sitc 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

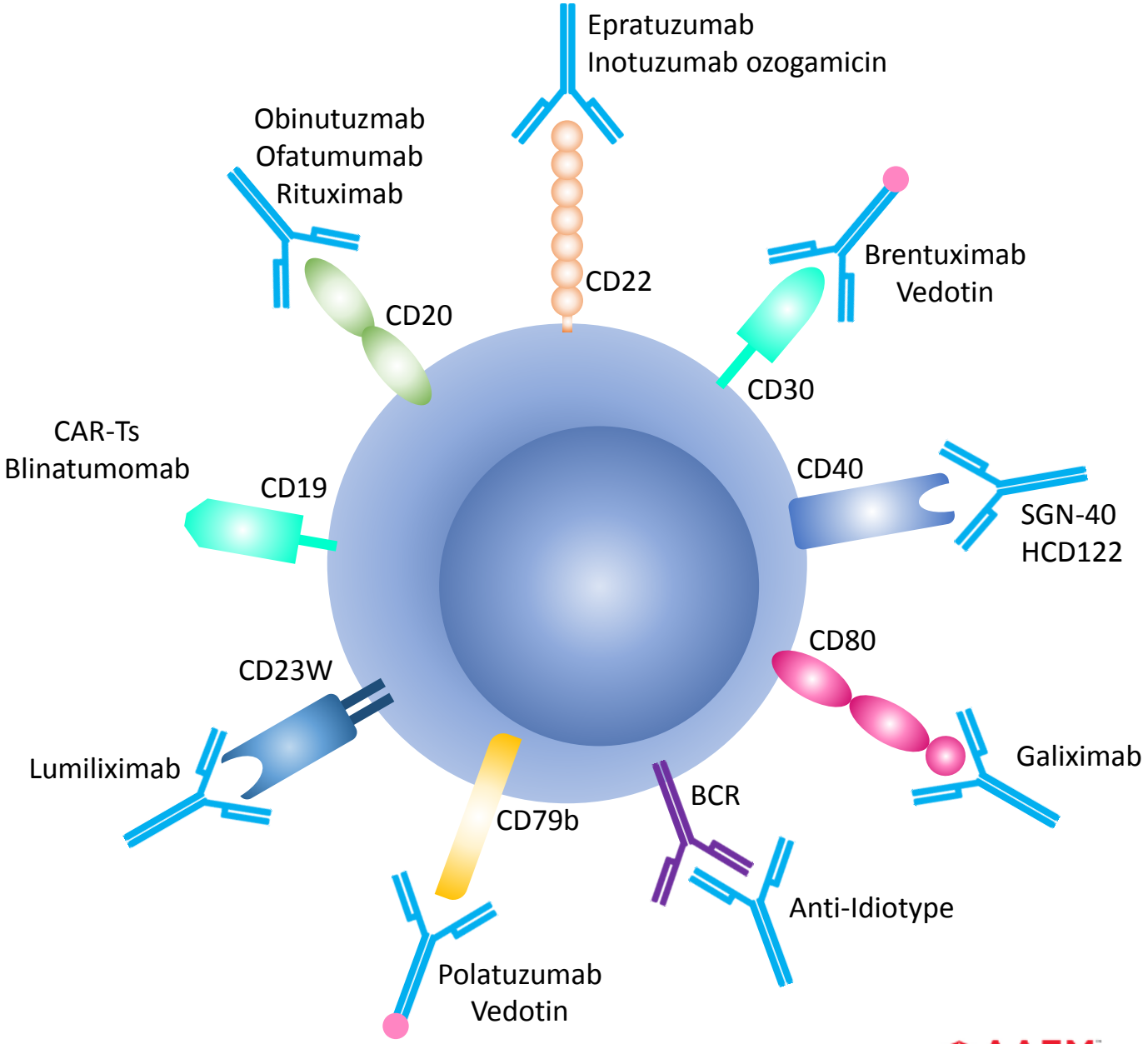
HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer

Disclosures

- Consulting fees from EUSA Pharma, Daiichi Sankyo, Kyowa Kirin, and Seattle Genetics
- Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: Seattle Genetics, EUSA

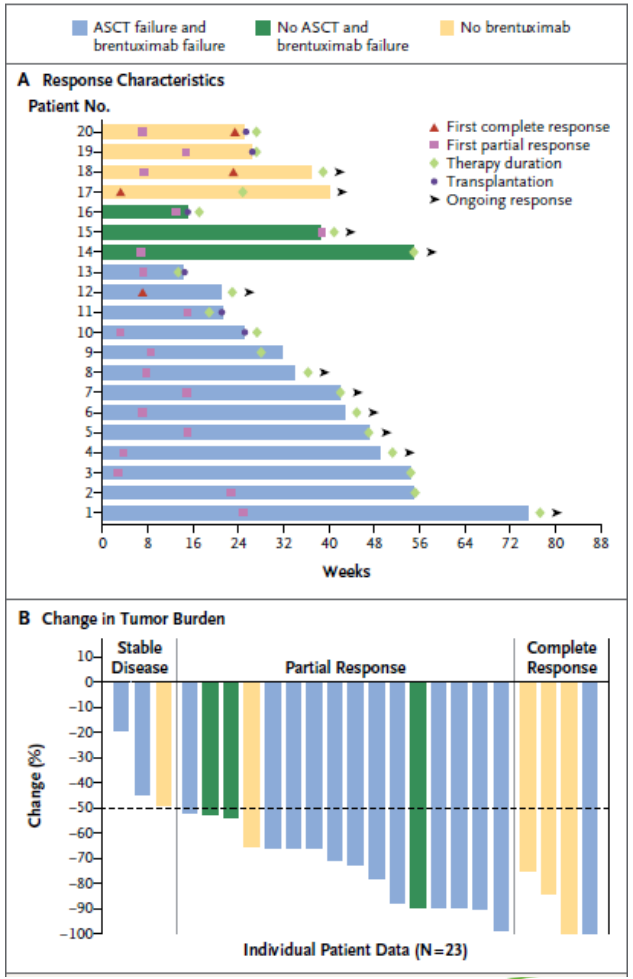
- I will be discussing non-FDA approved indications during my presentation.



Checkpoint inhibitors

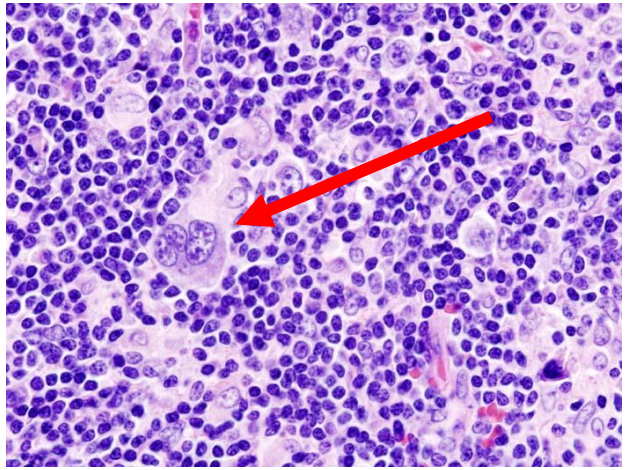
Classical Hodgkin lymphoma (cHL) is exquisitely sensitive to PD-1/PD-L1 blockade

- Response rates to PD-1 blockade of 65% to 87% to PD-1 blockade.
- Long term follow up demonstrates median PFS > 1 year.
- The response rate to PD-1 monotherapy in HL is much higher than what is typically seen in solid tumors



Why is cHL sensitive to PD-1/PD-L1 blockade?

- 9p24.1 amplification/CNAs present in 97% of cHL samples.

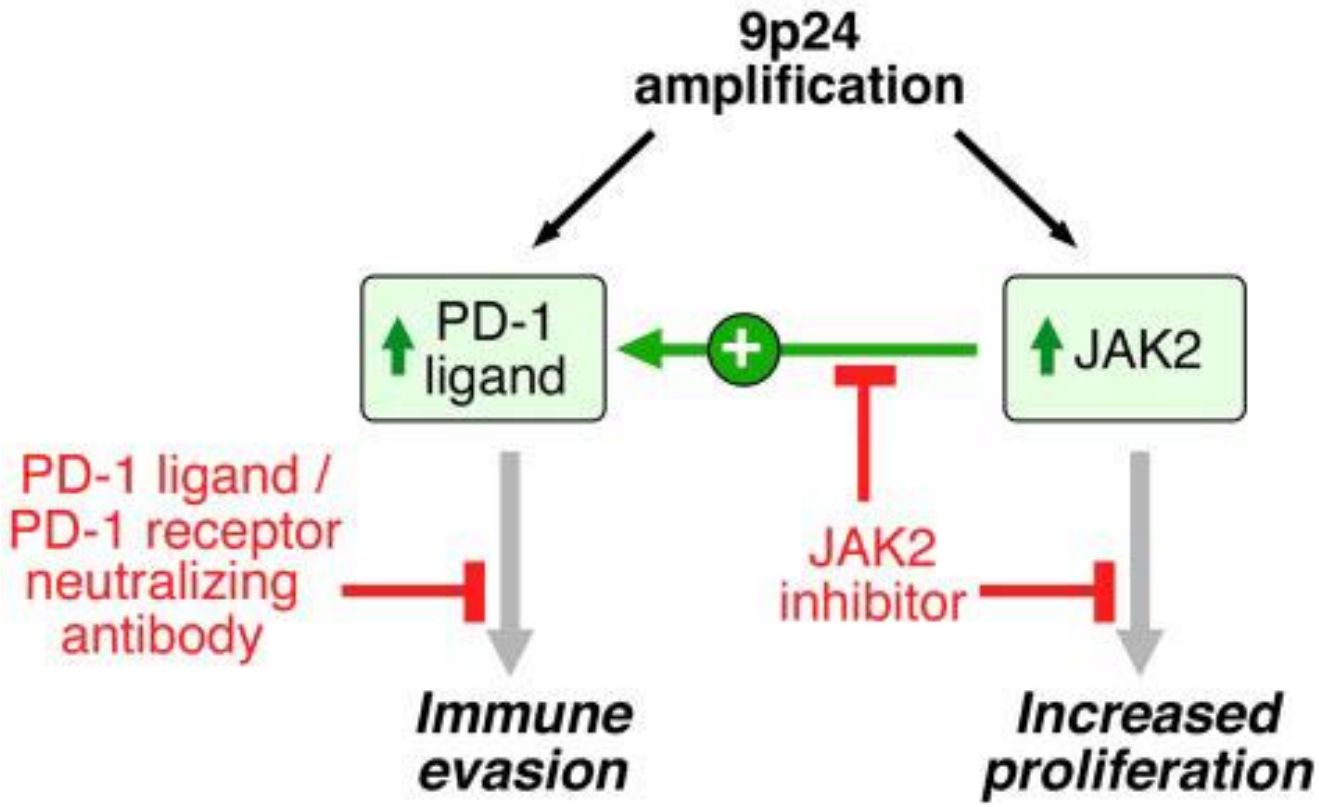


9p24.1 amplicon

PD-L1 (CD274)

PD-L2 (PDCD1LG2)

JAK2



FDA-approved Checkpoint inhibitors: Lymphoma

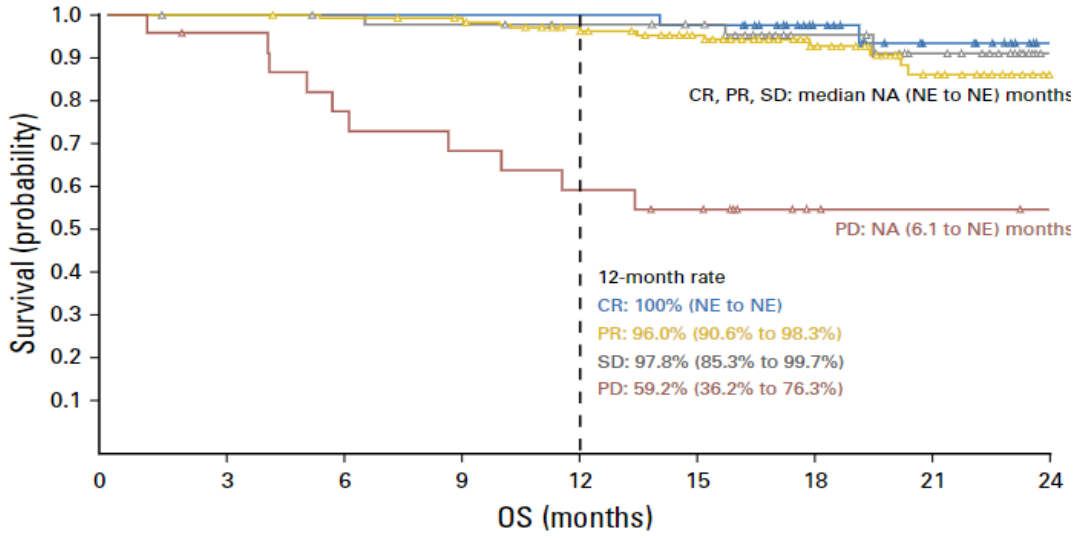
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg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

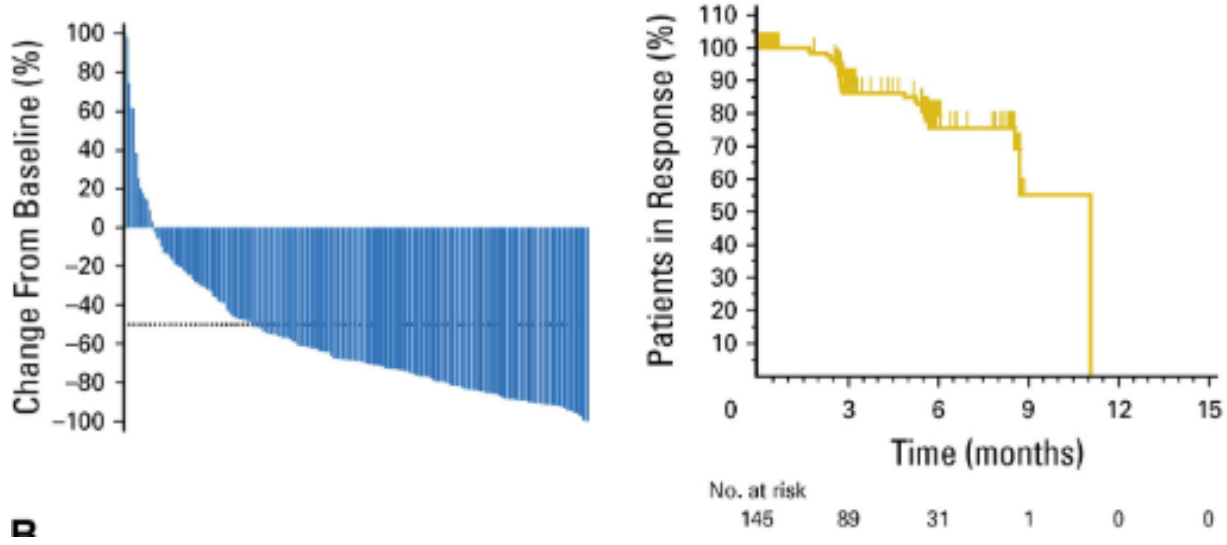
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

