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

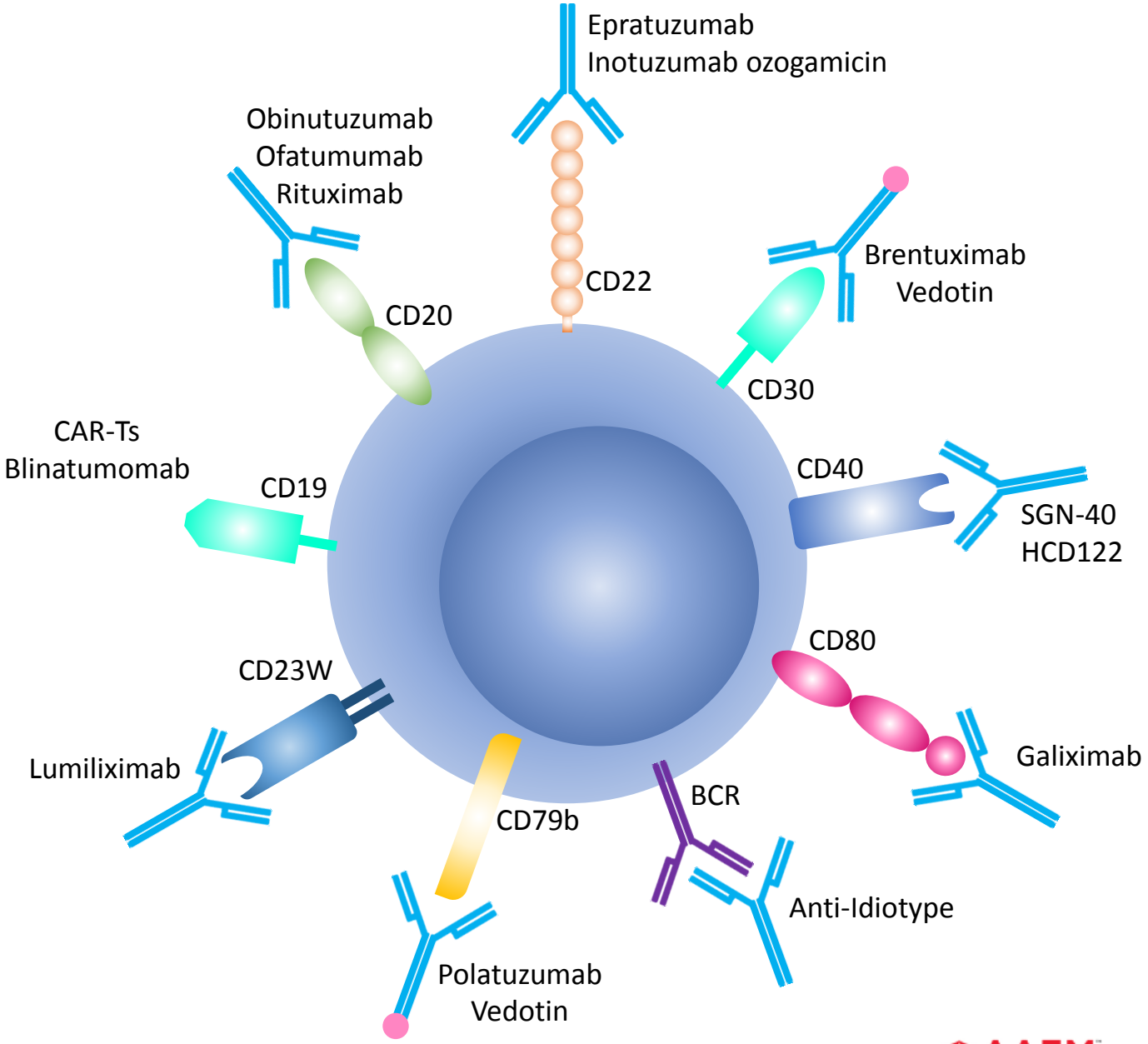
ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- I have no conflicts of interest to disclose.
- I will be discussing non-FDA approved indications during my presentation.



Checkpoint inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

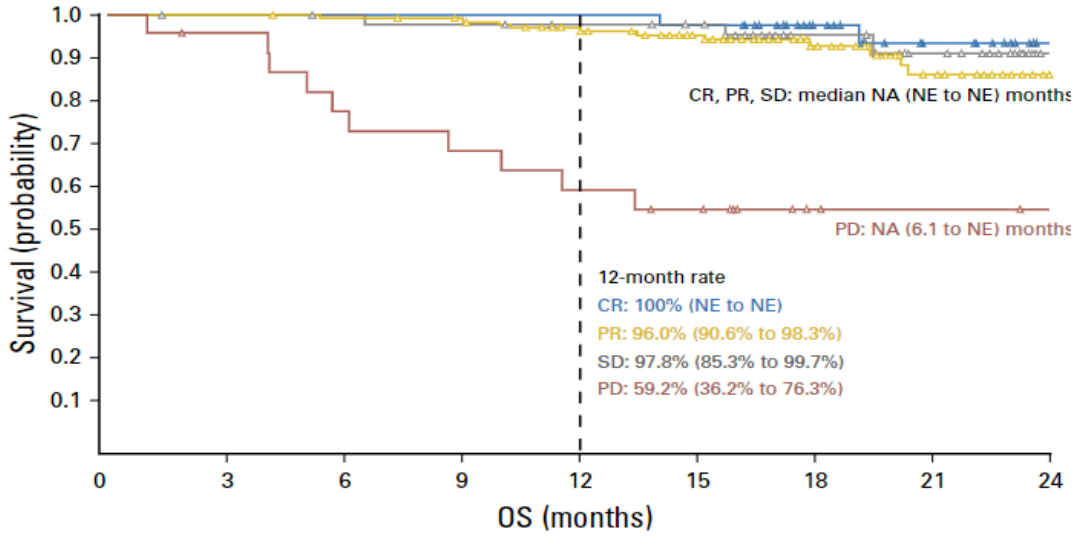
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg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

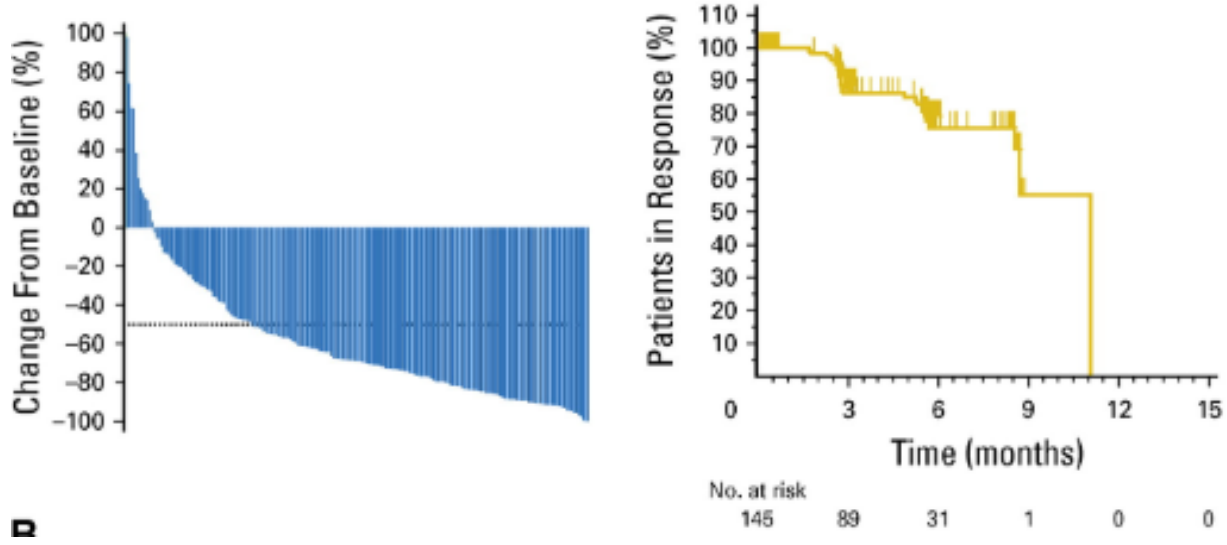
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

CR = 22.4%

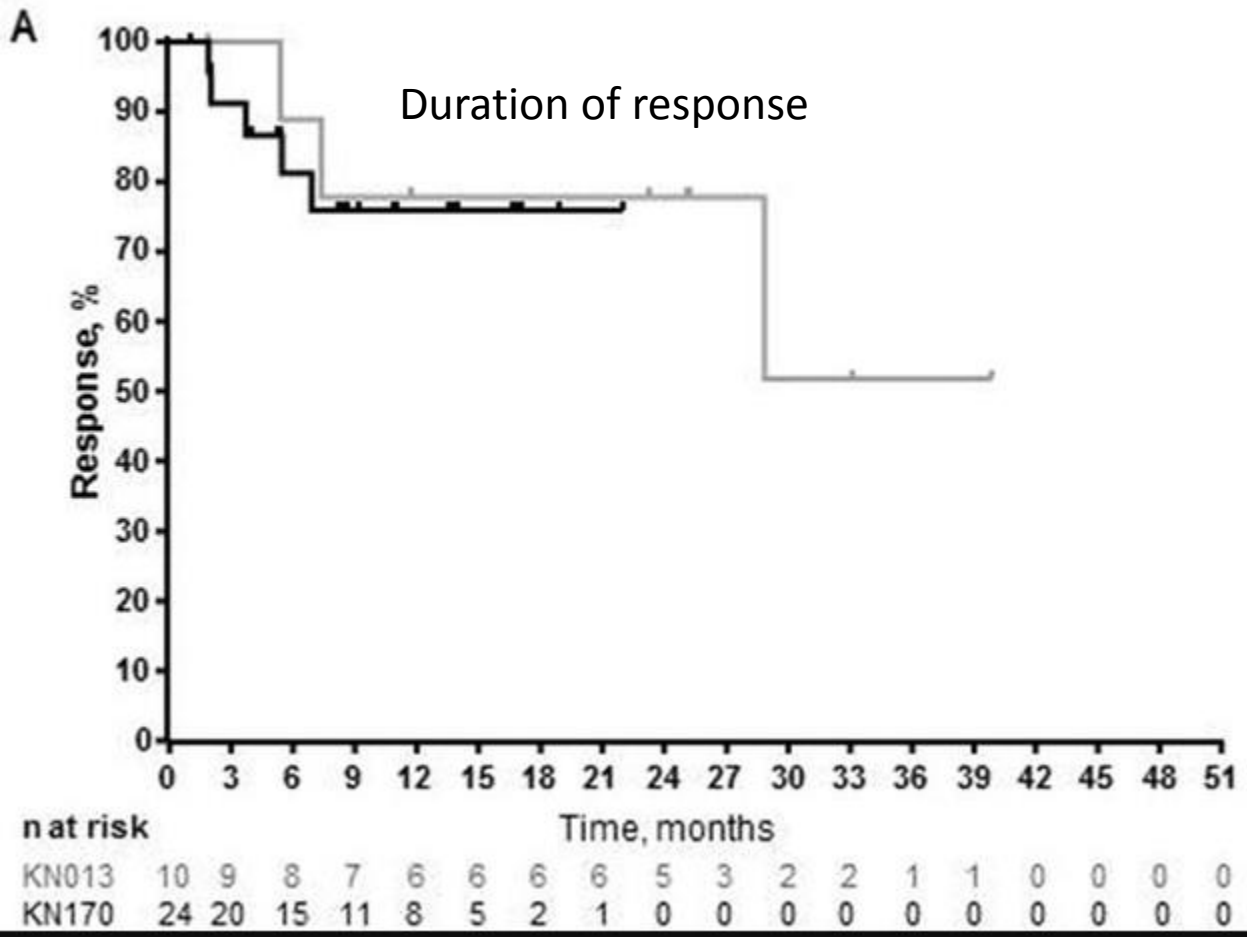
Activity seen regardless of PD-L1 expression

