Immunotherapy for the Treatment of Hematologic Malignancies

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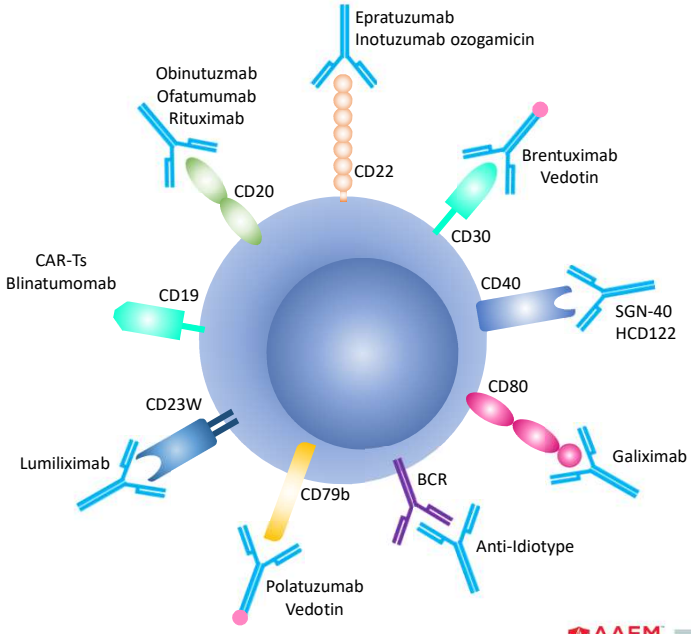
H.Lee Moffitt Cancer Center and Research Institute

Disclosures

- Contracted Research: Novartis-Research Funding
- I will be discussing non-FDA approved indications during my presentation.



Checkpoint inhibitors

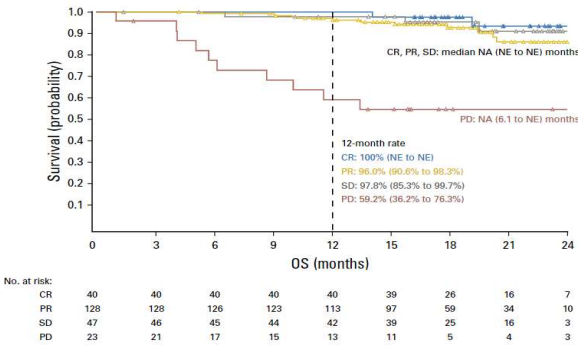
FDA-approved Checkpoint inhibitors: Lymphoma

Drug	Indication	Dose
Nivolumab	Classical **Hodgkin lymphoma**, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Adult/pediatric refractory classical **Hodgkin lymphoma** or relapsed after 3 previous therapies	200 mg Q3W or 400 mg Q6W adults 2 mg/kg (up to 200 mg) Q3W (pediatric)
Pembrolizumab	Adult/pediatric refractory **primary mediastinal large B-cell lymphoma** or relapsed after 2 previous therapies**	200 mg Q3W or 400 mg Q6W adults 2 mg/kg (up to 200 mg) Q3W (pediatric)

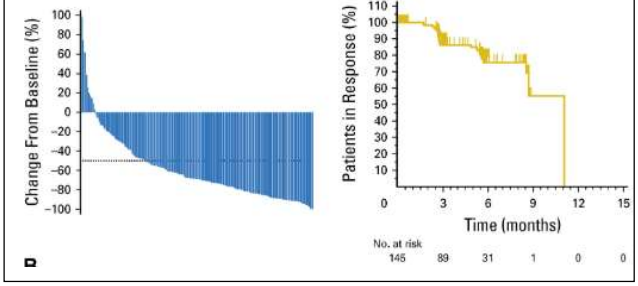
**Not recommended for patients with PBMCL that require urgent cytoreductive therapy.

