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

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Disclosures

- **Consulting Fees: Novartis, Gilead, BMS**

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

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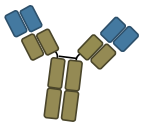
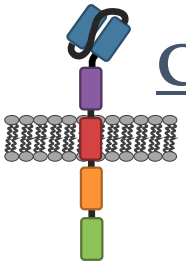
Cancer Immunotherapy

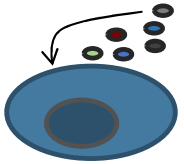
Monoclonal Antibodies



CARS



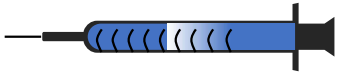
Cytokines



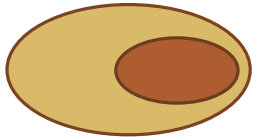
Checkpoint Inhibitors

Immunotherapy: treatment that uses the body's immune system to fight cancer

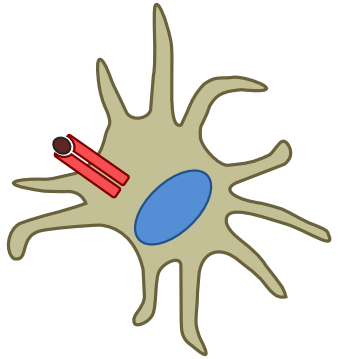
Cancer Vaccines



Adoptive Cell Transfer



Dendritic Cell Therapy



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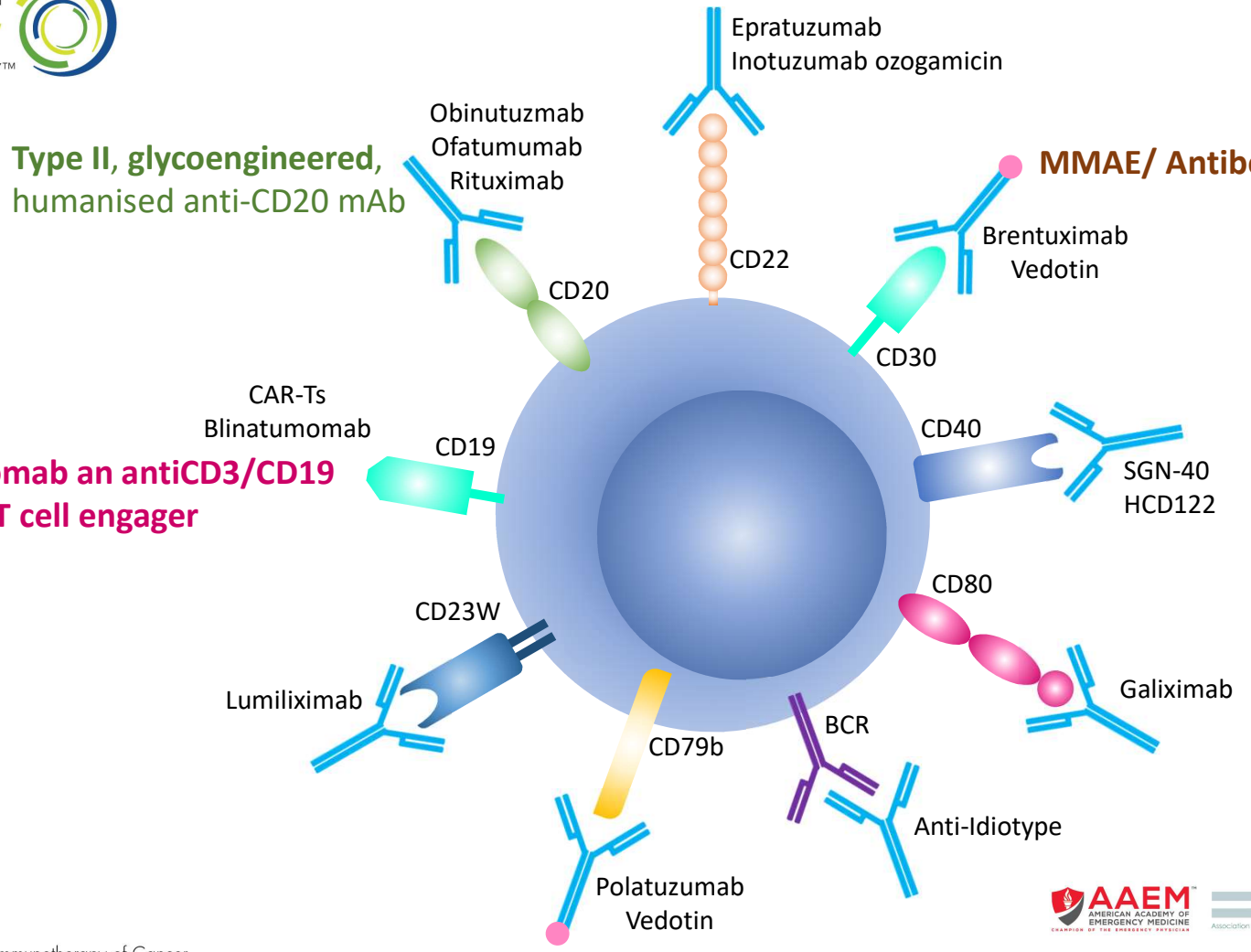
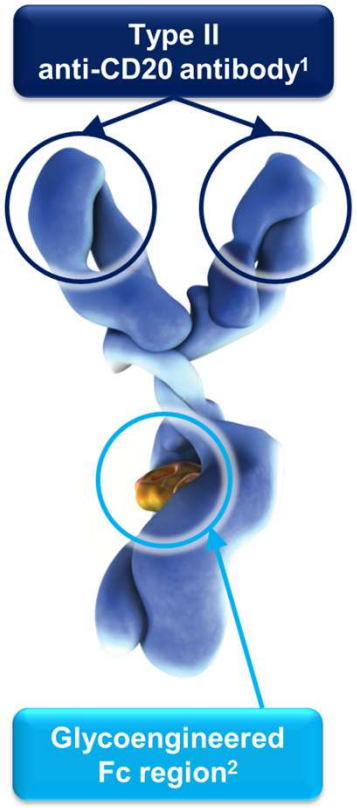
Monoclonal Antibody Therapy



Obinutuzumab – a better anti-CD20?

- The first **Type II**, **glycoengineered**, humanised anti-CD20 mAb[1–3]
  - Designed to provide an advancement in antibody technology[1,3]
- In preclinical studies comparing it with rituximab, GA101 showed:
  - Increased direct cell death induction[1,3]
  - Enhanced ADCC[1]
- GA101 is being evaluated in an extensive clinical trial programme in B-cell malignancies

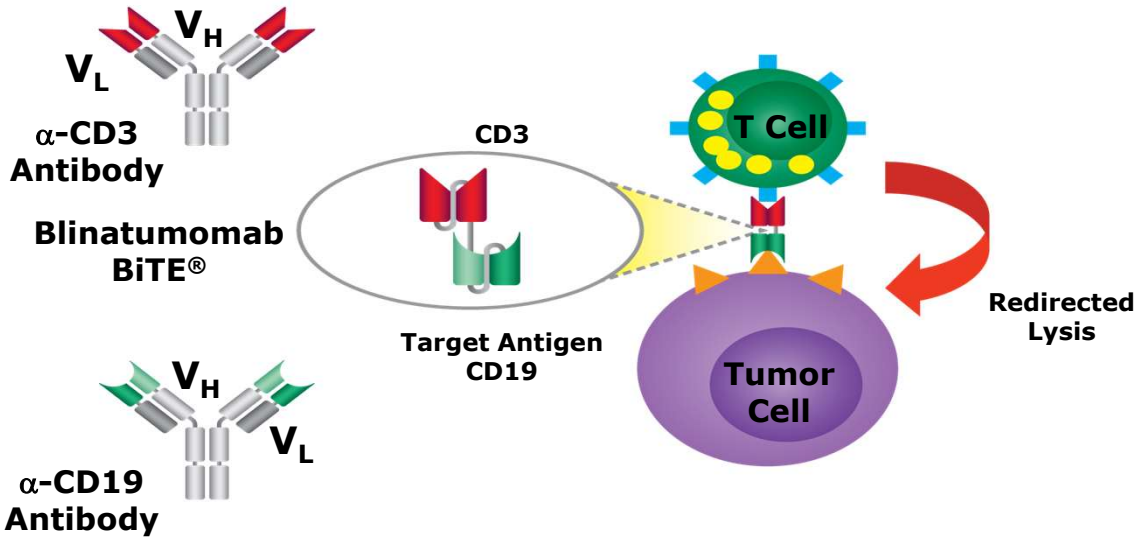


ADCC, antibody-dependent cell-mediated cytotoxicity; mAb, monoclonal antibody

1. Mössner E, *et al. Blood* 2010; 115:4393–4402; 2. Niederfellner G, *et al. Blood* 2011; 118:358–367;
3. Alduaij W, *et al. Blood* 2011; 117:4519–4529.