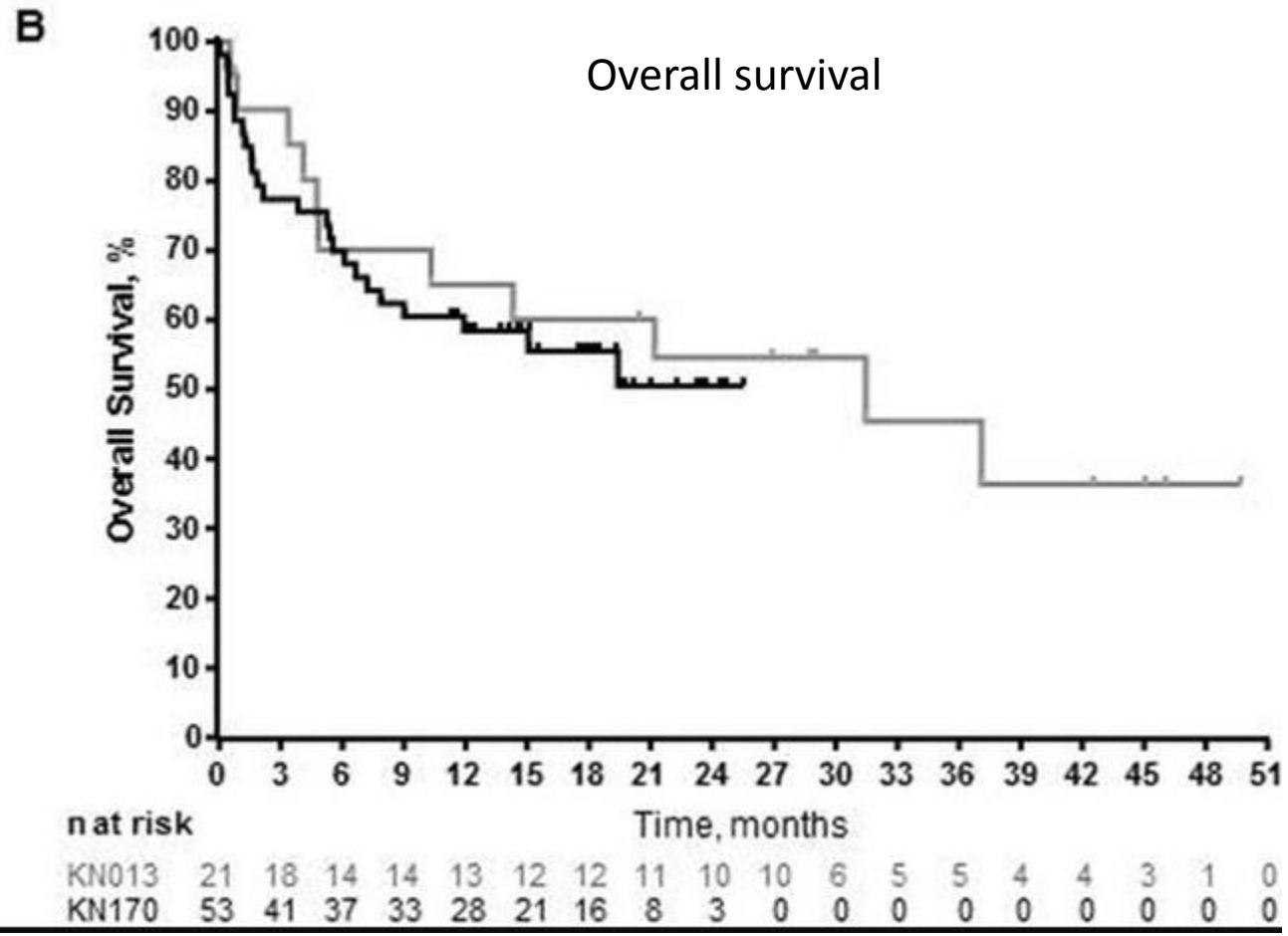


Armand, J Clin Oncol 2018.

Chen, J Clin Oncol 2017.

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

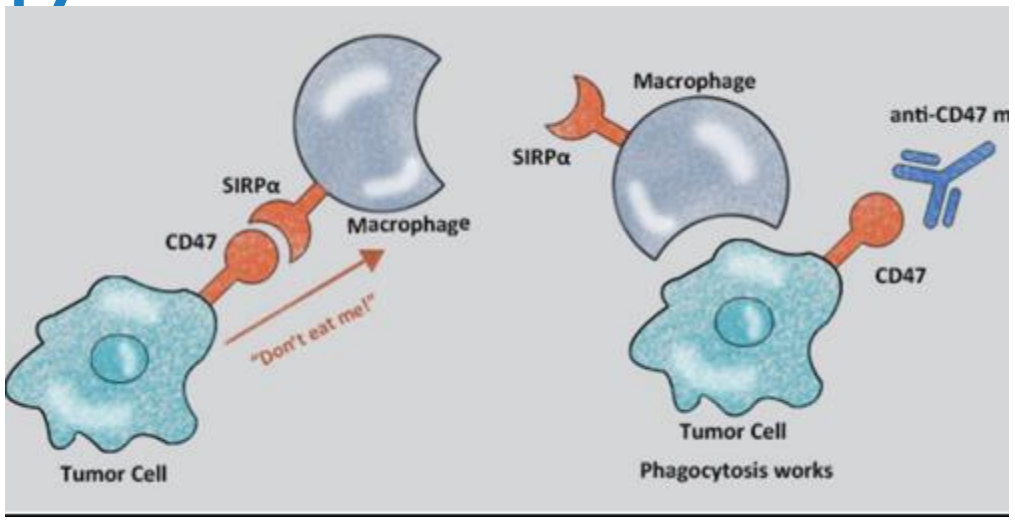


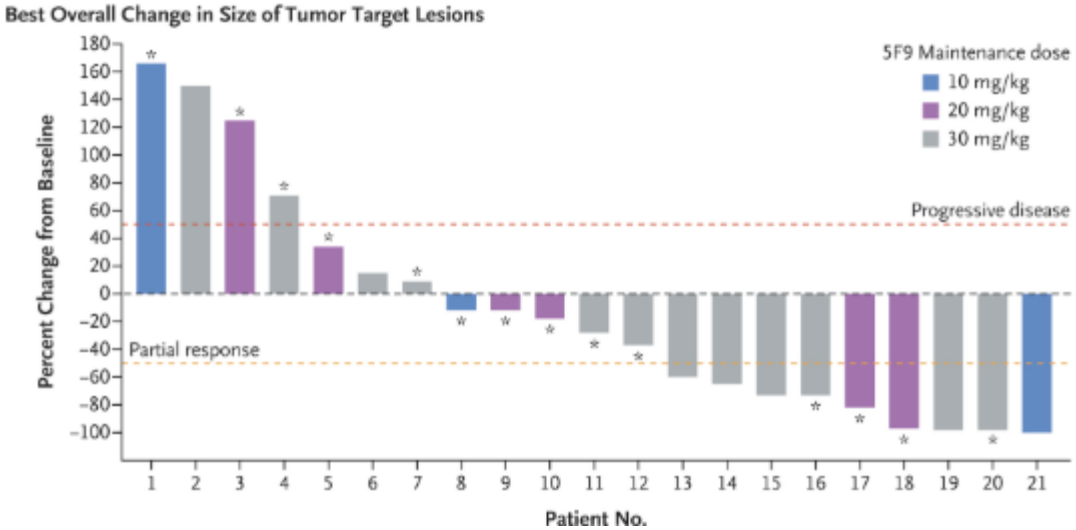


Armand, Blood 2018.

