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

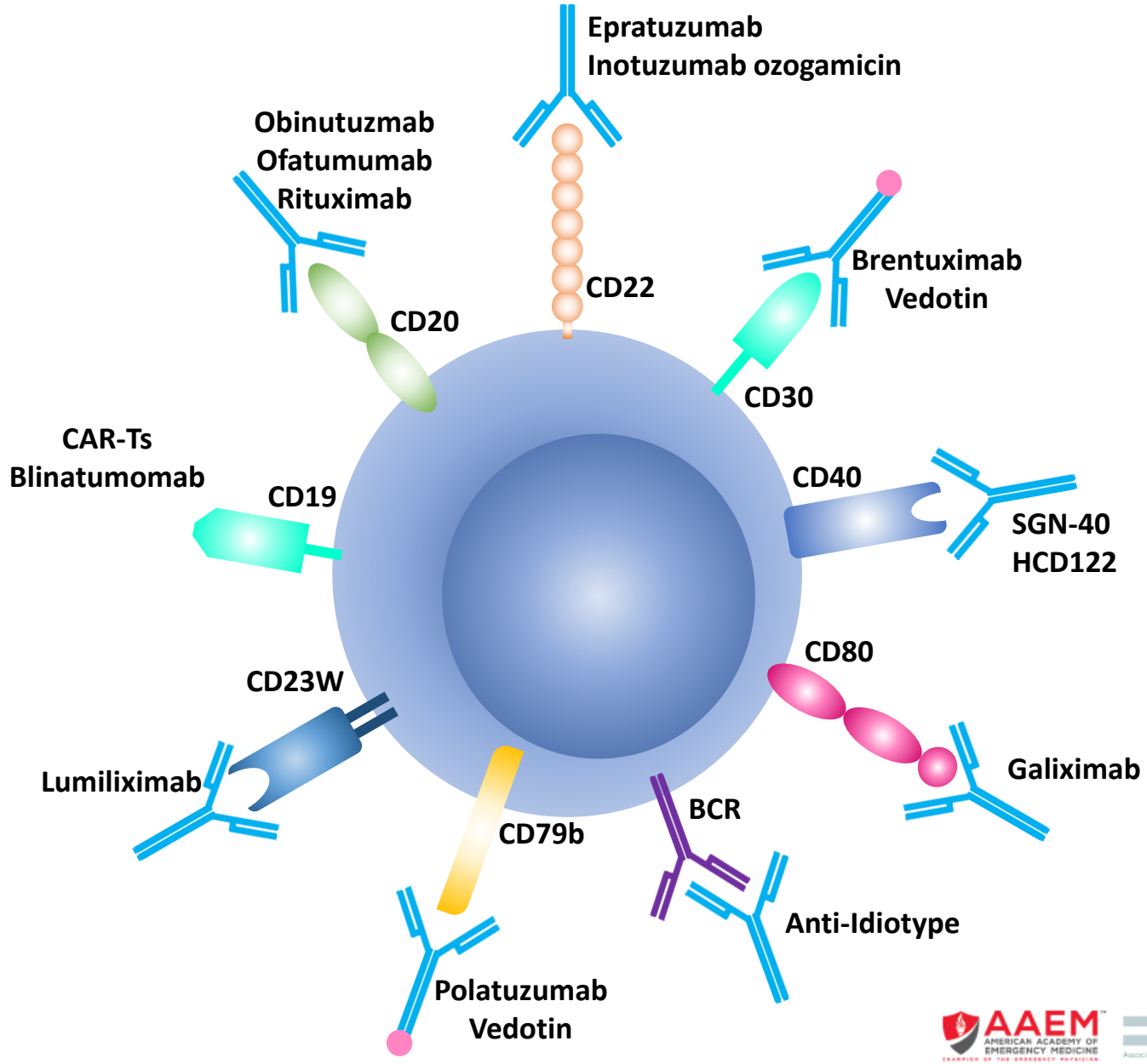
HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- Consultancy: OptumHealth
- Honoraria: Celgene, OptumHealth, Kite/Gilead
- Speakers Bureau: Celgene, Kite/Gilead, Agios, Sanofi
- Membership on a Advisory Board or Consultant: JUNO Therapeutics, KITE/Gilead, Novartis, CRISPR Therapeutics, OptumHealth
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapies Targeting B Cell Lymphoma



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Checkpoint Inhibitors

FDA-approved Checkpoint inhibitors: Lymphoma

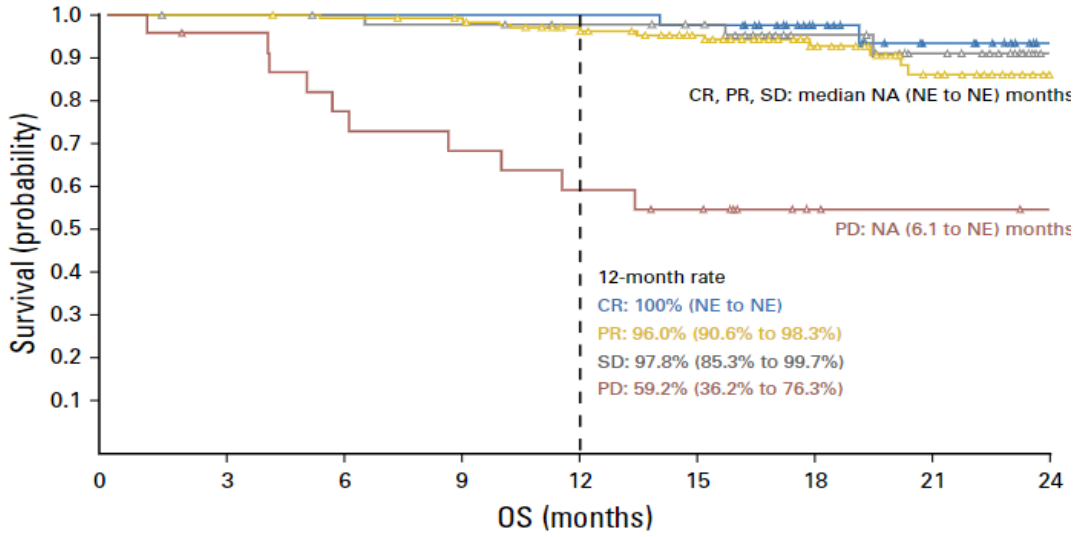
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg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

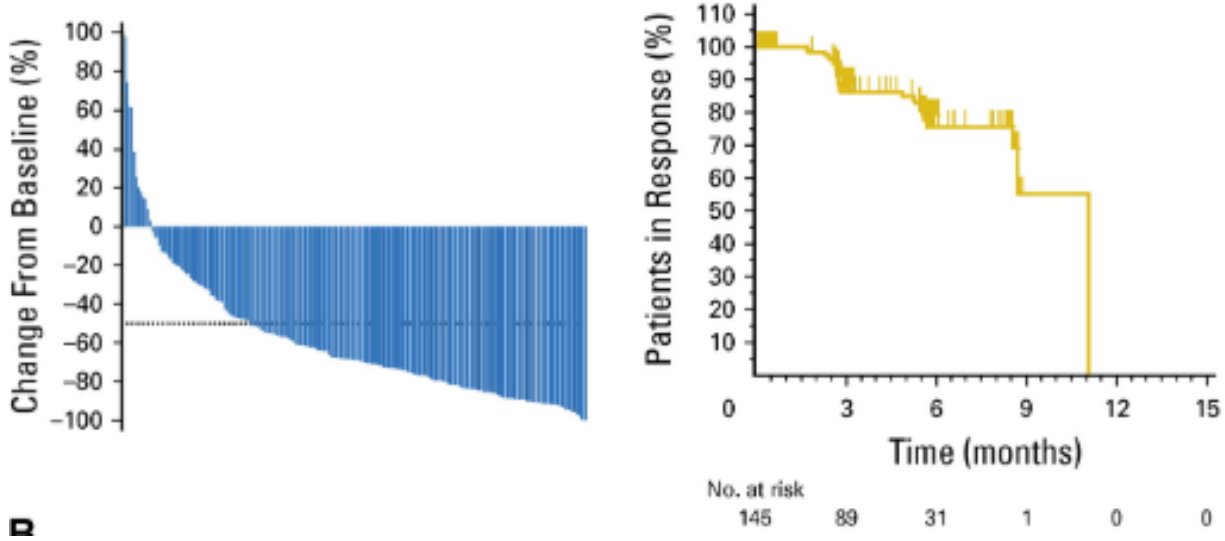
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