Checkpoint inhibitors: Hodgkin Lymphoma

Checkmate-205
ORR = 69%
CR = 16%

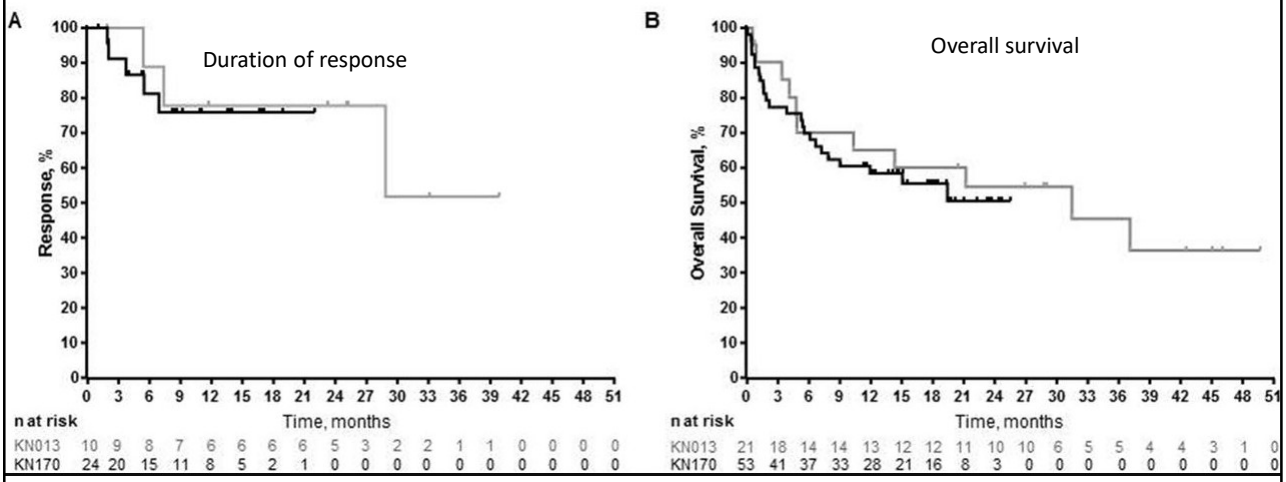


Keynote-087
ORR = 69%
CR = 22.4%
Activity seen regardless of PD-L1 expression



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

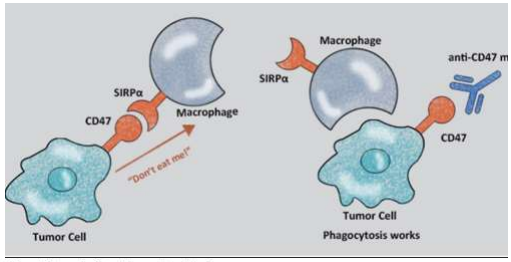
Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

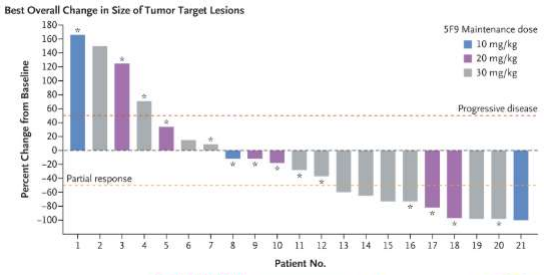


Armand, Blood 2018.