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%



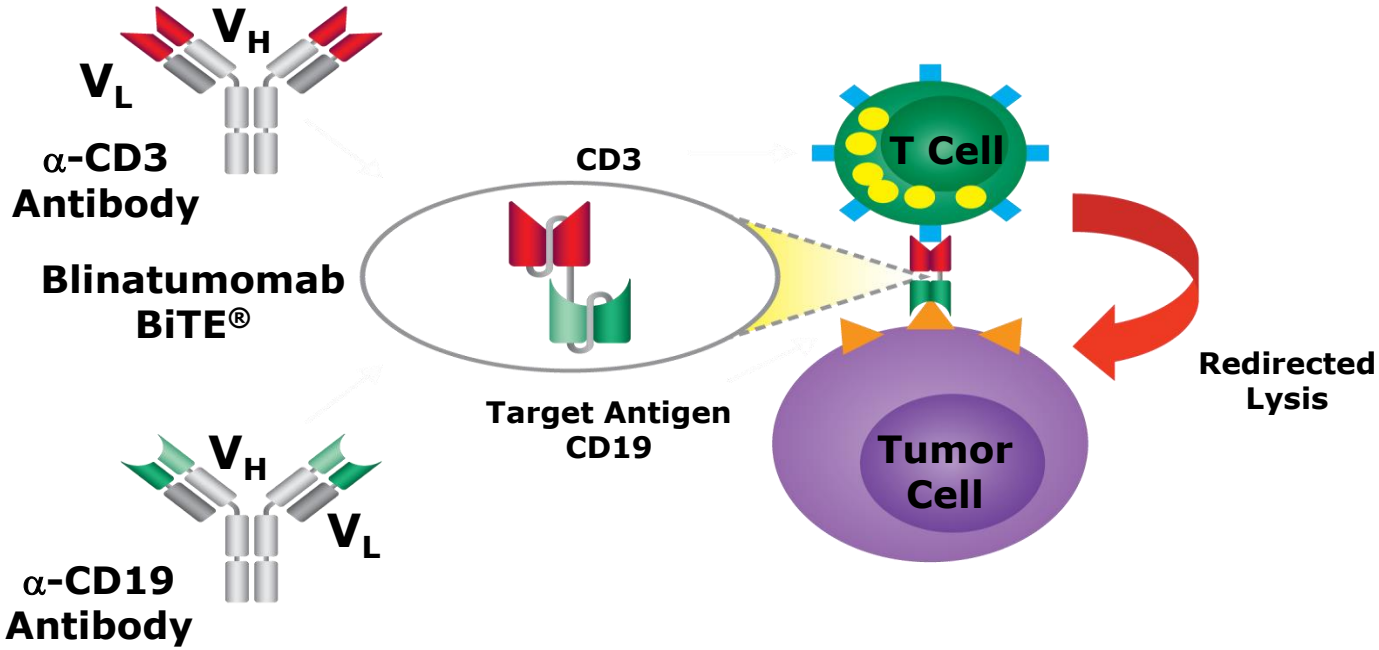


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

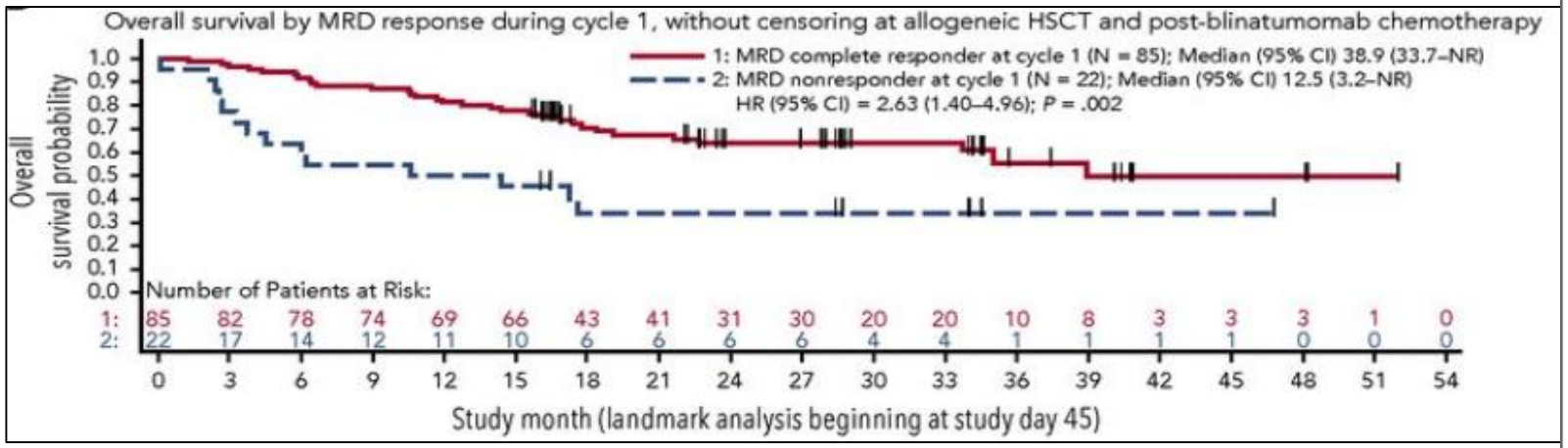
BiTE (Blinatumomab) Therapy

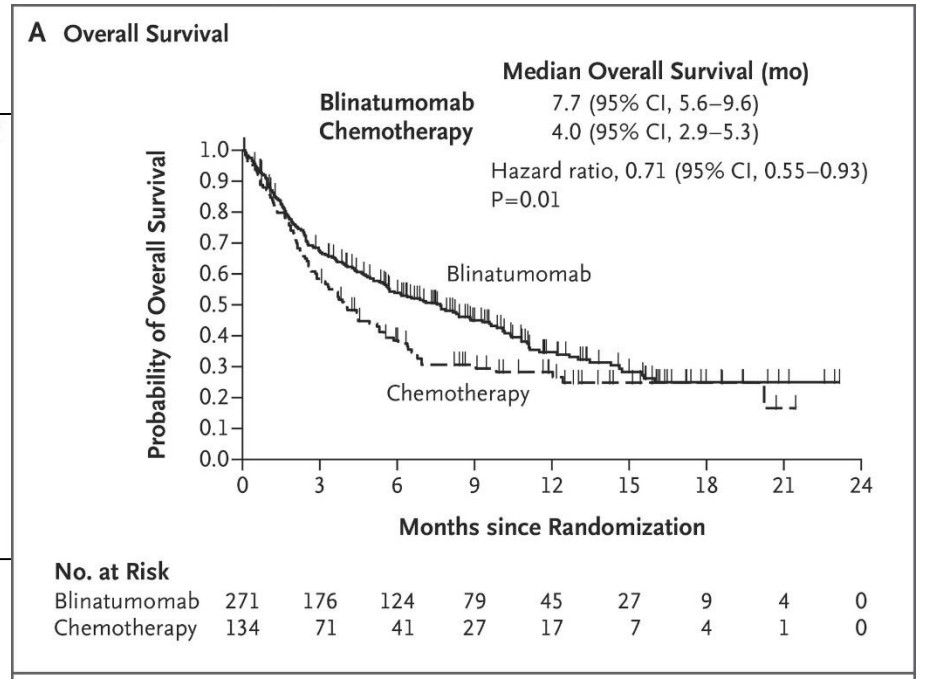
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



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 • Classical Hodgkin lymphoma, post auto-HSCT consolidation in high risk pts • Anaplastic large cell lymphoma ≥ 1 previous therapies
		2017	• Mycosis fungoides ≥ 1 previous therapies
		2018	cHL - first line with combination chemo ALCL, CD30+ PTCL- 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

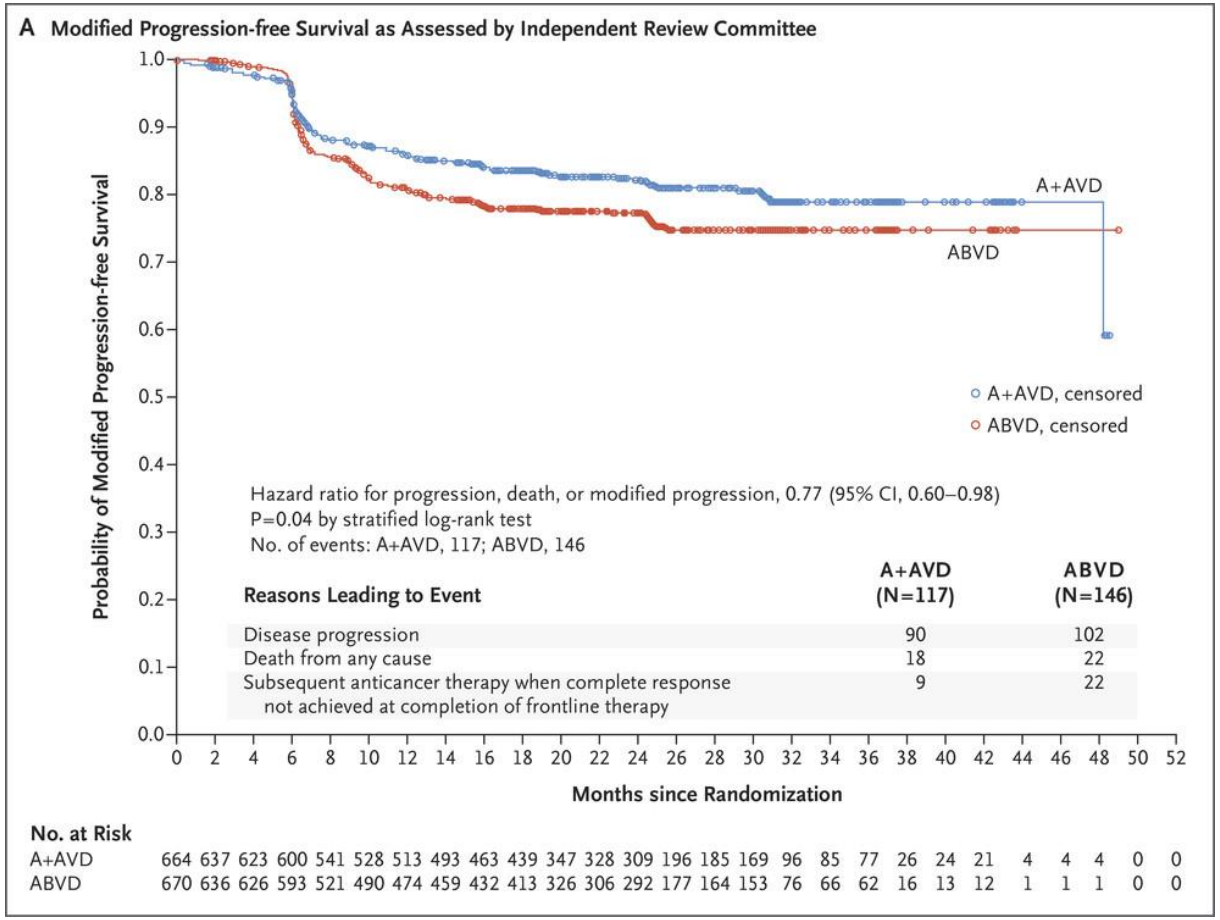
Brentuximab in newly dx cHL: Echelon-1 study

2-year modified progression-free survival rate,

A+AVD: 82.1% [95% confidence interval {CI}, 78.8 to 85.0]

ABVD: 77.2% [95% CI, 73.7 to 80.4]

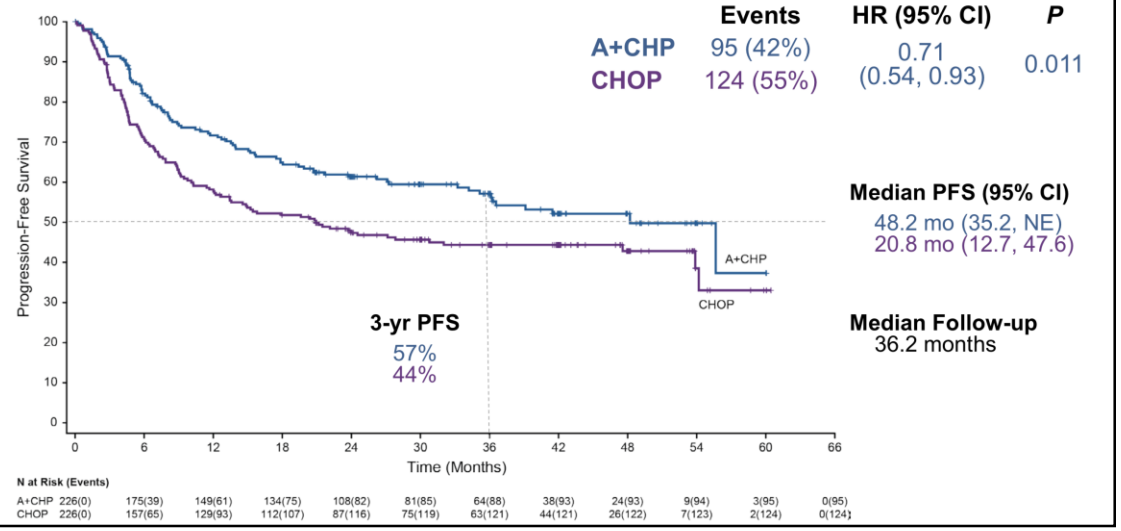
HR: 0.77 [95% CI, 0.60 to 0.98]; P=0.04



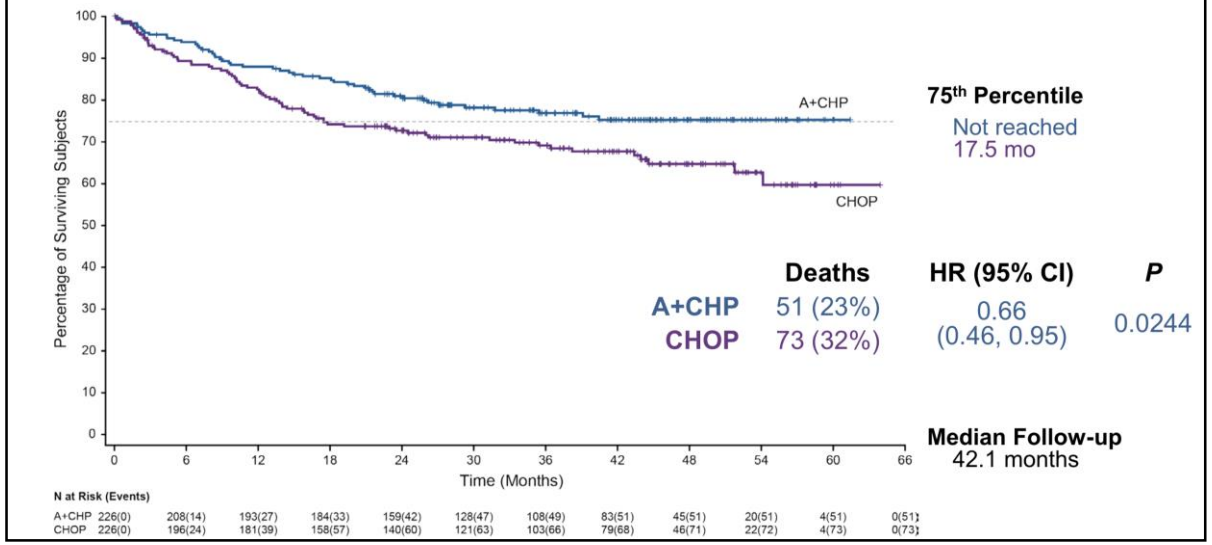
JM Connors et al. N Engl J Med 2018;378:331-344.