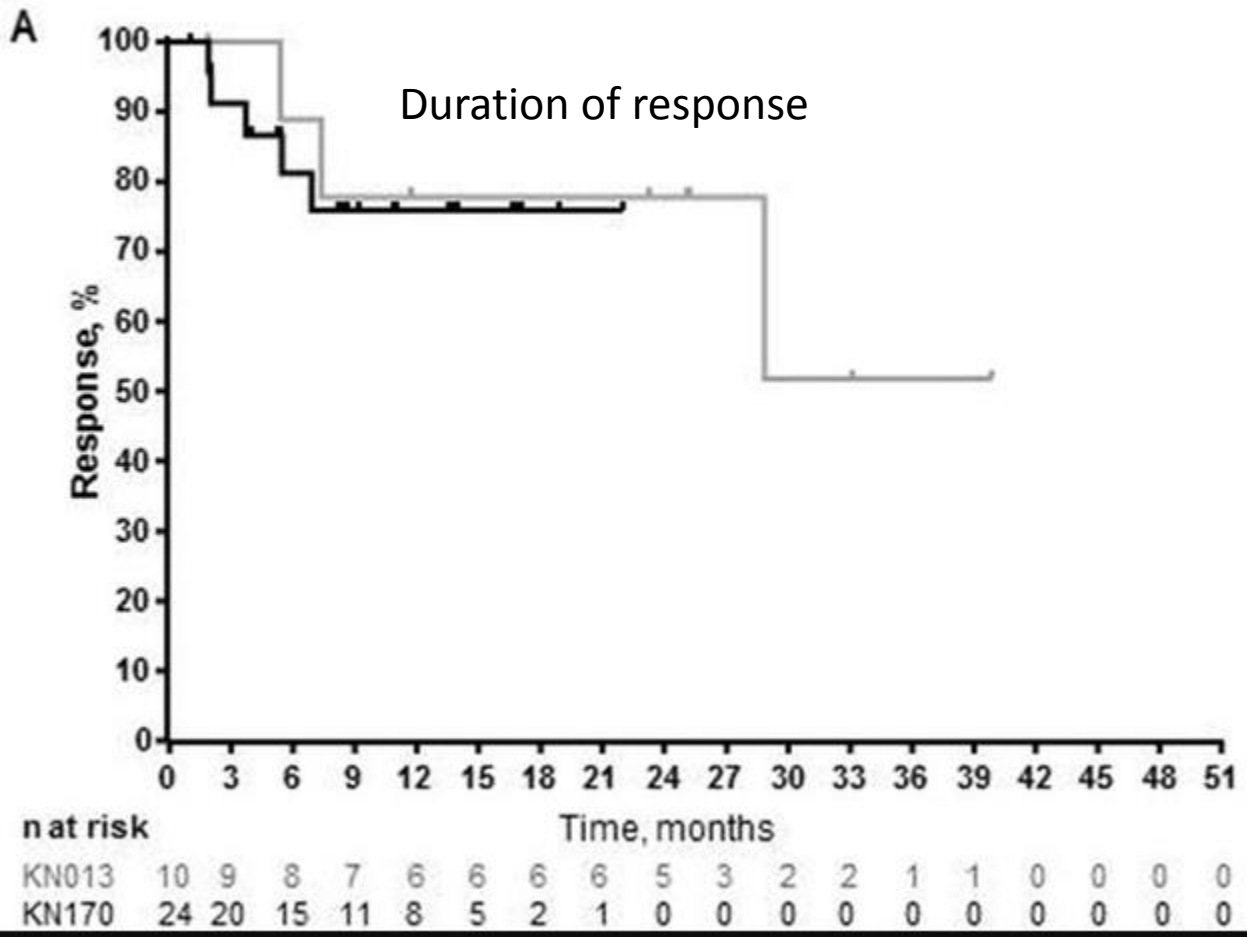
CR = 22.4%

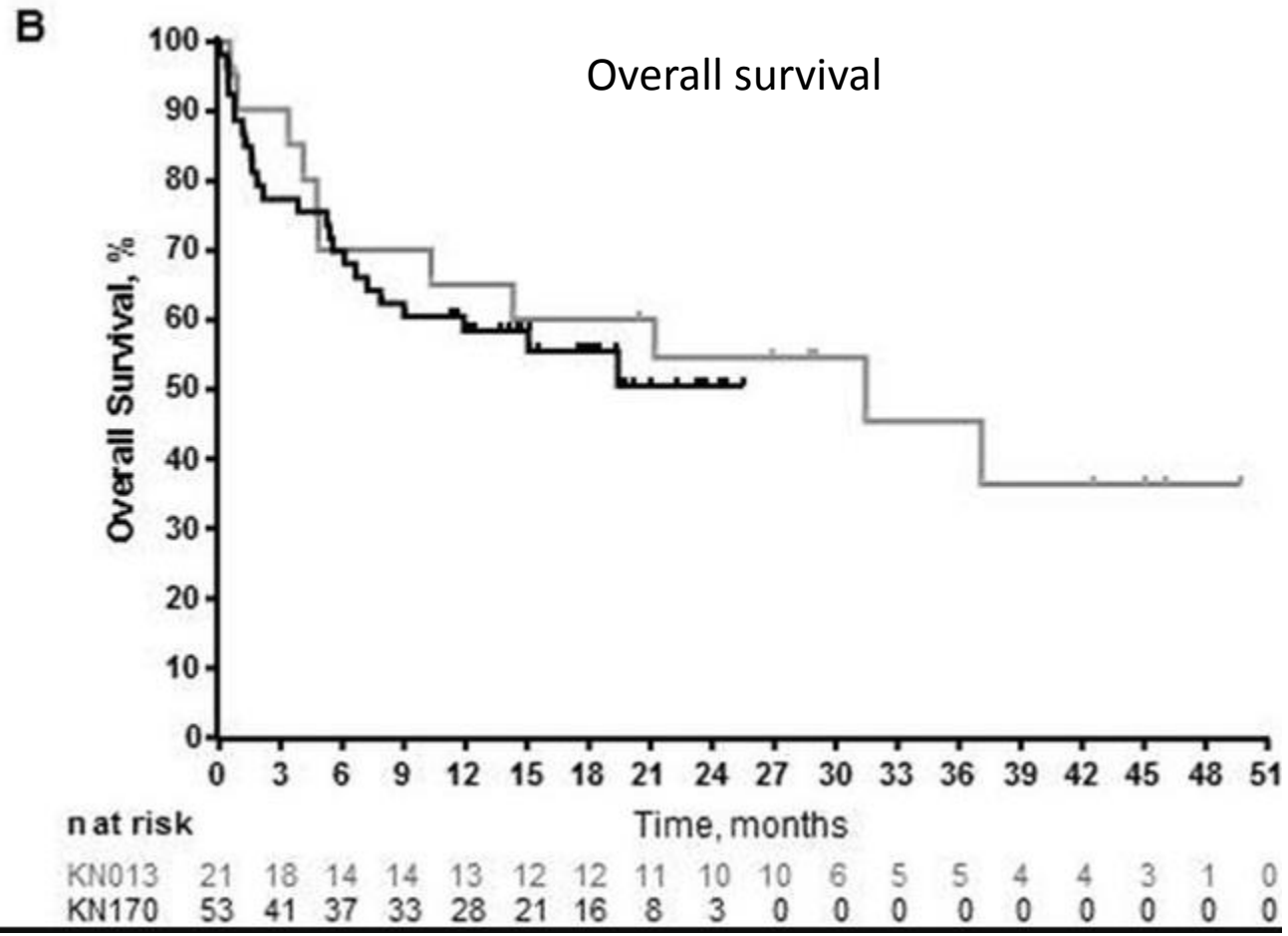
Activity seen regardless of PD-L1 expression



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

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

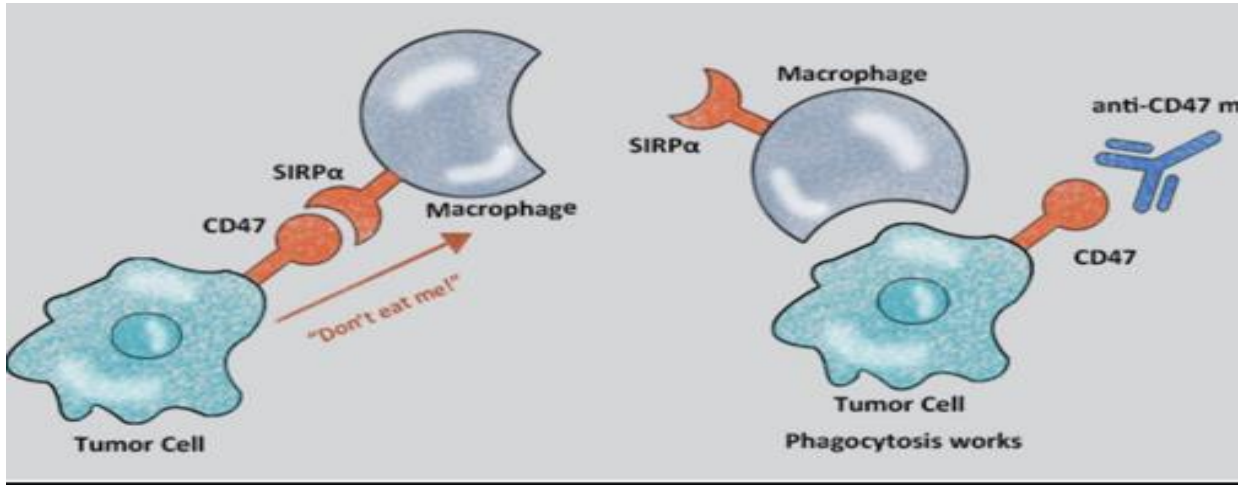


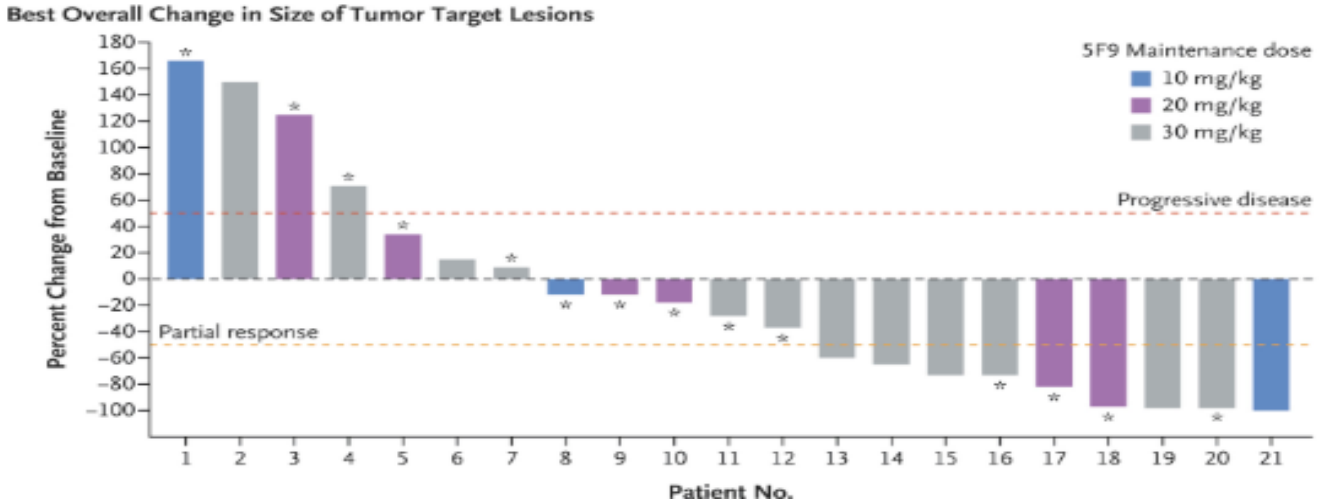


Armand, Blood 2018.