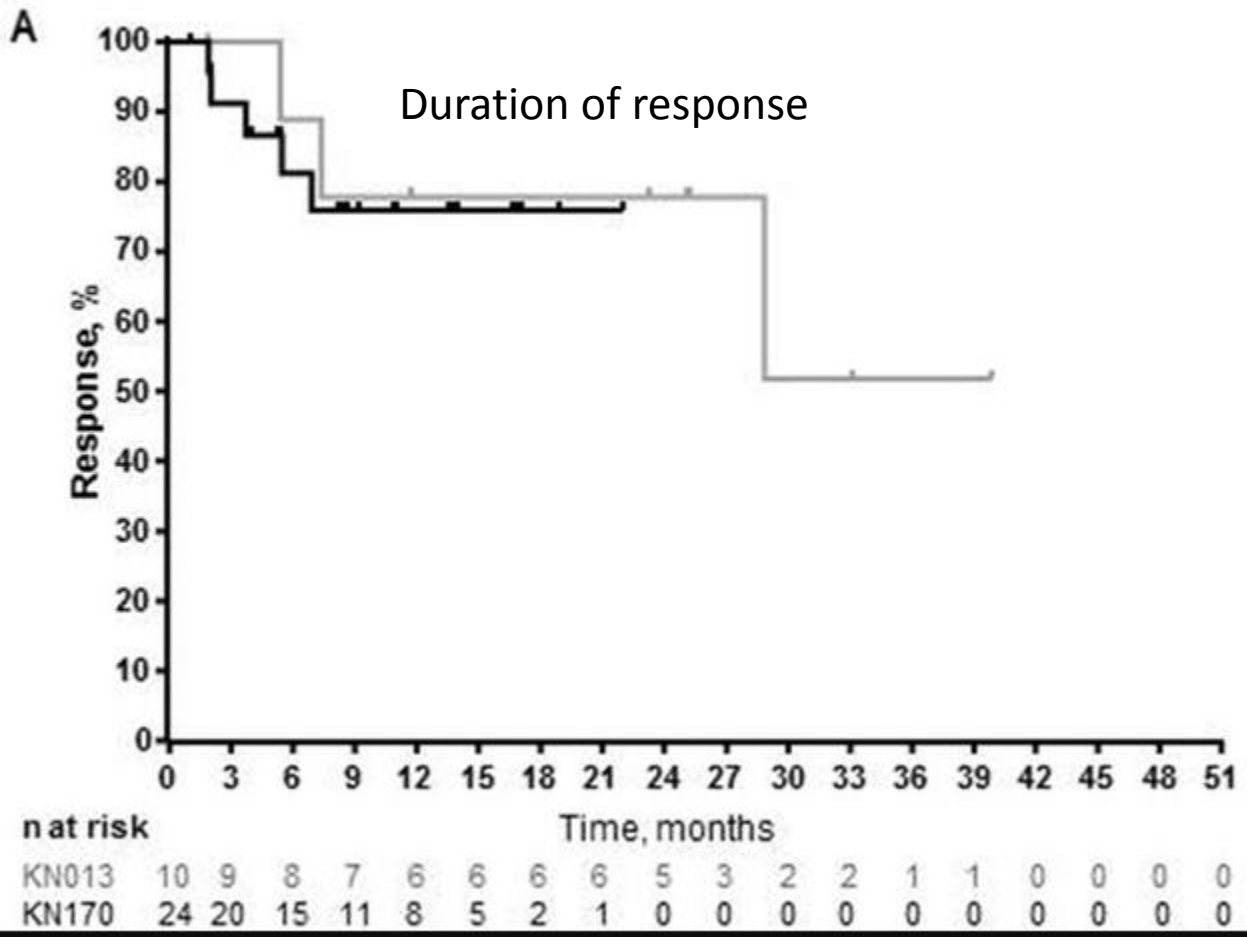
CR = 22.4%

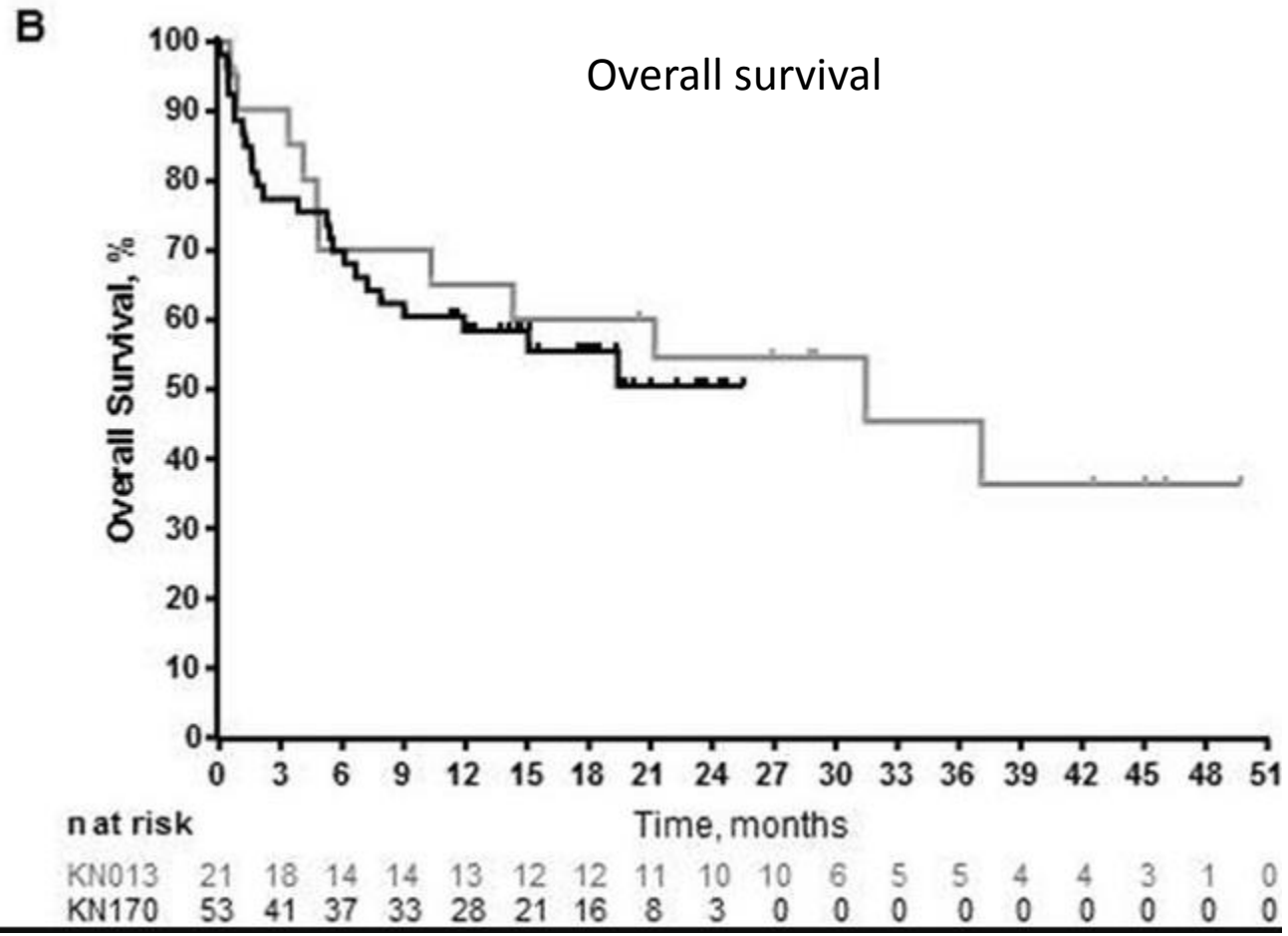
Activity seen regardless of PD-L1 expression



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

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

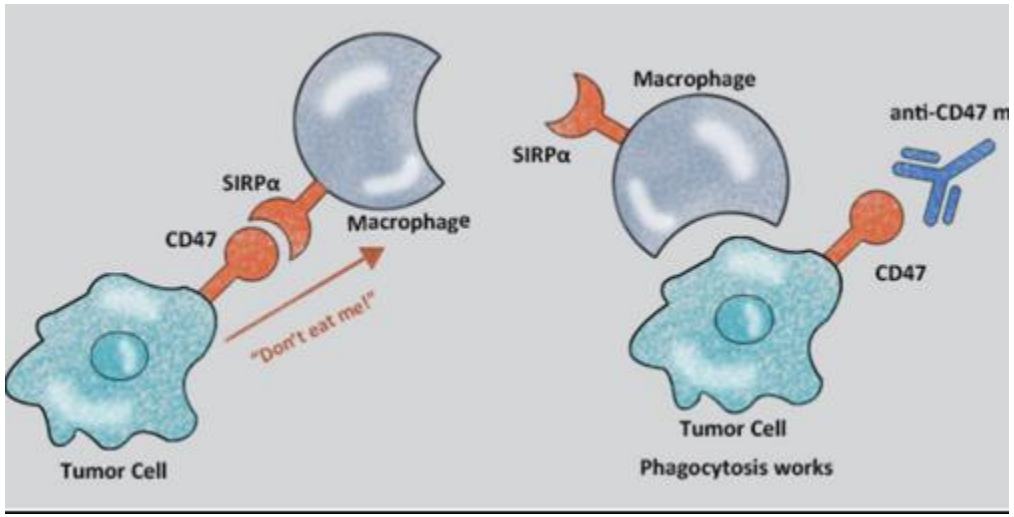


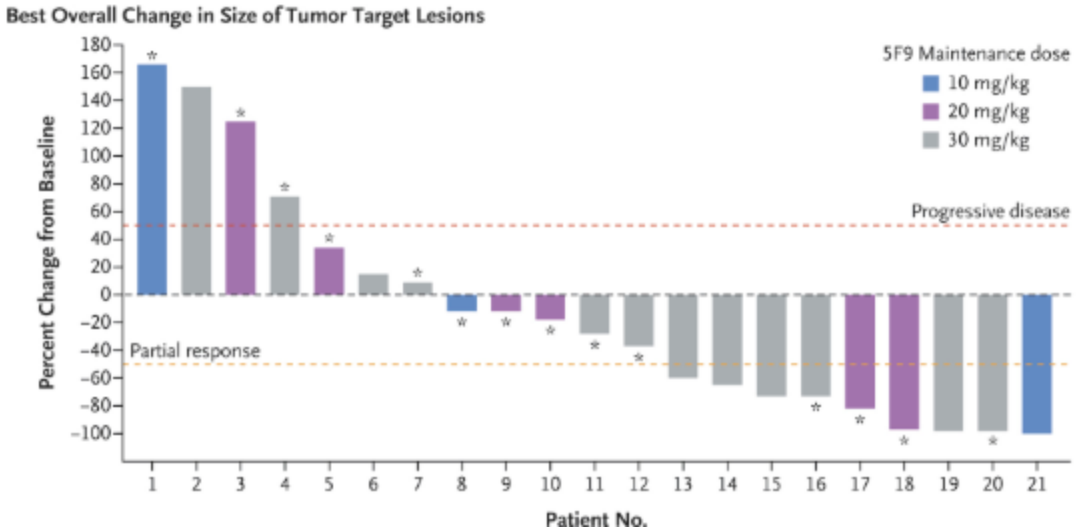


Armand, Blood 2018.

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.

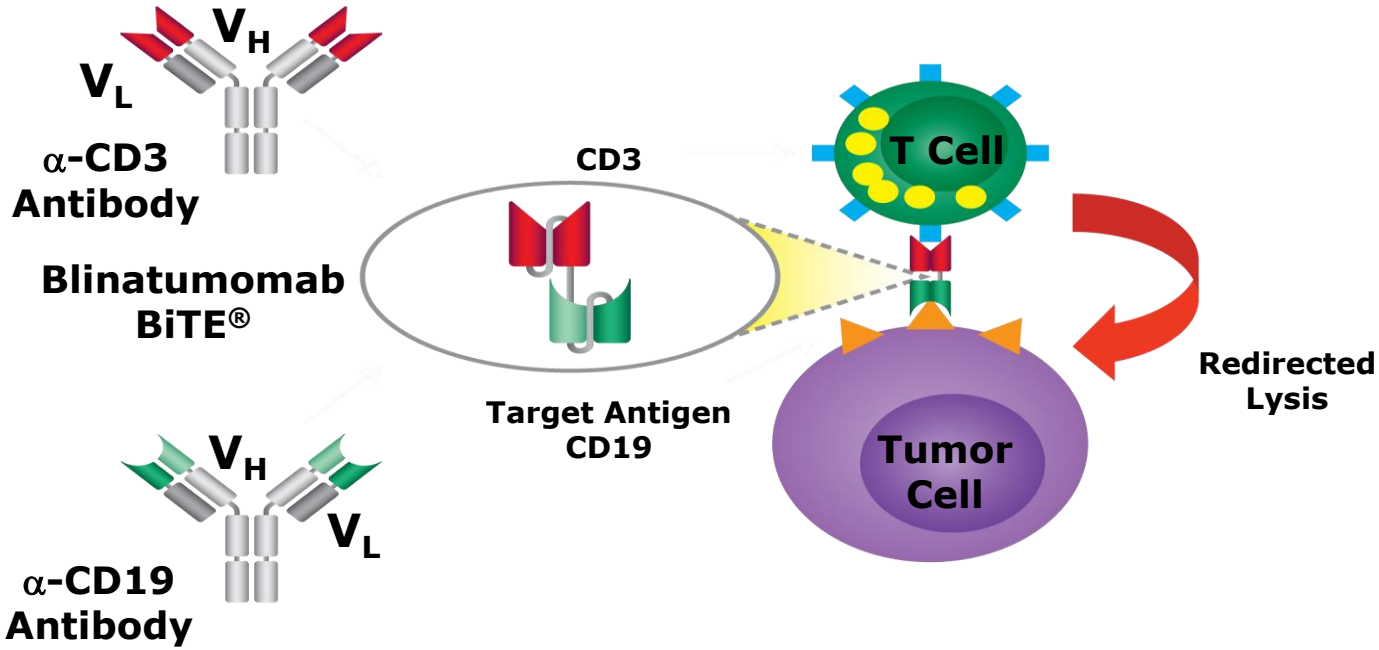
Bi-specific T-cell engagers (BiTEs)

Case

- 23 year old female with Ph- B-ALL.
- Treated on CALGB 10403 (AYA protocol) achieving CR.
- Relapsed 1 year following maintenance therapy.
- Bone marrow blasts 15%.
- Treatment?