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%



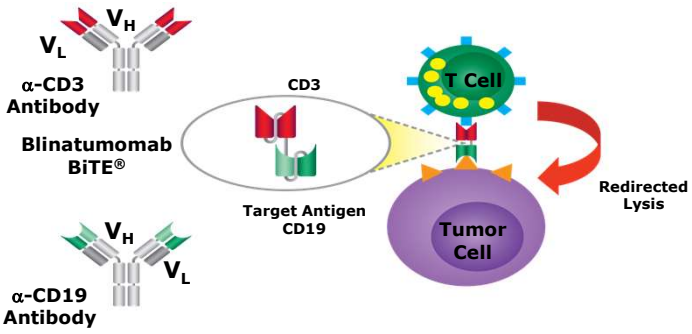


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

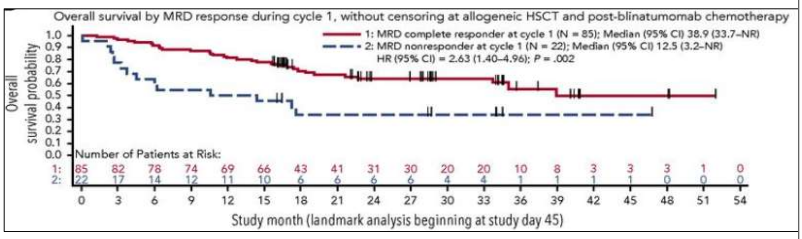
BiTE (Blinatumomab) Therapy

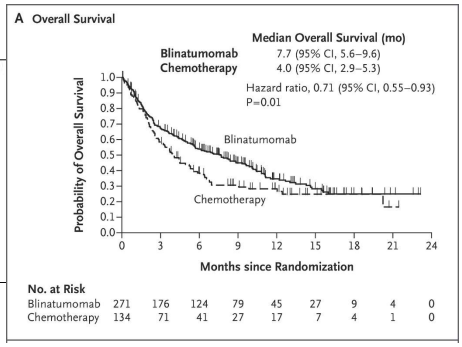
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





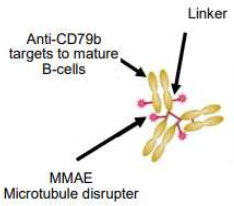
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

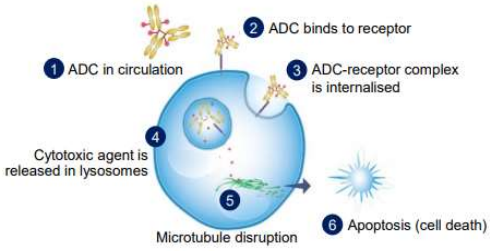
Antibody-drug conjugates (ADC)

FDA-Approved Antibody-Drug Conjugates

Drug	Target antigen	Indication
Brentuximab vedotin	CD30	**Classical Hodgkin lymphoma,** relapsed after HSCT or ≥2 previous therapies
		Cutaneous anaplastic large cell lymphoma or **CD30+ mycosis fungoides** ≥ 1 previous therapies
		Classical Hodgkin lymphoma - first line with combination chemo
		Classical Hodgkin lymphoma consolidation after auto-HSCT
Inotuzumab ozogamicin	CD22	Relapsed/refractory/MRD+ **B-cell ALL**
Polatuzumab vedotin (w/ bendamustine & rituximab)	CD79b	**DLBCL** ≥ 2 previous therapies
Gemtuzumab ozogamicin	CD33	**R/R or newly-diagnosed CD33+ AML** in adults or pediatric patients
Belantamab mafodotin	BCMA	**R/R multiple myeloma** after ≥ 4 prior 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

