib therapy

C. Move to transplant

D. Continue with blinatumomab but change TKI

Case Study 1

- **Question 2: What is the next step?**

A. Referral for CAR-T immunotherapy

Zuma-3 showed feasibility and efficacy of CAR-T after blinatumomab, small numbers.

B. Continue with blinatumomab/dasatinib therapy

MRD status after cycle 1 blinatumomab appears highly predictive of overall response. Able to optimize dasatinib dose for recent weight gain.

C. Move to transplant

Best outcomes with MRD negative and PCR/FISH negative, patient only s/p 1 cycle

D. Continue with blinatumomab but change TKI

Mutation resistance testing negative, optimized dose for recent weight gain.

Case Study 1

- Cycle 2: FISH Ph+ 1.6%, PCR 1.1%, MRD and CNS negative
- Cycle 3: FISH Ph+ negative, PCR 0.7%, MRD and CNS negative
- Proceeded to BMT workup
- Screening chest CT notable for pneumonia. BAL positive for CMV, as well as low level viremia
- Initiated therapy with ganciclovir, Cytogam and continued dasatinib
- Repeat chest CT and BAL negative
- Underwent a myeloablative BMT (TBI, TT, CY conditioning) with a 10/10 MUD male donor with CSA and MTX GVHD prophylaxis
- In remission, 100% donor, peak grade III skin GVHD

Case Study 2

- Diagnosed with ALL, CNS-1 in 2010 at age 17 after presenting with fatigue, SOB, abnormal CBC
- Originally enrolled on COG AALL0232. Cryptic deletion of 9p21 and extra copy of chromosome 5
- Recurrent neurologic toxicity related to HD MTX (slurred speech and CN palsies), decision made to remove from study and use Capizzi MTX instead. Required Erwinia substitution for PEG-ASP due to infusion reaction.
- Completed therapy 2014
- Relapsed May 2018. CNS-1, no clonal evoluation. CD 10, 19, 22 positive
- Started treatment with modified CALGB 10403 with omission of PEG-ASP

Case Study 2

- **Question 1: What would you do next?**

A. Referral for CAR-T immunotherapy

B. Continue with cytotoxic chemotherapy and BMT referral

C. Initiate blinatumomab therapy and BMT referral

D. Initiate inotuzumab therapy and BMT referral

Case Study 2

- **Question 1: What would you do next?**

A. Referral for CAR-T immunotherapy

Potential option-however patient has Medicaid and no precedent for Medicaid coverage for CAR-T therapy

B. Continue with cytotoxic chemotherapy and BMT referral

Potential option- some limitations given history of PEG-Asp allergy and MTX encephalopathy. BMT referral as early as possible helps expand options for the patient.

C. Initiate blinatumomab therapy and BMT referral

Excellent therapeutic choice but complicated social situation and concern to be able to manage continuous infusion and logistics of blinatumomab.

D. Initiate inotuzumab therapy and BMT referral

Excellent choice for bridging therapy and BMT referral as early as possible helps expand options for the patient. INO-VATE ALL trial showed significantly longer PFS compared to standard therapy

Case Study 2

- Patient received 2 cycles of inotuzumab. Course complicated by E coli bacteremia. Patient in remission. He has a matched sibling donor.
  - **Question 2: What is the next step?**

A. Referral for CAR-T immunotherapy

B. Continue with inotuzumab therapy.

C. Move to transplant.

D. Consider completion of therapy.

Case Study 2

- Patient received 2 cycles of inotuzumab. Course complicated by E coli bacteremia. Patient in remission. He has a matched sibling donor.

- **Question 2: What is the next step?**

A. Referral for CAR-T immunotherapy

Potential option-however patient has Medicaid and no precedent for Medicaid coverage for CAR-T therapy

B. Continue with inotuzumab therapy.

Potential option- median # cycles of 3 in INO-VATE trial. However, patient in remission and has had therapy related complications.

C. Move to transplant.

Patient is in remission and had a matched sibling donor.

D. Consider completion of therapy.

Needs definitive therapy for best chance of cure.

Case Study 2

- Patient went to myeloablative TBI based transplant with matched sibling donor. Offered participation in defibrotide clinical trial due to increased risk of VOD. Patient declined.
- 16 months s/p BMT, one year evals 100% donor. Mild chronic GVHD