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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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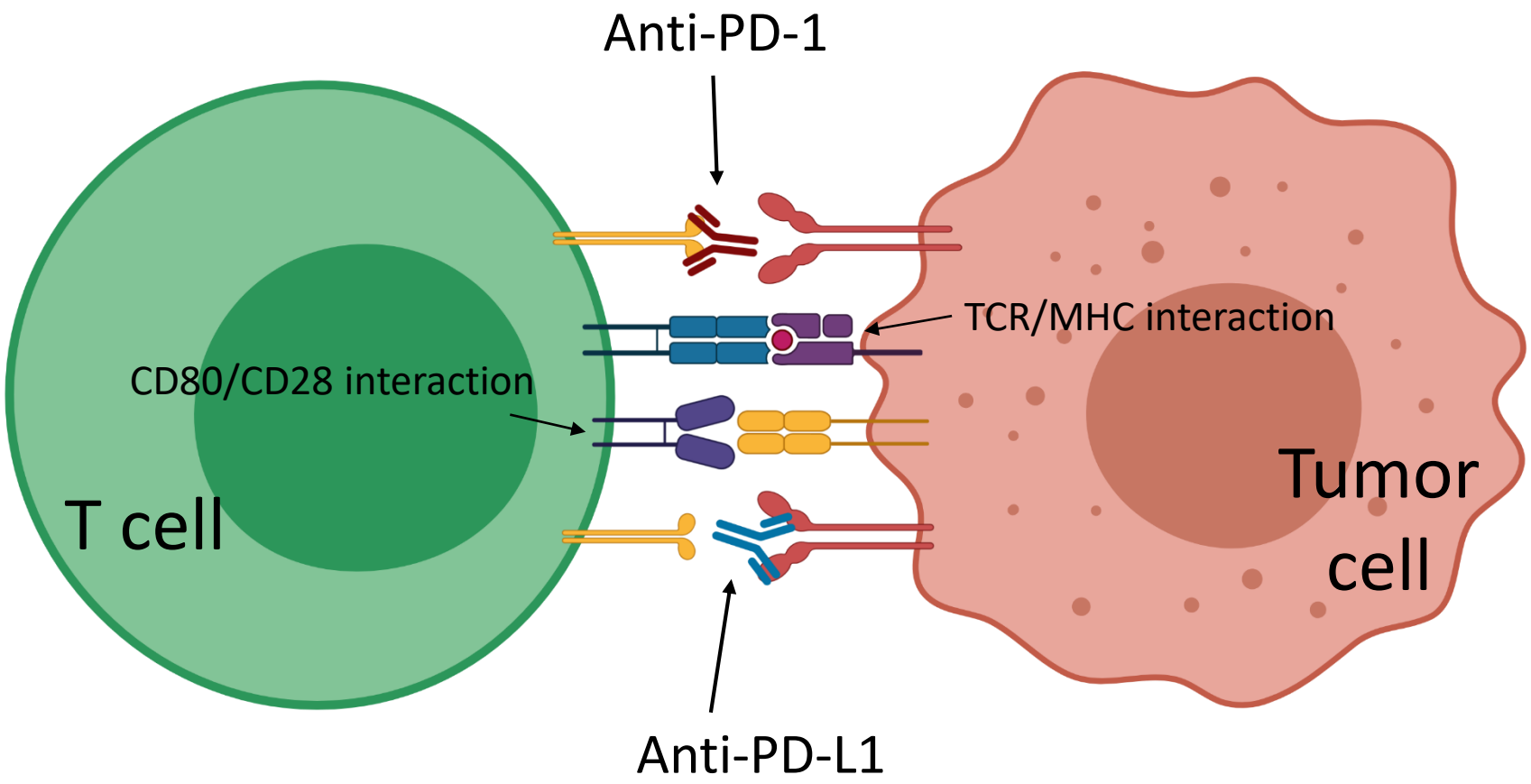
Disclosures

- Consulting Fees: Janssen/Pharmacyclics
- I will be discussing non-FDA approved indications during my presentation.