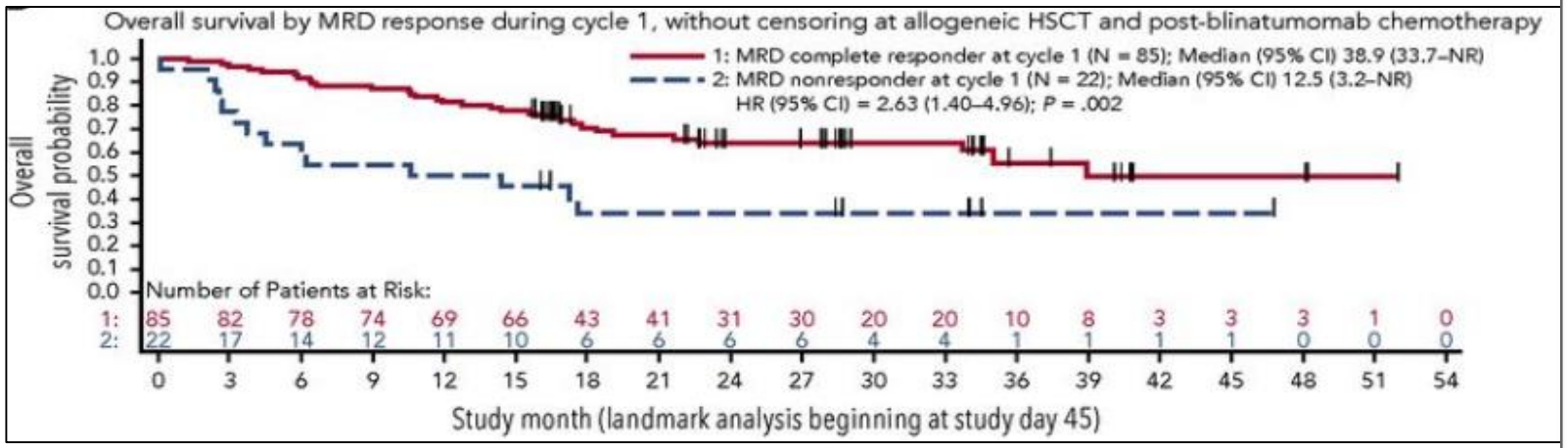
BiTE (Blinatumomab) Therapy

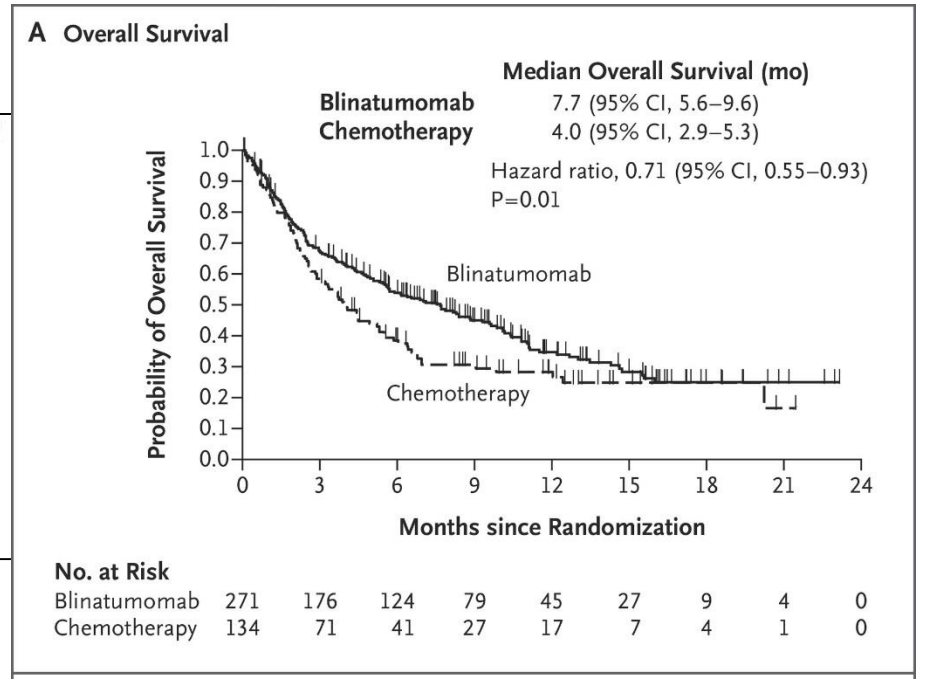
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





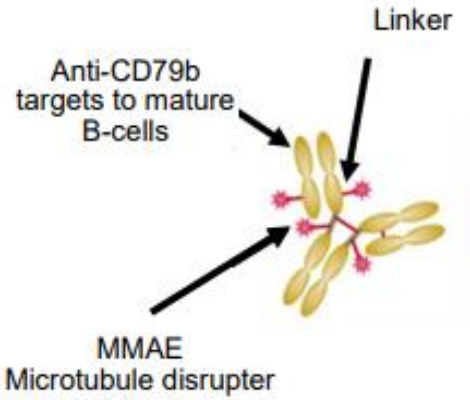
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

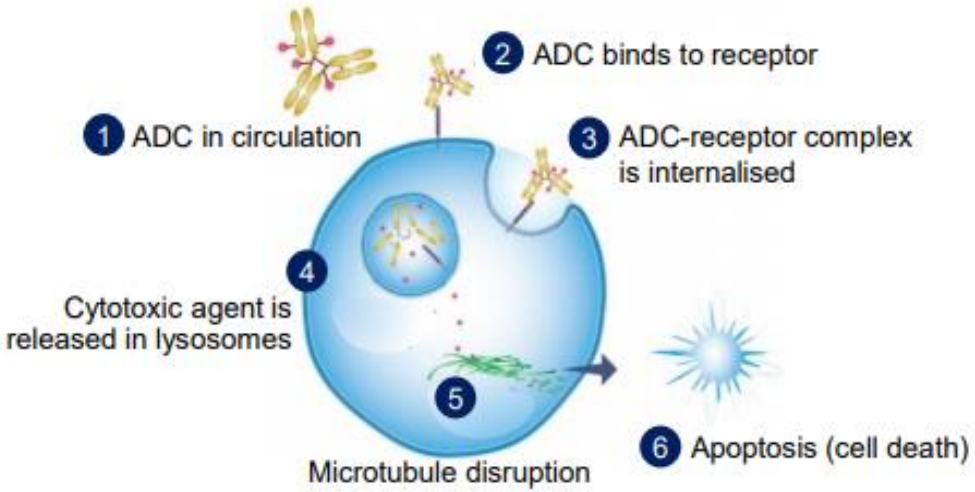
Antibody-drug conjugates (ADC)

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

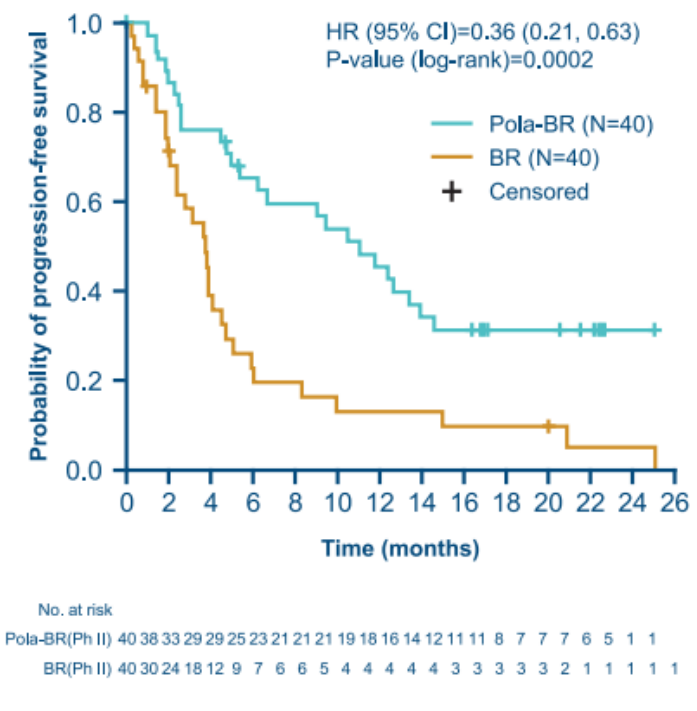
Slide credit: Tilly et al. ICML 2019

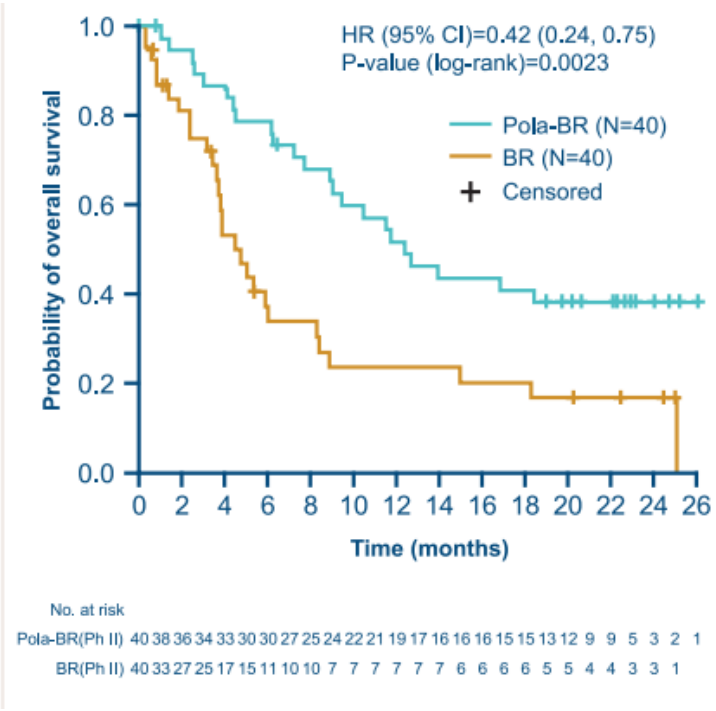
Polatuzumab vedotin: DLBCL

- 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

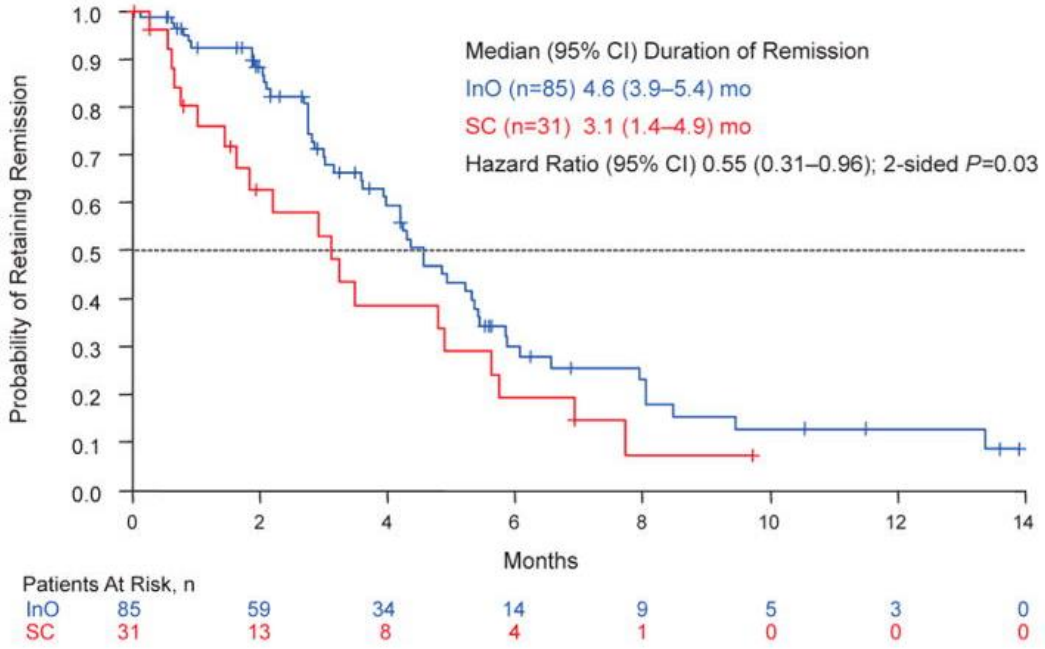


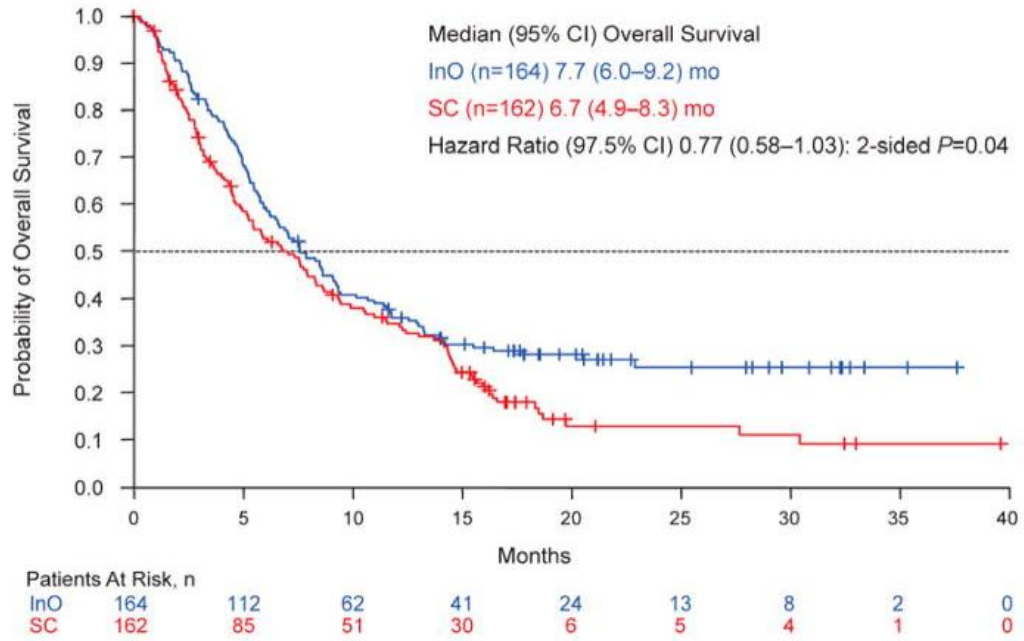


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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



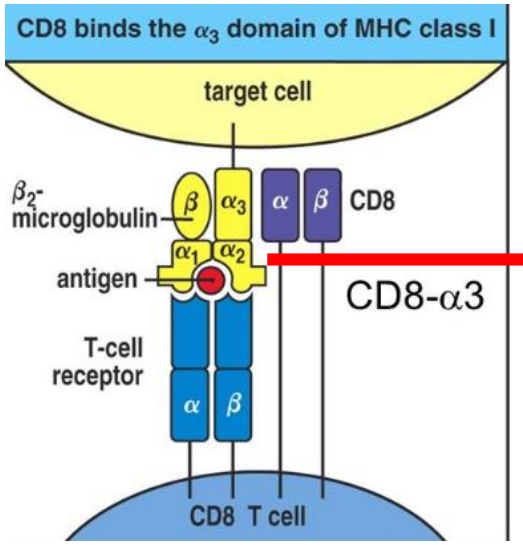


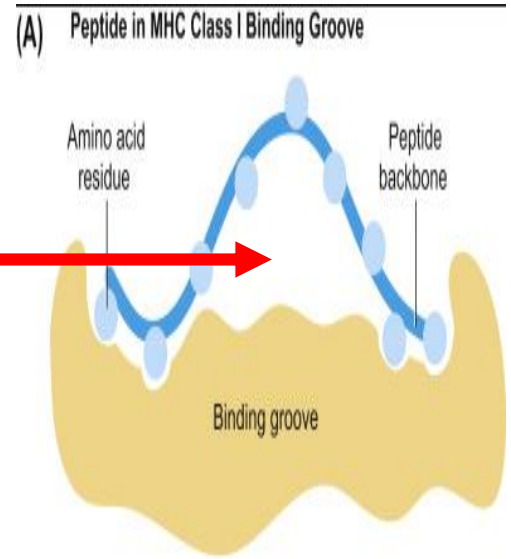
Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