Brentuximab in newly dx CD30+ PTCL: Echelon-2 study

Progression-free Survival

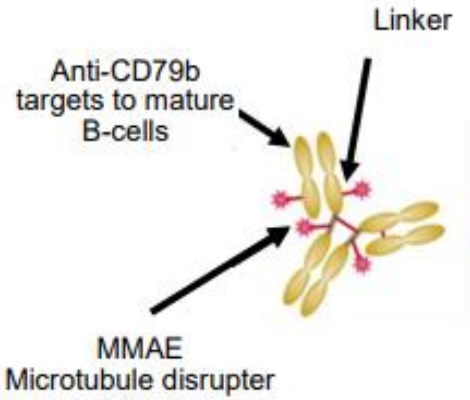


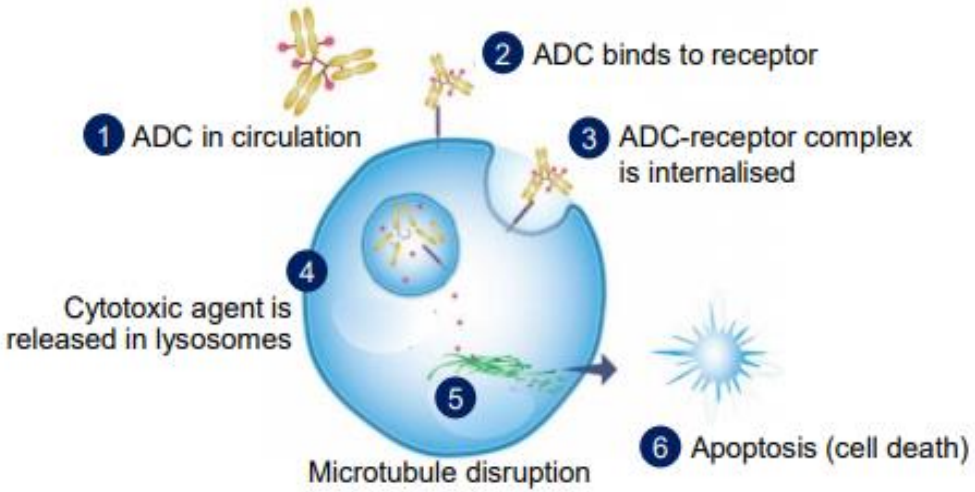
Overall Survival



Horwitz et al. Abstract 997. ASH 2018

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

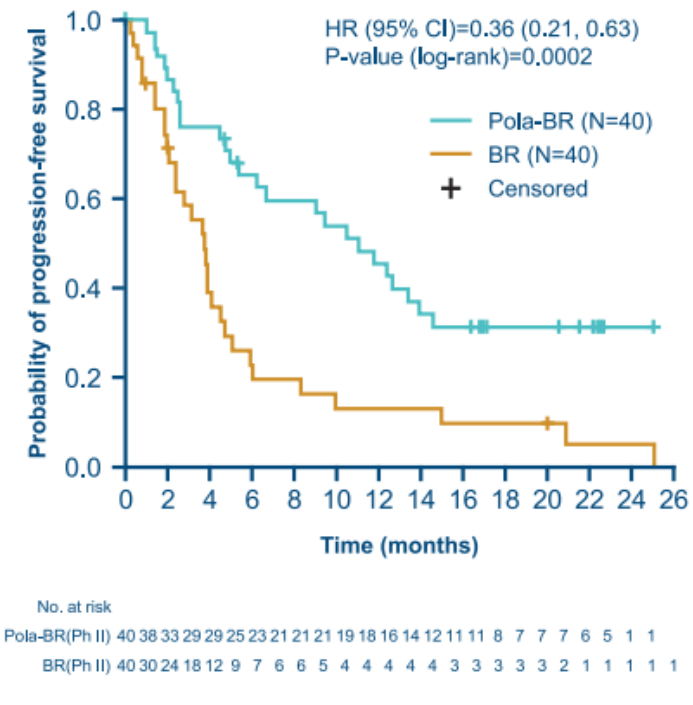
Slide credit: Tilly et al. ICML 2019

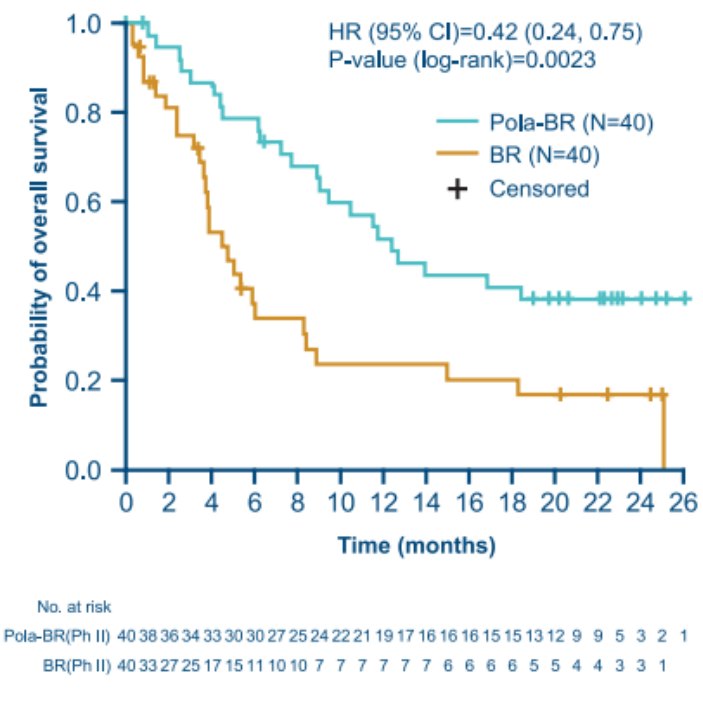
Polatuzumab vedotin: DLBCL

- 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

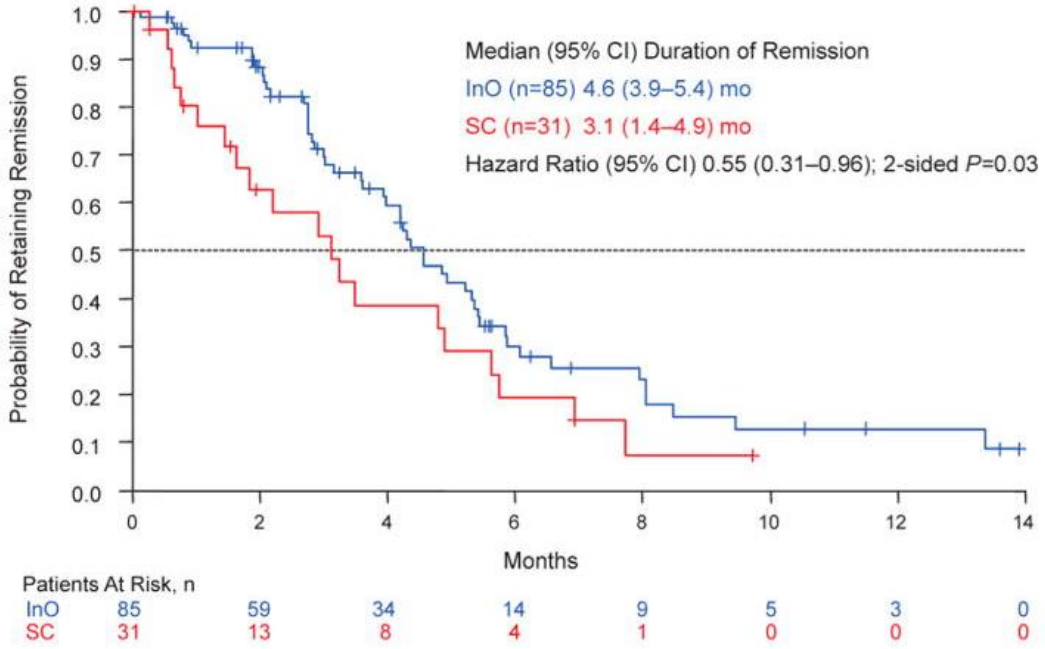