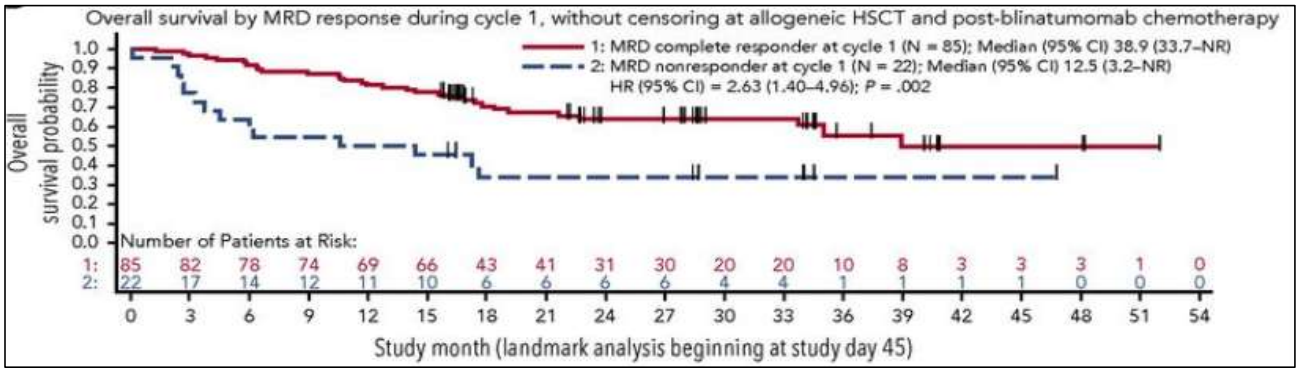
BiTE (Blinatumomab) Therapy

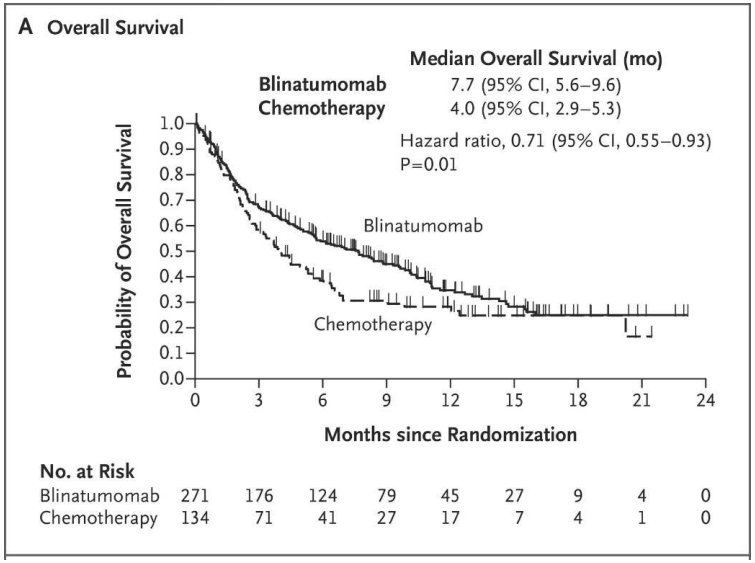
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





- Blinatumomab is administered as a continuous infusion
- Common adverse events include neurotoxicity and cytokine release syndrome, most often in first cycle of therapy
- Demonstrated improvements over standard-of-care for both MRD-positive B-ALL and relapsed/refractory B-ALL

Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

CD20/CD3 targeting BiTEs in development

BSA (Company)	Descriptor	Development phase (disease)
REGN1979 (Regeneron)[3]	Full-length IgG4	Phase I (NHL, CLL and lymphoma)*
XmAb13676 (Xencor)[4]	IgG-like with modified Fc region	Phase I (NHL, CLL)
Mosunetuzumab (Roche/Genentech)[1]	Fully humanised, IgG1-like with modified Fc region	Phase I/II (NHL)
CD20-TCB (Roche/Genentech)[2]	Fully humanised, IgG1-like 2:1 format with fully silent Fc region	Phase I/II (NHL)
GEN3013 (GenMab)	DuoBody with IgG4 Fab-arm	Phase I/II (NHL)

These antibodies have the potential to overcome the PK limitations associated with blinatumomab

- 1. Sun LL, et al. Sci Transl Med 2015;7:287ra70; 2. Bacac M, et al. Oncoimmunol 2016;5:e1203498
- 3. Smith EJ, et al. Sci Rep 2015;5:17943; 4. Chu SY, et al Blood 2014;124:3111

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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

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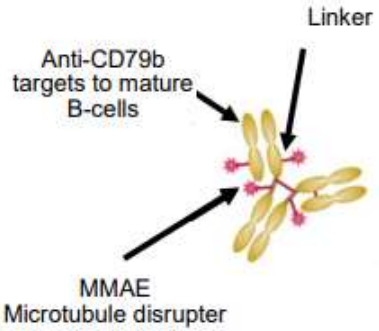
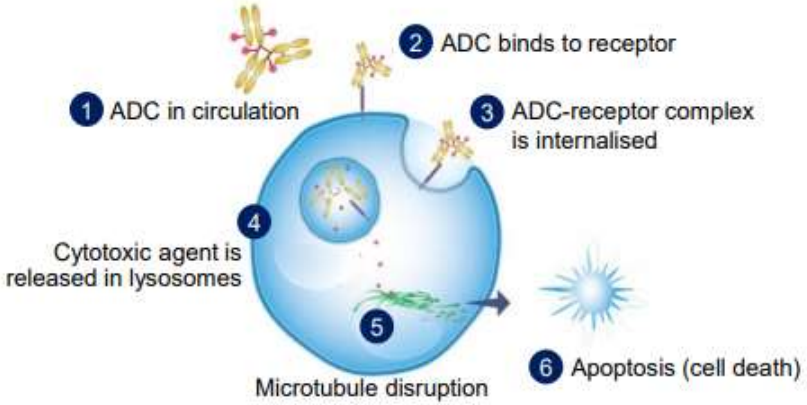
Polatuzumab vedotin: DLBCL