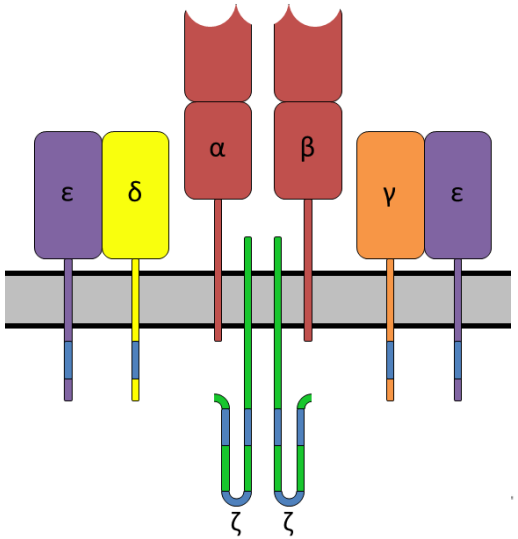
CD8+ T-cell destruction Destruction of target cell

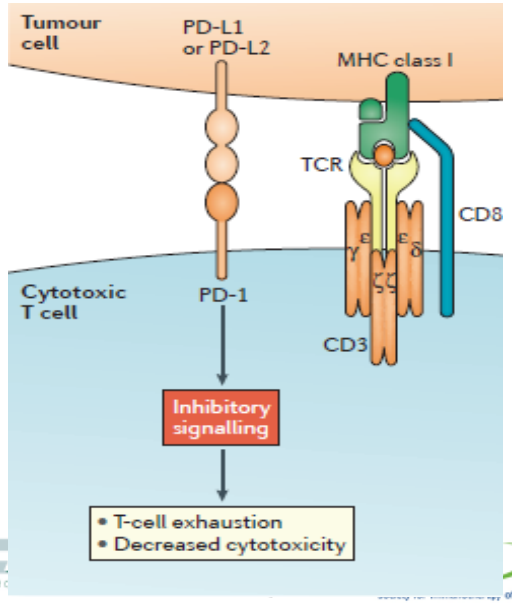
- Peptide not recognized as “self”
  - Pathogen peptide
  - Cancer peptide
- MHC-1 must be able to “present” peptide on cell surface





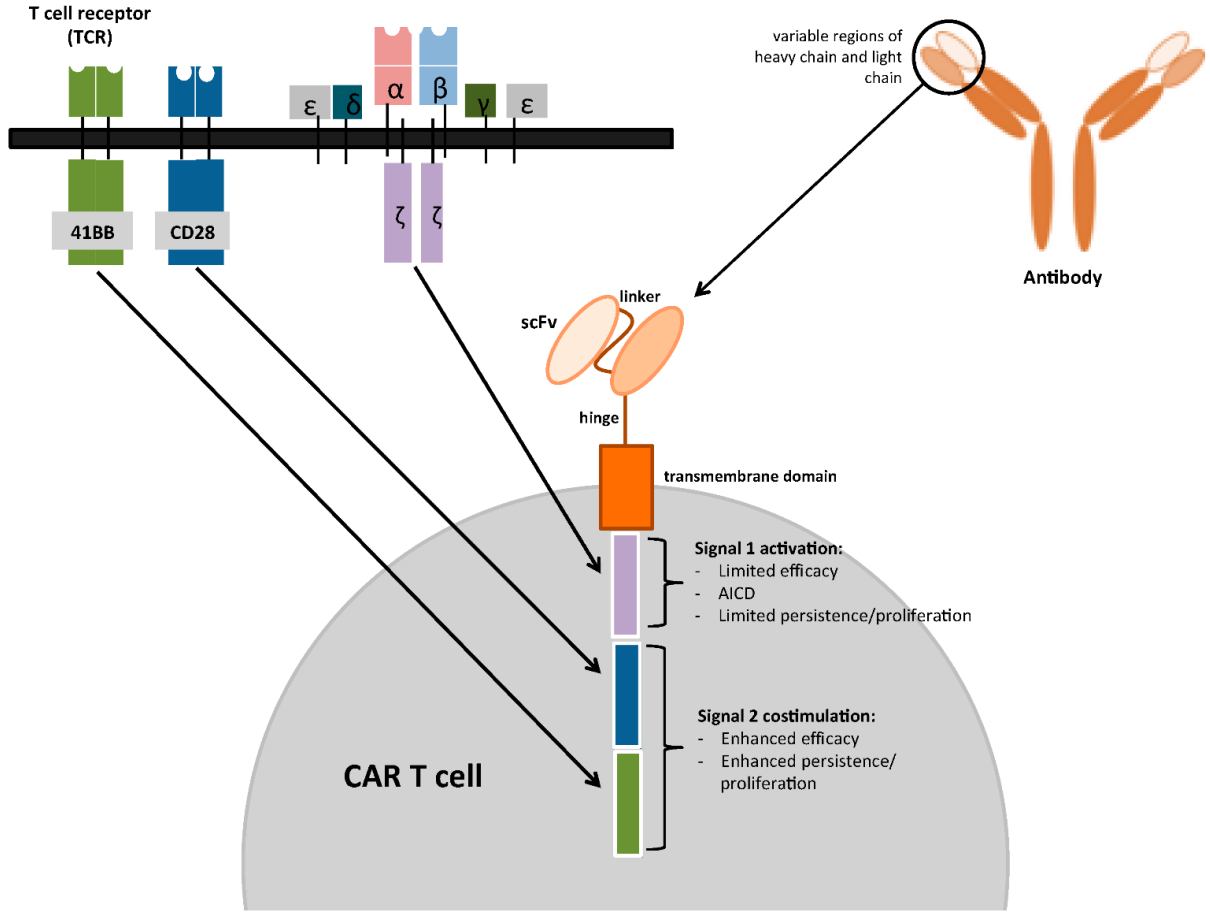
- CD8+ T-cell must have specific TCR for peptide/MHC-1 complex.
- CD8+ T-cell must be activated and not inhibited by checkpoints
  - CTLA4
  - PD-L1/L2





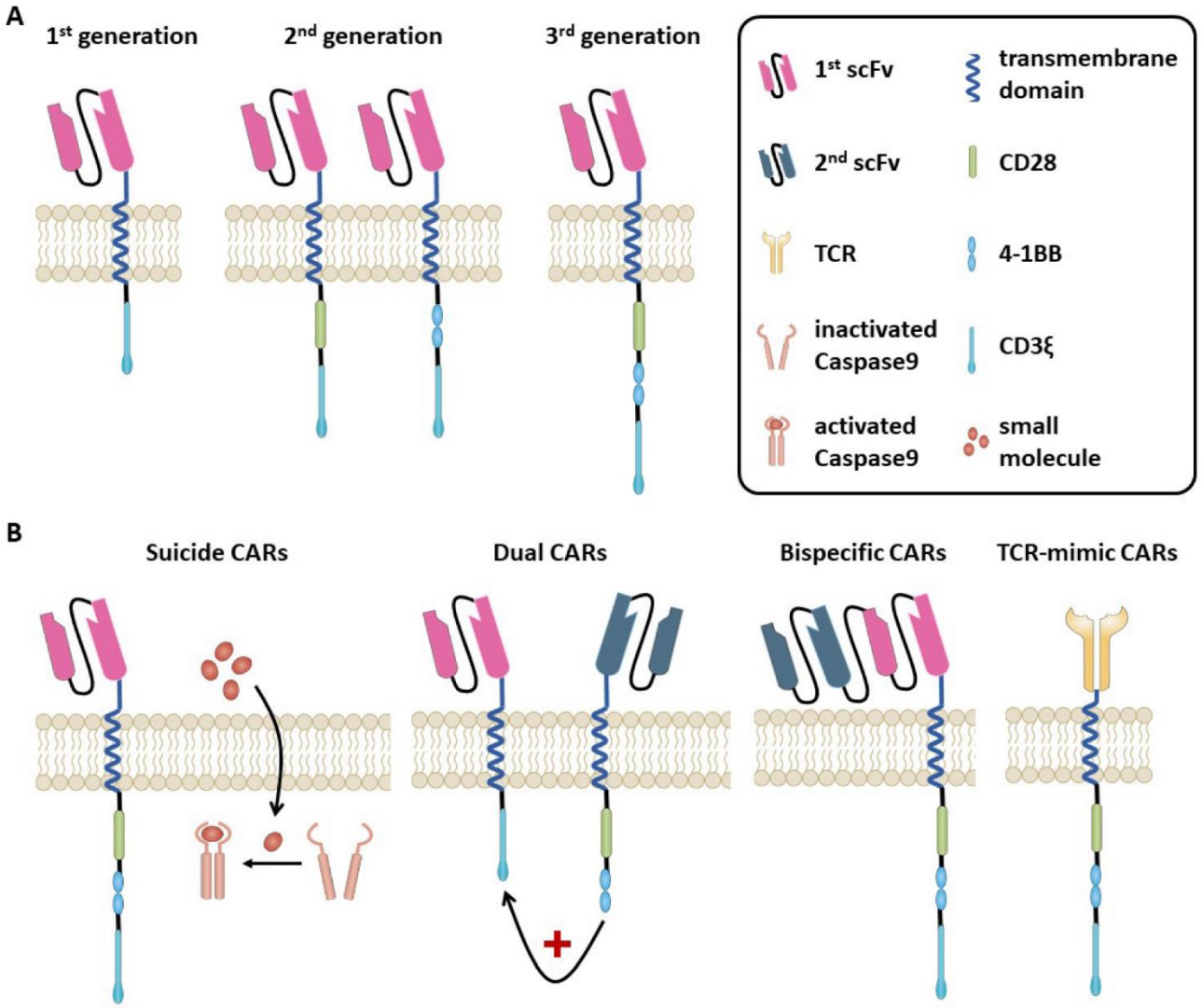
Chimeric antigen receptors

- 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.