Outline: Major immunotherapies under development

- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Immune checkpoint inhibitors



FDA-approved checkpoint inhibitors: lymphoma

Drug	Indication	Dose
Nivolumab	Classical **Hodgkin lymphoma (cHL)**, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Adult/pediatric refractory **cHL** 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 (PMBL)** 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.

Efficacy of approved checkpoint inhibitors: lymphoma

Study	Treatment	Patient population	Overall response rate	Complete response rate	Landmark OS
CheckMate 205	Nivolumab	Brentuximab vedotin-naïve **cHL**	65%	29%	1-year: 92%
		Bretuximab vedotin after auto-HCT **cHL**	68%	13%	1-year: 93%
		Bretuximab vedotin before/after auto-HCT **cHL**	73%	12%	1-year: 90%
KEYNOTE-087	Pembrolizumab	**cHL** progressed after ASCT and BV	78.3%	26%	3-year: 86.3%
		cHL after salvage chemo and BV, ineligible for ASCT	64.2%	26%	3-year: 85.7%
		cHL progressed after ASCT without BV treatment	71.7%	31.7%	3-year: 87.6%
KEYNOTE-013	Pembrolizumab	**PMBL** with relapse/ineligible for ASCT	48%	33%	1-year: 65%
KEYNOTE-170	Pembrolizumab	**PMBL** ineligible for ASCT with progression on ≥ 2 previous therapies	45%	13%	1-year: 58%

cHL: Classical Hodgkin lymphoma; PMBCL: primary mediastinal B cell lymphoma

Armand, J Clin Oncol 2018; Zinzani, ASH 2019.

In development: Immune checkpoint inhibitors in AML

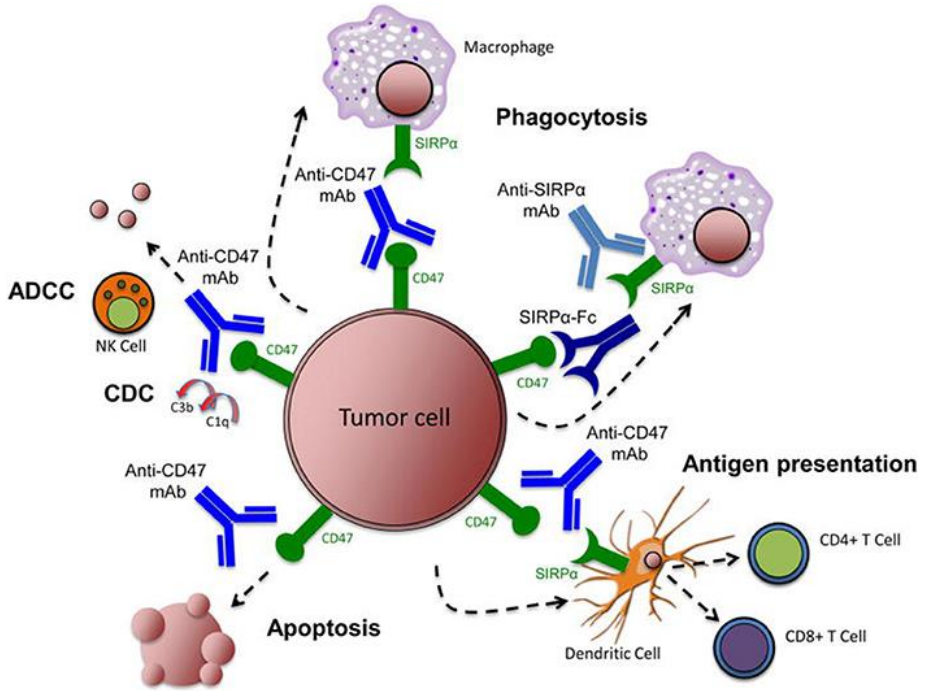
Study	Population	Treatment(s)	ORR	Median OS (months)	Status
NCT02775903	Untreated AML	Azacitidine + durvalumab	20%	13.0	Active, not recruiting
		Azacitidine	23%	14.4	
NCT02397720	Relapsed/refractory AML	Azacitidine + nivolumab	33%	6.4	Recruiting
		Azacitidine + nivolumab + ipilimumab	44%	10.5	
NCT02768792	Relapsed/refractory AML	HiDAC followed by pembrolizumab	46%	8.9	Active, not recruiting
NCT02845297	Relapsed/refractory AML	Azacitidine + pembrolizumab	31%	10.8	Recruiting
	Newly diagnosed AML, ≥ 65 years of age		70.5%	13.1	