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.

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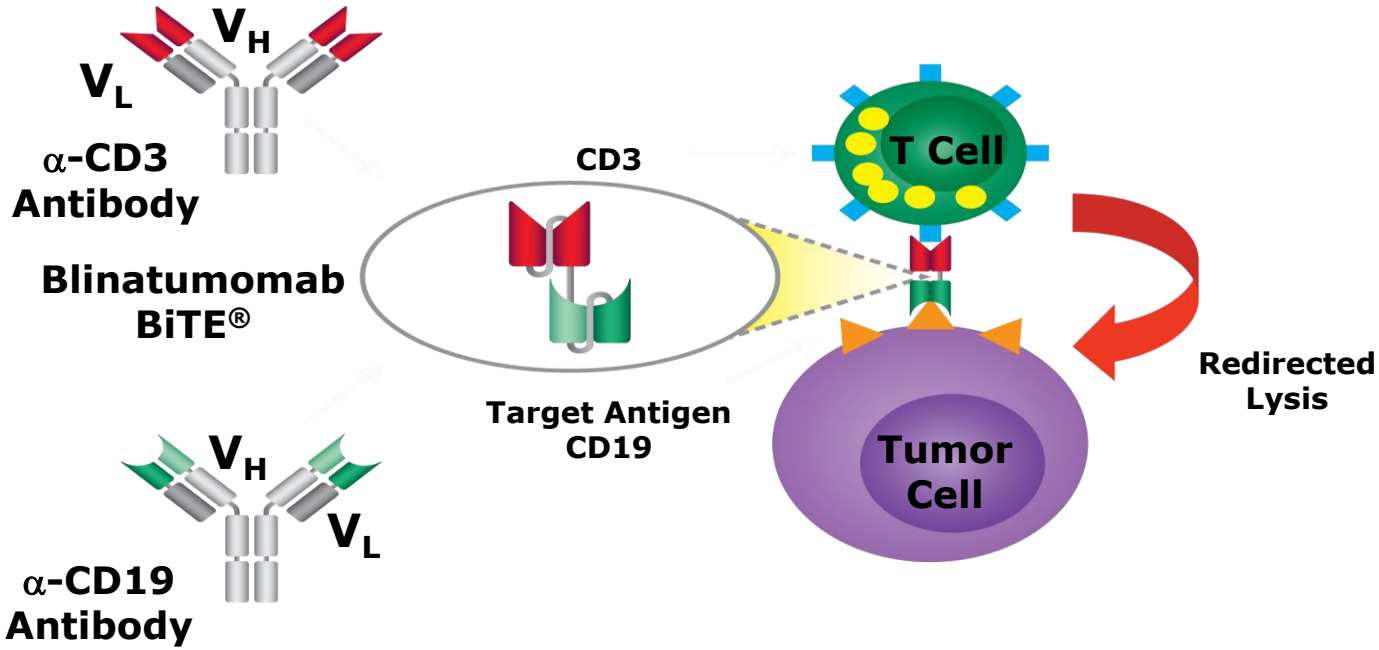
Bi-specific T-cell Engagers (BiTEs)

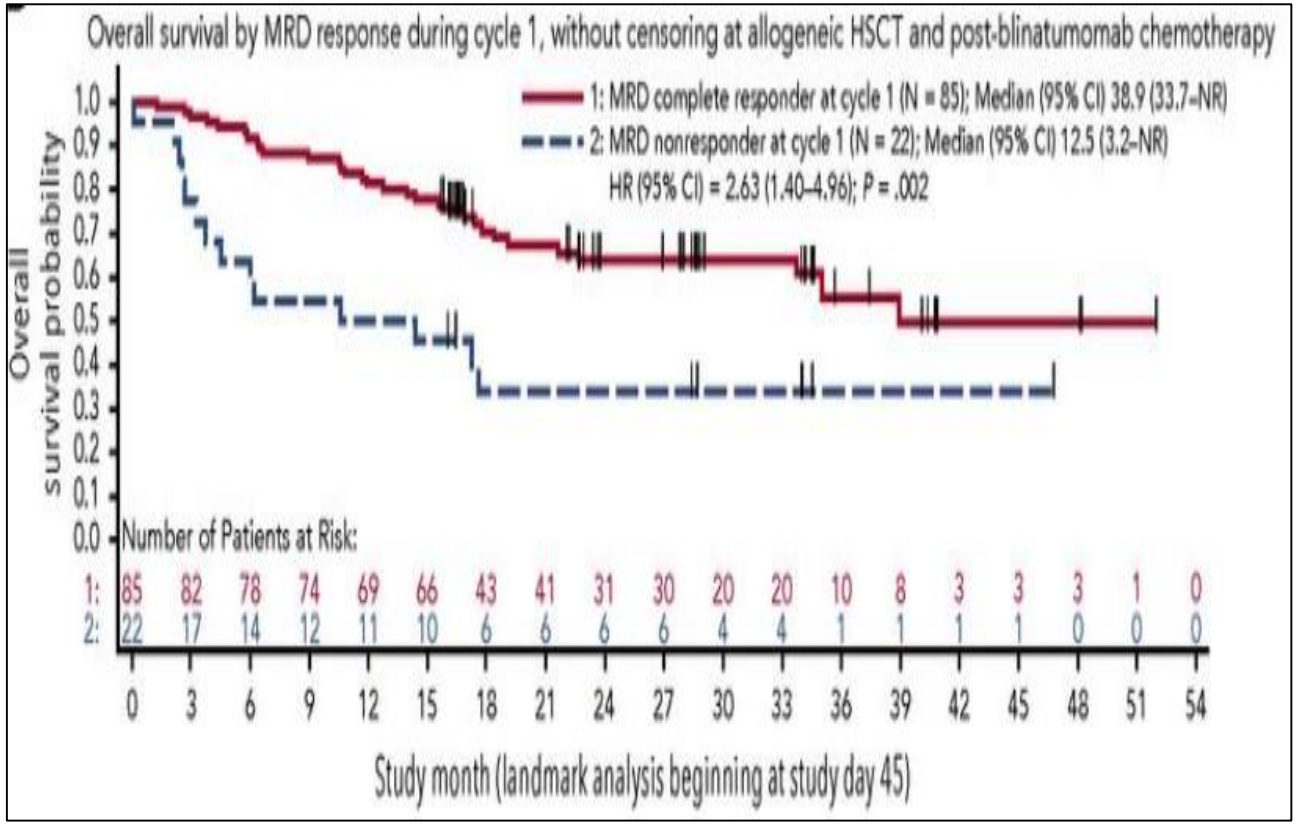
BiTE (Blinatumomab) Therapy

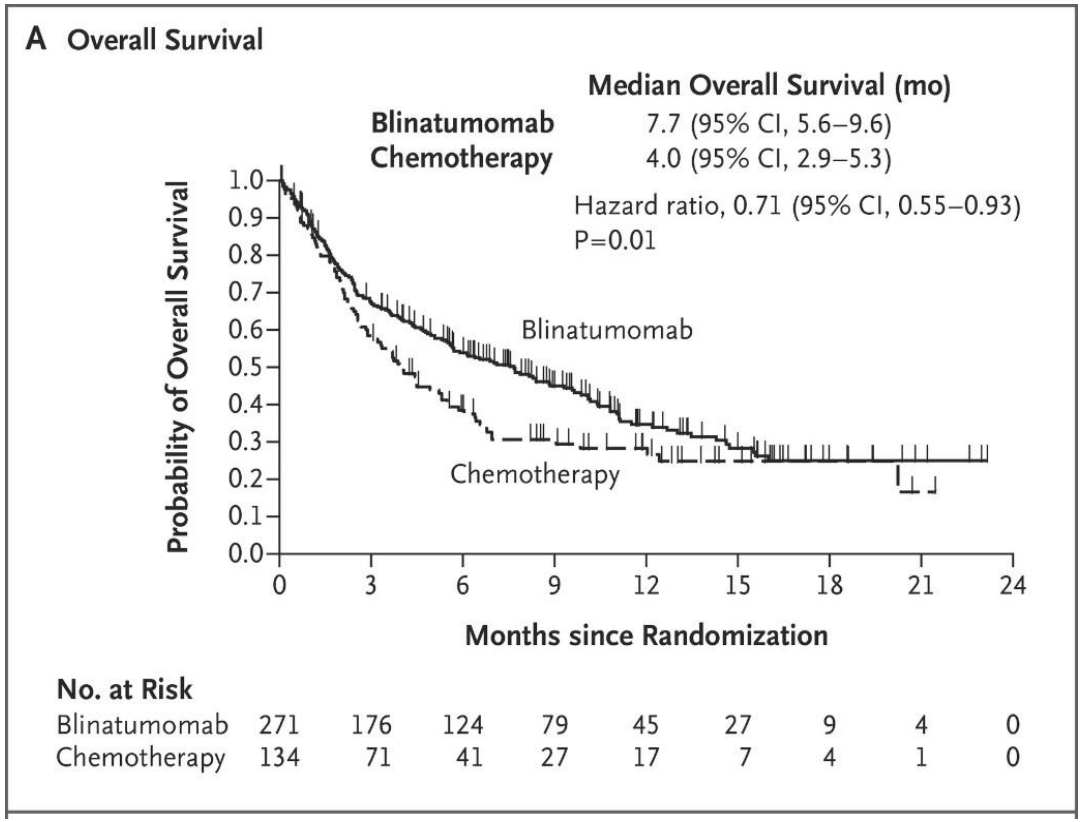
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
  - Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
  - Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