6-8 Days Streamlined and Manufacturing Process for anti-CD19 CAR T Cells

Apheresis product shipped to CMO

↓

Lymphocyte enrichment

↓

T cell activation with anti-CD3 Ab

↓

Retroviral vector transduction of CAR gene

↓

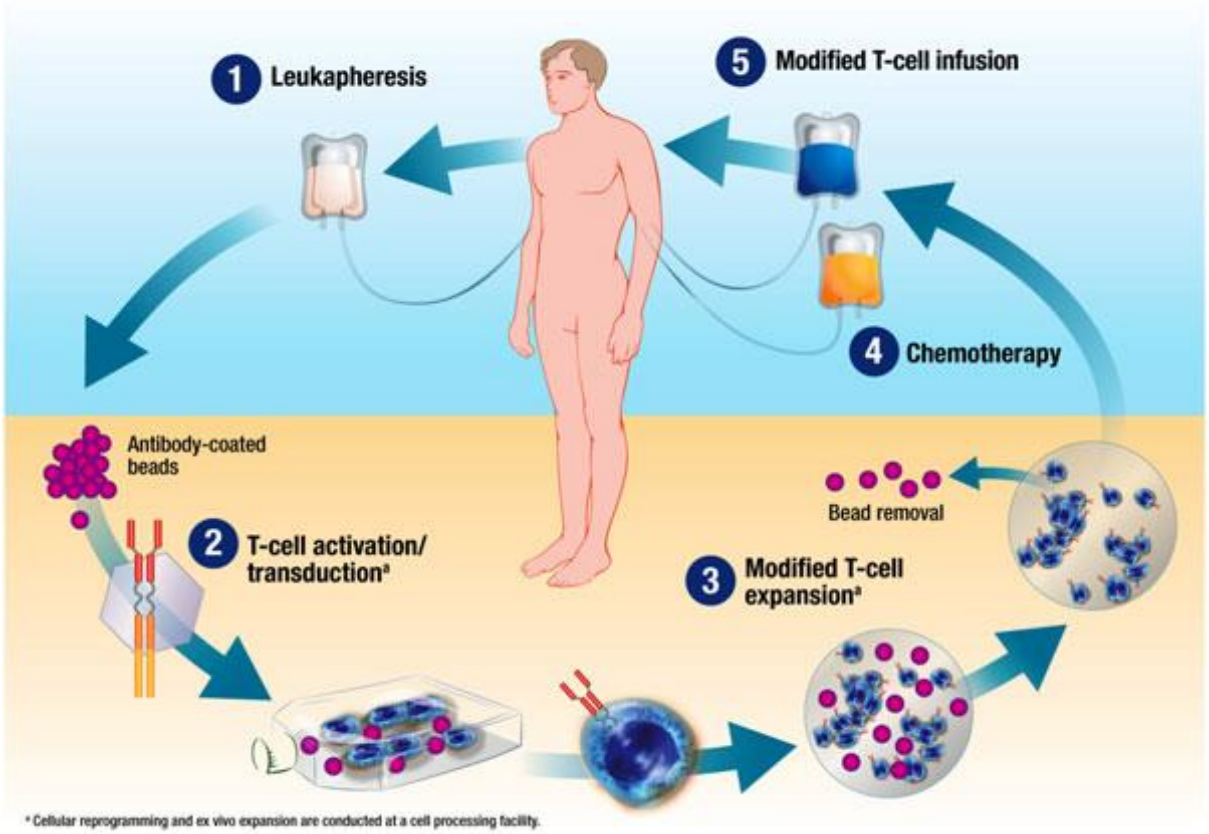
T cell expansion

↓

Harvest , cryopreserve product

↓

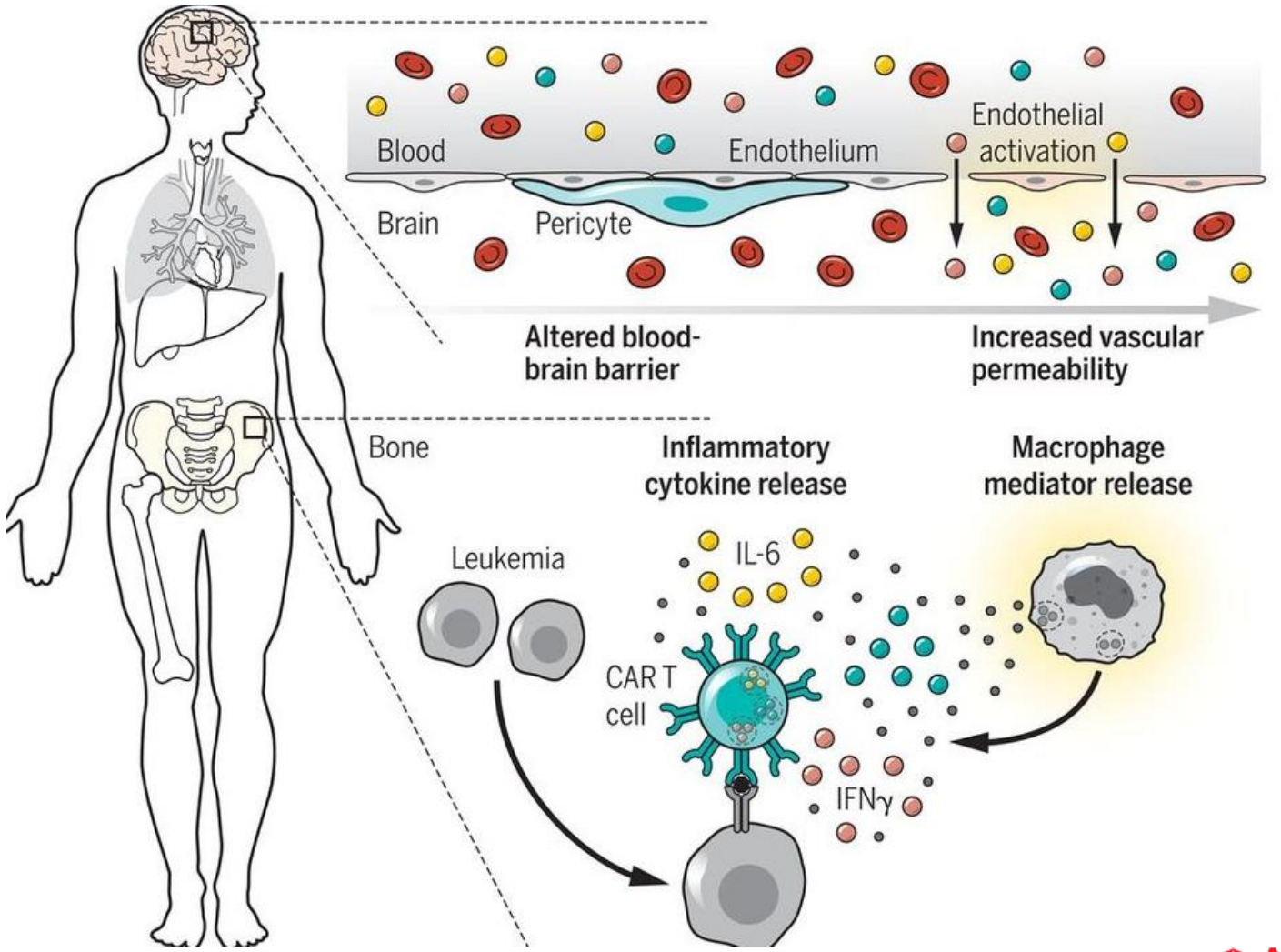
Ship product; ready for bedside use



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

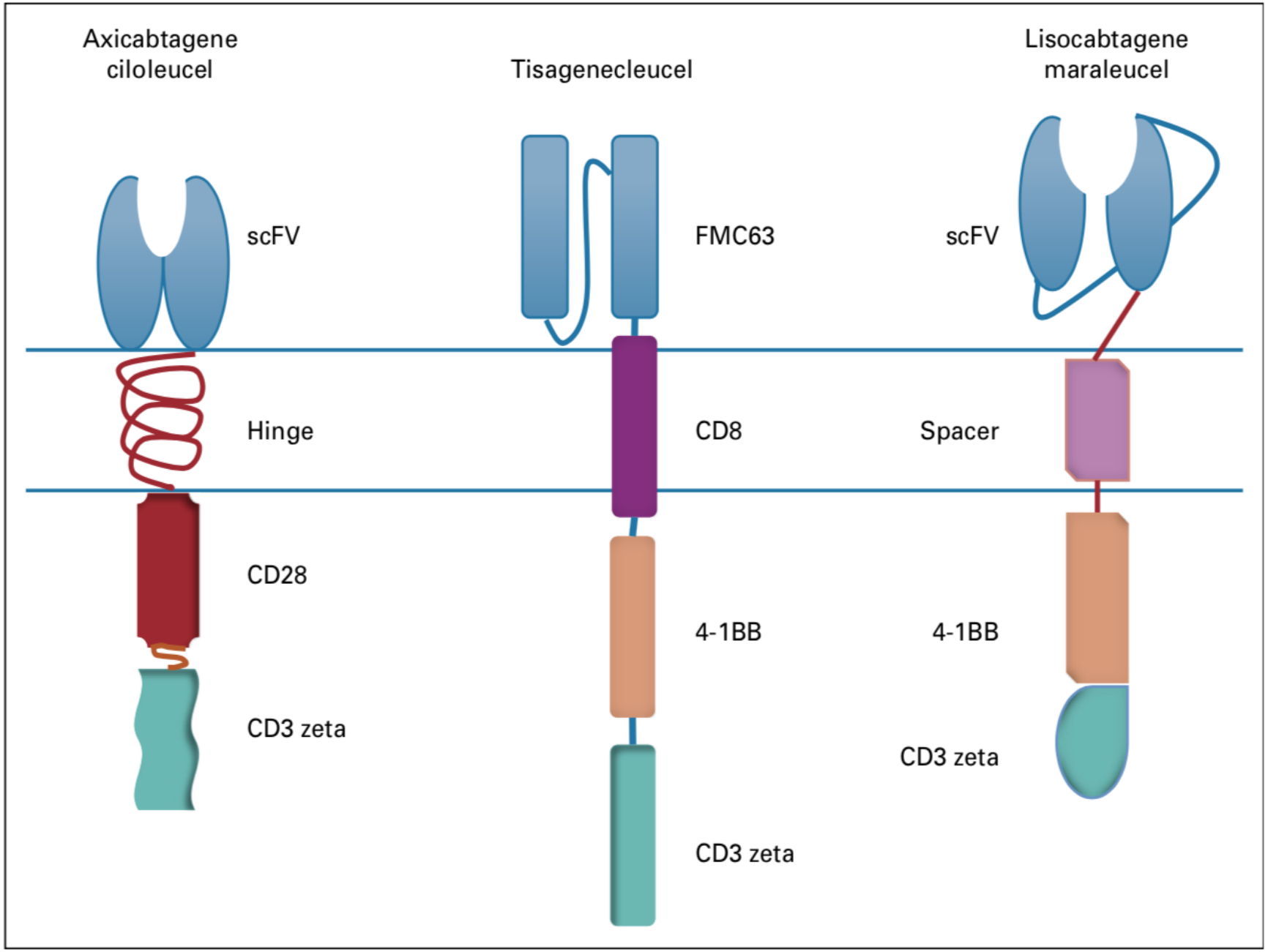
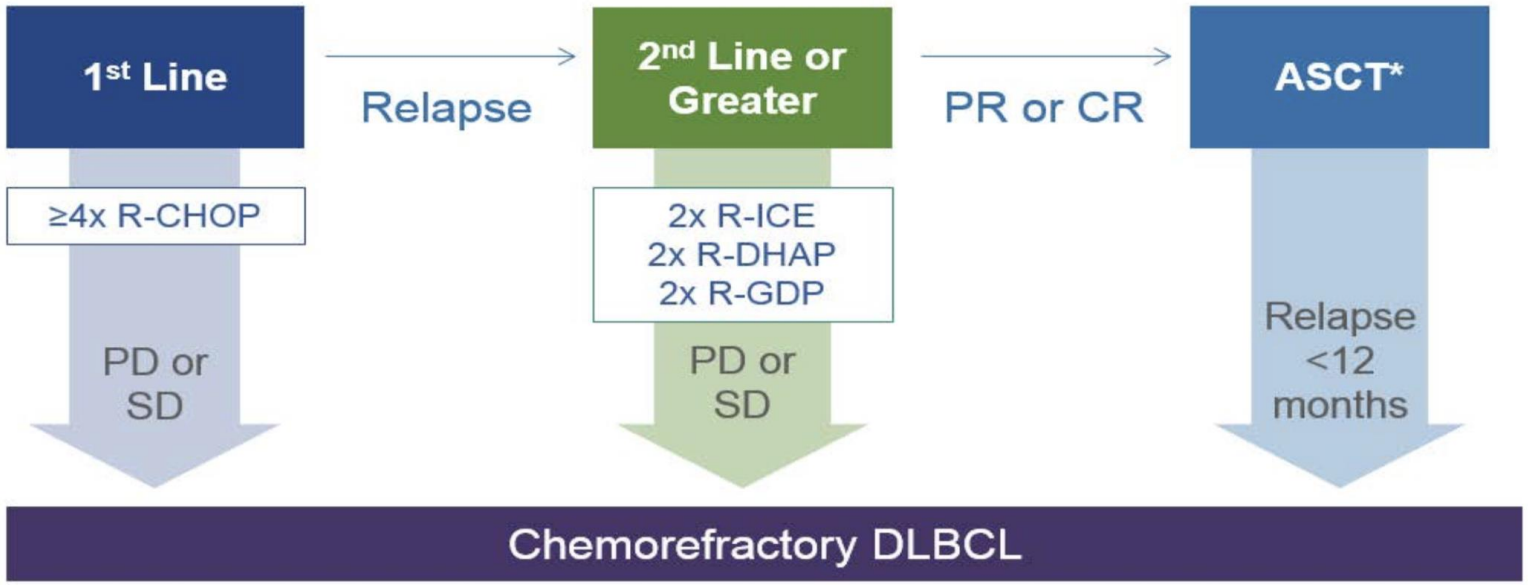


FIG 1. Depictions of three anti-CD19 CAR T-cell constructs in clinical development. Axicabtagene ciloleucel (left) contains a CD28 costimulatory domain in addition to a CD3 zeta domain, whereas tisagenecleucel (middle) and lisocabtagene maraleucel (right) contain a 4-1BB costimulatory domain in addition to a CD3 zeta costimulatory domain. scFV, signal chain variable fragment.

Standard of care for relapsed disease

- Salvage chemotherapy:
  - RICE
  - R-DHAP
  - RGDP
  - R-ESHAP
- If chemosensitive disease:
  - High dose chemotherapy with ASCT

There is a substantial unmet need for patients with Diffuse Large B cell Lymphoma



DLBCL is the most common subtype of NHL

Outcomes in chemorefractory DLBCL are poor

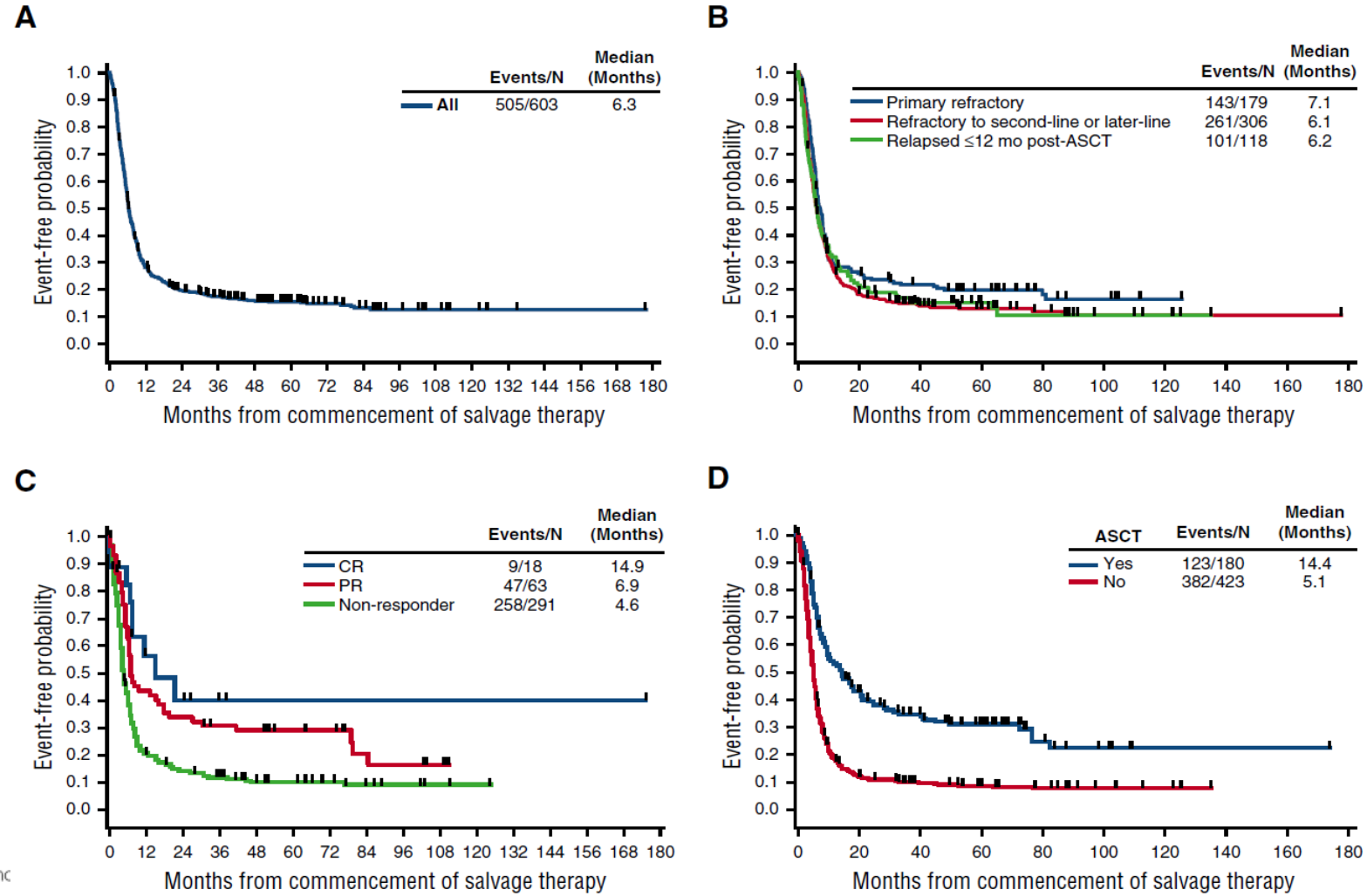
- **ORR: 26%, CR: 8%**
- **Median OS 6.6 months**

ZUMA-1: first multicenter trial of CD19 CAR T therapy in aggressive NHL

Phase 1 of ZUMA-1: ongoing CRs in 43% at 12+ months

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Diffuse Large B-Cell Lymphoma