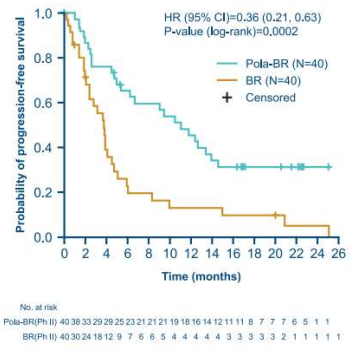
Slide credit: Tilly et al. ICML 2019

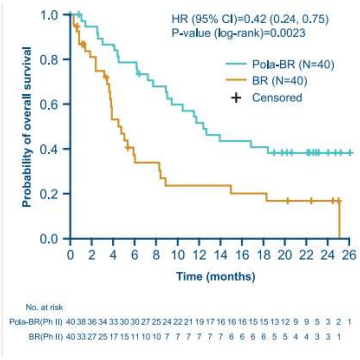
Polatuzumab vedotin: DLBCL

- 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

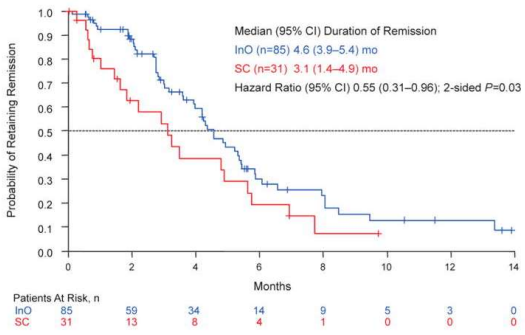


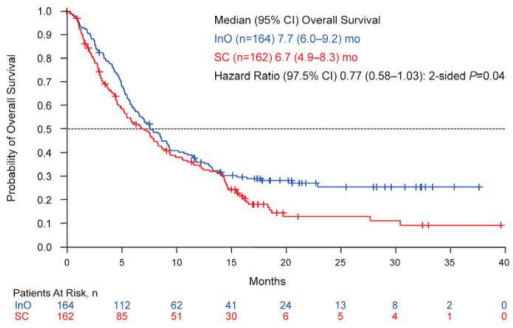


Sehn, Blood 2018.

Inotuzumab ozogamicin for B-ALL

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

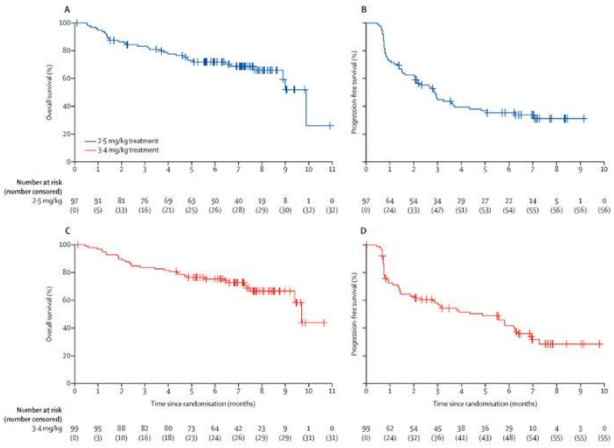




Kantarjian, NEJM 2016.

Belantamab mafodotin for R/R Multiple Myeloma

- Anti-BCMA antibody-drug conjugate
- ORR: 34% of patients (3% achieved CR)
- Black box warning for ocular toxicity

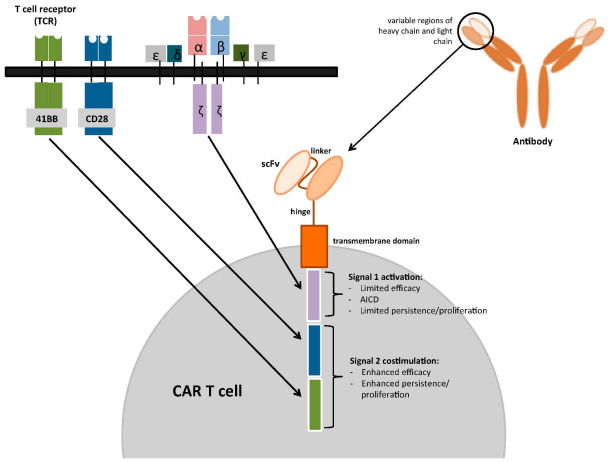


Lonial et al, Lancet 2019

Chimeric Antigen Receptor Therapy (CAR T)