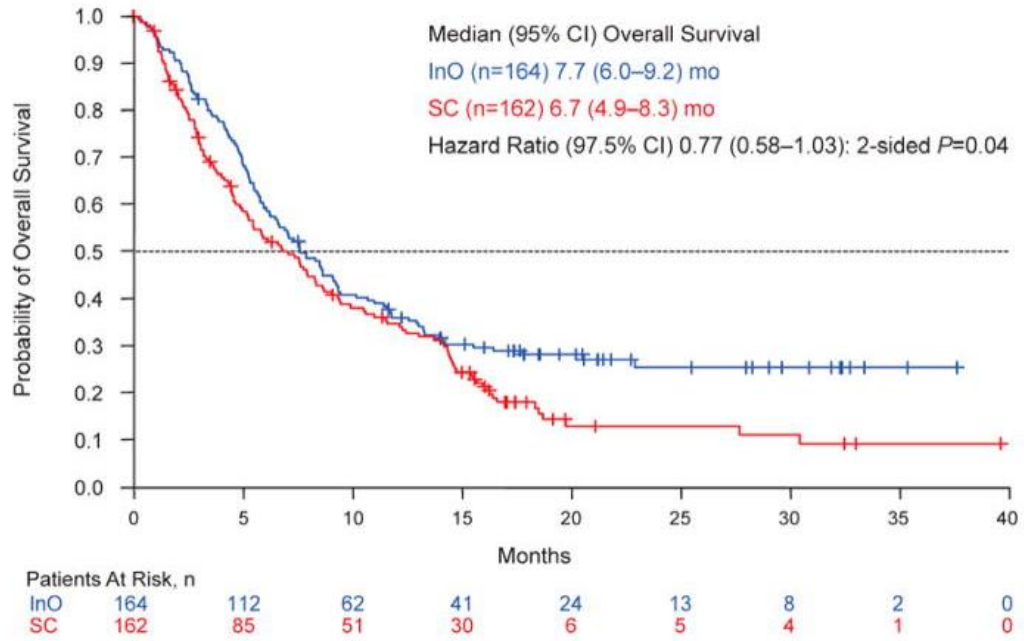


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



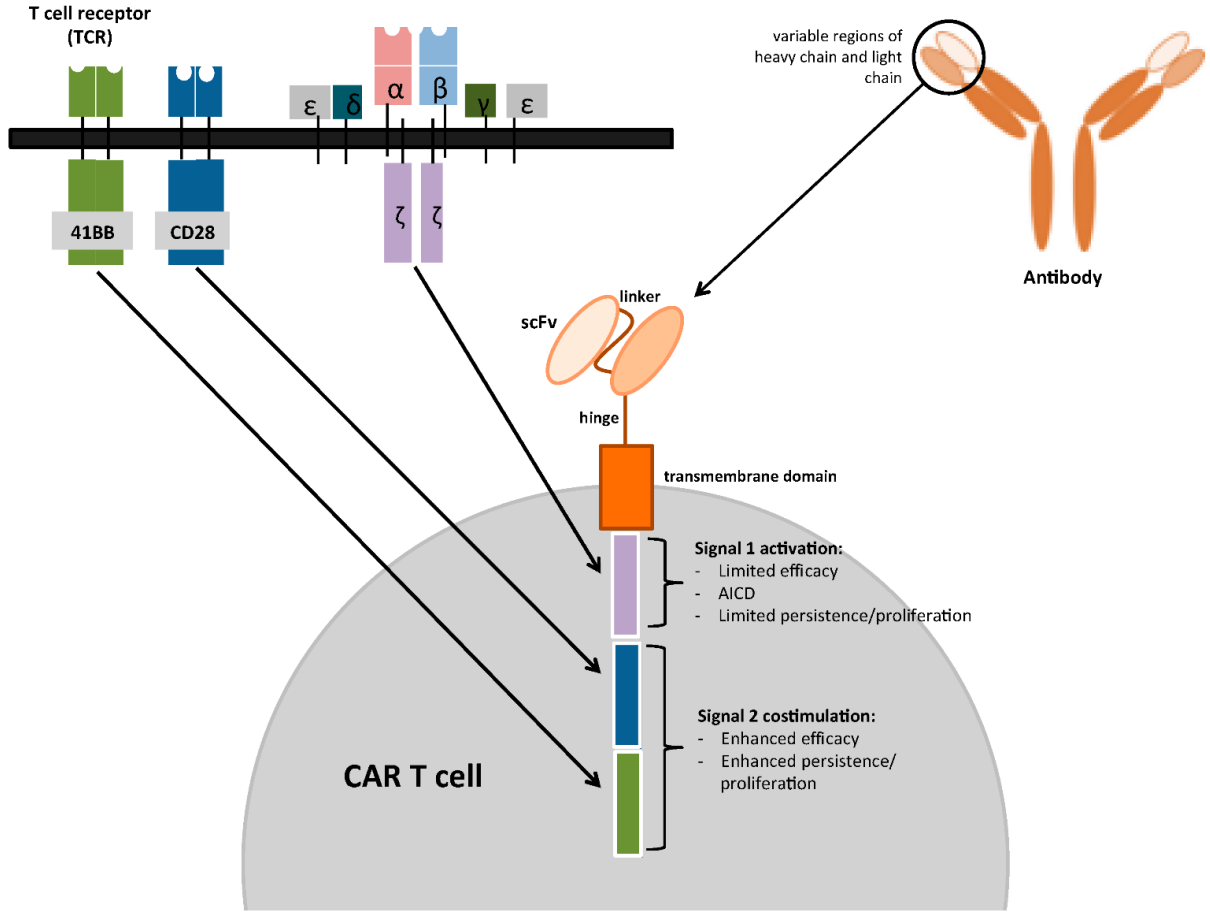


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

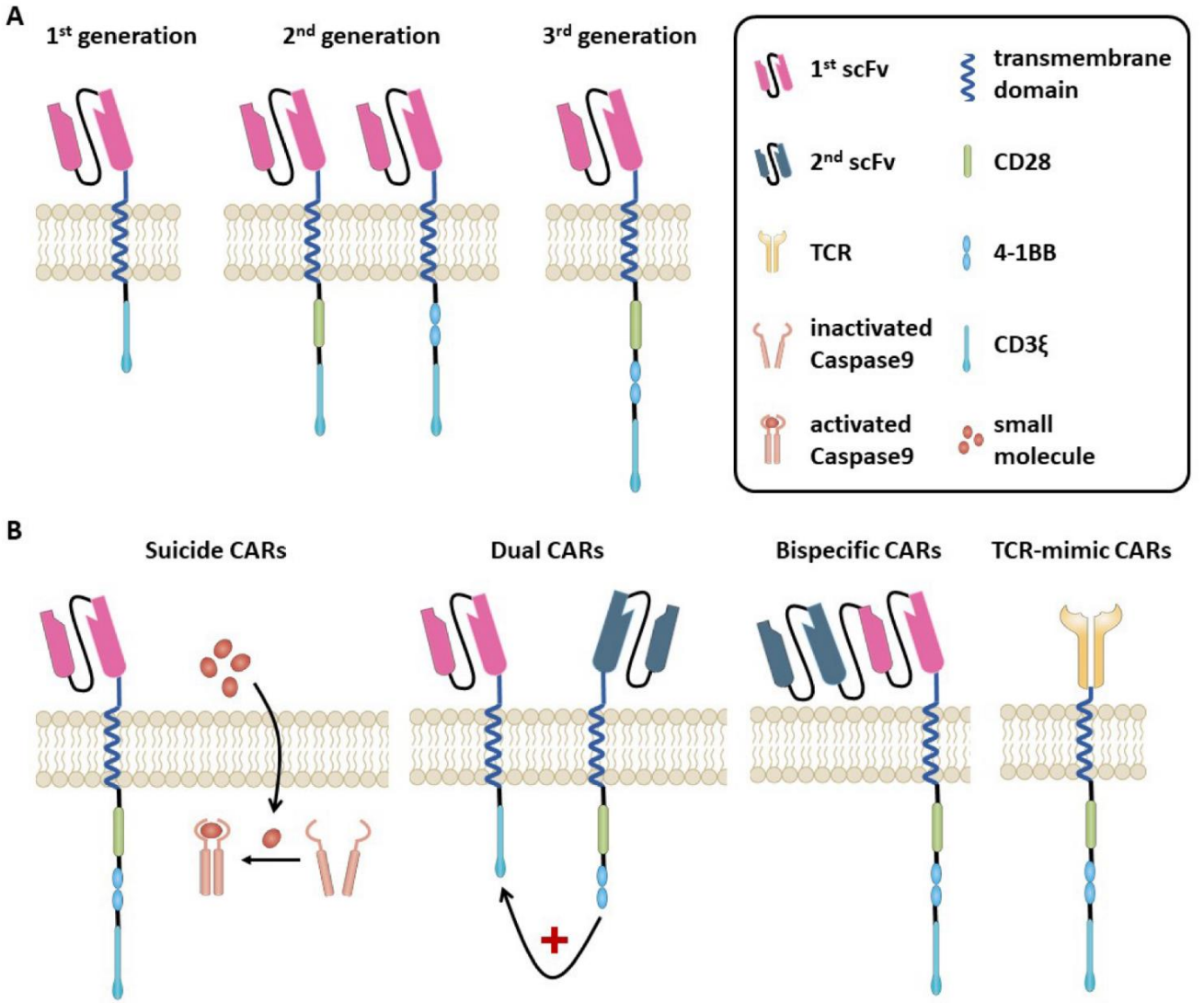
Chimeric antigen receptors

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



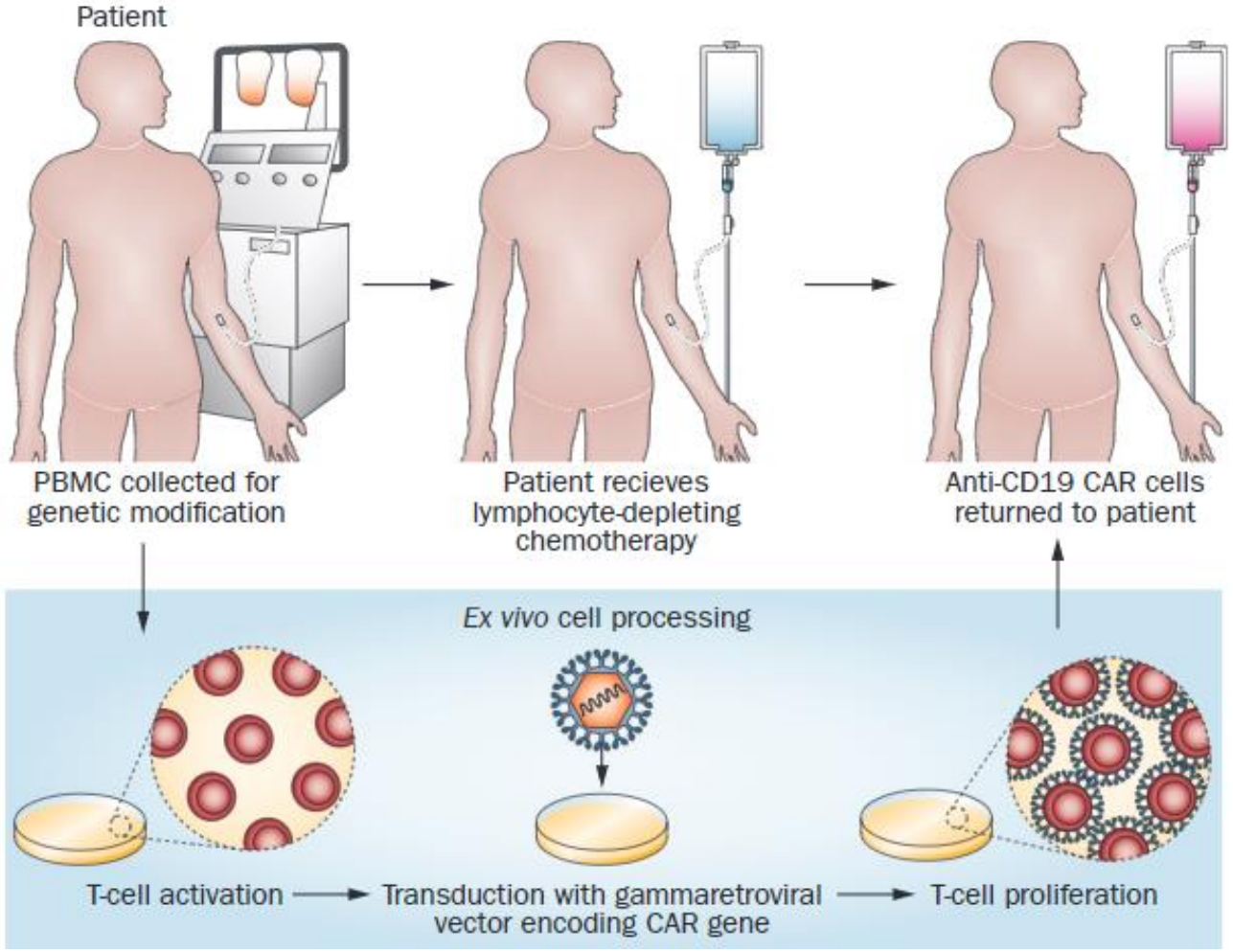
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

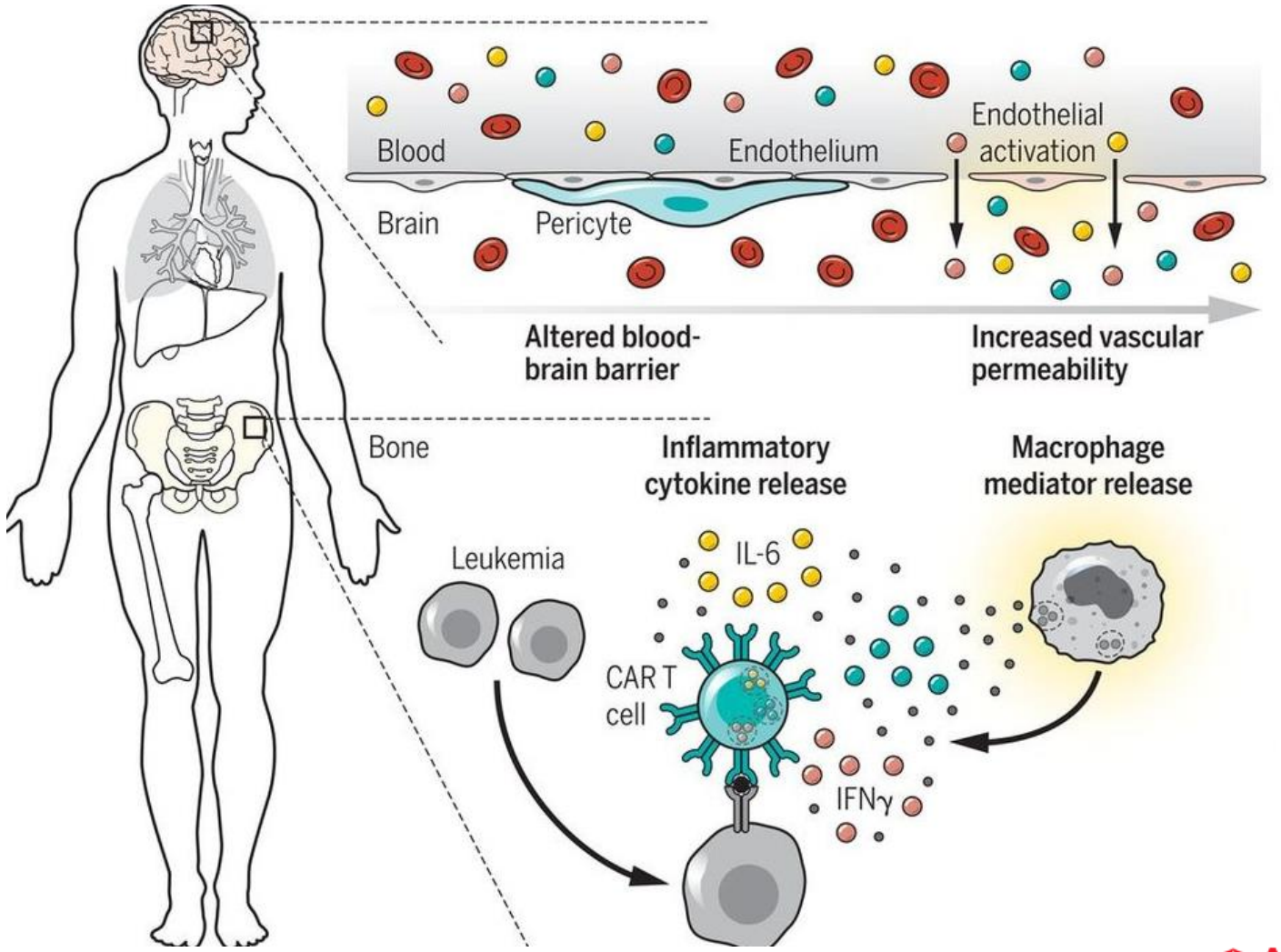


Kochenderfer, Nat Rev Clin Oncol 2013.