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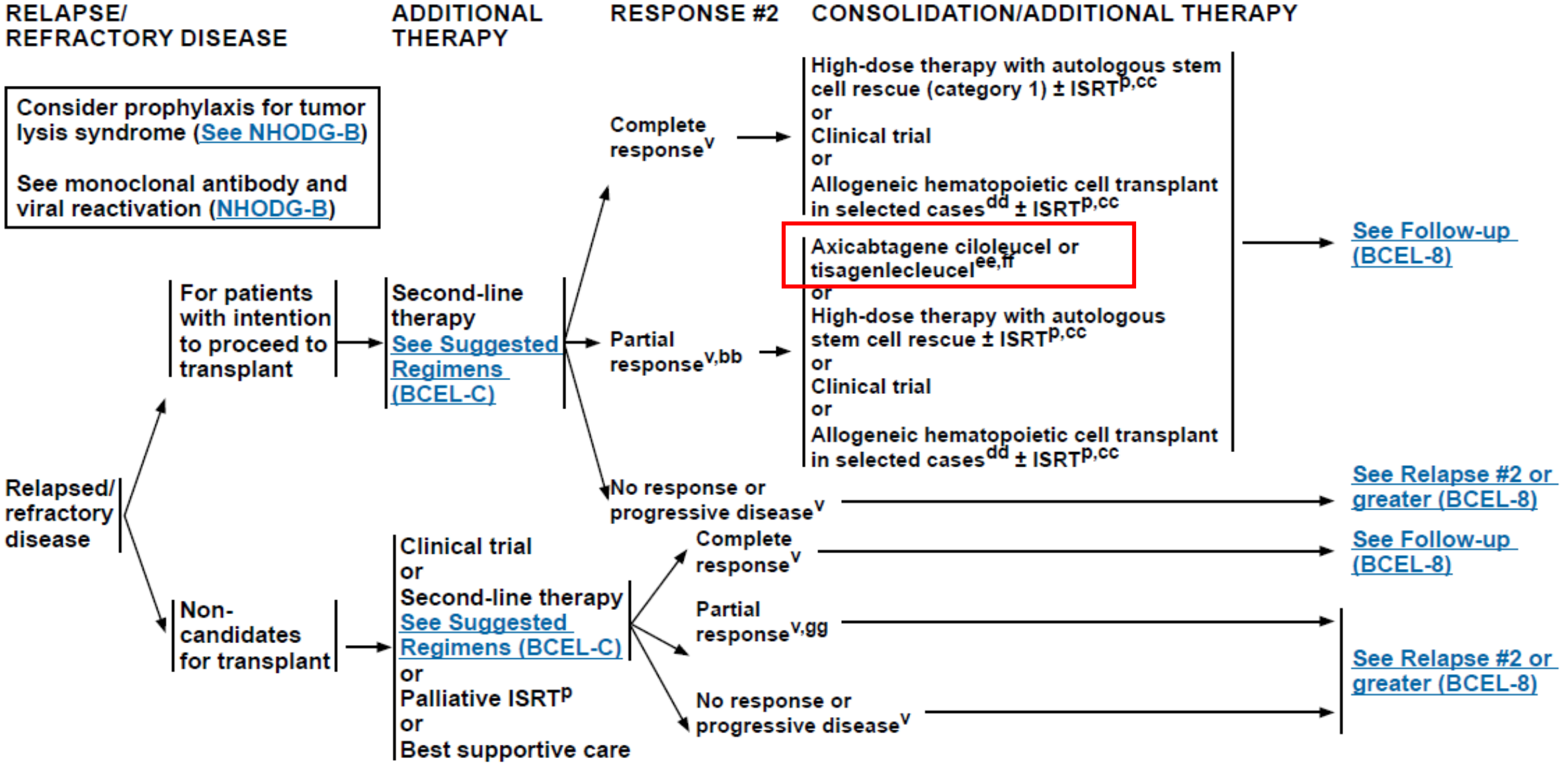
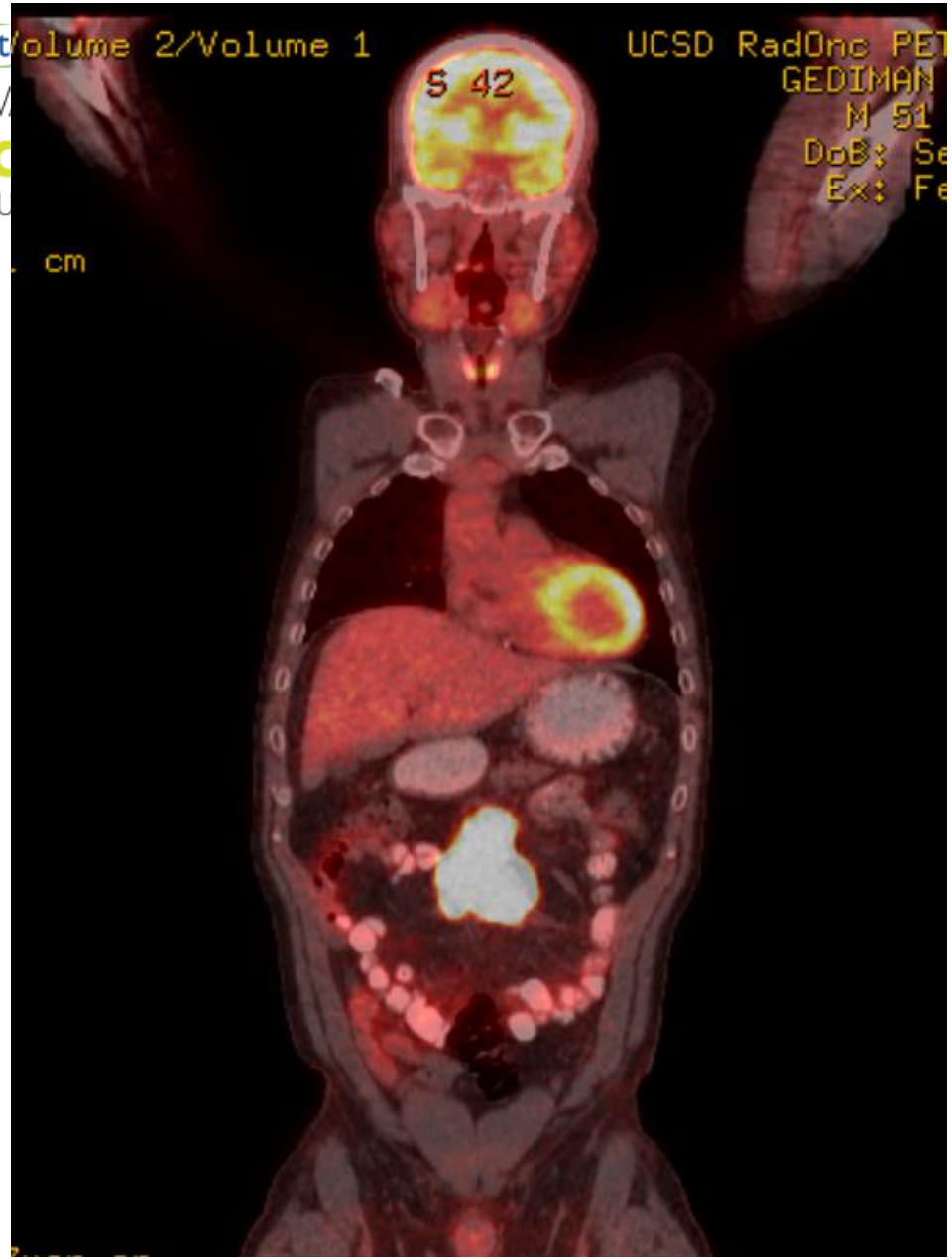


Case

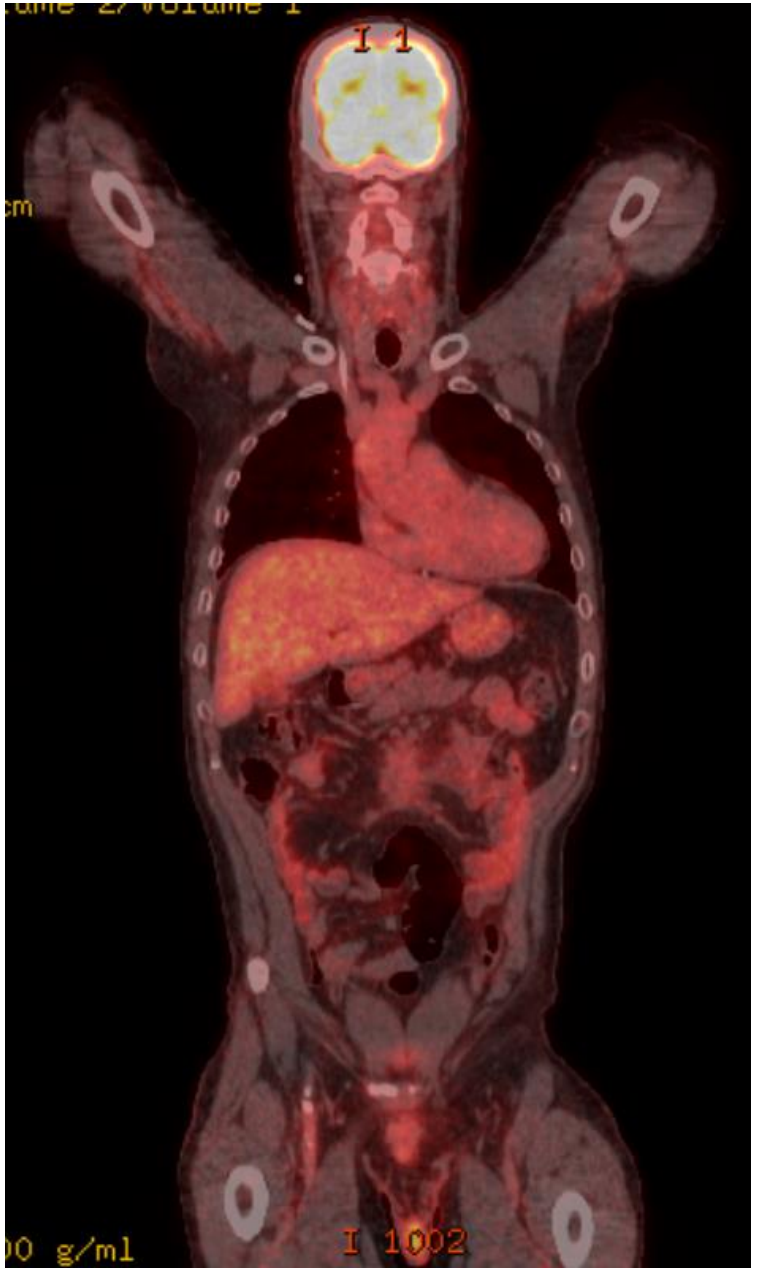
51 year old male with a history of stage IIIB DLBCL s/p 6 cycles of R-CHOP (completed 8/30/16). He initially had a good response to therapy but then presented with disease in the abdomen immediately after completing chemotherapy. He subsequently progressed through RICE and R-Gem-Ox. He was placed on trial with a CD19 directed CAR T-cell.



2/27/17

CAR T infusion

3/9/17



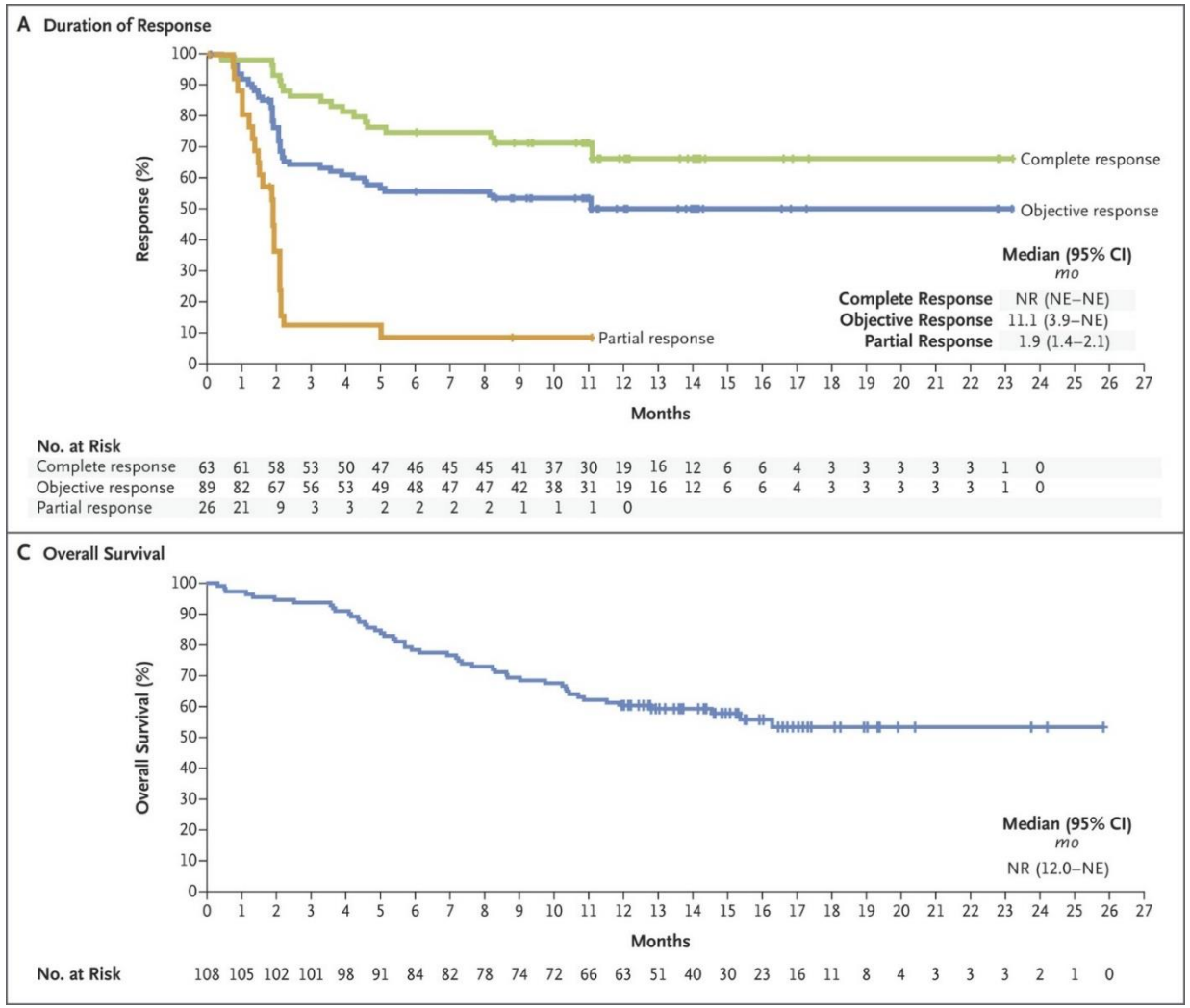
4/3/17

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)

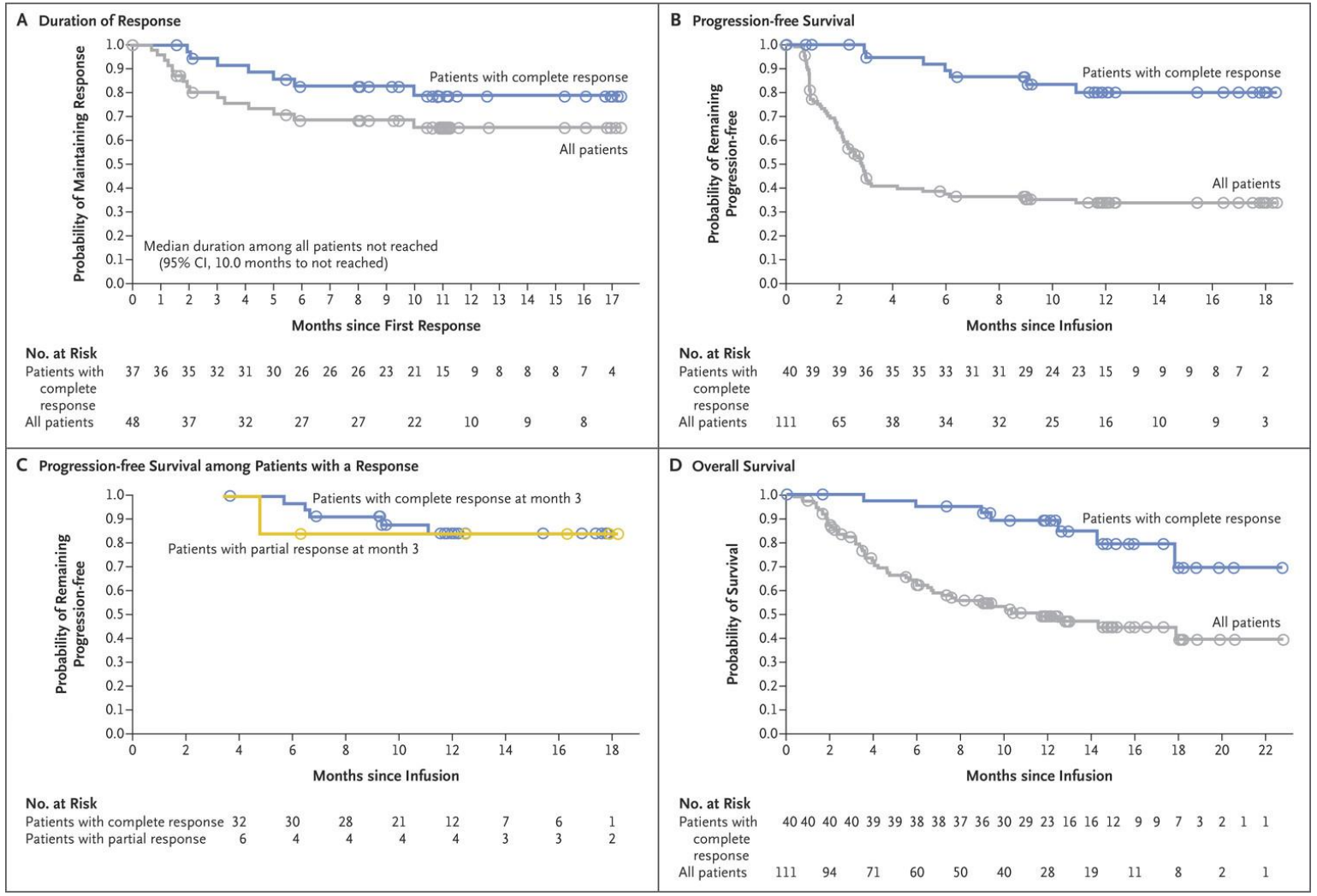
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