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

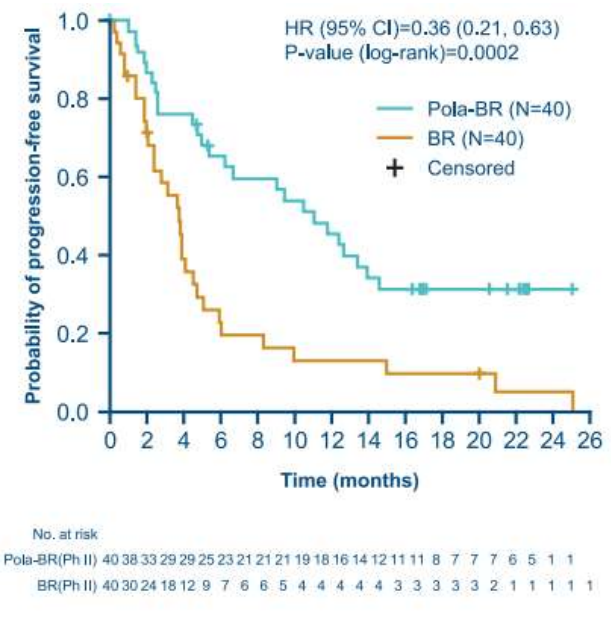
Slide credit: Tilly et al. ICML 2019

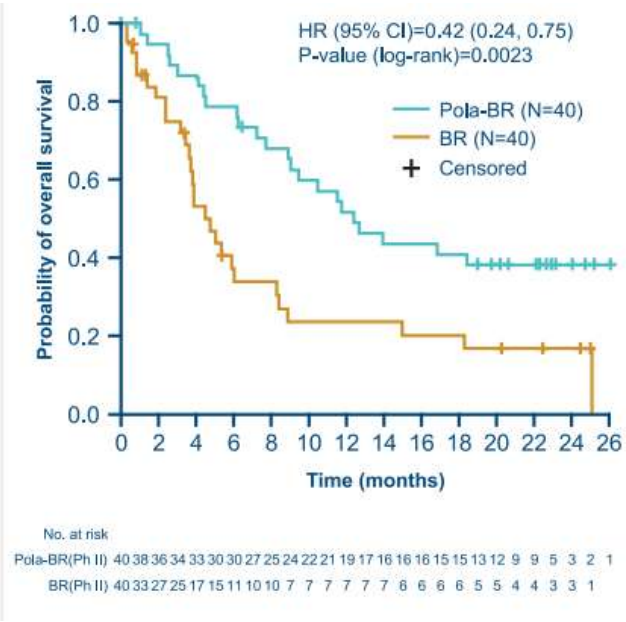
Polatuzumab vedotin: DLBCL

- 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

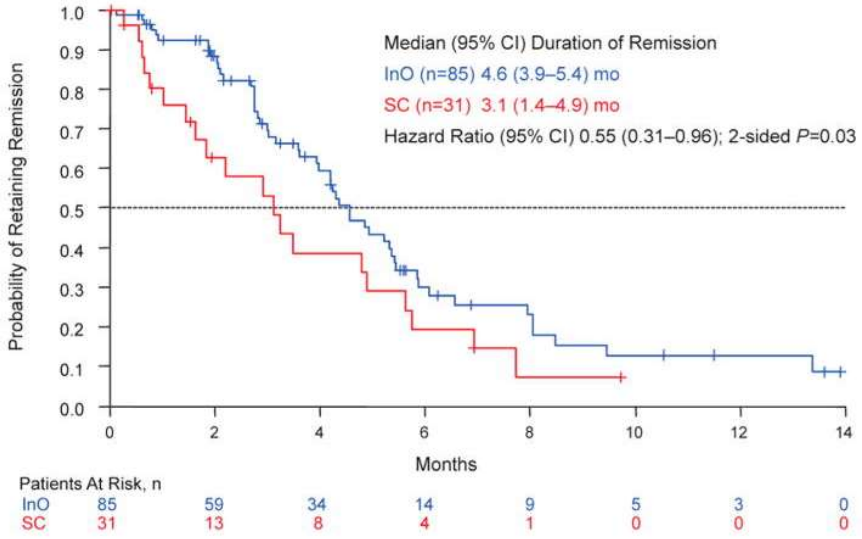


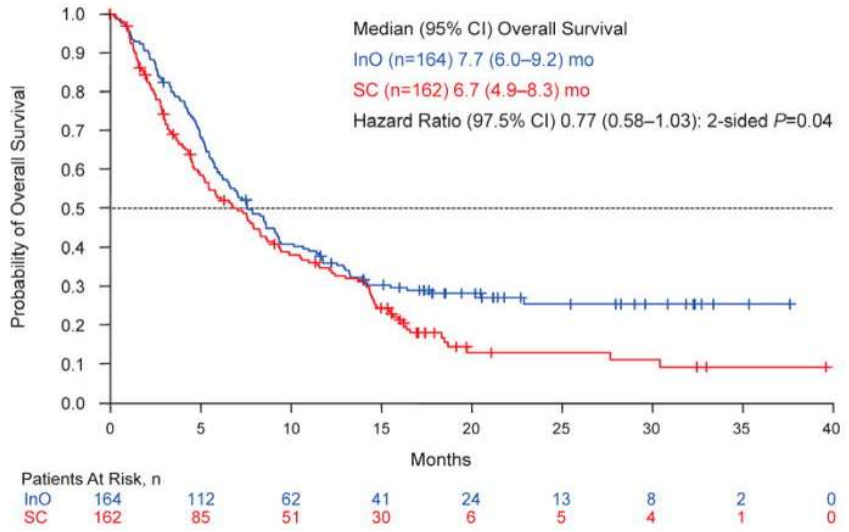


Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

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

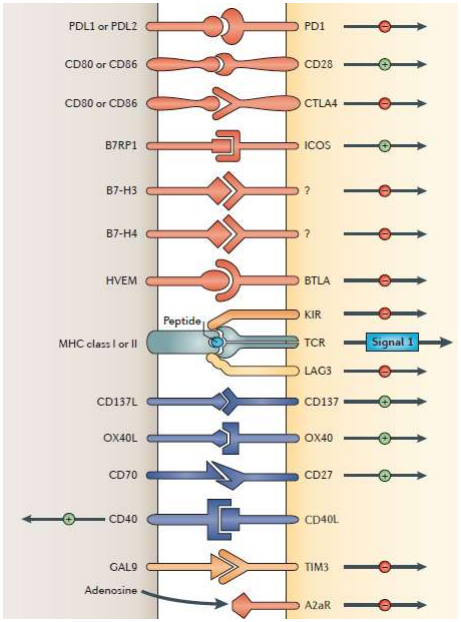




Kantarjian, NEJM 2016.

Role of the Immune Checkpoint

- We need the immune system to fight pathogens and help eliminate abnormal cells
- We also need to have controls on this system
  - Maintain tolerance and prevent injury to self tissue
- The immune checkpoint is the series of inhibitory signals for this system
  - While designed for self control, these signals can be exploited by cancer cells



Cancer Cell **T-cell**

Pardoll , 2012, *Nat Rev Can*, **5**, 252-265

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)

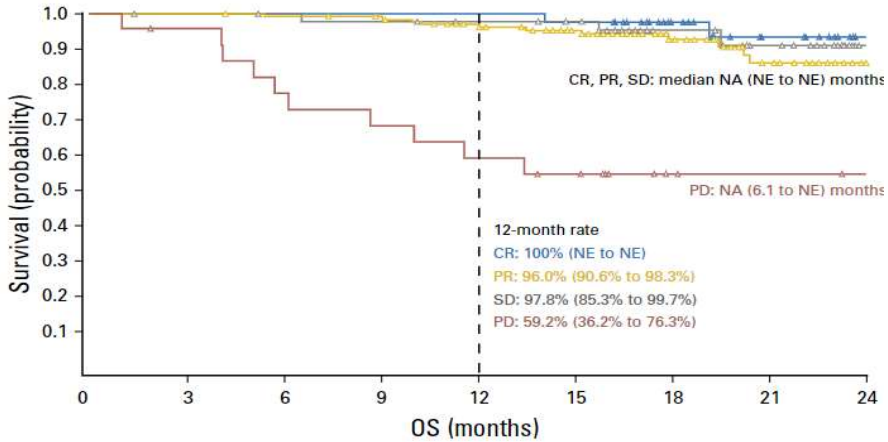
**Not recommended for patients with PBMCL that require urgent cytoreductive therapy.

Checkpoint inhibitors: Hodgkin Lymphoma

Checkmate-205

ORR = 69%

CR = 16%



No. at risk:

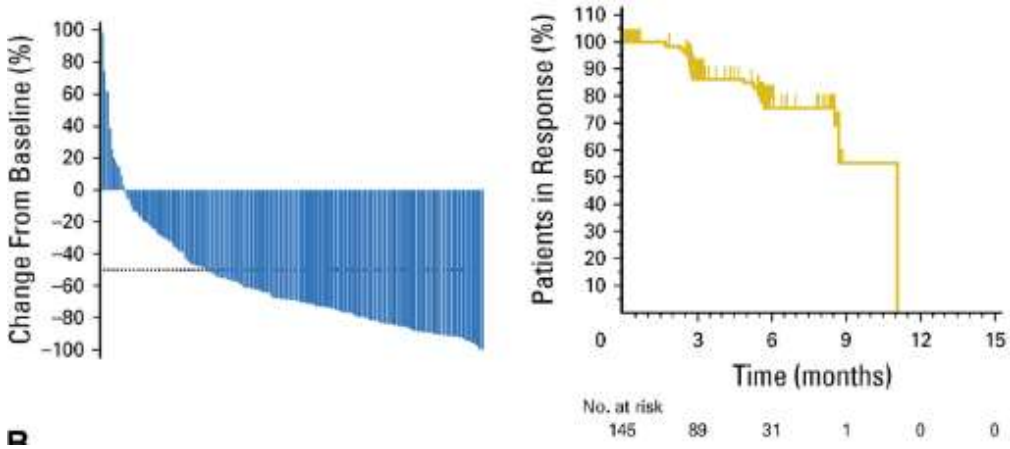
CR	40	40	40	40	40	39	26	16	7
PR	128	128	126	123	113	97	59	34	10
SD	47	46	45	44	42	39	25	16	3
PD	23	21	17	15	13	11	5	4	3

Keynote-087

ORR = 69%

CR = 22.4%

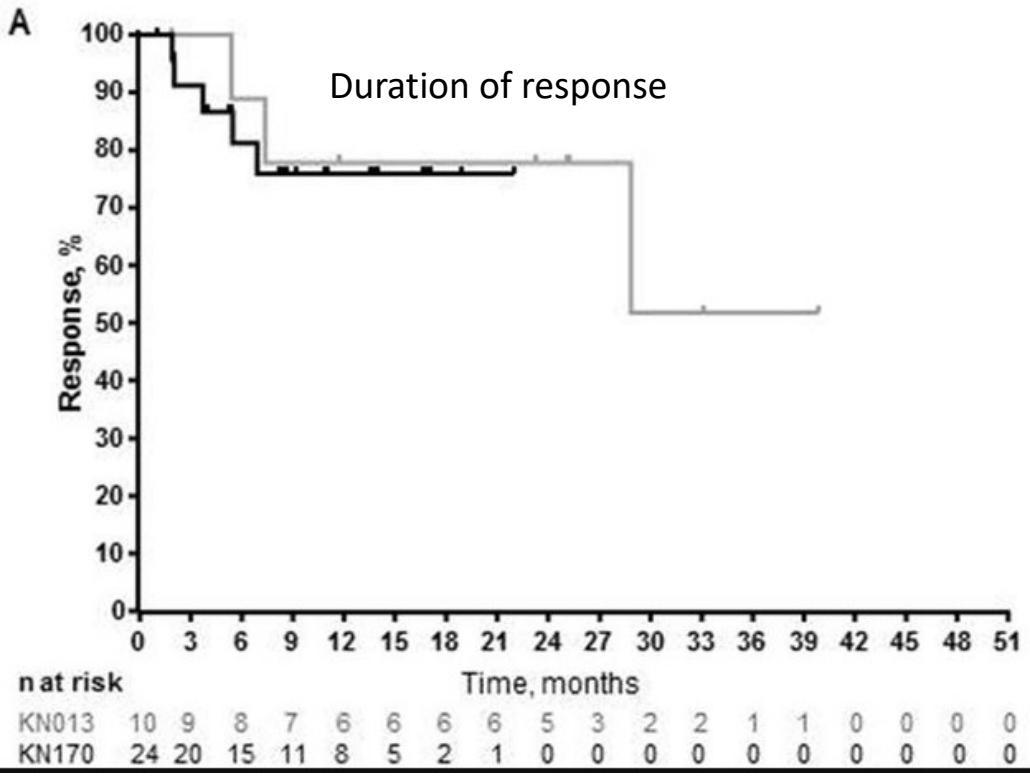
Activity seen regardless of PD-L1 expression