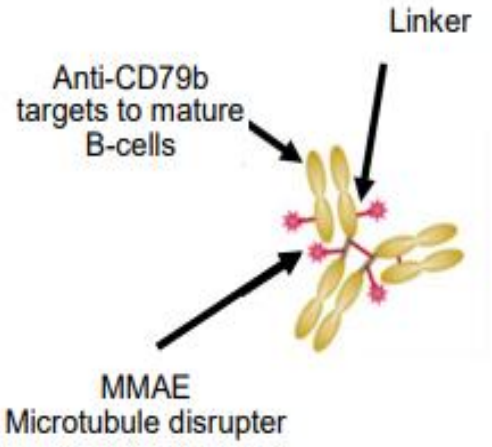
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

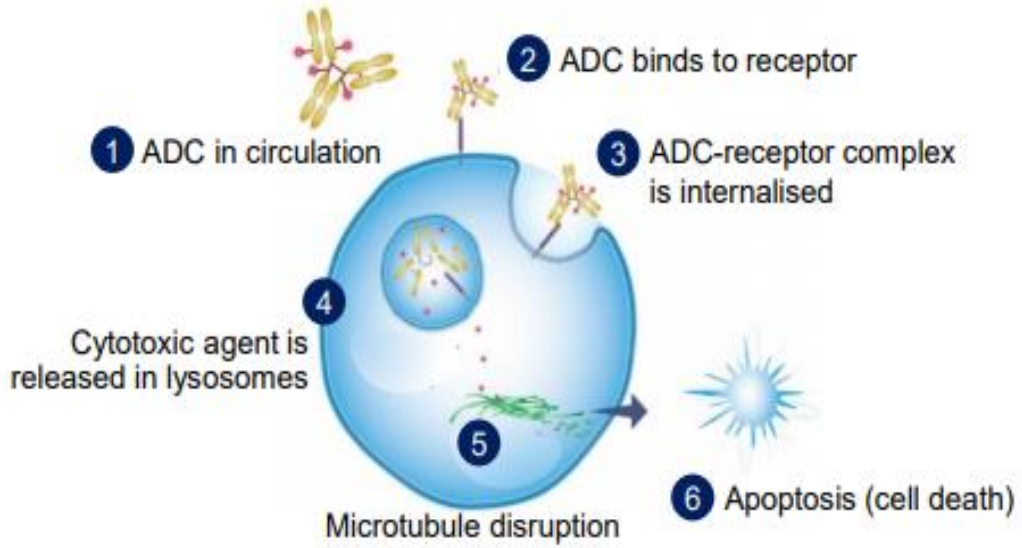
Antibody-drug conjugates (ADC)

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]

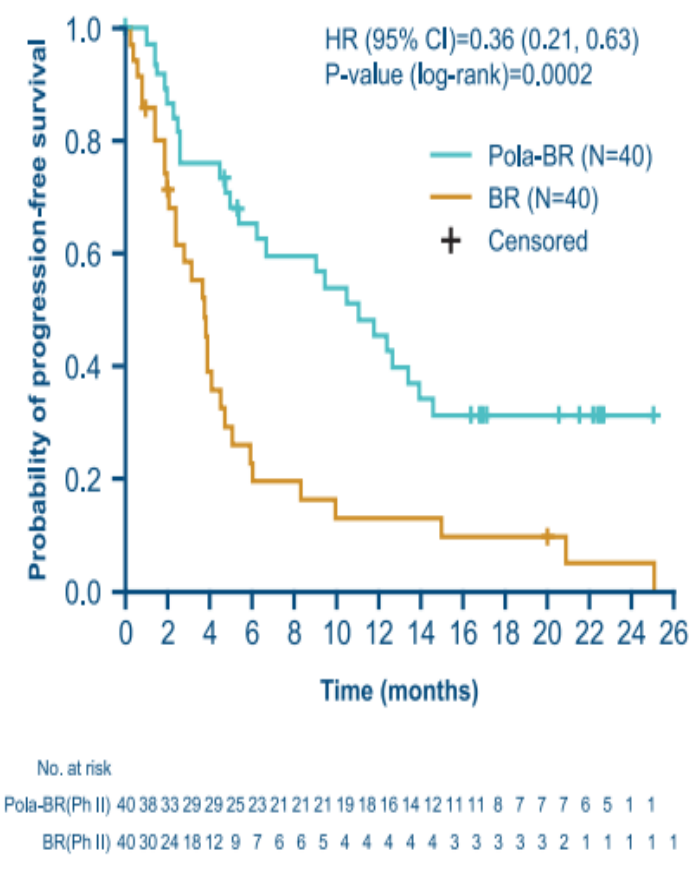
ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E

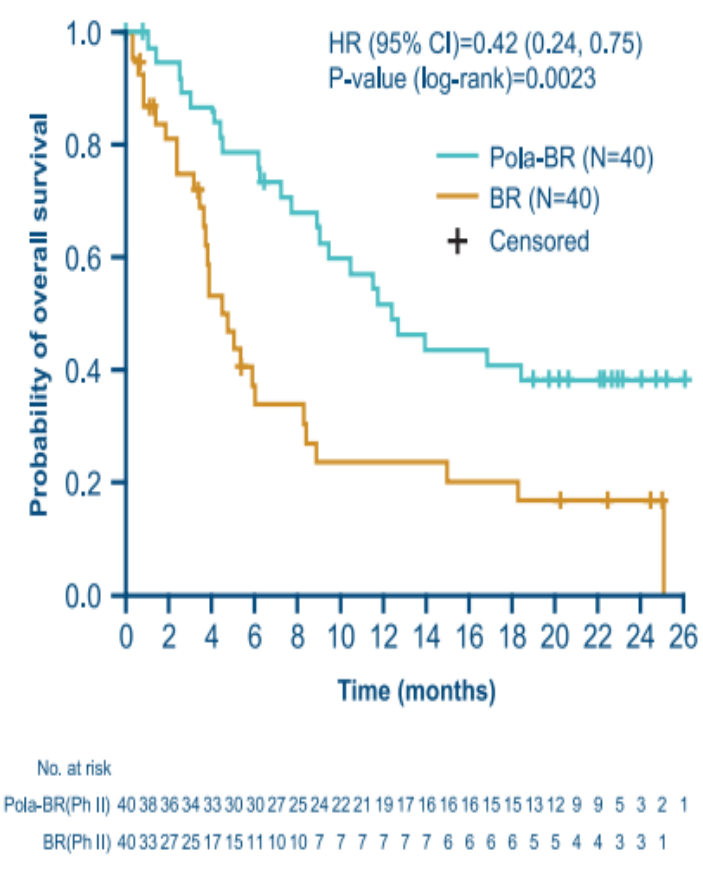
1. Palanca-Wessels A, et al. Lancet Oncol 2015;16:704–15; 2. Morschhauser F, et al. Lancet Hematology 2019;6:e254–65; 3. Sehn H, et al. Blood 2018;132:1683