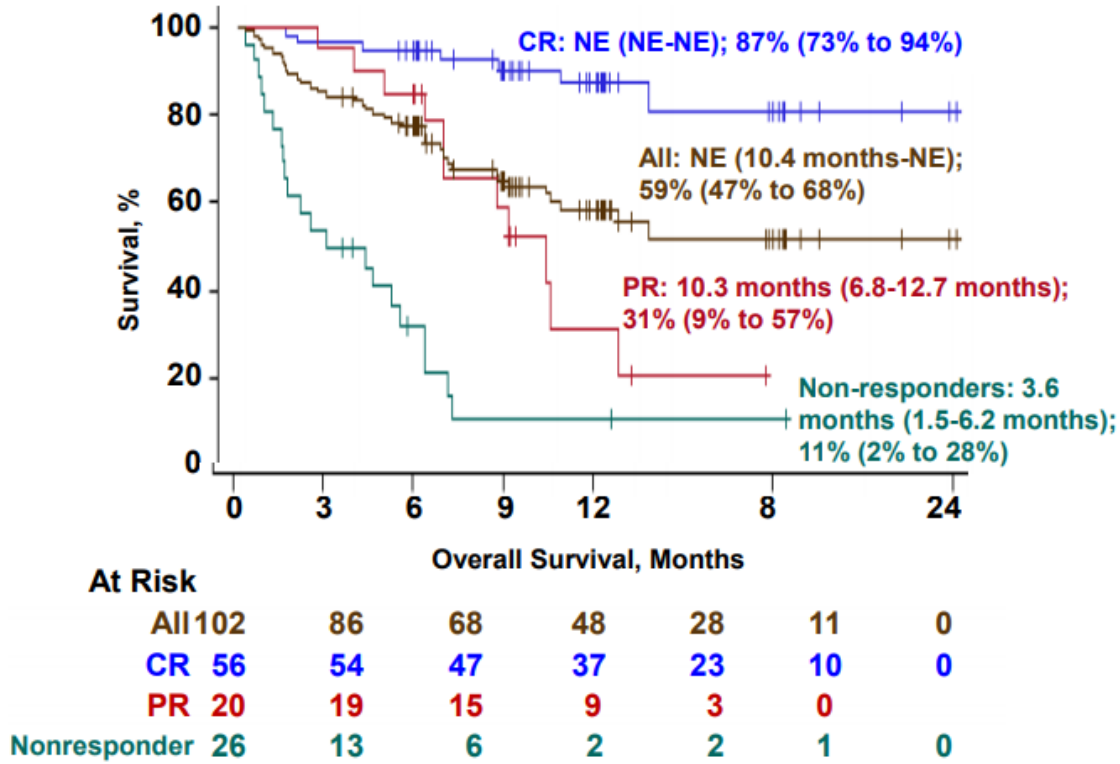
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

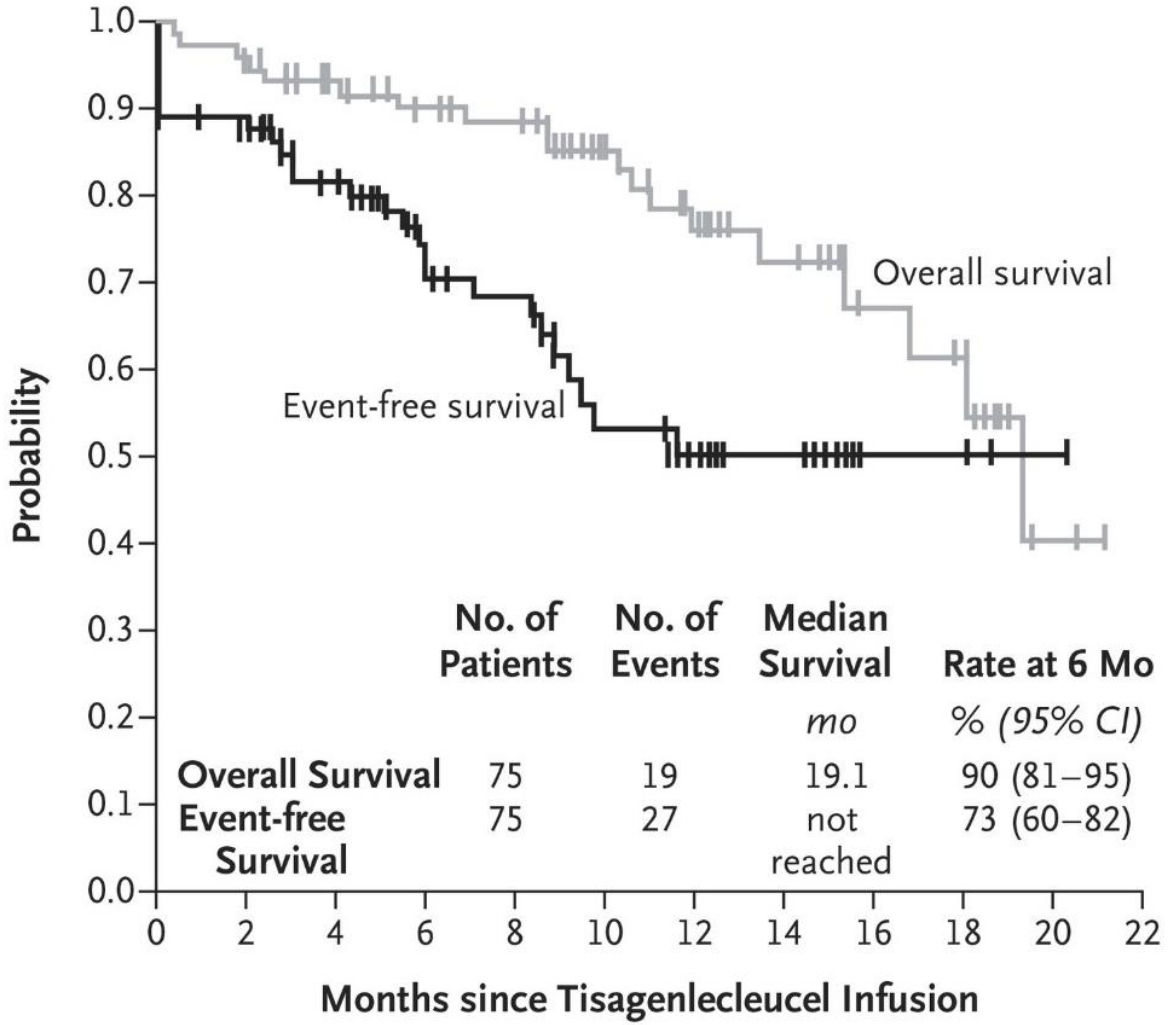
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

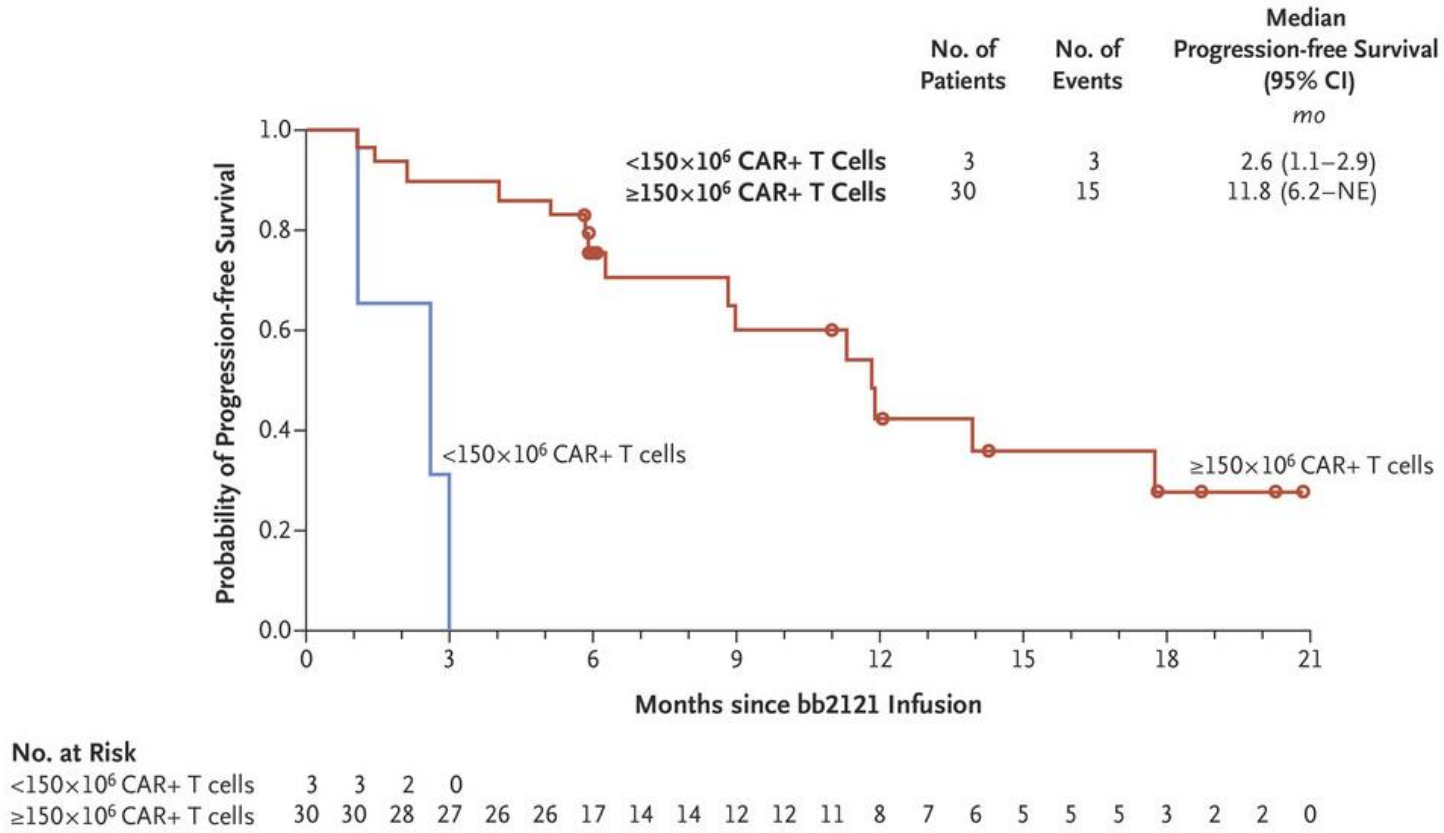


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

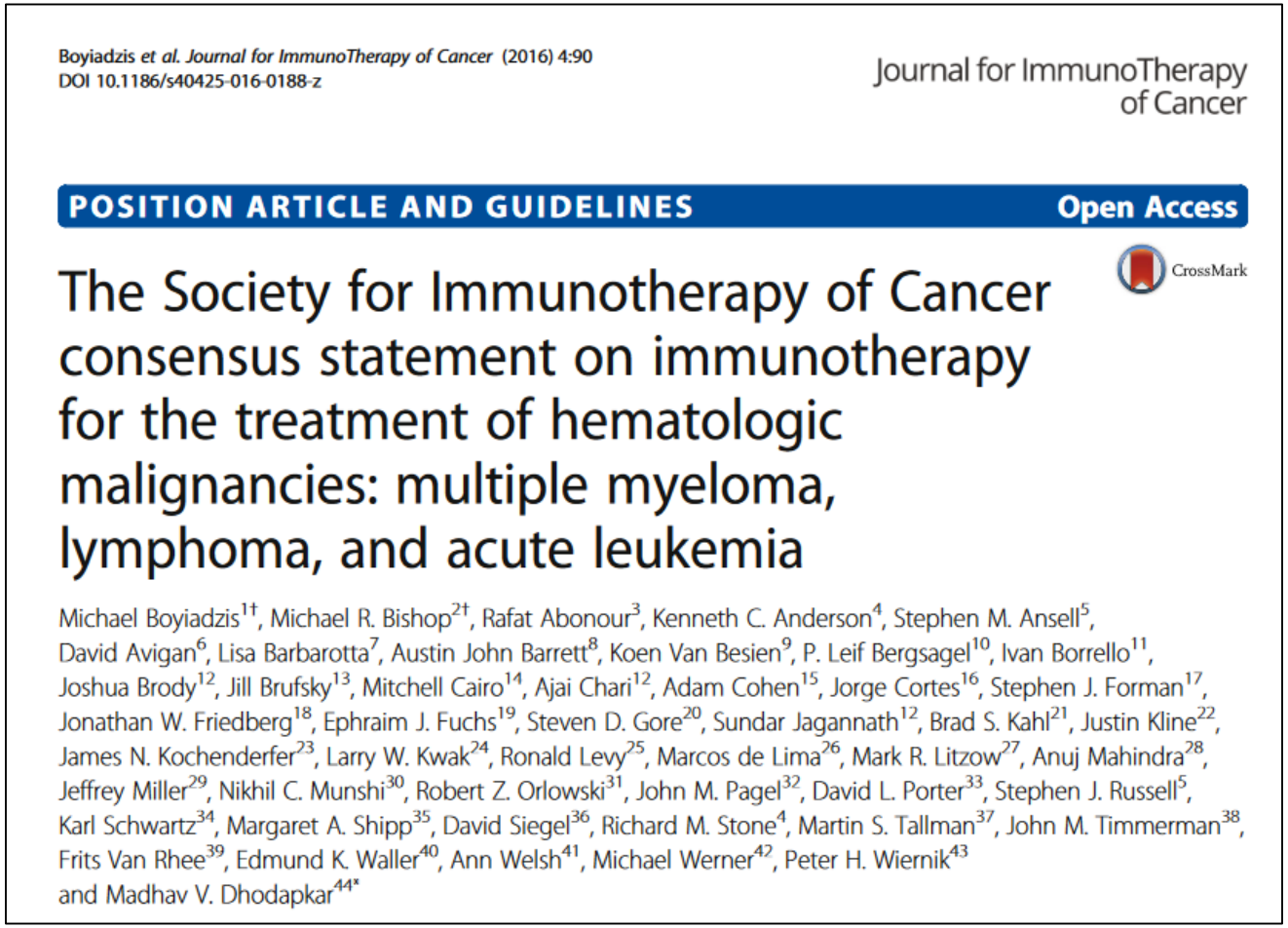


Raje, NEJM 2019.