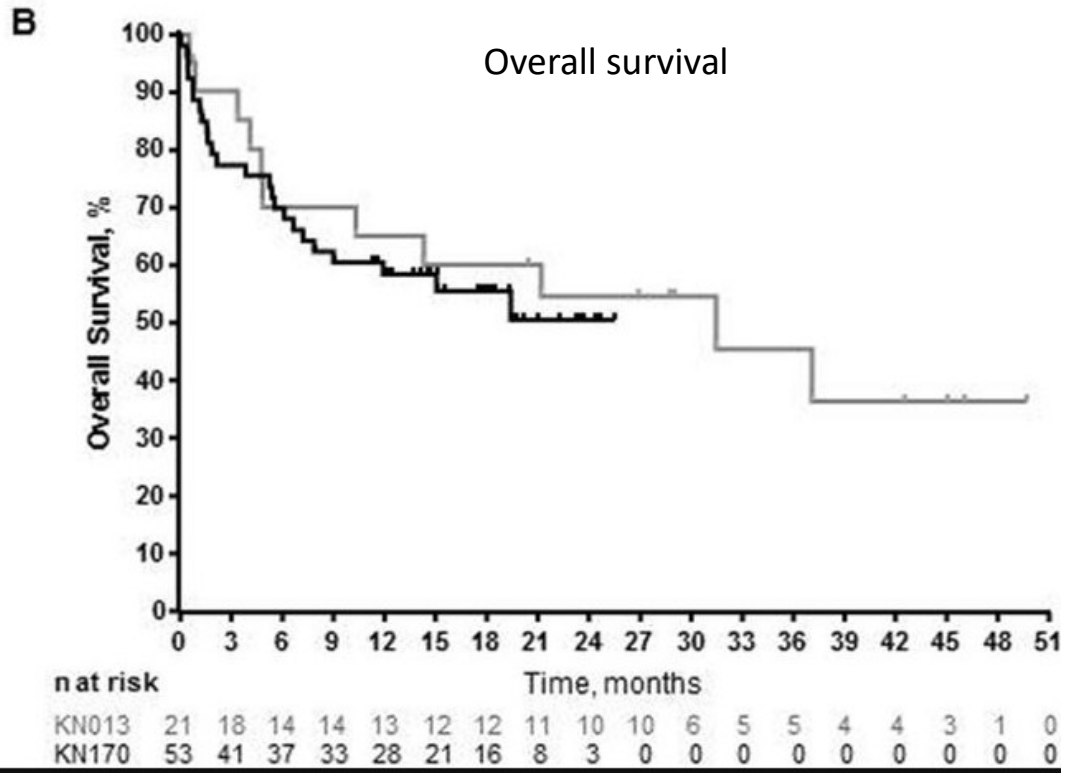


Armand, J Clin Oncol 2018.

Chen, J Clin Oncol 2017.

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

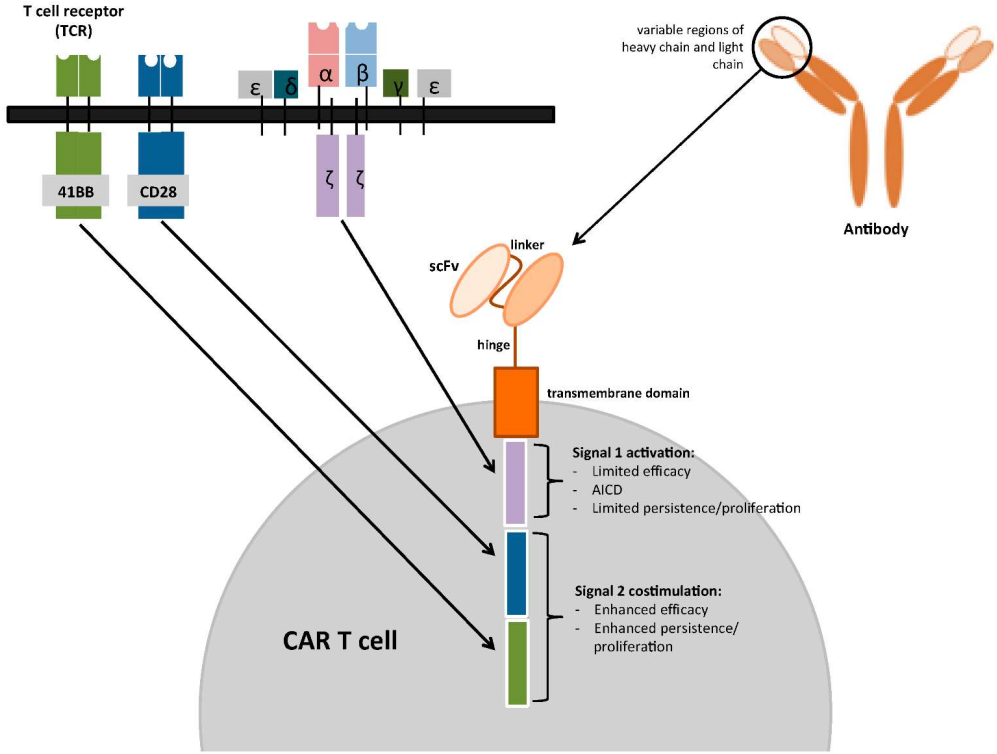




Armand, Blood 2018.

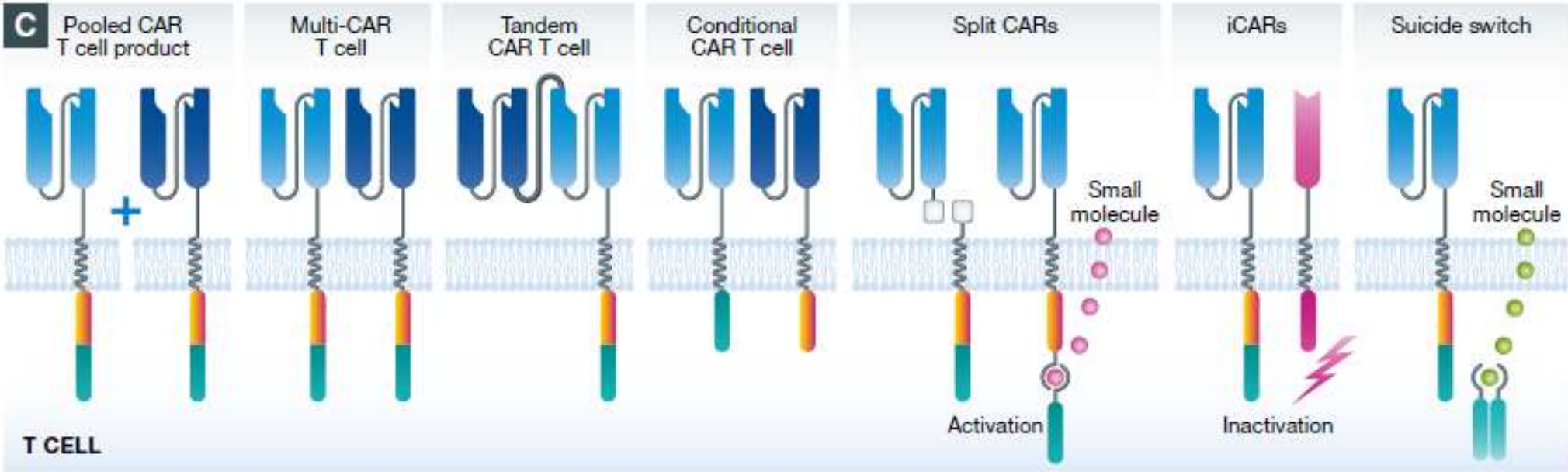
Chimeric antigen receptors

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



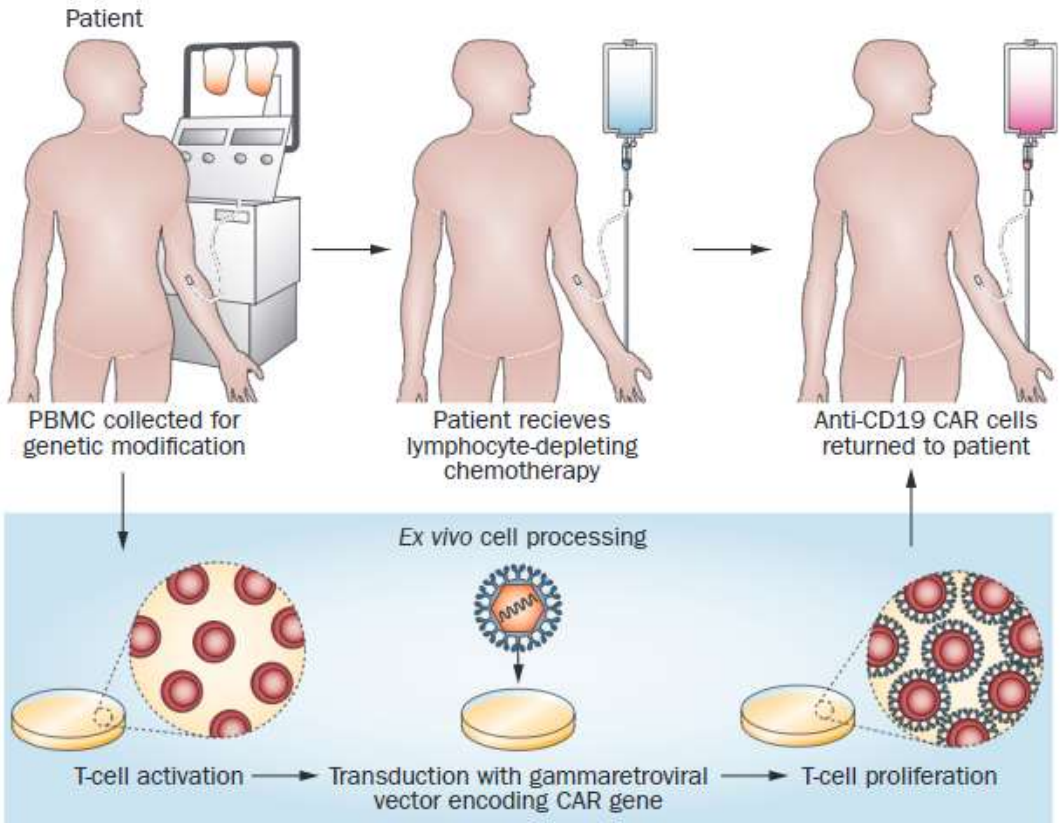
Klampasta, Cancers 2017.