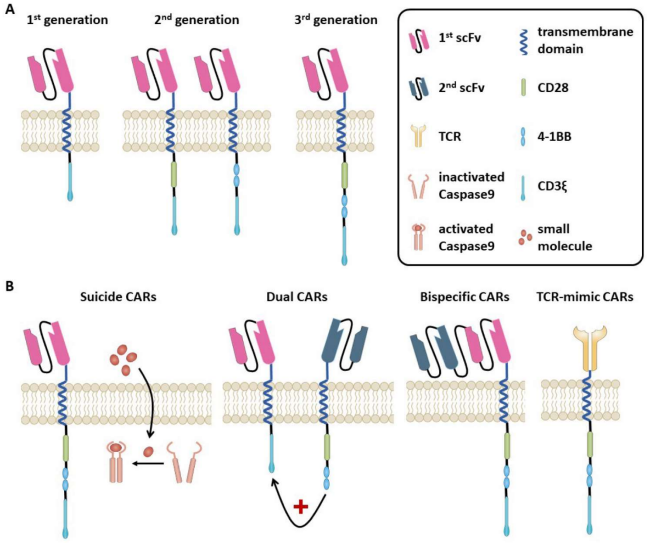
Chimeric antigen receptors

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



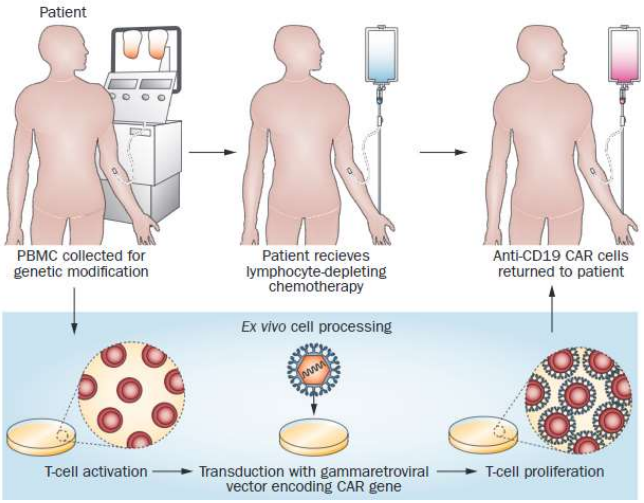
Klampasta, Cancers 2017.

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

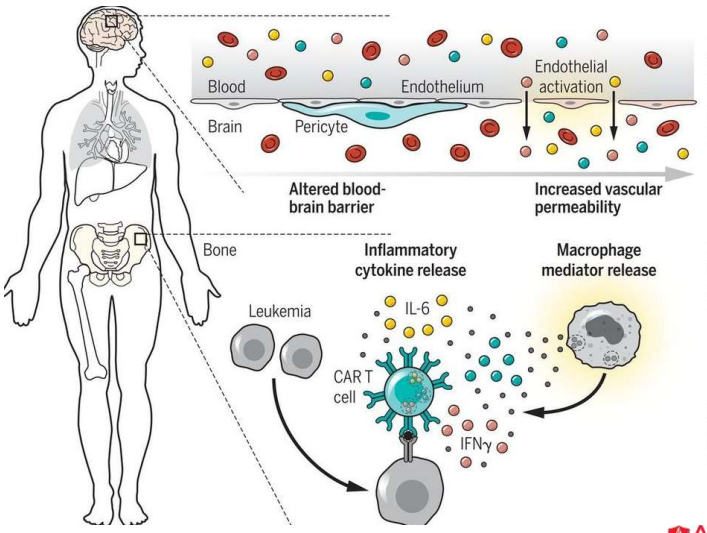


Kochenderfer, Nat Rev Clin Oncol 2013.

CAR T Side Effects

- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- B cell aplasia
- Prolonged Cytopenias
- 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	Target/co-stimulatory domain	Indication	Dose
Axicabtagene ciloleucel	CD19/CD28	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	CD19/4-1BB	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	CD19/4-1BB	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
Brexucabtagene autoleucel	CD19/CD28	Adults with mantle cell lymphoma (MCL) who have not responded to or who have relapsed following other treatments	2 x 10^6 CAR-positive, viable T cells per kg bodyweight (up to 2x10^8)