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



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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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Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

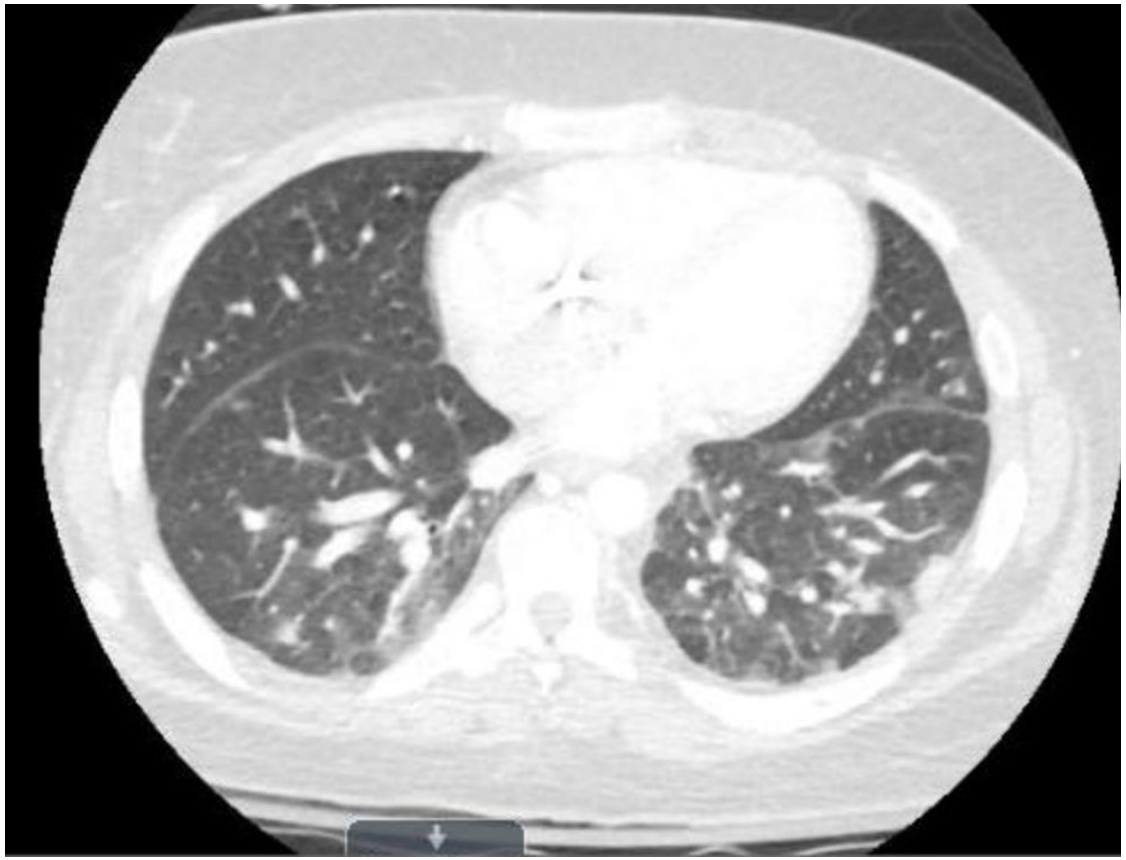
Case Studies

Case Study 1

- 23 year old female with Down's syndrome who was diagnosed with Ph- B-ALL in 2013. She was treated on a large COG stugye (AALL1131) and went into CR.
- In June of 2018 she presented with thrombocytopenia and a WBC of 25,000. A bone marrow biopsy was performed and was consistent with relapsed B-ALL (>90% B-lymphoblasts in marrow). Immunophenotype: CD19+, CD20+, CD22+, CD34+.
- How would you treat?
- She was treated on clinical trial with blinatumumab and pembrolizumab. Unfortunately, after a few cycles of therapy she had no response.

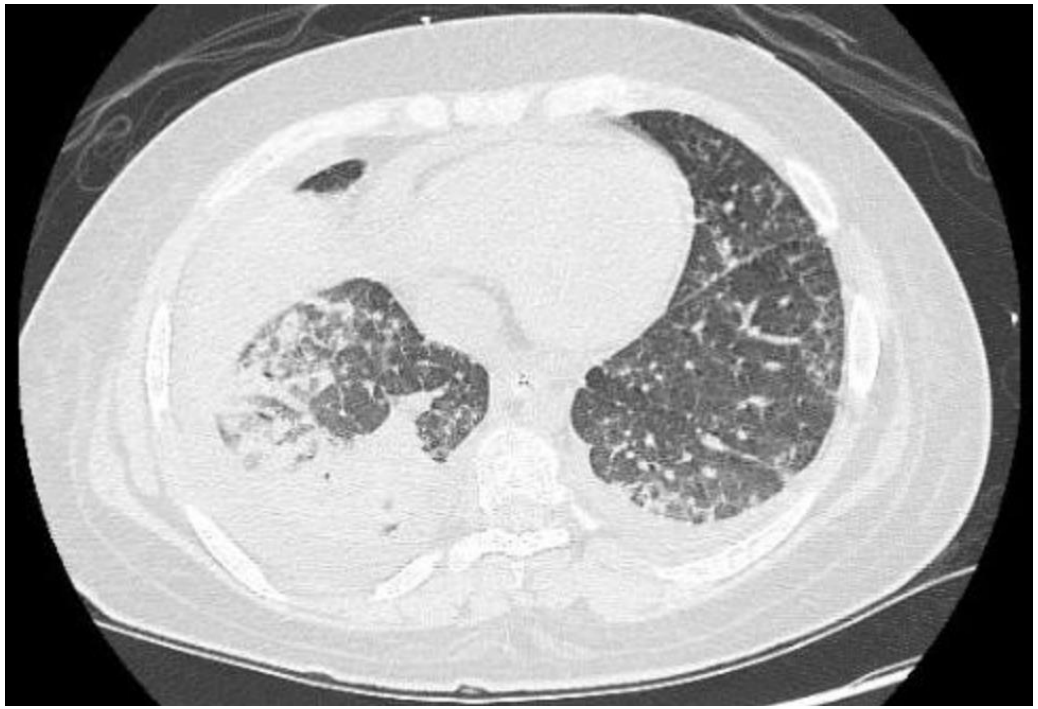
Case 1

- She developed thoracic and cervical lymph node enlargement and lung nodules.
- Bronchoscopy with BAL negative for infection, flow positive for blasts.
- Numerous LP's with no CNS involvement.
- How would you treat this patient now?



23 yo old with B-ALL

- She was enrolled onto ZUMA-3 a study of axicabtagene ciloleucel in adults with relapsed B-ALL.
- Received Flu/Cy conditioning followed by CART on 12-7-18.
- 12/12 developed fevers to 101. Started on cefepime.
- What grade of CRS?
- Grade 1 – no intervention
- 12/13 developed hypotension requiring low dose vasopressor.
- What grade of CRS and how would you treat?
- Grade 2- given tocilizumab.
- 12/15 developed rapidly progressive hypoxemic respiratory failure. Intubated. FiO2 70-100%. PEEP 18.
- What grade of CRS and how would you treat?
- Grade 4 – given more tocilizumab, methylprednisolone 1000 mg/day x 3 days, and anakinra.

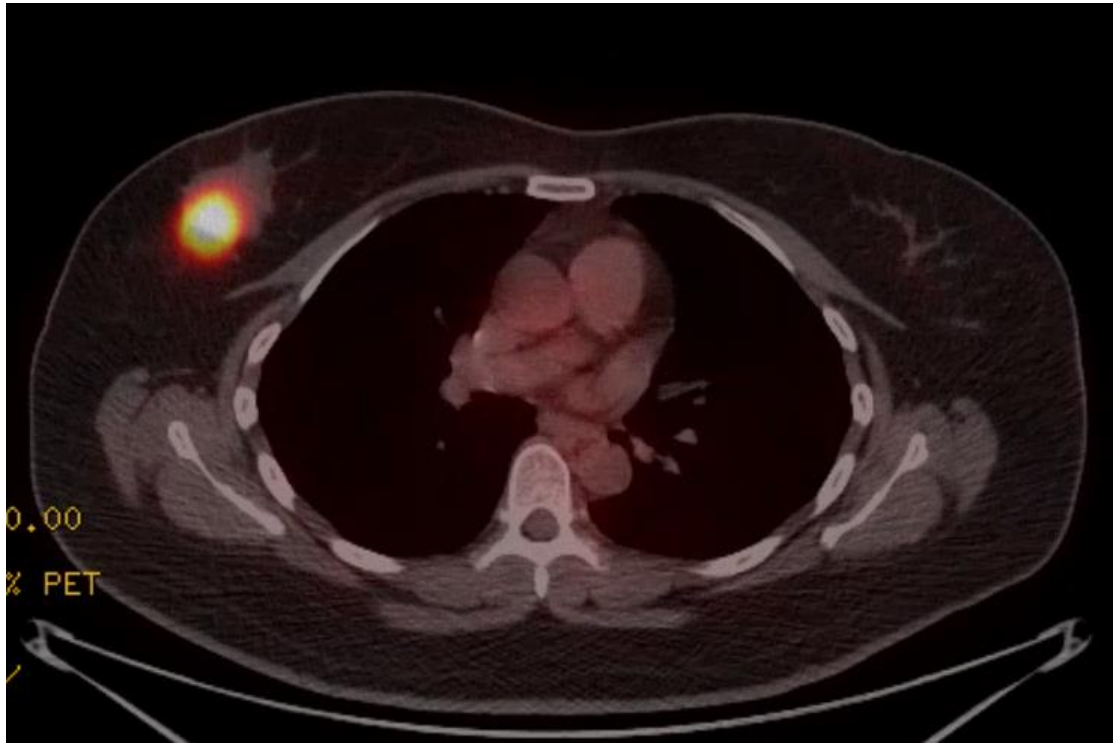


Case Study 1

- She was in the hospital for over 2 months and slowly recovered.
- At discharge she was off oxygen.
- She is now close to 1 year post CART and in a continuous MRD negative CR with no further therapy after CART.

Case Study 2

- 45 year old female with a history of polymyositis (treated with rituximab, Remicade, Enbrel, methotrexate, and prednisone) developed a right breast mass 5/18.
- Right breast core biopsy with grade 3 (A or B not specified) follicular lymphoma. CD20+, BCL2+, BCL6+, CD10+, CD21+, c-MYC (20-30%)+ by IHC. KI-67 40%. Cytogenetics not performed.
- Bone marrow biopsy with focal involvement (5%) by low grade follicular lymphoma.
- PET/CT with markedly hypermetabolic (SUV 14.9) 5 cm right breast mass.
- She was treated with 6 cycles of RCHOP achieving a CR.



- In February of 2019 she presented with an enlarging right breast mass. Repeat biopsy revealed grade 3B follicular lymphoma, cannot rule out transformation to DLBCL. BMBx with no evidence of lymphoma.
- 45 year old female with grade 3B follicular lymphoma with a remission duration of 5 months after treatment with RCHOP. What would you do next?
  - A: CD19 directed CART
  - B: Salvage chemotherapy (RDHAP, RICE, etc.) and if a response proceed with autologous stem cell transplantation.
  - C: Copanlisib
  - D: Revlimid/Rituximab

Case Study 2

- 45 year old female with grade 3B follicular lymphoma with a remission duration of 5 months after treatment with RCHOP. What would you do next?
  - A: CD19 directed CART – Not approved for follicular lymphoma, even grade 3B. Also, approval in DLBCL requires two lines of prior chemotherapy.
  - **B: Salvage chemotherapy (RDHAP, RICE, etc.) and if a response proceed with autologous stem cell transplantation. Treated grade 3B follicular lymphoma as you would treated DLBCL.**
  - C: Copanlisib – PI3K inhibitor approved for relapsed follicular lymphoma who have received at least 2 prior systemic therapies. Also, pivotal study excluded patients with grade 3B disease [M. Dreyling. JCO. 2017].
  - D: Revlimid/Rituximab – Pivotal study excluded grade 3B disease [J. Leonard. JCO. 2015]. Not unreasonable in patients not fit for chemotherapy and ASCT.

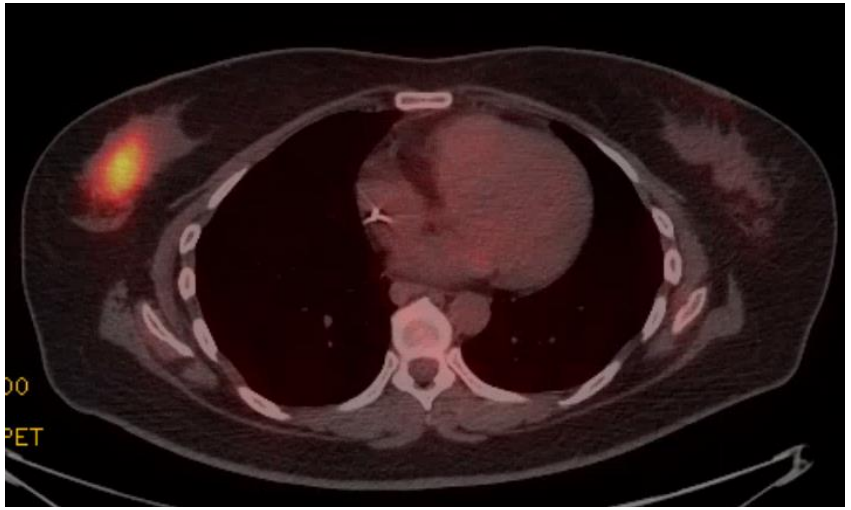
Case Study 2

- Treated with 2 cycles of RDHAP.
- PET/CT with progressive disease in right breast.
- Repeat biopsy of the right breast with at least DLBCL vs. high grade B-cell lymphoma not otherwise specified.
- What would be your treatment recommendation?
  - A: More chemotherapy followed by an allogeneic stem cell transplantation.
  - B: Ibrutinib
  - C: Axicabtagene ciloleucel (Yescarta)
  - D: Nivolumab

- What would be your treatment recommendation?
  - A: More chemotherapy followed by an allogeneic stem cell transplantation – This is a valid option, however, most would take to CART first.
  - B: Ibrutinib – Limited single agent activity in DLBCL. More active in ABC type vs germinal center origin DLBCL [W. Wilson. Nature Medicine. 2015].
  - **C: Axicabtagene cilolecel (Yescarta)**
  - D: Nivolumab – Very limited activity in relapsed DLBCL [S. Ansell. JCO. 2018].

- She was treated Flu/Cy conditioning followed by axicabtagene ciloleucel.
- Treatment was complicated by grade 2 CRS requiring 2 doses of tociluzumab.

Pre-CART PET/CT



Day +100 PET/CT