Clinical development of CAR T cells



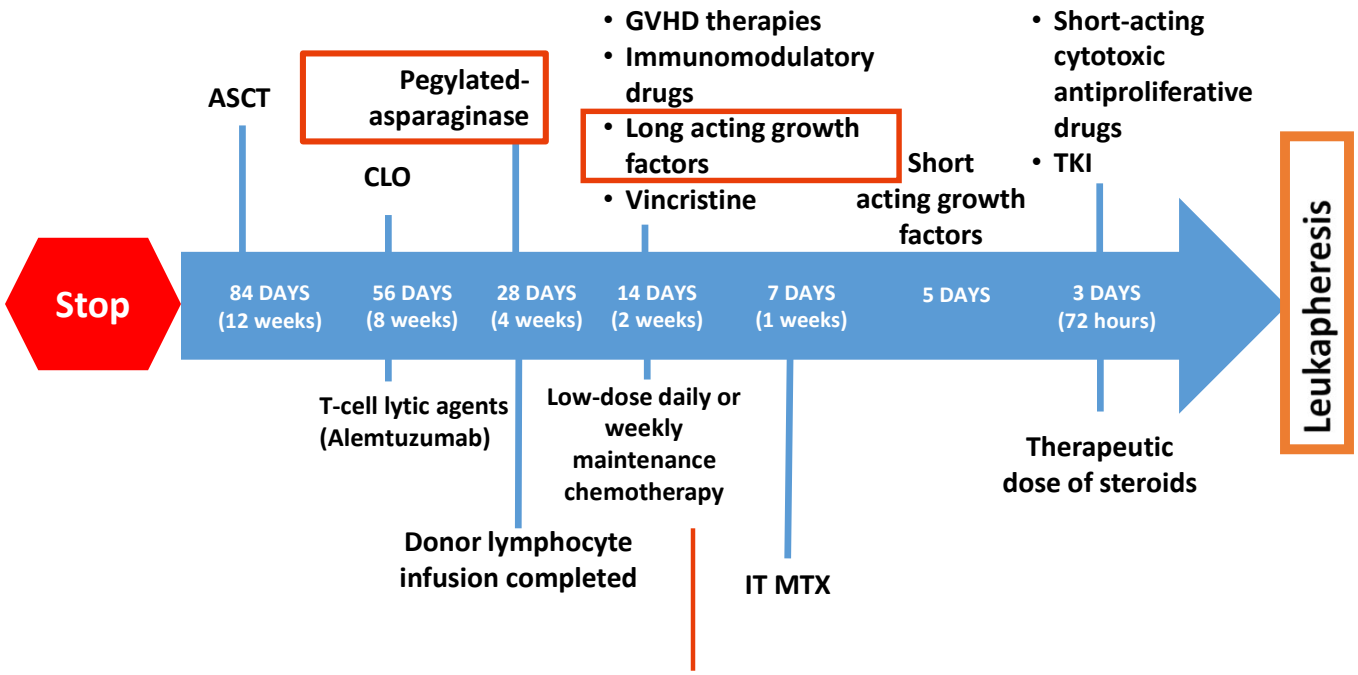
Hartmann et al. (2017), EMBO Molecular Medicine

CAR T manufacturing and administration



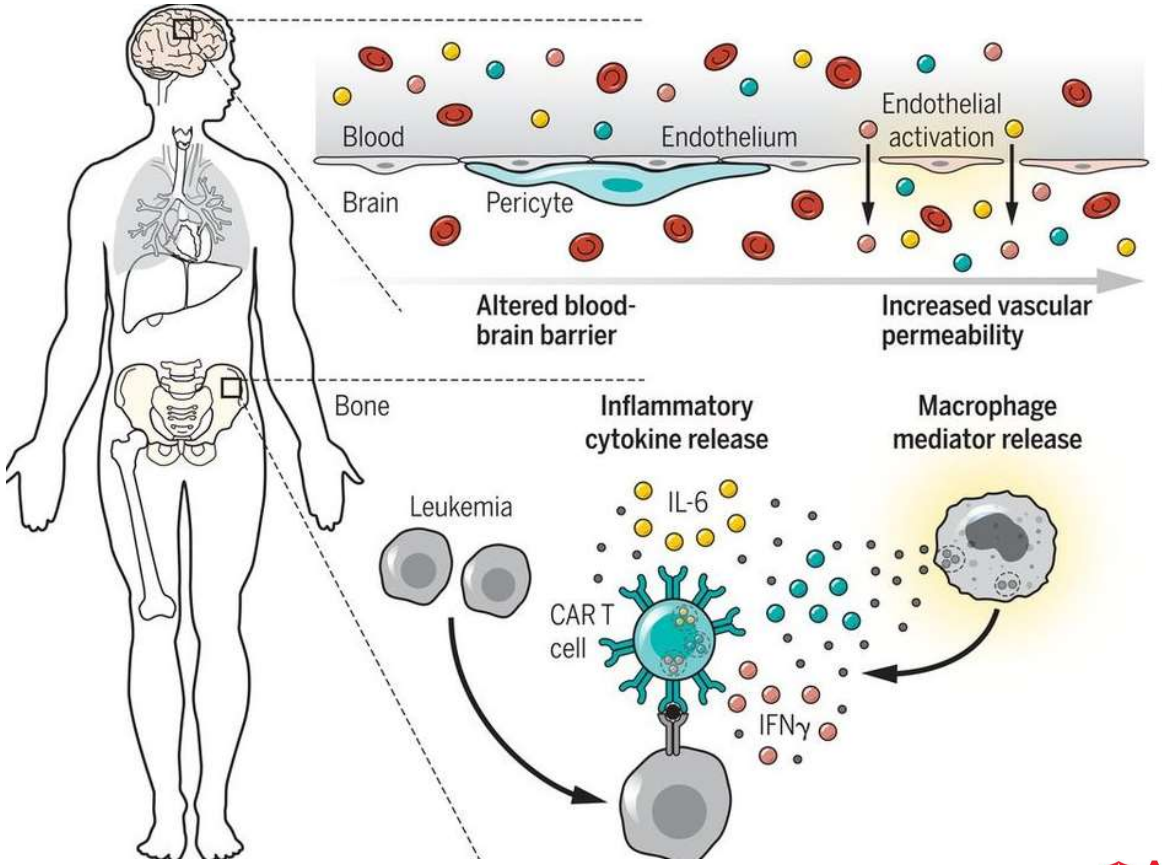
Kochenderfer, Nat Rev Clin Oncol 2013.