ASH 2019: Zeidan, Daver, Zeidner, Gojo.

In development: Macrophage checkpoint: CD47

Treatment	Populations	ORR	CRR	Median DOR
Azacitidine + magroliumab	Untreated MDS	91.7%	50%	NR (>4.9 months)
	Untreated AML	63.6%	41%	NR (>5.8 months)

- CD47 is expressed on some cancer cells
- CD47 signaling through SIRPα prohibits macrophage phagocytosis of cancer cells – "don't eat me"
- Blocking interaction of CD47 and SIRPα promotes adaptive immune responses and boosts tumor cell phagocytosis



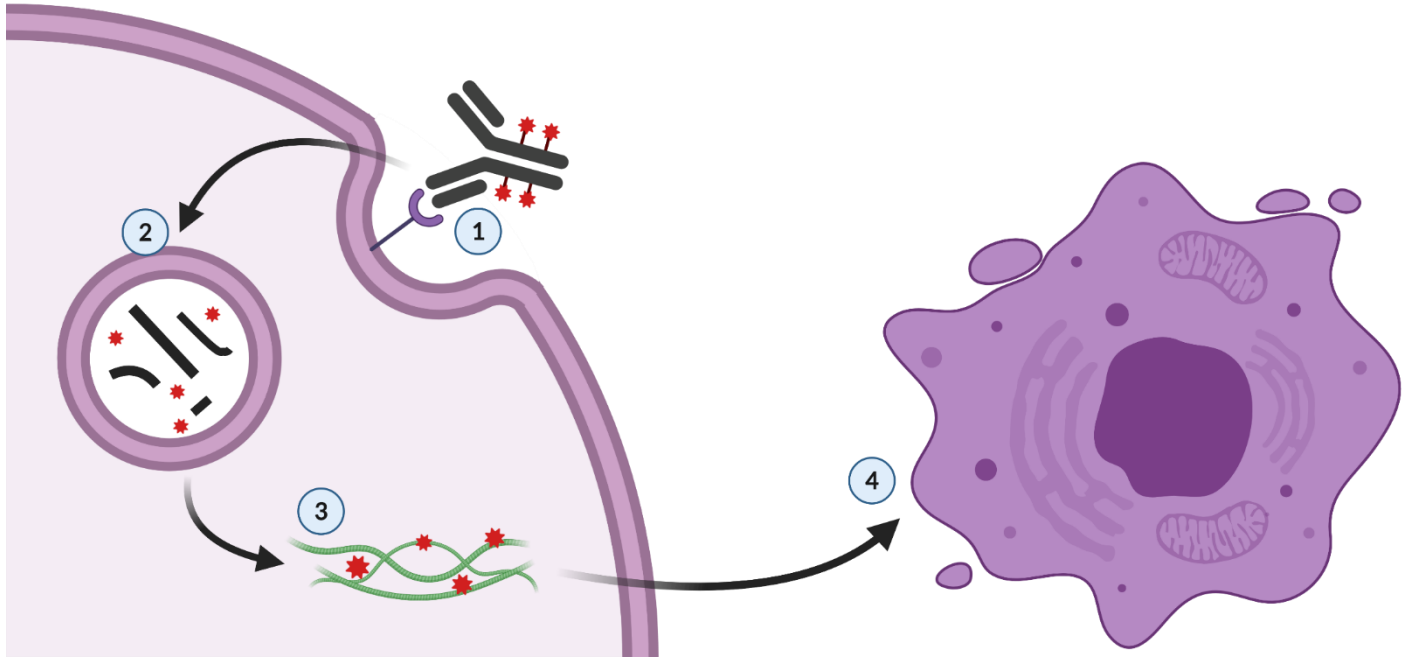
Sallman, ASH 2019.
Zhang, Front Immunol 2020.