Eligibility considerations for CAR

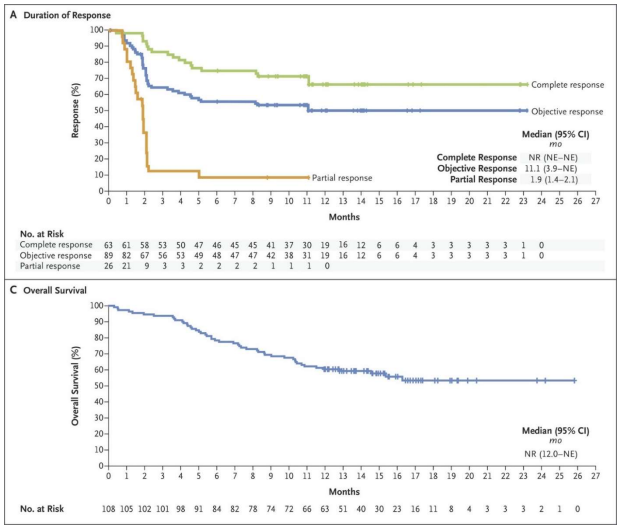
- Disease
  - Relative stability during CAR T manufacturing (~2-6 weeks)
  - Bridging therapy (chemo, RT, steroids, lenalidomide, ibrutinib)
  - CNS control
- Patient
  - Adequate cell counts
  - DVT, bleeding, infection, neuro disorders
  - Functional status: at screen vs. day of CAR T infusion
- Other
  - Social support, reimbursement

Challenges with CAR T Cell Therapy

- Overcoming Resistance
  - Antigen Escape
  - Hostile Tumor Microenvironment
  - Limited Persistence
- Toxicity Management
  - CRS and NT
  - Prognostic markers of toxicity
  - Prophylactic Strategies
- Expanding Access
  - Financial Toxicity
  - Overcoming prolonged manufacturing periods

CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

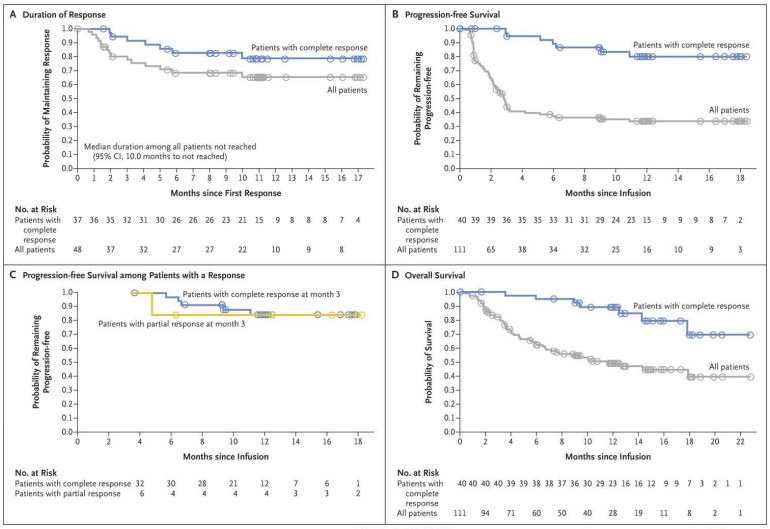
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

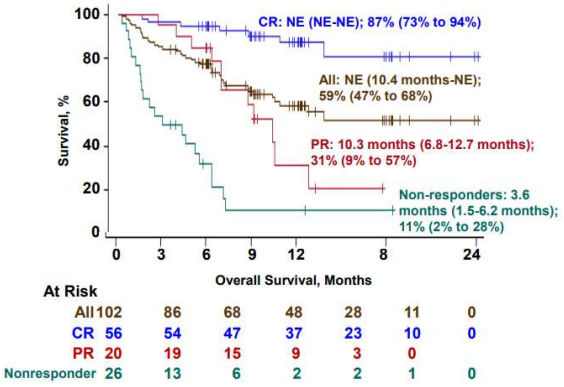
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

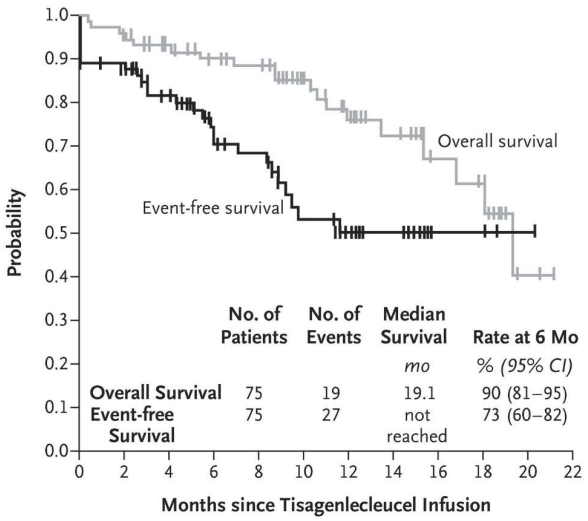
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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