Leukapheresis washout: JULIET & ELIANA



1. Schuster SJ et al. *N Engl J Med*. 2019;380:45-56.
2. Maude SL et al. *N Engl J Med*. 2018;378:439-48.

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

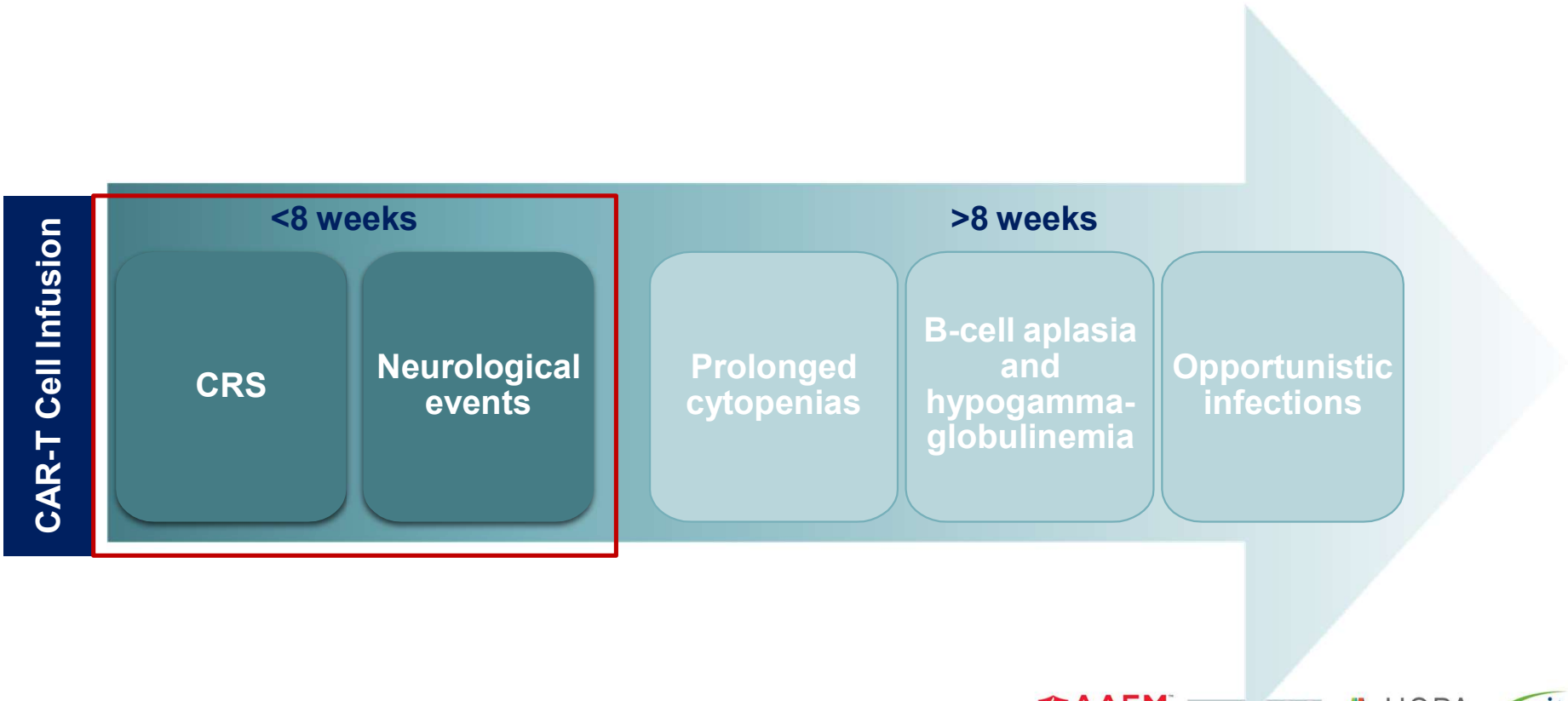
Treatment

Steroids
Anti-epileptics

Tocilizumab
Steroids

June et al. Science 2018

CAR-T Cell Therapy-Associated Safety Events



CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

CAR-T Cell Therapy Complications

Efficacy	Safety
Bridging therapy	Bridging therapy
Disease burden (tumor volume and LDH)	Disease burden (tumor volume and LDH)
ECOG PS >2	ECOG PS >2
High pretreatment inflammatory markers	High pretreatment inflammatory markers
ALC at apheresis	High total bilirubin
Medical comorbidities: Low cardiac EF, low CrCl	Medical comorbidities: Low cardiac EF, low CrCl

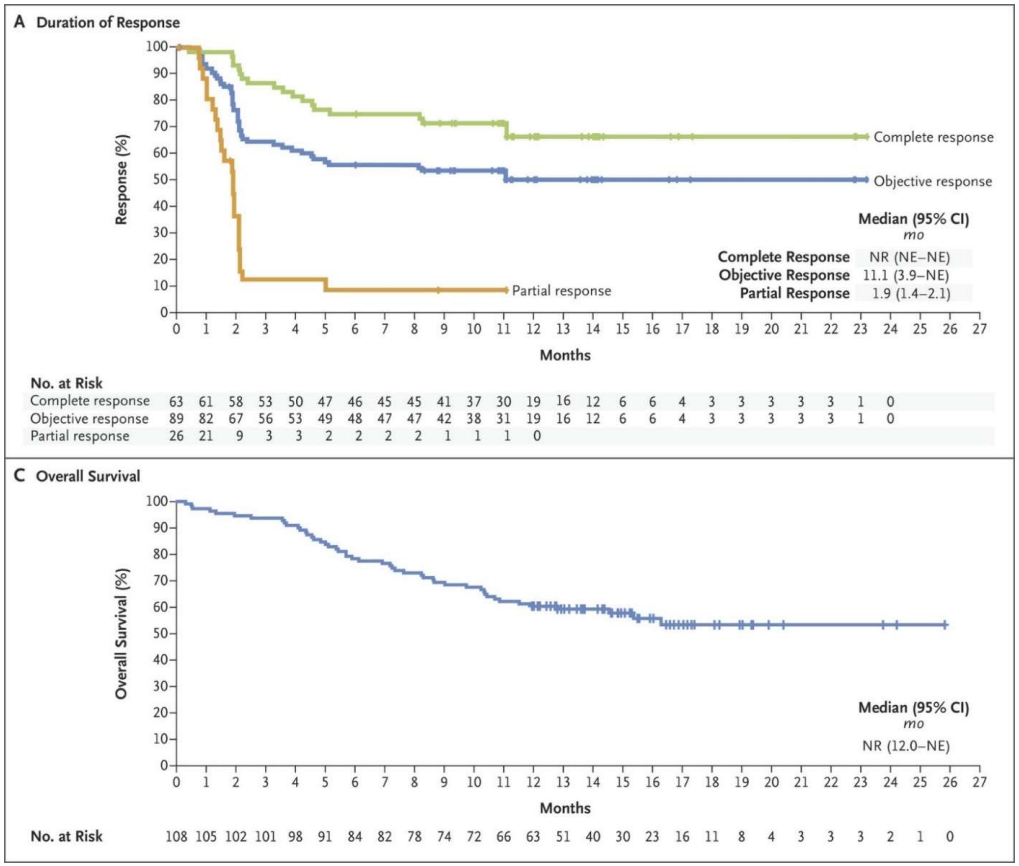
Note: The information/recommendations presented here come from personal/institutional experience
ALC, absolute lymphocyte count; CAR, chimeric antigen receptor; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group performance status; EF, ejection fraction; LDH, lactate dehydrogenase.

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)

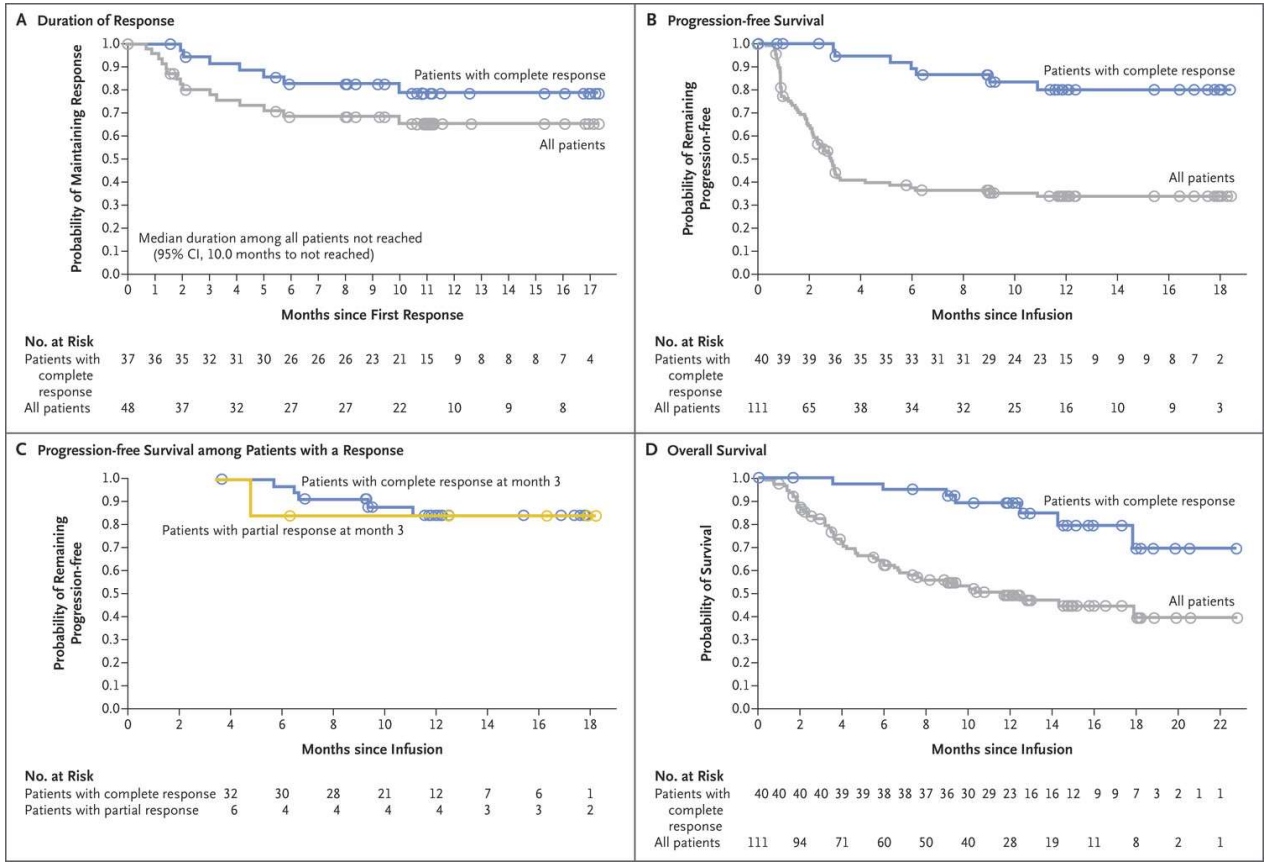
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