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

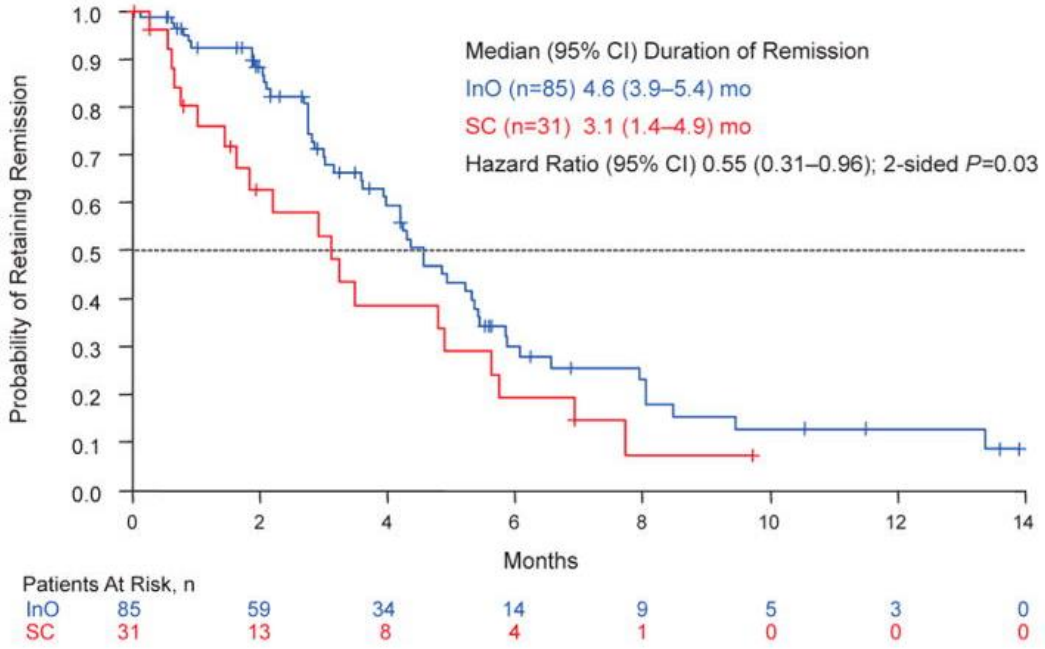


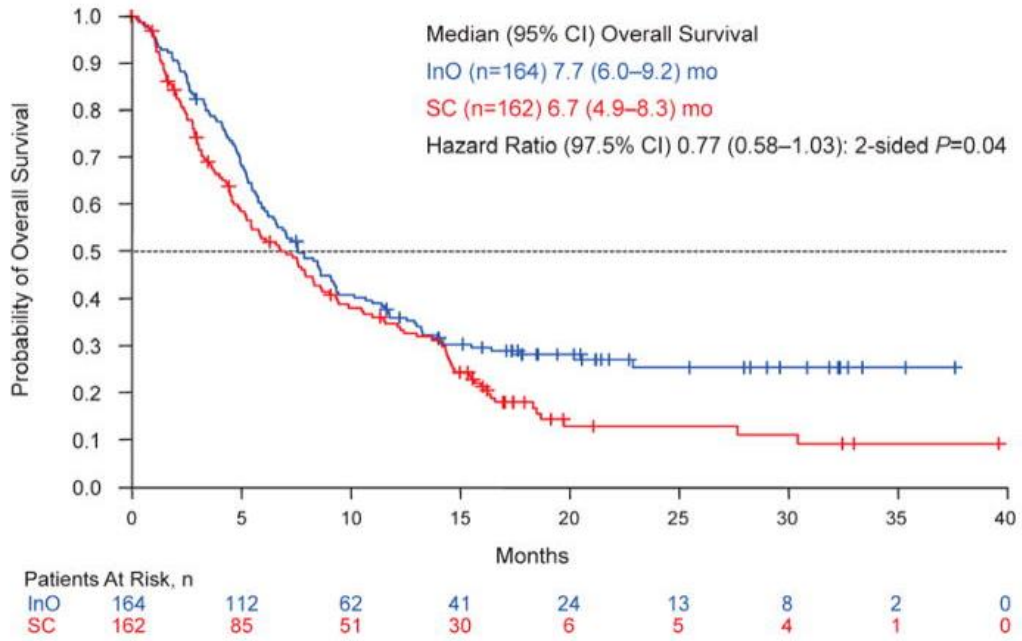


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



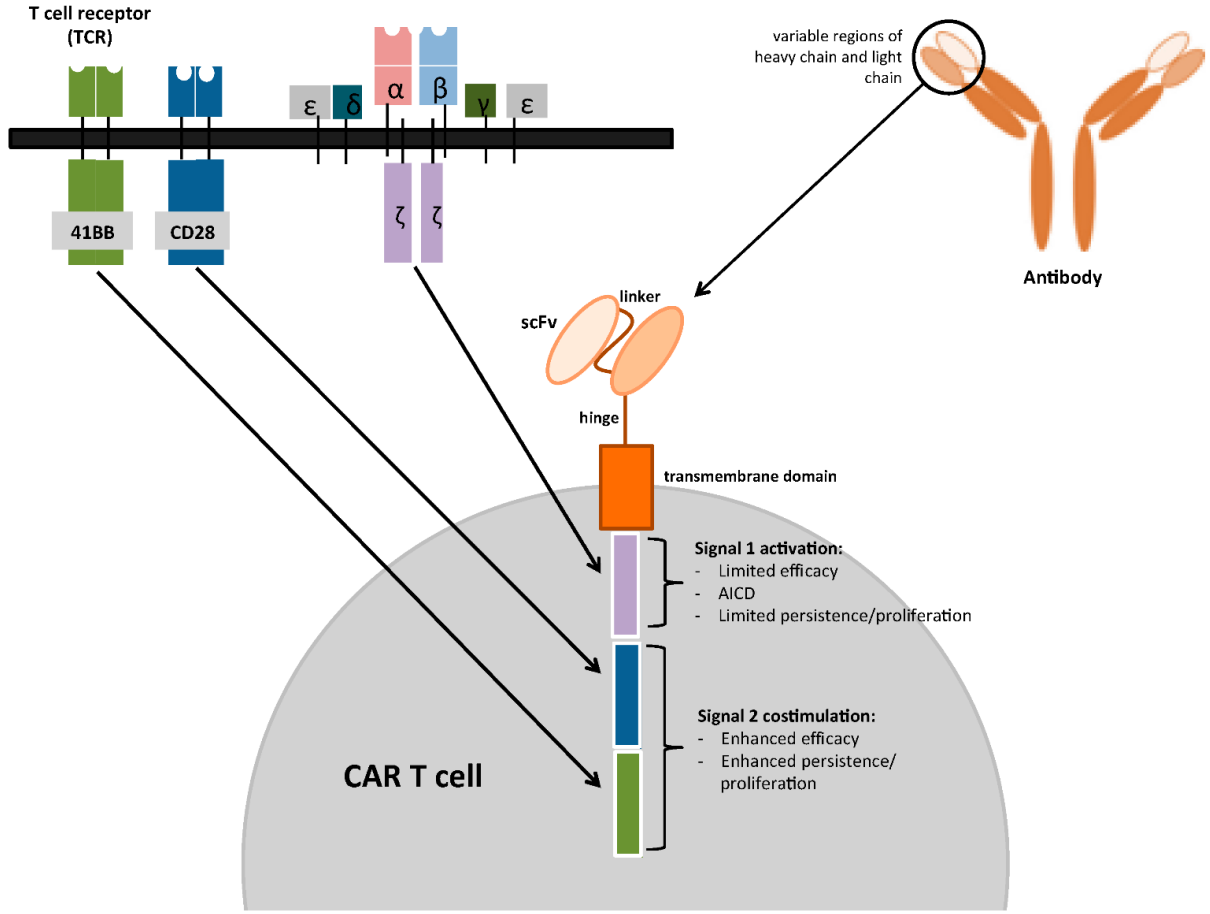


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor T cell Therapy (CAR T)