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

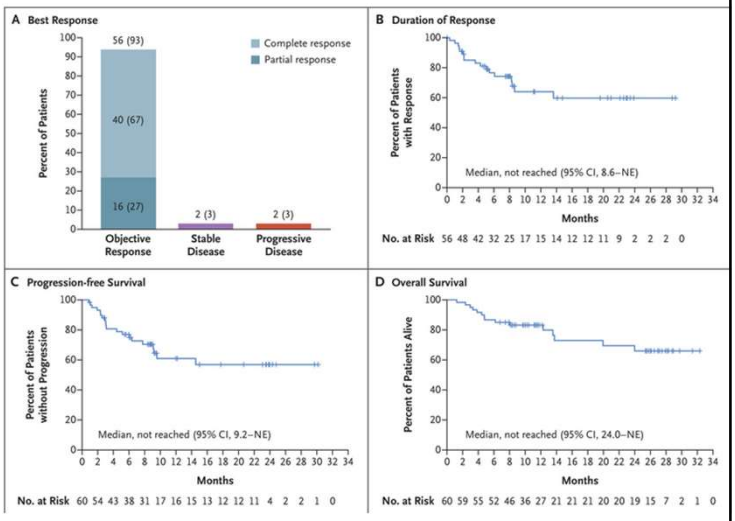
- CD19/4-1-BB
- ORR = 81%
- CR = 60%, CRi = 21%
- CRS grade ≥3 = 47%
- Neurotox grade ≥3 = 13%



Maude et al. NEJM 2018

CD19 CAR for MCL: Brexucabtagene autoleucel

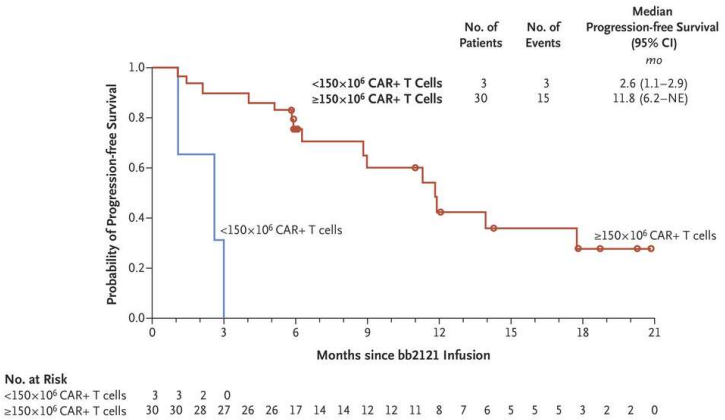
- CD19/KTE-X19
- ORR = 87%
- CR = 62%
- CRS grade ≥3 = 15%
- Neurotox grade ≥3 = 31%



Wang et al, NEJM 2020

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%

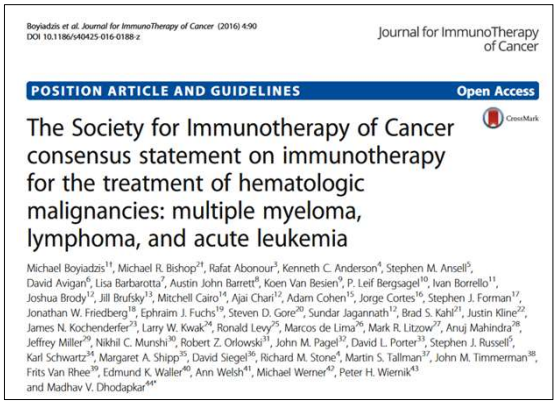


Raje, NEJM 2019.