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

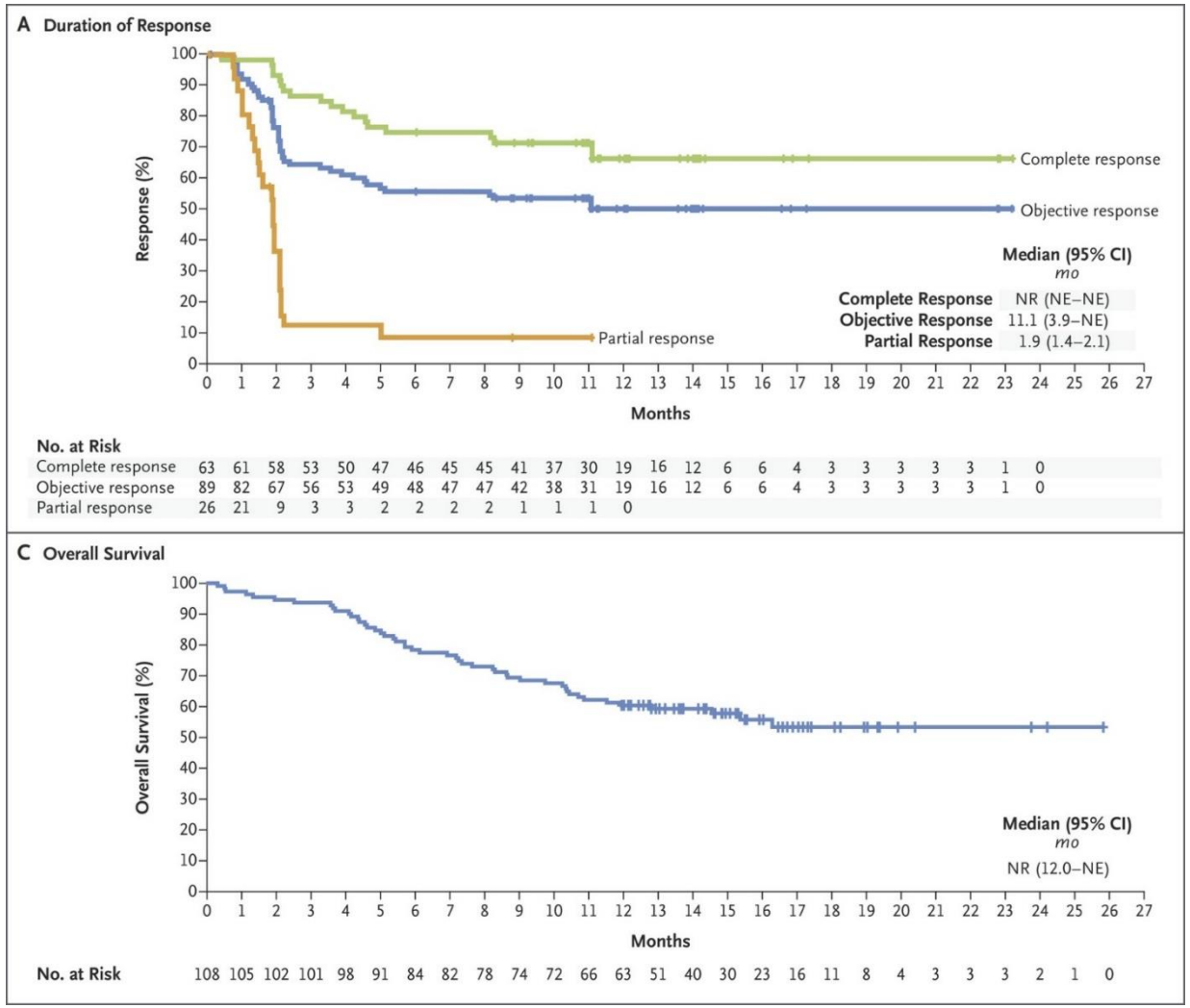
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight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

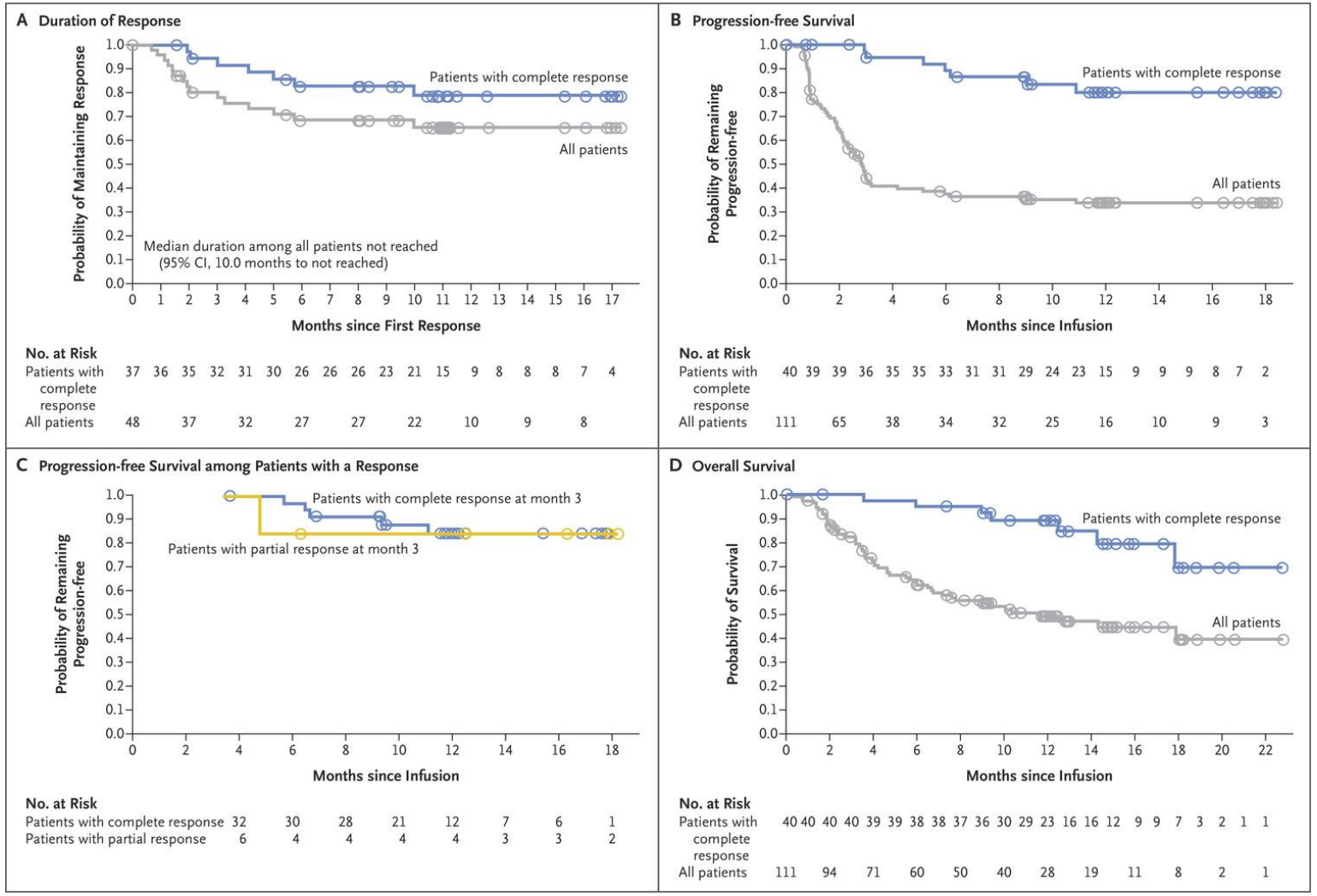
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

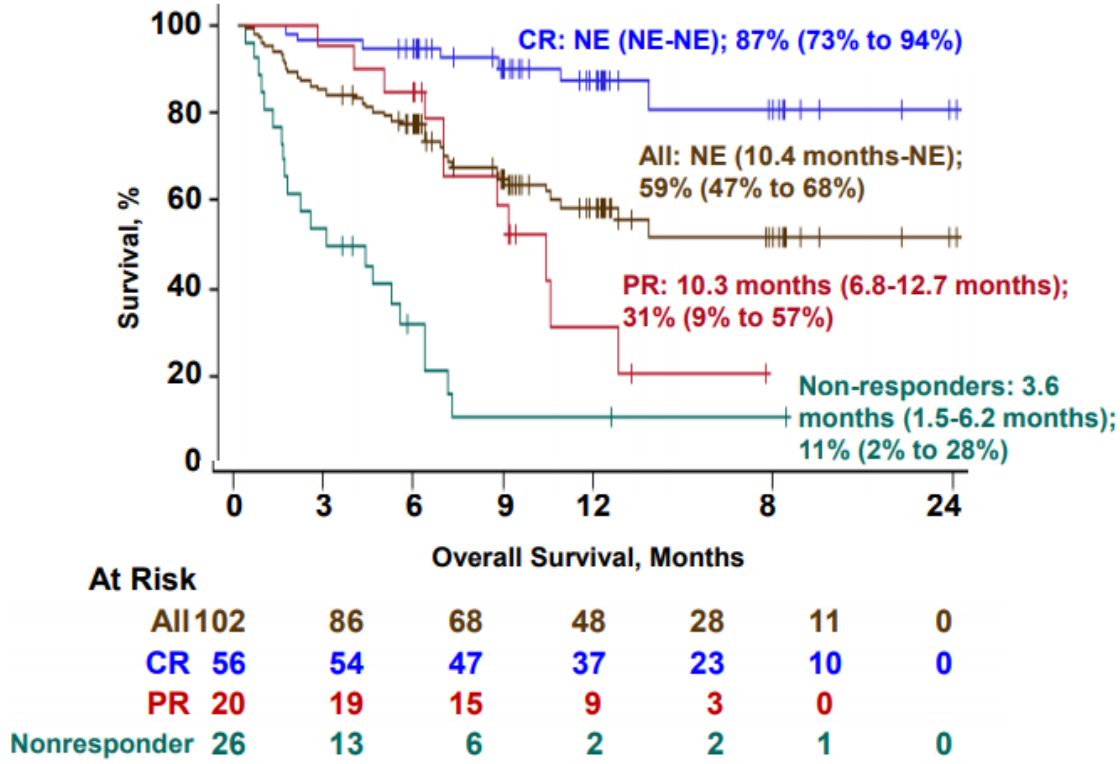
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

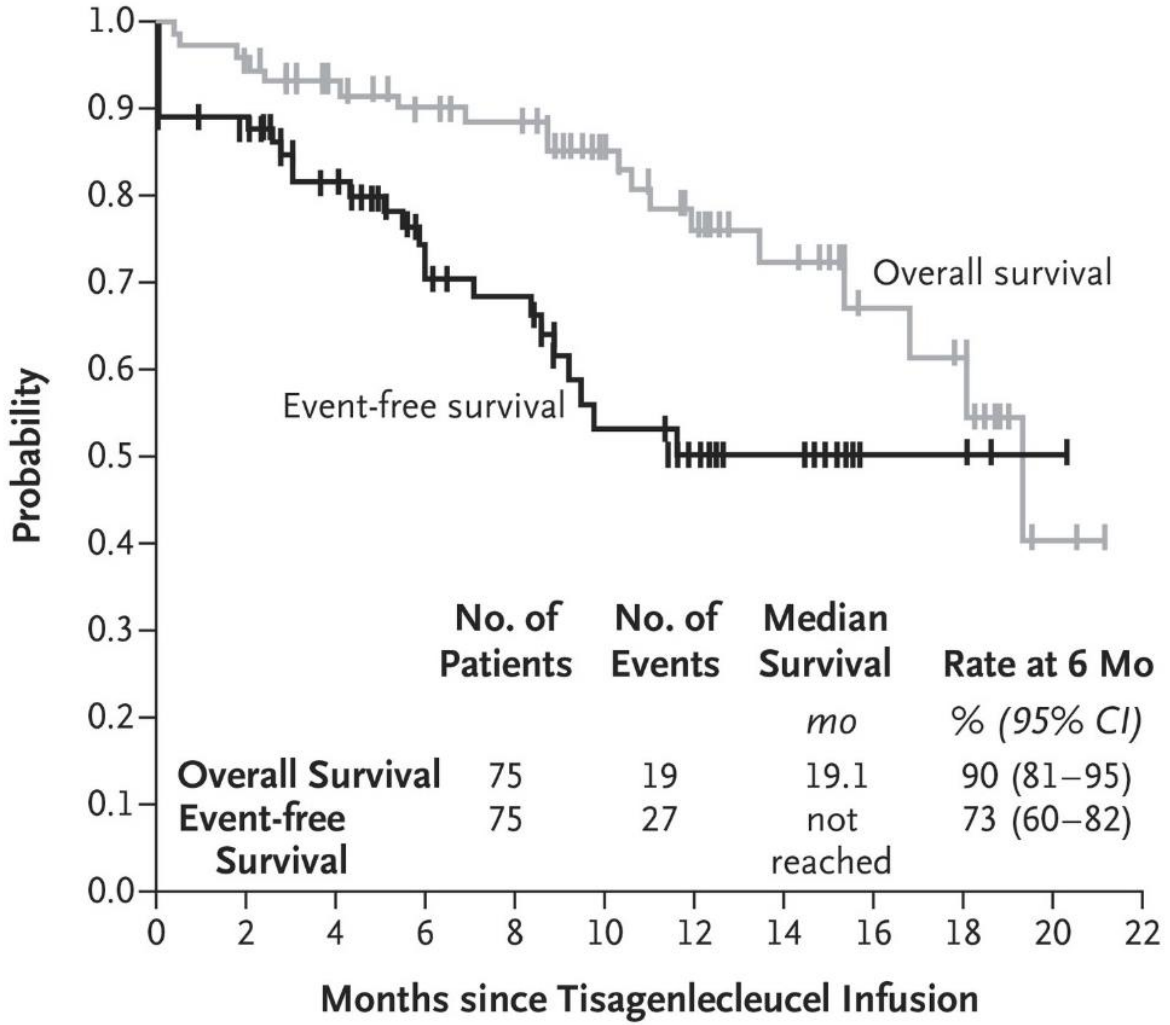
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