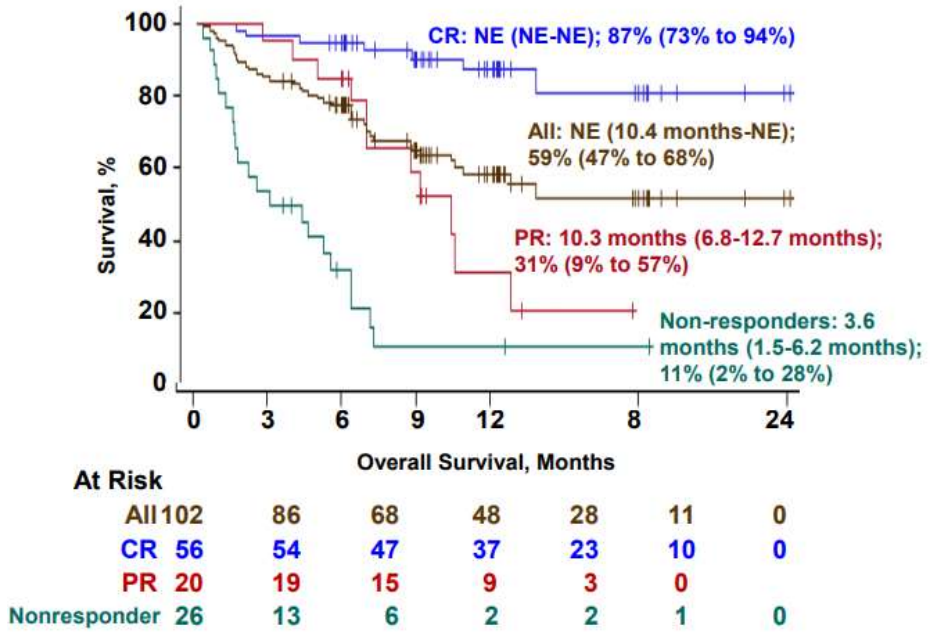
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

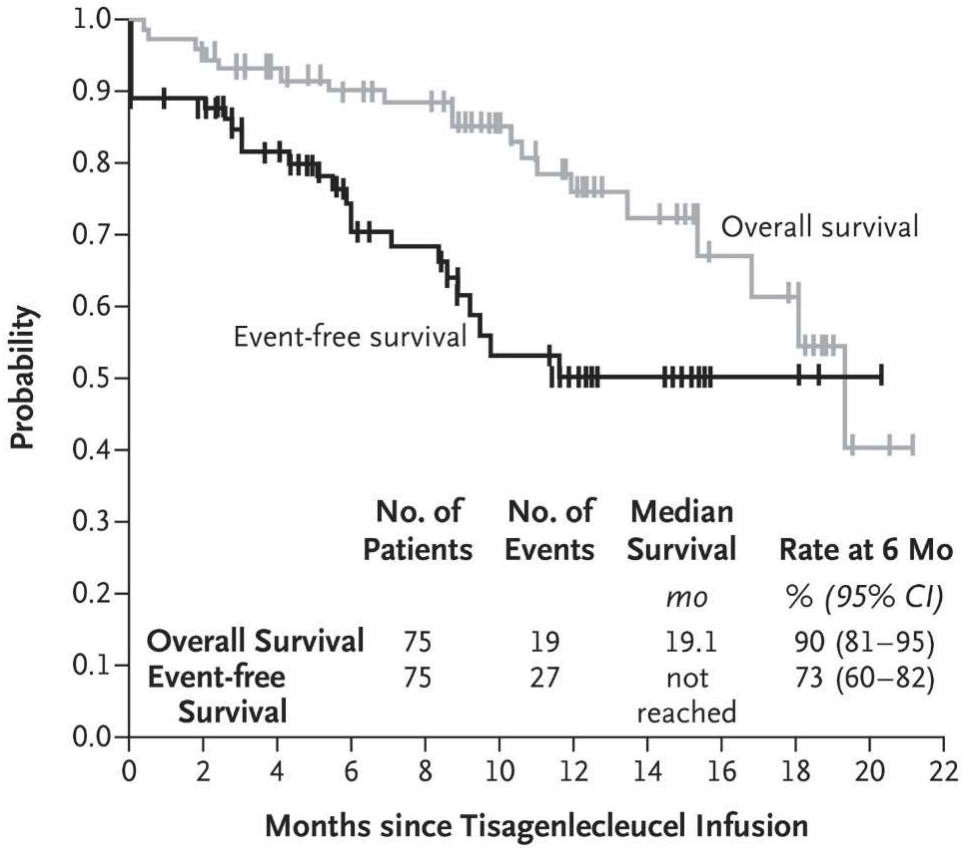
- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%



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%

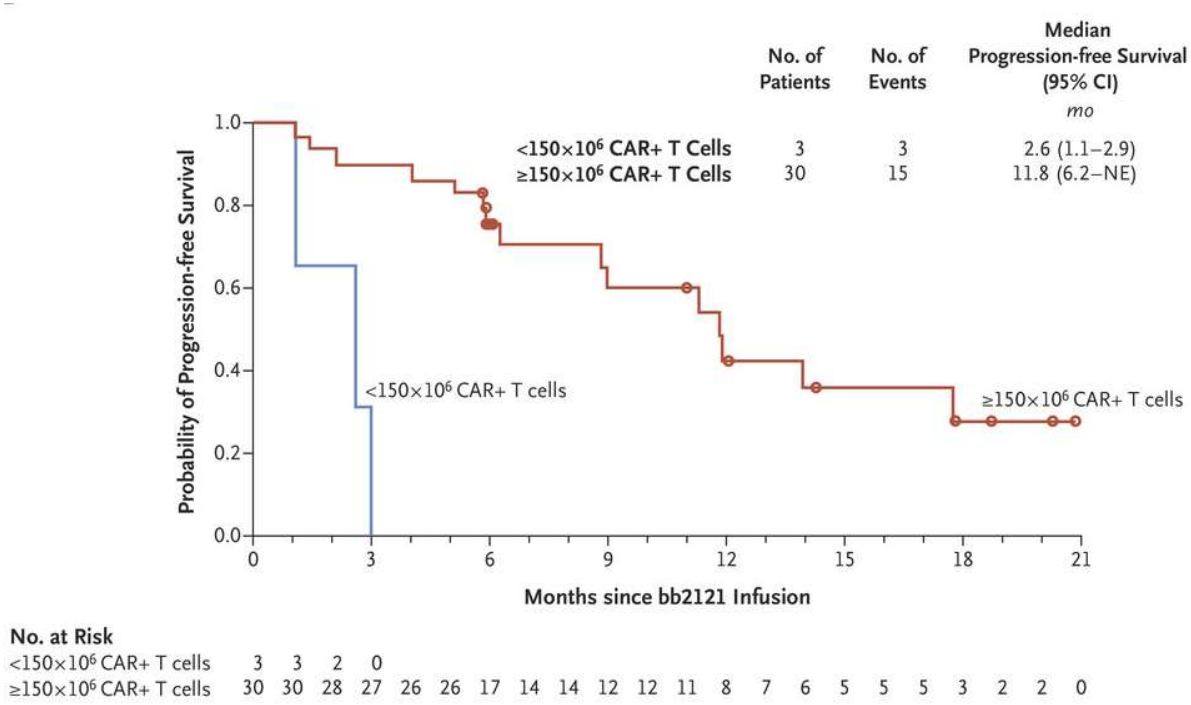


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

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%

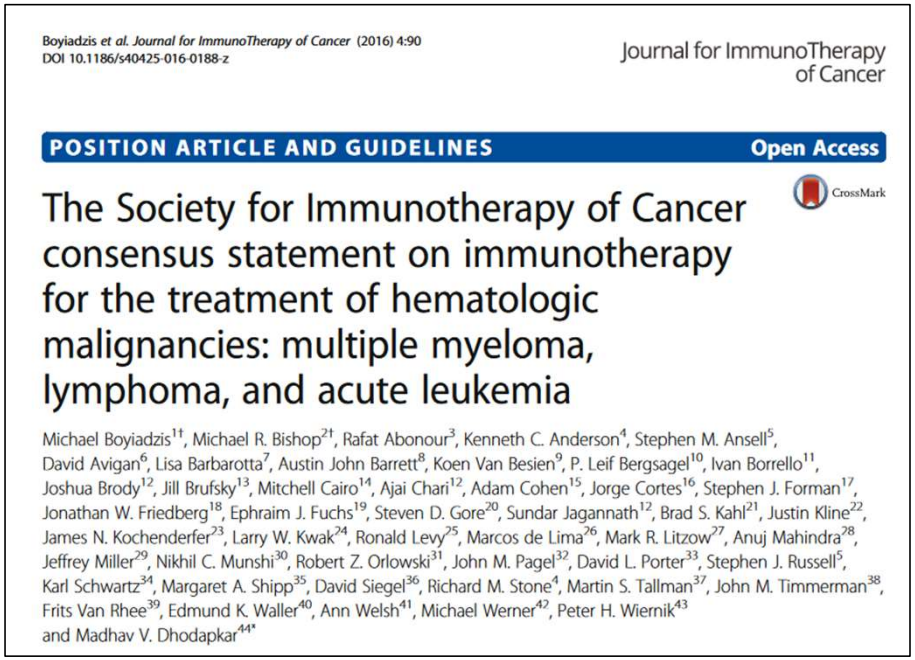


Raje, NEJM 2019.