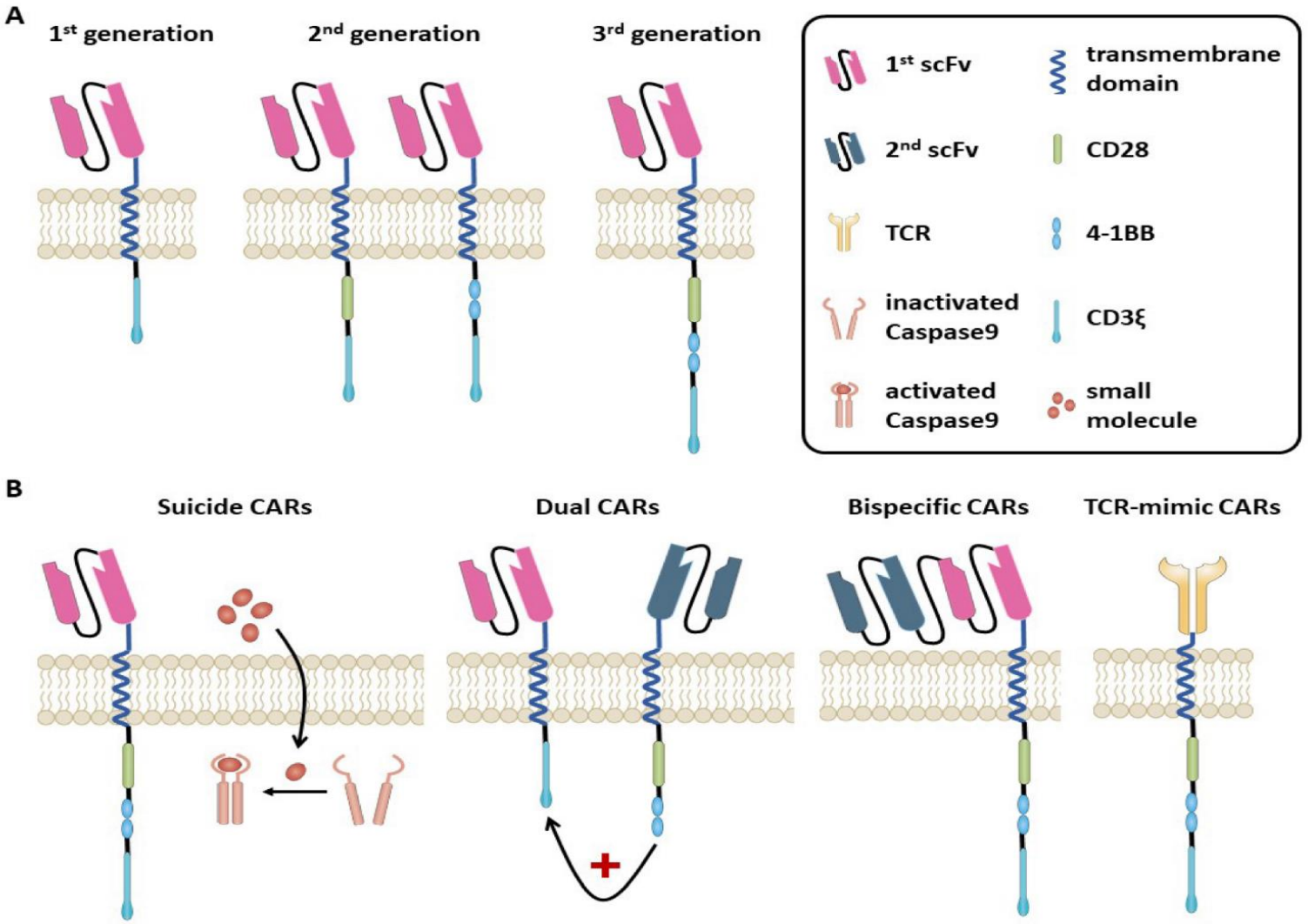
Chimeric Antigen Receptors

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



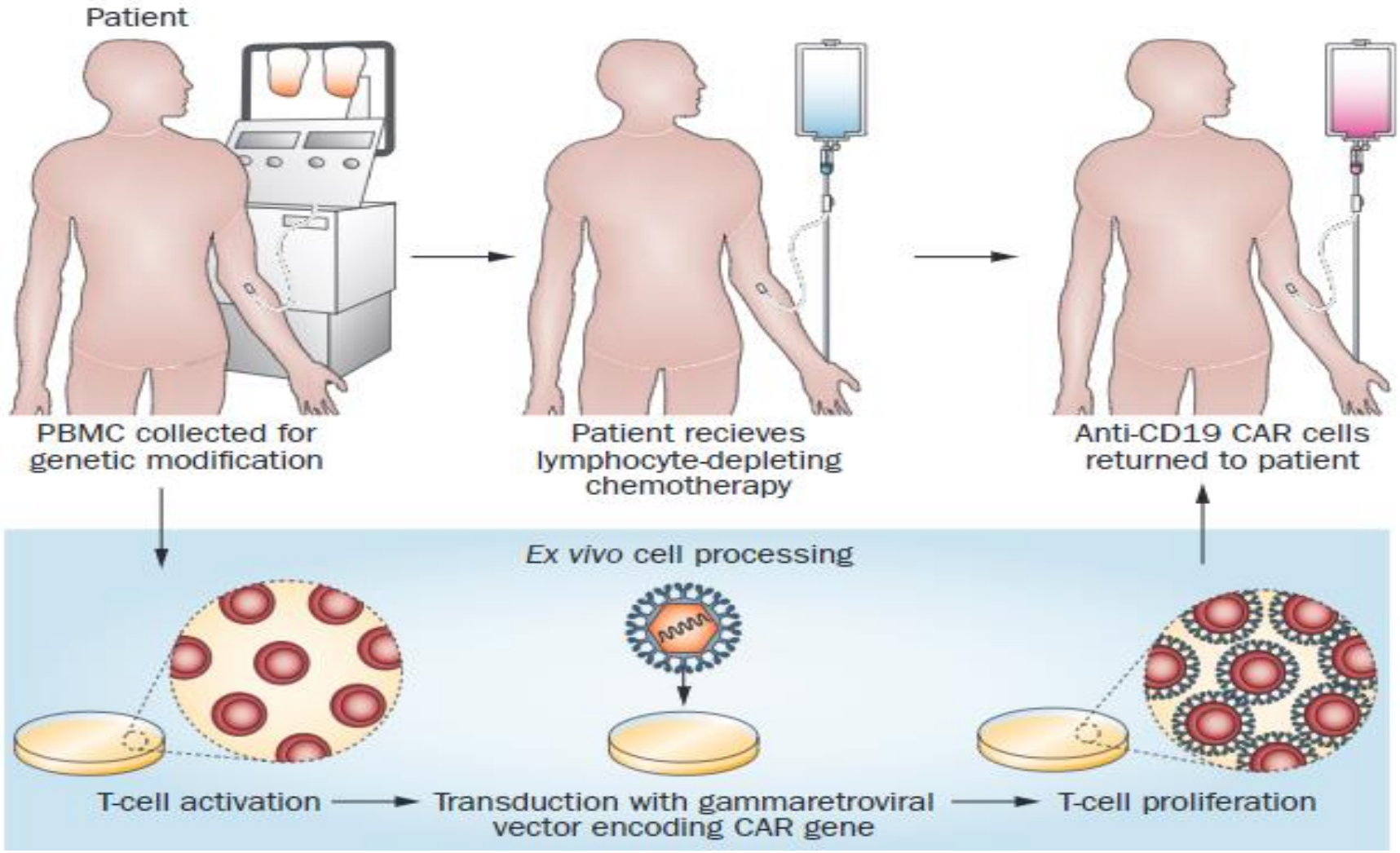
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T Manufacturing and Administration

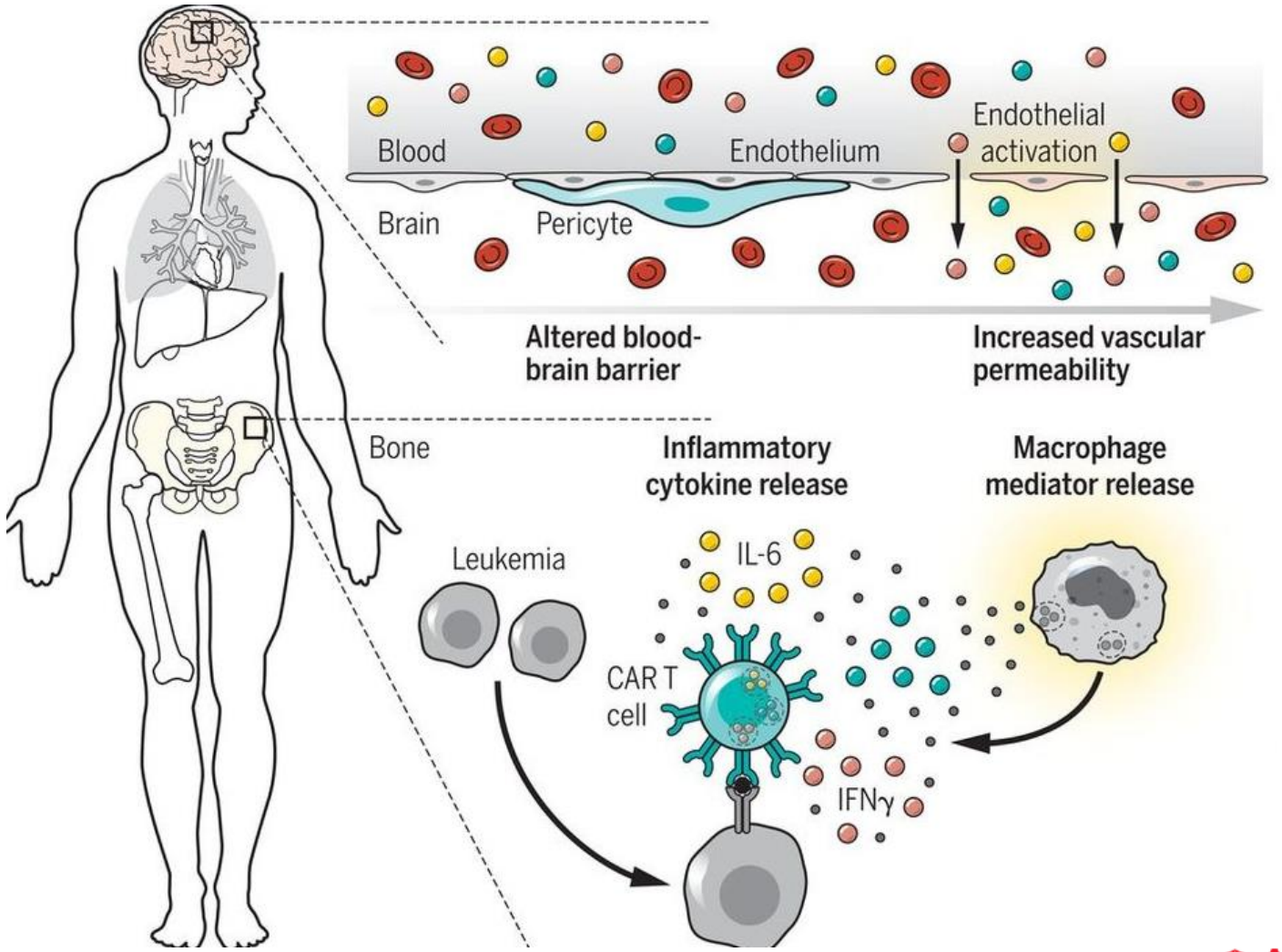


Kochenderfer, Nat Rev Clin Oncol 2013.

CAR T Side Effects

- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- B Cell aplasia
- Macrophage Activation Syndrome (MAS)/HLH
- Tumor Lysis Syndrome

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

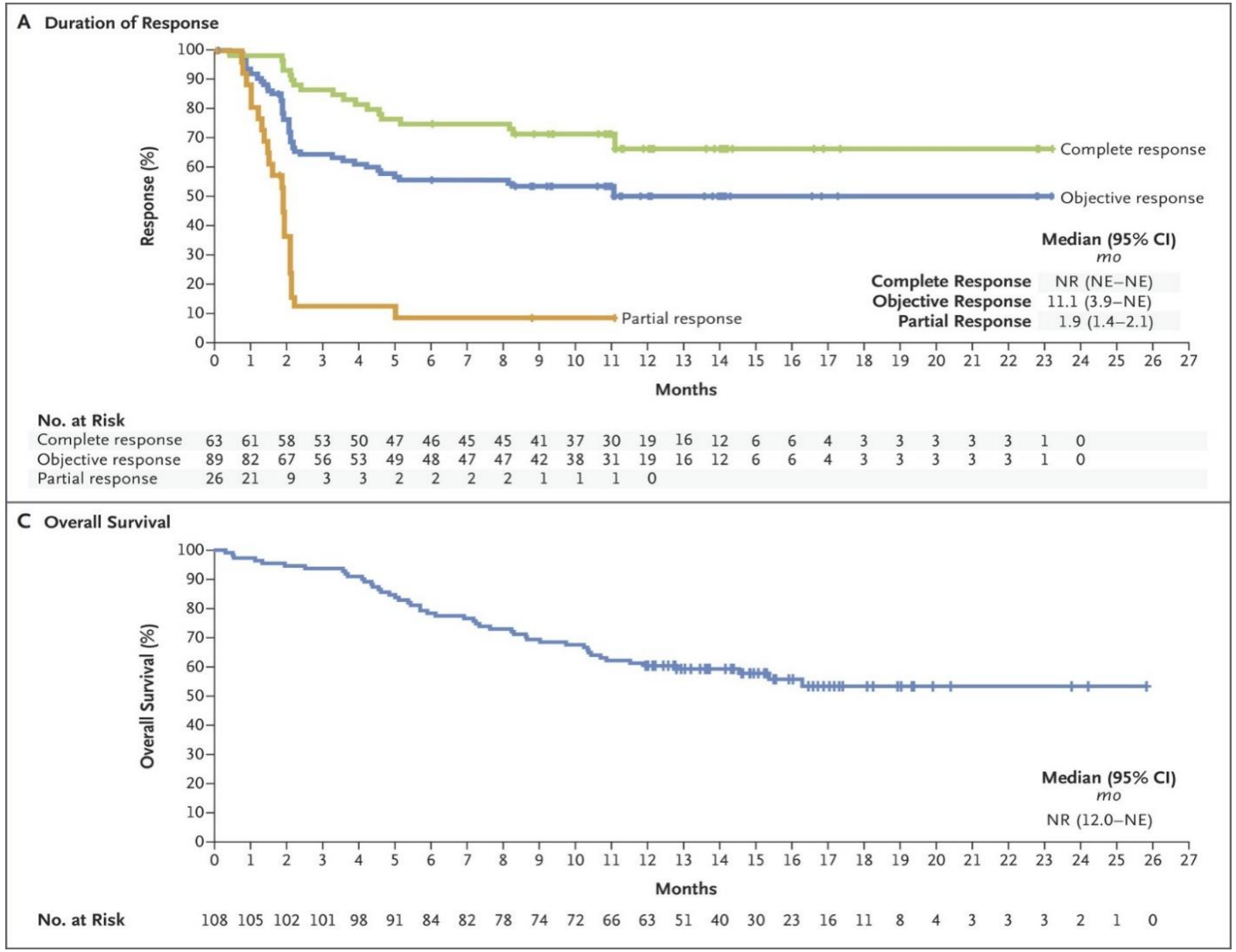
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight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

CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

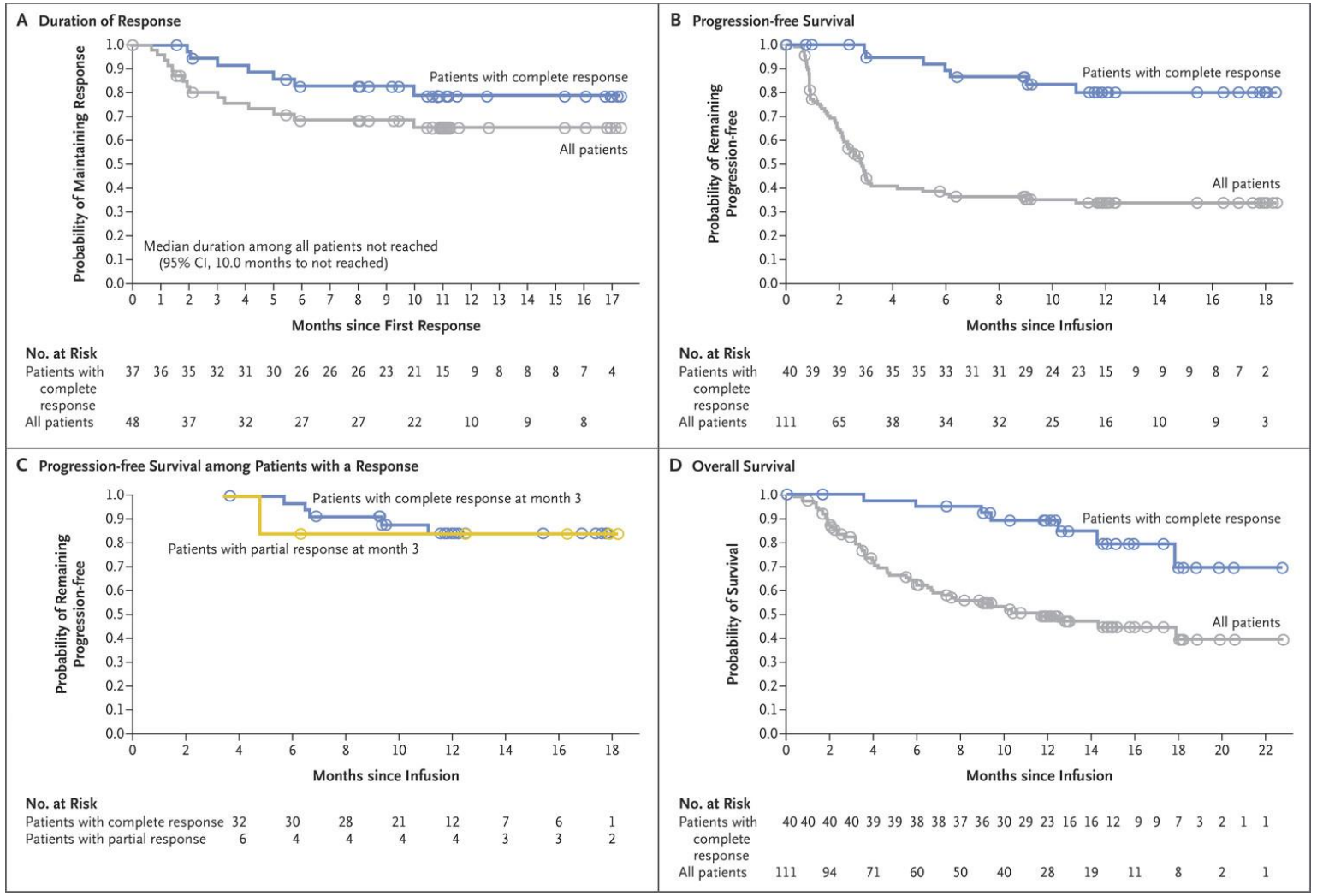
- Target: CD19
- Construct: CD3/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- Toxicities:
  - CRS grade ≥3 = 13%
  - Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

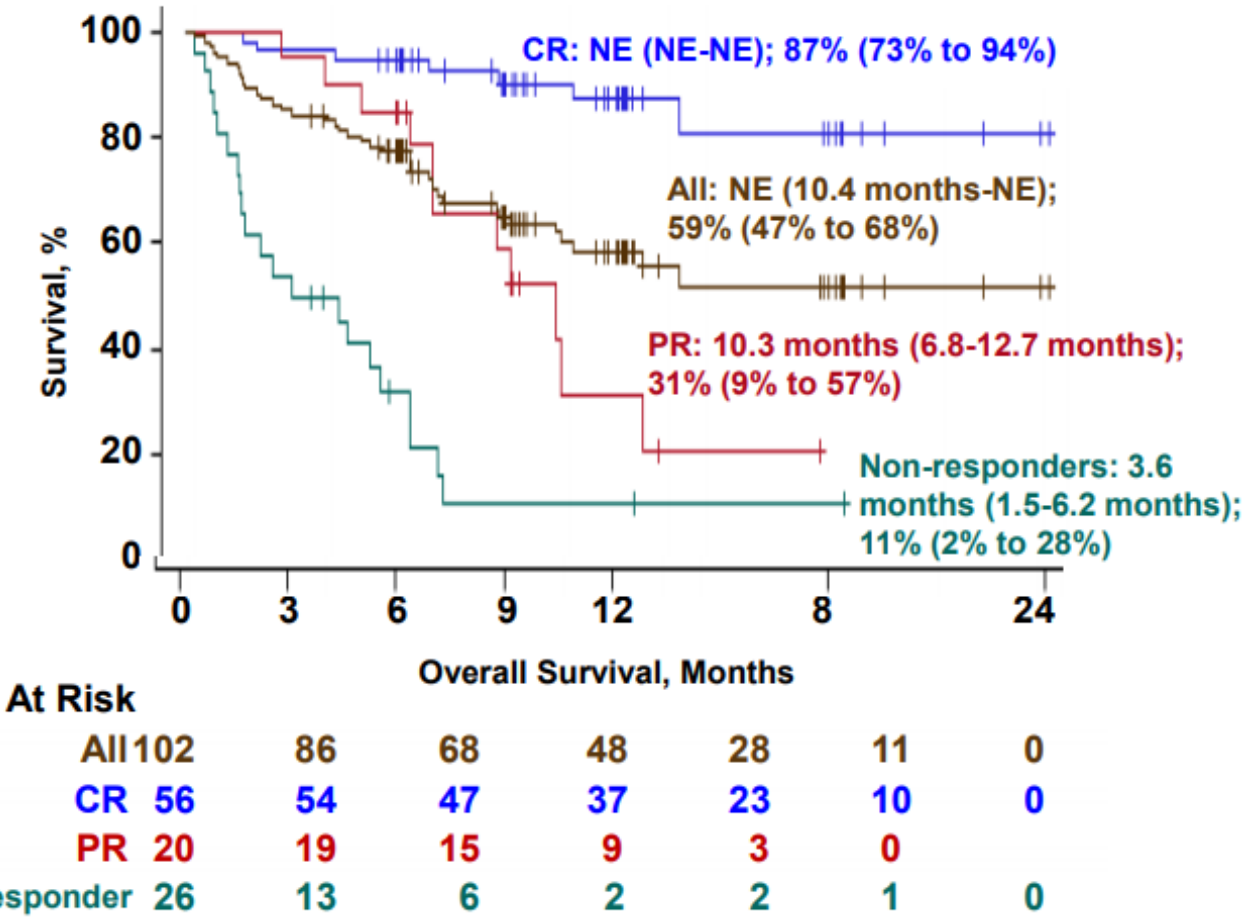
- Target:CD19
- Construct: CD3/4-1BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- Toxicities:
  - CRS grade ≥3 = 18%
  - Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