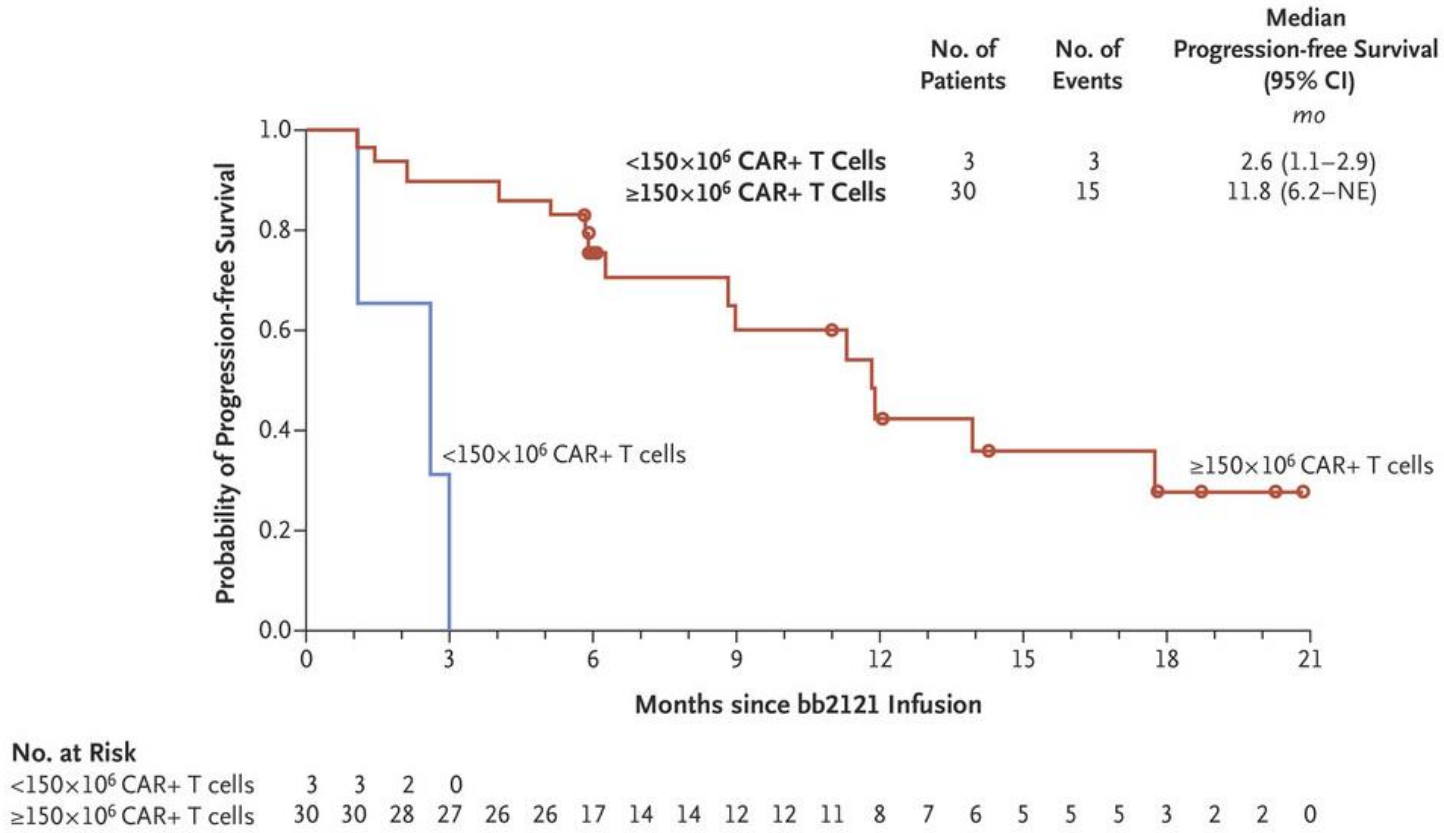


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

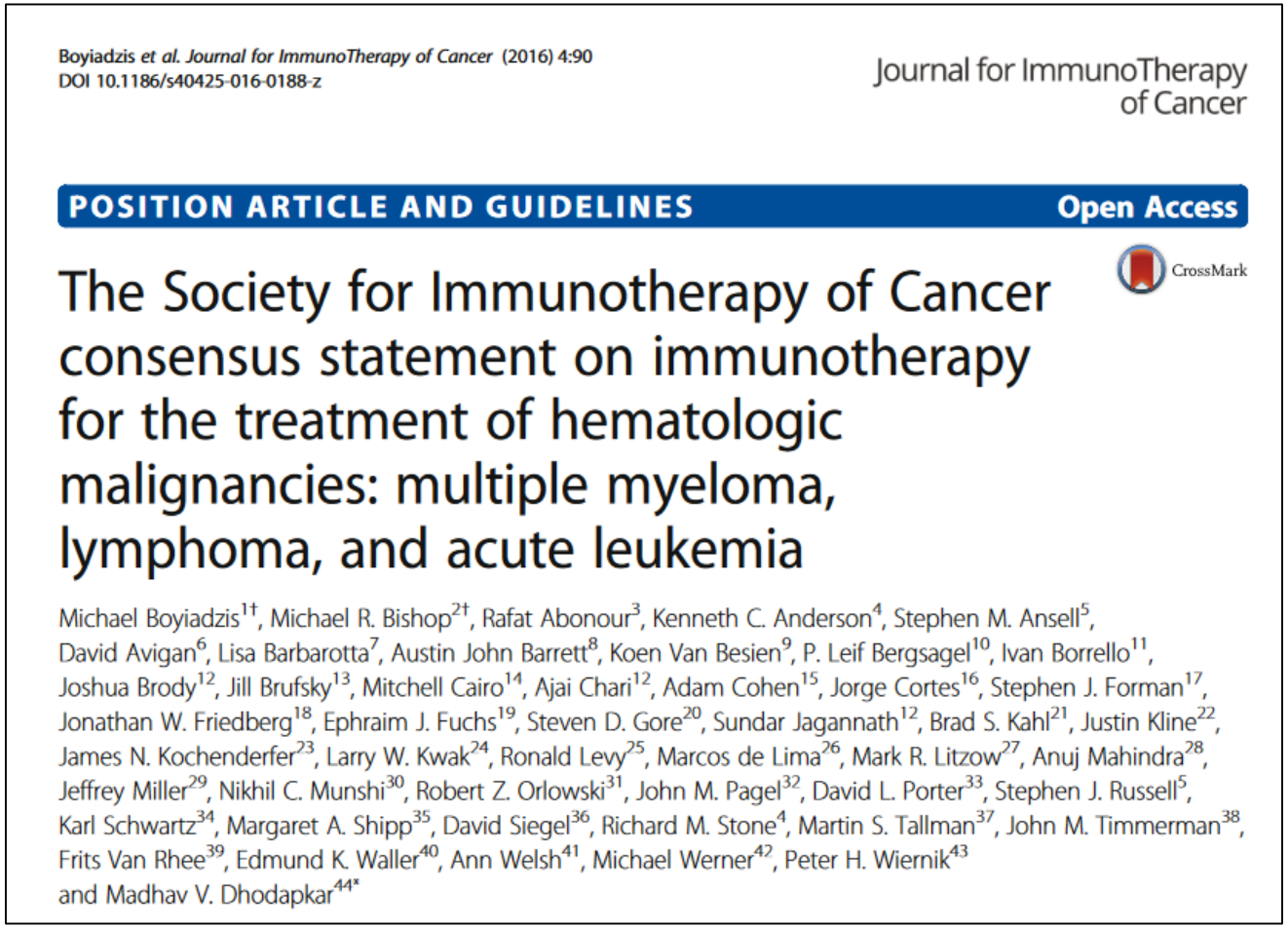


Raje, NEJM 2019.

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: DLBCL

Ms. P is an 80 year old woman with DLBCL, non-GCB subtype, negative for double hit cytogenetics, stage 4 disease (suspected lung involvement). At diagnosis, she looked quite frail, ECOG PS 1-2; her comorbidities include Crohn's disease, colostomy and h/o iatrogenic bowel perforation.

1st line therapy: mini R-CHOP x 1 cycle

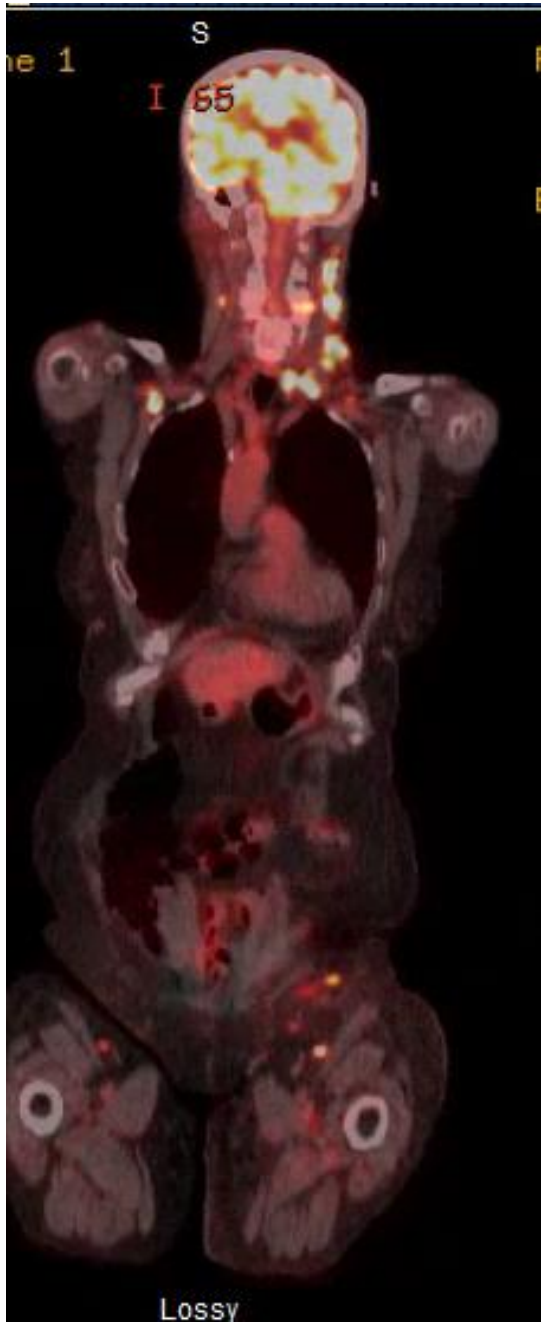
2nd line therapy: lenalidomide-rituximab → remission for 1 year