Outline

- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Antibody-drug conjugates

1. Antibody binds to receptor on tumor cell
2. ADC is internalized and broken down
3. Drug payload performs its MOA (here, microtubule disruption)
4. Apoptosis is induced in target cell



FDA-approved antibody-drug conjugates

Drug	Target antigen	Indication
Brentuximab vedotin	CD30	**cHL** - relapsed after HSCT or ≥2 previous therapies
		cHL - consolidation after auto-HSCT
		cHL- first line with combination chemo
		CD30+ peripheral T-cell lymphomas - first line with combination chemo
		Systemic anaplastic large cell lymphoma (ALCL) ≥ 1 previous therapies
		Cutaneous ALCL or **CD30+ mycosis fungoides** ≥ 1 previous therapies
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

Efficacy of approved ADCs – brentuximab vedotin

Study	Treatment(s)	Patient population	Overall response rate	Complete response rate	Landmark OS
NCT00848926	Brentuximab vedotin	Relapsed/refractory **cHL** after failed auto-SCT	75%	33%	5-year: 41%
NCT00866047	Brentuximab vedotin	Relapsed/refractory **sALCL**	86%	66%	5-year: 60%
ECHELON-1	Brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine	Previously untreated stage III or IV **cHL**	2-year modified PFS rate: 82.1%		
	Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)		2-year modified PFS rate: 77.2%		
AETHERA	Brentuximab vedotin	Unfavorable-risk relapsed or primary refractory **cHL** after auto-SCT	Median PFS: 42.9 months		
	Placebo		Median PFS: 24.1 months		

Chen, Blood 2016; Pro, Blood 2017; Connors, N Engl J Med 2018; Moskowitz, Lancet 2015.

Efficacy of approved ADCs

Study	Treatment(s)	Patient population	Key outcomes
INO-VATE	Inotuzumab ozogamicin	Relapsed/refractory **B cell precursor ALL**	CR/CRi rate: 73.8% vs 30.9% Median OS: 7.7 vs 6.2 months 2-year OS: 22.8% vs 10%
	Standard-of-care chemo		
GO29365	Polatuzumab vedotin + bendamustine & rituximab	Relapsed/refractory **DLBCL**	CRR: 40.0% vs 17.5% Median PFS: 9.5 vs 3.7 months Median OS: 12.4 vs 4.7 months
	Bendamustine & rituximab		
ALFA-0701	Gemtuzumab ozogamicin + daunorubicin + cytarabine	De novo **AML**	CR/CRp rate: 81.5% vs 73.6% Median OS: 27.5 vs 21.8 months Median EFS: 17.3 vs 9.5 months
	Daunorubicin + cytarabine		
DREAMM-2	Belantamab mafodotin	R/R **multiple myeloma** after IMiD, PI, and anti-CD38	ORR: 31% Median PFS: 2.9 months

Sehn, J Clin Oncol 2020; Kantarjian, Cancer 2019; Lambert, Haematologica 2018.