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



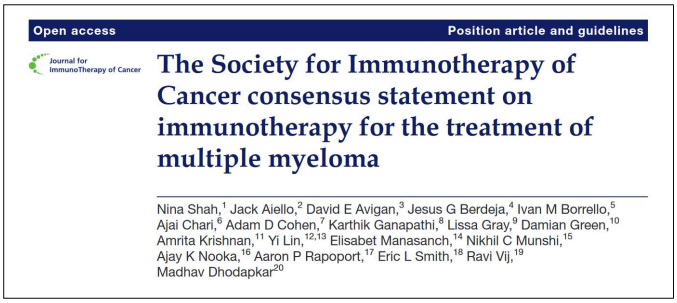
Boyiadzis et al. Journal for ImmunoTherapy of Cancer (2016) 4:90
DOI 10.1186/s40425-016-0188-z

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*]



Open access — Position article and guidelines

Journal for ImmunoTherapy of Cancer

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of multiple myeloma

Nina Shah,[1] Jack Aiello,[2] David E Avigan,[3] Jesus G Berdeja,[4] Ivan M Borrello,[5] Ajai Chari,[6] Adam D Cohen,[7] Karthik Ganapathi,[8] Lissa Gray,[9] Damian Green,[10] Amrita Krishnan,[11] Yi Lin,[12,13] Elisabet Manasanch,[14] Nikhil C Munshi,[15] Ajay K Nooka,[16] Aaron P Rapoport,[17] Eric L Smith,[18] Ravi Vij,[19] Madhav Dhodapkar[20]

Case Studies

The Case of Patient KO

- 49 year old male with standard risk Ph negative B-ALL treated with HyperCVAD
- PMH: Type II DM and HTN
- Achieves morphologic CR but remains MRD
- Presents to your clinic for discussion of next treatment options

The Case of Patient KO

- What would you be your next treatment line?

A) Blinatumomab
B) Inotuzumab
C) Tisagenlecleucel
D) Chemotherapy

The Case of Patient KO

- What would you be your next treatment line?

A) Blinatumomab
B) Inotuzumab
C) Tisagenlecleucel
D) Chemotherapy

Per NCCN guidelines, Blinatumomab and allogeneic stem cell transplantation are category one recommendations

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The Case of Patient KO

- Patient was treated with 2 cycles of Blinatumomab, achieved MRD negative CR
- Hospital course complicated by grade 1 CRS which resolved with supportive care
- Received allogeneic stem cell transplantation and remains in remission

The Case of Patient JB

- 62 yo F diagnosed with DLBCL (GCB subtype) in 2017 with extensive intra-abdominal disease and bone marrow involvement. Treated with R-CHOP with progressive disease after 3 cycles.
- Salvage chemotherapy with R-ICE with progressive disease with new peritoneal metastases which were confirmed to be DLBCL on repeat biopsy.
- Patient evaluated in clinic for 3rd line treatment options. Remains fit with KPS 90%. PMH significant for Atrial Fibrillation, Type II DM, and HTN.

The Case of Patient JB

Which of the following is NOT a treatment option

1. Autologous Stem Cell Transplantation
2. Additional Chemotherapy
3. CD19 Targeted CAR T Cell Therapy
4. Polatuzumab vedotin

The Case of Patient JB

Which of the following is NOT a treatment option

1. **Autologous Stem Cell Transplantation**
2. Additional Chemotherapy
3. CD19 Targeted CAR T Cell Therapy
4. Polatuzumab vedotin

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The Case of Patient JB

- Patient met eligibility criteria for treatment with axicabtagene ciloleucel.
- Hospital course complicated by grade 2 CRS which resolved with tocilizumab and supportive care
- Remains in CR at 18 months post therapy

Key Questions to consider

➢Would you recommend bridging chemotherapy or radiation?

➢Should patient be considered for allogeneic stem cell transplant?

Questions?

- You can contact me at Rawan.Faramand@moffitt.org for any further questions.