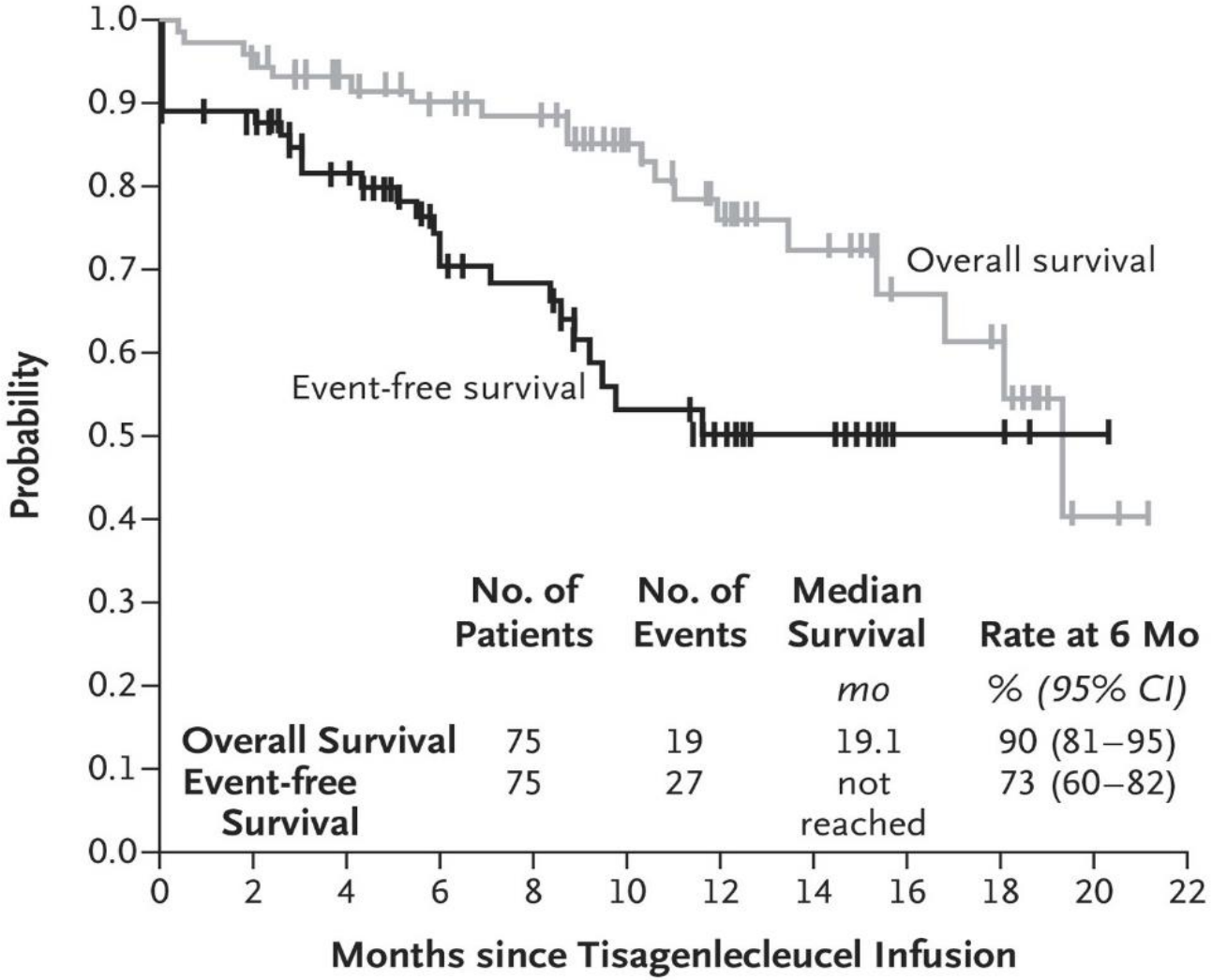
- Target: CD19
- Construct: CD3/4-1-BB,
- CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- Toxicities:
  - CRS grade ≥3 = 1%
  - Neurotox grade ≥3 = 13%



Abramson JS, et al. HemaSphere. 2018;2(S1): Abstract S800.

CD19 CAR in B-ALL: ELIANA (Tisa-cel)

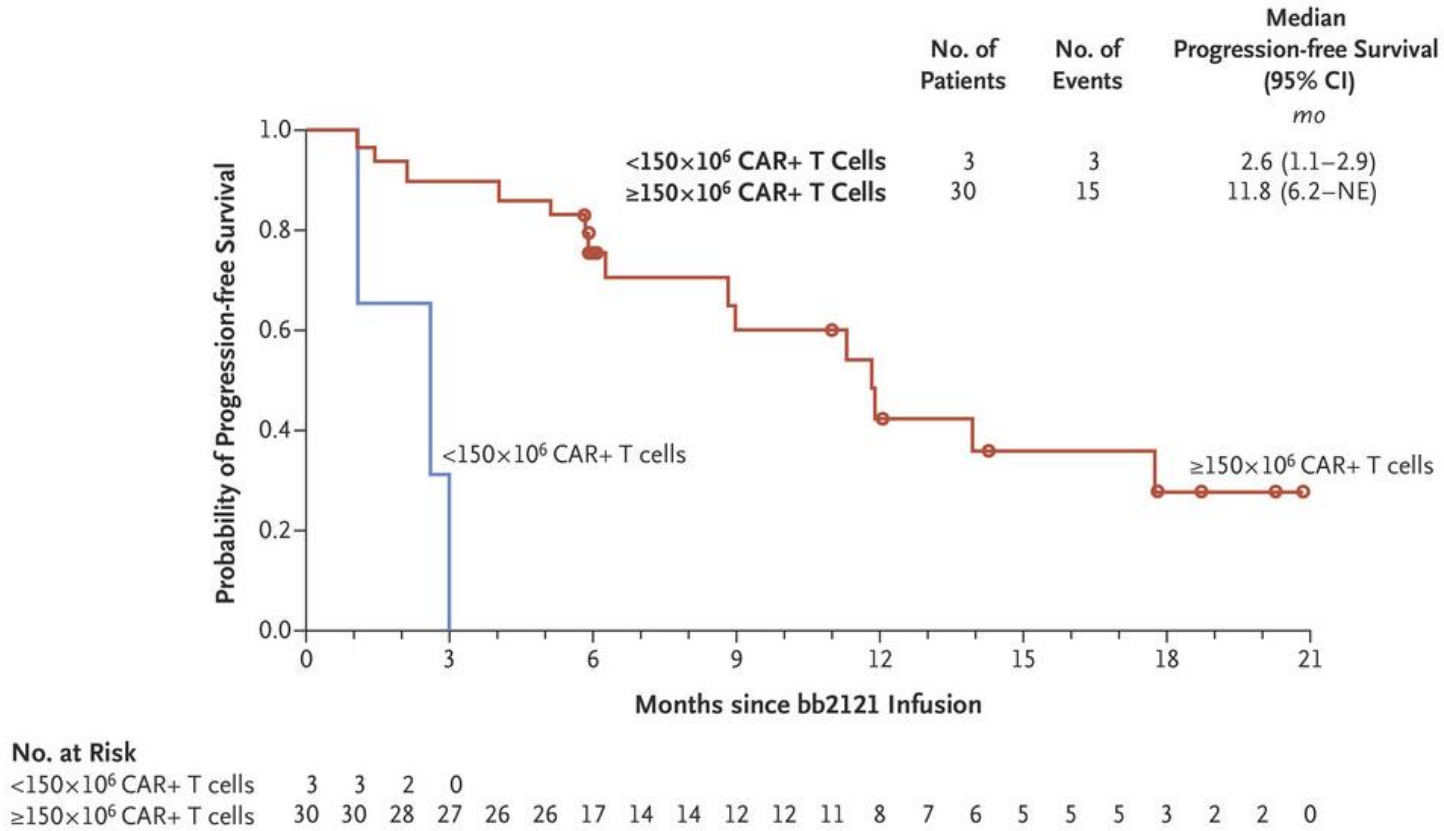
- Target: CD19
- Construct: CD3/4-1BB
- ORR = 81%
- CR = 60%, CRi = 21%
- Toxicities:
  - CRS grade ≥3 = 47%
  - Neurotox grade ≥3 = 13%



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 (≥ 3 lines) patients with relapsed/refractory multiple myeloma
  - ORR: 85%, CR: 45%



Raje, NEJM 2019.

Immunotherapy for the Treatment of Hematologic Malignancies

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 Study

Case Study 1

- **64-yr-old male presents with a 2 month h/o increasing bilateral axillary adenopathy, occasional night sweats, mild fatigue, and ~10-15 lb weight loss**
- **Right axillary lymph node biopsy: Morphologic features c/w DLBCL. Cells expressed CD19, CD20, MUM-1, CD10, and BCL-2; c-myc was (-). Ki-67 = 30-40%**
- **PET-CT was FDG-avid in cervical, axillary, and retroperitoneal lymph nodes. Bone marrow was (-) for involvement. LDH = 324; IPI = 3**

Case Study 1

His best options for therapy is:

1. **R-CHOP**
2. **DA-EPOCH-R**
3. **Polatuzumab vedotin +/- Bendamustine**
4. **Clinical trial**

Case Study 1

- He was treated with R-CHOP x 6 and achieved a PET (-) CR.
- He relapsed 10 months later with a biopsy proven recurrence in a right cervical lymph node. The pathology demonstrated DLBCL. The cells now expressed c-myc which was verified by FISH. The Ki-67 = 70-80%.
- The patient is fatigued, but his organ functions and his performance status are good.

Case Study 1

His best options for therapy is:

1. **R-ICE followed by close observation**
2. **R-ICE followed by maintenance rituximab**
3. **R-ICE followed by autologous HSCT**
4. **R-ICE followed by allogeneic HSCT**
5. **Clinical trial**

Case Study 1

- **The patient was treated with R-ICE x 2 cycles.**
- **PET-CT following cycle 2 of R-ICE by demonstrated a 40% reduction in prior adenopathy and a new FDG-avid lesion in the liver.**
- **The patient's organ functions and performance status remain stable.**
- **HLA typing of his sibling reveals no matches, but he has several well matched volunteer donors on a preliminary search.**

Case Study 1

His best option for therapy is:

1. **R-Gem-Ox followed by autologous HSCT**
2. **Allogeneic HSCT**
3. **CAR T cells**
4. **Checkpoint inhibitor**
5. **Clinical trial**

Case Study 1

- Recommended to receive CAR T cells. Undergoes leukopheresis with successful production of CAR T cells in 3 weeks
- Receives lymphodepleting chemotherapy (fludarabine and cyclophosphamide) followed by CAR T cell infusion (Day 0)without complication.
- Day+4: Fevers (Tmax = 39.4) with tachycardia (HR = 115), BP = 90/86, O2 saturation = 96% on 2L via NC. No focal signs of infection. CRP that morning was 37. Neuro exam intact. Receives single dose of Tocilizumab with resolution of symptoms.
- Discharged Day+14 in good condition
- Day+28: CT scan which show >50% reduction in prior adenopathy. Asymptomatic
- Day+60: Doing well without signs or symptoms of CRS or neurologic toxicity.
- Day+90: Doing well. PET-CT demonstrates 90% reduction in lymphadenopathy that are all FDG(-)