In development: Novel ADCs in clinical trials

Trial	Indication	Treatment(s)	ADC target antigen	Phase
NCT03544281	R/R multiple myeloma	GSK2857916 + lenaolidomide + dexamethasone	BCMA	2
		GSK2857916 + bortezomib + dexamethasone		
NCT03386513	CD123+ AML, BPDCN or ALL	IMGN632	CD123	1/2
NCT03424603	R/R B cell malignancies	STRO-001	CD74	1
NCT03682796	R/R B cell lymphoma	TRPH-222	CD22	1
NCT04240704	CLL or NHL	JBH492	CCR7	1
NCT03833180	Pre-treated hematologic malignancies	VLS-101	ROR1	1

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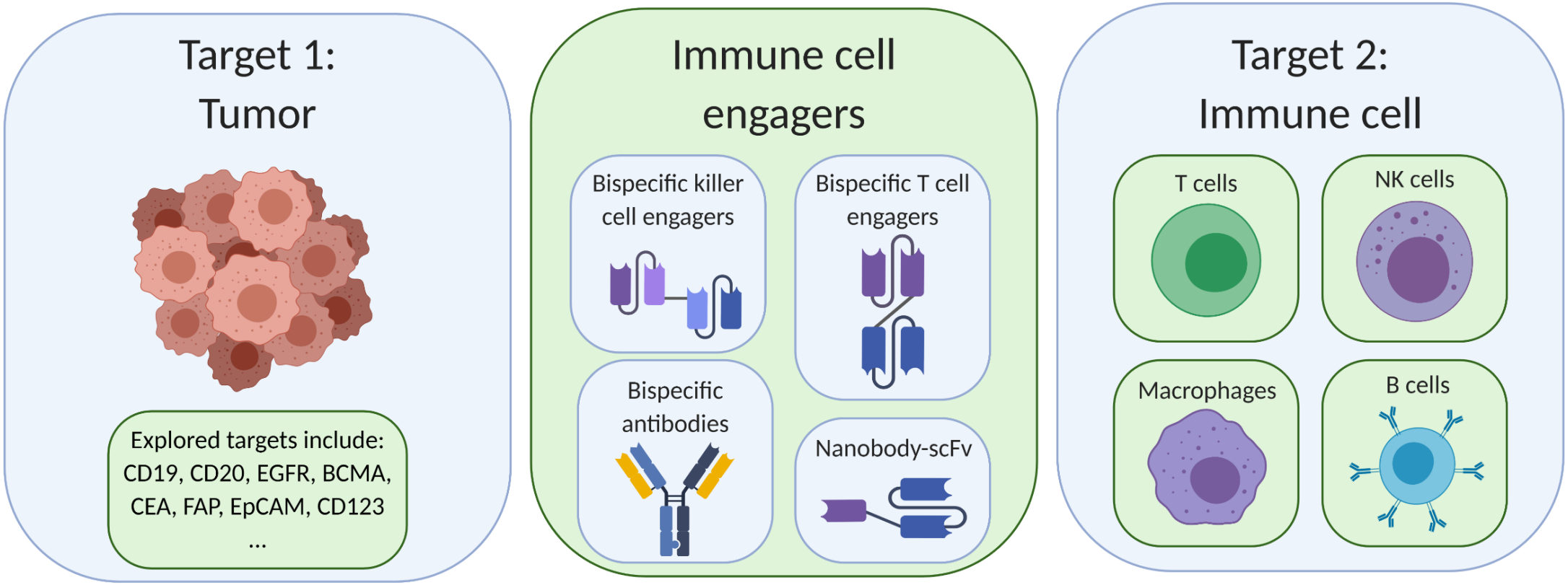
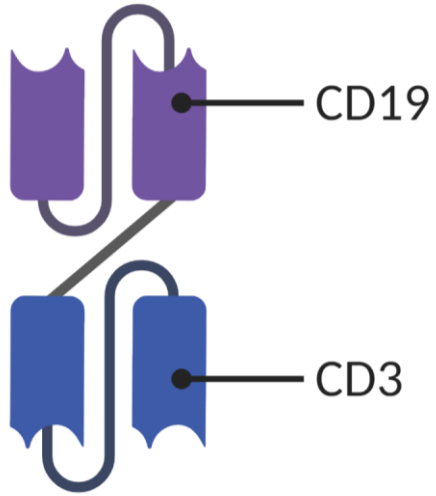
Bispecifics in immunotherapy