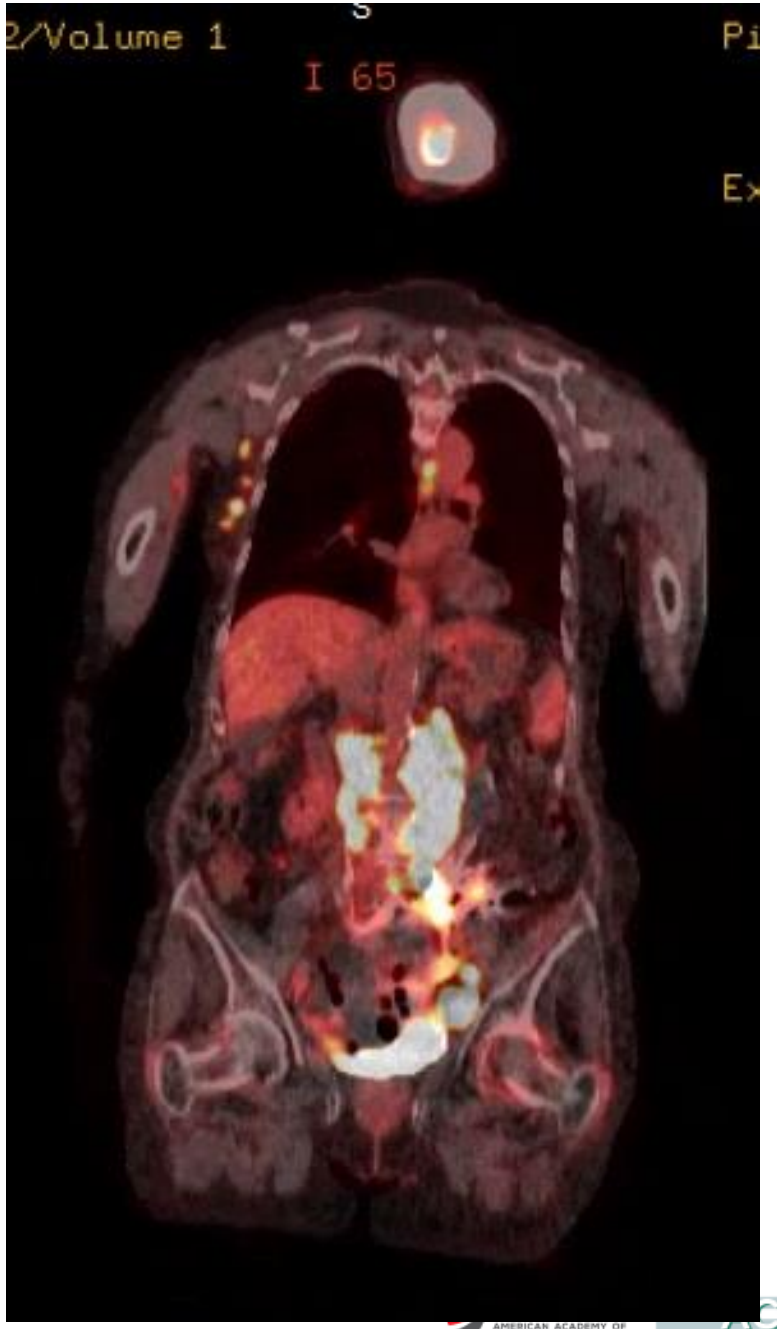
She came to our clinic with new onset left neck adenopathy. On exam, she had palpable cervical and axillary lymphadenopathy.

Question 1: What will be the next step?

1. PET scan
2. Repeat biopsy
3. Change therapy
4. Hospice consult

- What will be the next step?
  1. PET scan- correct, imaging is needed to discern burden and location of disease
  2. Repeat biopsy- correct- to ensure that the diagnosis and markers are unchanged. Patient has been on lenalidomide which can lead to secondary malignancies.
  3. Change therapy- correct- if patient desires further therapy, other options need to be considered once diagnosis is confirmed
  4. Hospice consult- correct- shared decision making, patient should be offered hospice services if further therapy undesirable





Case Study 1

PET 9/11/2019 confirmed relapse, biopsy showed non-germinal center B-cell phenotype, double-expressor lymphoma with high Ki67. Patient in interested in further therapy

Question 2: What will be the most appropriate treatment option?

1. Salvage therapy such as ICE/DHAC followed by autologous stem cell transplant
2. Anti CD-19 CAR-T cell therapy
3. Ibrutinib
4. Polatuzumab-rituximab-bendamustine
5. Single agent rituximab

Case Study 1

Question 2: What will be the most appropriate treatment option?

1. Salvage therapy such as ICE/DHAC followed by autologous stem cell transplant- incorrect, patient unfit for such therapy
2. Anti CD-19 CAR-T cell therapy- incorrect, patient unfit for such therapy, plus large burden of disease with rapid progression
3. Ibrutinib- incorrect, responses short-lived, concomitant anticoagulation
4. Polatuzumab-rituximab-bendamustine- correct, ability to dose adjust based on tolerance, longest duration of response in this scenario
5. Single agent rituximab- possible, though responses short-lived, as patient rituximab refractory.

- Patient was given first cycle with rituximab-Polatuzumab (bendamustine omitted) which she tolerated well. Lymph nodes regressed clinically at next clinic visit. Bendamustine added with cycle #2 at 50% dose reduction, adjusted for GFR.

Case Study 2- HL

- A 37-year-old Caucasian woman with relapsed/refractory HL presented with gradual onset cholestatic jaundice and constitutional symptoms for 2 months
- Initially diagnosed with mixed cellularity classical HL 4 years back when she presented with painless cervical lymphadenopathy and intense pruritus while 20 weeks pregnant. She had no laboratory evidence of liver involvement at diagnosis, staging scans could not be performed due to her gravid state.
- She received 3 cycles of ABVD followed by successful delivery of a healthy baby girl at 32 weeks gestation. Thereafter, she completed 3 additional cycles of ABVD and achieved a complete metabolic response (CMR).
- 1st relapse: Six months later, she developed intense pruritus, PET and biopsy confirmed relapse. She received ICEx 2 followed by HDC-ASCT and attained CMR on day+100.
- 2nd relapse: 21 months later. She initiated therapy with 20 mg lenalidomide on a clinical trial; restaging PET after 3 cycles showed stable disease. She had been on lenalidomide for an additional 3 months, when she developed progressively worsening cholestatic jaundice.

What will be the next step?

1. Stop all hepatotoxic drugs
2. Evaluation by a liver specialist and workup of cholestatic jaundice
3. Liver biopsy
4. PET scan to evaluate for recurrent disease

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The patient was admitted twice at an outside hospital where suspecting drug-induced liver injury, all medications, including lenalidomide, aspirin, oral contraceptives and fluoxetine were discontinued, albeit with no improvement.

Antimitochondrial antibody (AMA), antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver-kidney-smooth muscle (LKM) antibody, hepatitis A, B, C, CMV and EBV work-up was negative.

Ceruloplasmin, thyroid stimulating hormone and alpha-1 antitrypsin levels were normal.

Ferritin was elevated at 1682 ng/ml; however, serum iron levels were normal.

Liver biopsy showed intracellular and intracanalicular cholestasis with mild intracellular iron deposition, no evidence of lymphoma.

PET scan showed worsening adenopathy in the thoracic cavity and neck consisting with progression of HL, however no intra-abdominal disease was noted.

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At this point, her liver function tests showed

- total bilirubin 28.3 mg/dL, direct- 25 mg/dL
- ALT 131 IU/L, AST 126 IU/L, ALP 733 IU/L, INR 1.31.

A diagnosis of paraneoplastic idiopathic cholestasis was considered.

How would you treat this patient?

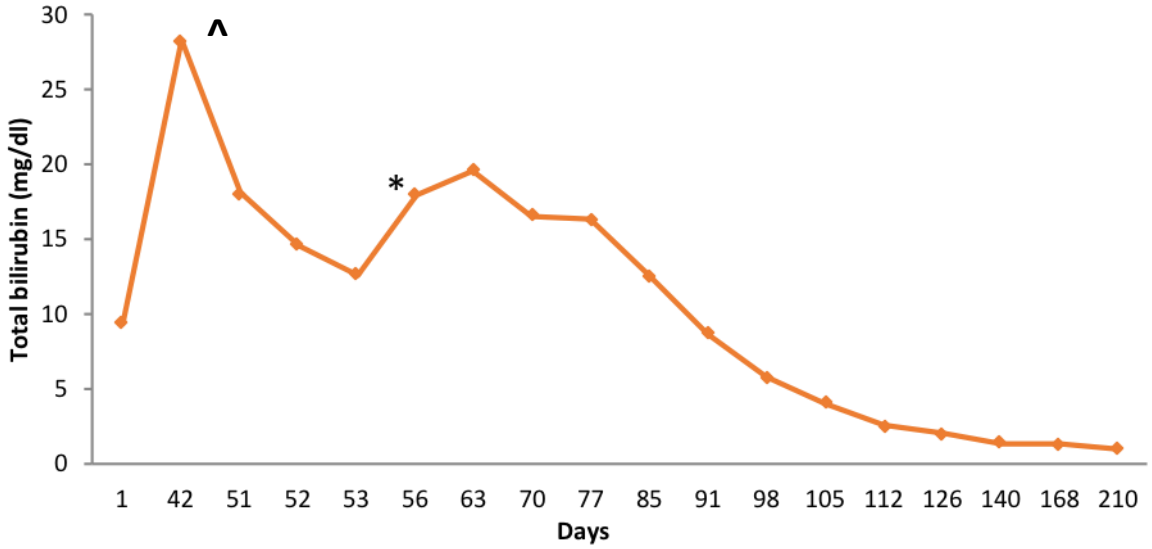
1. Gemcitabine
2. Bendamustine
3. Brentuximab
4. Nivolumab
5. Cyclophosphamide
6. High-dose steroids

- How would you treat this patient?

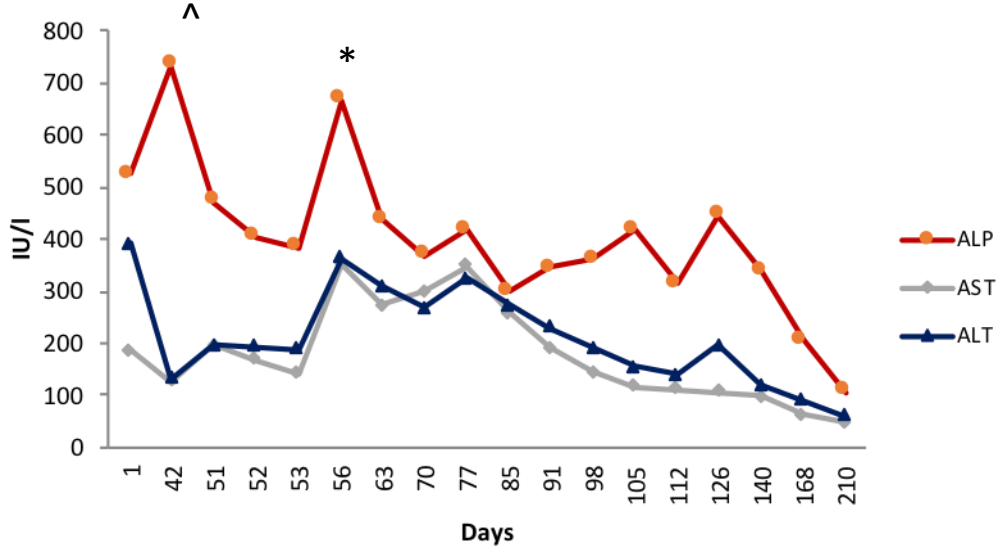
1. Gemcitabine- incorrect, contraindicated for this degree of hyperbilirubinemia
2. Bendamustine- incorrect, contraindicated for this degree of hyperbilirubinemia
3. Brentuximab- incorrect, contraindicated for this degree of hyperbilirubinemia
4. Nivolumab- correct
5. Cyclophosphamide- correct
6. High-dose steroids- correct

- The patient received 3 doses of intravenous cyclophosphamide 100 mg/m2 and intravenous methylprednisolone 125 mg once a day.
- Three days later, the patient initiated single agent nivolumab 3 mg/kg every 2 weeks.
- Imaging studies confirmed a partial remission after 3 cycles of nivolumab.
- Two years later, the patient continues to respond to nivolumab, she has deferred an allogeneic stem cell transplant.

A



B



Total bilirubin (A) and liver function enzyme (B) levels prior and after therapy with cyclophosphamide (^) and nivolumab (*).

- Questions?

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