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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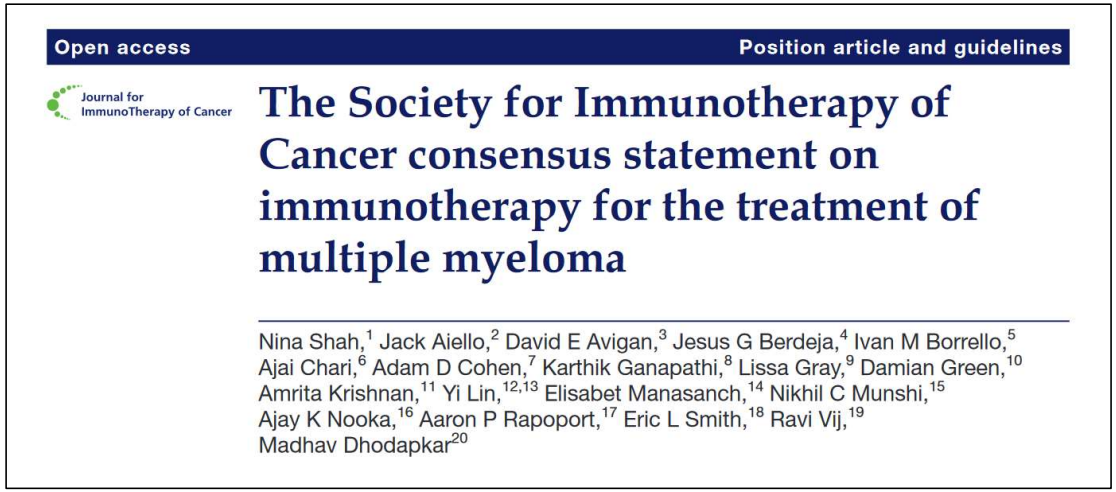

Open access — Position article and guidelines

Journal for ImmunoTherapy of Cancer

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

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Case #1

- 63F Follicular Grade-3A stage IIIA , extensive lymphadenopathy, + marrow monoclonal B cells April 2017 treated with R-CHOP x 6 and maintenance R over 2 years EOT CT improved (PR), PET not done

- Progression November 2019 12x12cm L mass hemi-thorax, path dual-HIT (FISH BCL-2, cMYC) DLBCL, ki>90%- Salvage GDPx2 PET remains 13DU

- **Question #1 – Treatment options**
- (i) proceed with autograft
- (ii) escalate to ICE and proceed to autograft
- (ii) consider CD19 directed CART therapy
- (iii) clinical trial
- (iv) Polatuzumab/Benda/Rituximab

Case #1

- 63F Follicular Grade-3A stage IIIA , extensive lymphadenopathy, + marrow monoclonal B cells April 2017 treated with R-CHOP x 6 and maintenance R over 2 years at EOT CT improved, PET not done

- Relapsed November 2019 12x12cm L mass hemi-thorax, path dual-HIT (FISH BCL-2, cMYC) DLBCL, ki>90%- Salvage GDP x 2 PET remains 13DU

- **Question #1 – Treatment options**
- (i) proceed with autograft - probably not if refractory
- (ii) escalate to ICE and proceed to autograft – may be an option, especially if too unstable
- (ii) consider CD19 directed CART therapy – if disease can be stabilized to collect
- (iii) clinical trial – always an option
- (iv) Polatuzumab/Benda/Rituximab – effects of benda (T cell fitness) if CART a later option

Case #1

- 63F Follicular Grade-3A stage IIIA , extensive lymphadenopathy, marrow monoclonal B cells April 2017 treated with R-CHOP x6 and maintenance R over 2 years EOT CT improved (PR), PET not done

- Progression November 2019 12x12cm L mass hemi-thorax, path dual-HIT (FISH BCL-2, cMYC) tDLBCL, ki>90%- Salvage GDPx2 PET remains 13dv-

- **Question #2 – Proceed with CD19 CART (bridging with IF radiation) Risk of CRS/ICANs**
- (i) tumor bulk
- (ii) serum LDH
- (iii) ECOG (lymphoma driven)
- (iv) inflammatory status
- (v) cell dose administered

Case #1

- 63F Follicular Grade-3A stage IIIA , extensive lymphadenopathy, marrow monoclonal B cells April 2017 treated with R-CHOP x6 and maintenance R over 2 years EOT CT improved (PR), PET not done

- Progression November 2019 12x12cm L mass hemi-thorax, path dual-HIT (FISH BCL-2, cMYC) tDLBCL, ki>90%- Salvage GDPx2 PET remains 13dv-

- **Question #2 – Proceed with CD19 CART (bridging with IF radiation) Risk of CRS/ICANs**
- (i) tumor bulk – risk of organ compromise, may have greater CRS grade 3 / 4
- (ii) serum LDH –only independent multivariable analysis to predict severe CRS
- (iii) ECOG (lymphoma driven) – eligible to 0,1
- (iv) inflammatory status – CRP/ferritin –prefer to infuse at a lower level
- (v) cell dose administered – Kymriah higher dose may correlate with CRS

CASE #1 Clinical course post CART 41BB product infusion

- Day +1 Temp 39.7, BP 95/70, O2 sats 90% R/A- admit-2L NS
  - BP soft – ICU –single pressor NE and increased O2 CRP 250/ Ferritin 8000 CRS grade 2 (vs 3) Toci #1
  - 6h later increasing neurological symptoms and O2 Airvo -2nd Toci given and single dose of dex 10mg iv
  - Next day decision to dex 10mg iv q 6h x 72h (02 needs)
  - Grade 3 CRS, liver, Fibrinogen concentrates – ICU 4 days- resolved and steroids stopped, ICE ICANS resolved
- Day 10 discharged back to outpatient CRP <1, ferritin 600, LDH trending down 390 off O2 support
- Status day +30 PET markedly improved (80% reduction metabolic burden) but not CR, remains neutropenic (<0.5), IgG <4g, plts 20
- Septra, Fluconazole, Acyclovir, Levaquin, irradiated bld products, IVIgG sc home, grastofil
- back to referring center?
- Next PET- was treatment successful or not?

CASE #1 Clinical course post CART 41BB product infusion

- Day +1 Temp 39.7 (CRS temp often higher than neutropenic fever), BP 95/70, O2 sats 90% R/A- admit- 2L NS
  - BP soft – ICU –single pressor NE (ICU readiness important) and increased O2 CRP 250/ Ferritin 8000 CRS grade 2 (vs 3) Toci #1
  - 6h later increasing neurological symptoms and O2 Airvo -2nd Toci given and single dose of dex 10mg iv
  - Next day decision to dex 10mg iv q 6h x 72h (02 needs) (concern with lympholytic effect of corticosteroids)
  - Grade 3 CRS, liver, Fibrinogen concentrates – ICU 4 days- resolved and steroids stopped, ICE ICANS resolved
- Day 10 discharged back to outpatient CRP <1, ferritin 600, LDH trending down 390 off O2 support
- Status day +30 PET markedly improved (80% reduction metabolic burden) but not CR, remains neutropenic (<0.5), IgG <4g, plts 20
- Septra, Fluconazole, Acyclovir, Levaquin, irradiated bld products, IVIgG sc home, grastofil
- back to referring center?
- Next PET- was treatment successful or not? (Need d + 90 PET – if still positive improving and no new sites of disease/asymptomatic – monitor vs next line of treatment)

Case #2

- 27M presents with advanced stage cHL, bulky mediastinum >10cm, also neck, axillary and abdominal adenopathy, Hasenclever 5/7. marked SOBOE prednisone and ABVD x 2 No PET, PET-2 was positive escBEACOPP x 4- EOT PET negative/complete metabolic response, ?radiation to bulk -declined
- Decision to aggressive surveillance PET at 6months – Positive 3 sites DU>5U asymptomatic – re biopsy? GDPx 2 CR by CT –autograft: Melphalan/Etoposide

- **Question #1 – Treatment options post SCT**
- (i) re image PET at 1month
- (ii) maintenance Brentuximab as per “Althera” trial
- (iii) Checkpoint inhibitor if any positive disease
- (iv) IFR to sites of positive disease

Case #2

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- Decision to aggressive surveillance PET at 6months – Positive 3 sites DU>5U asymptomatic – re biopsy? GDPx 2 CR by CT –autograft: Melphalan/Etoposide

- **Question #1 – Treatment options post SCT**
- (i) re image PET at 1month -yes
- (ii) maintenance Brentuximab as per “Althera” trial yes eligible relapsed <12m or “refractory”
- (iii) Checkpoint inhibitor if any positive disease - possible
- (iv) IFR to sites of positive disease – may depend on pattern of residual disease

Case #2

- 27M presents with advanced stage cHL, bulky mediastinum 10cm, neck, axillary and abdominal adenopathy, Hasenclever 5/7. SOBOE and starts prednisone and ABVD x 2, PET-2 positive escBEACOPP x 4 EOT PET negative, ?radiation to original bulk -declined
- Decision to PET at 6months – Positive 3 sites DU>5u – re biopsy? GDPx2 –autograft Melphalan/Etoposide
- Maintenance Brentuximab x 16 cycles q21d

- **Question #2 – If subsequent relapse and progression**
- (i) checkpoint - Nivolumab
- (ii) stem cell transplant – haplo-identical donor