Commonly CD3 on T cells, CD16 for NK and macrophages, etc

Clinical use of immune cell engagers

Drug	Indications
Blinatumomab	Relapsed/refractory B-ALL
	B-ALL in 1st or 2nd complete response with MRD ≥ 0.1%

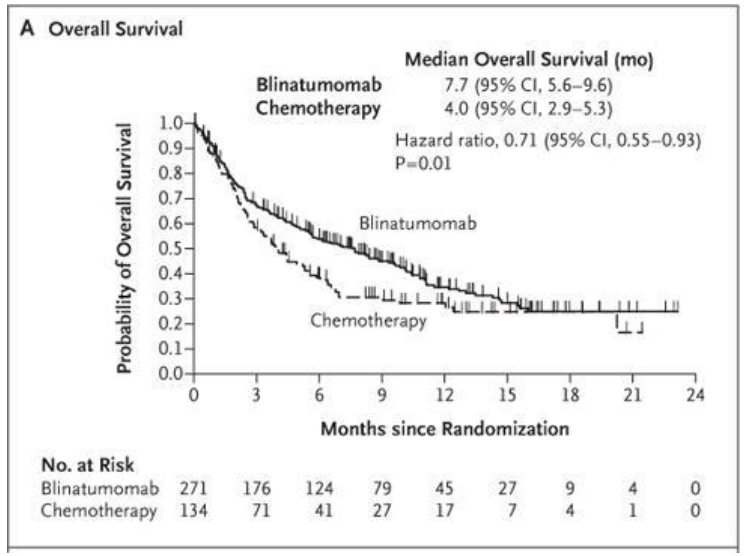


Blinatumomab prescribing information.

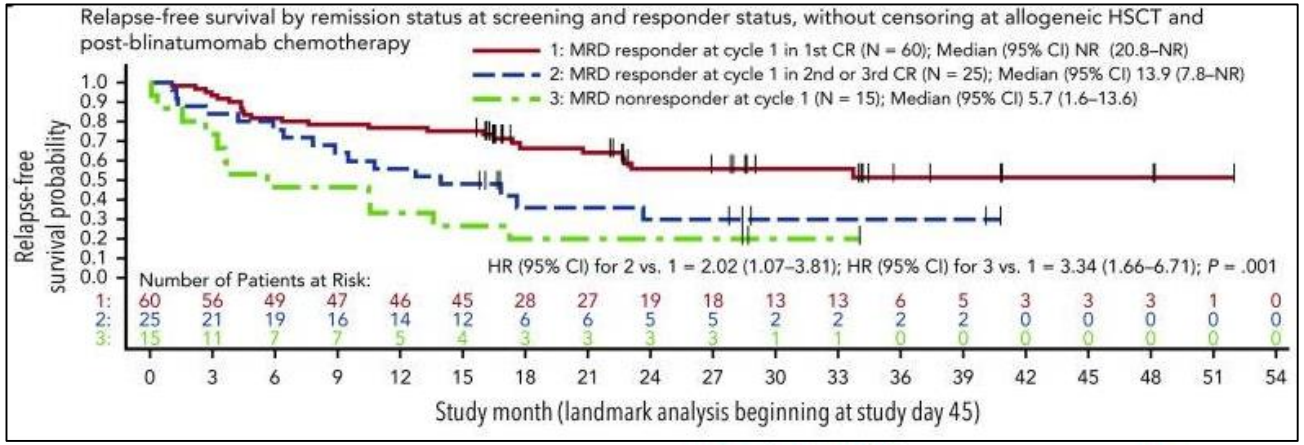
Blinatumomab in R/R B-ALL

Trial	Patient population	Treatment	Key outcomes
NCT02013167	Adults with R/R B-ALL	Blinatumomab	Median OS: 7.7 vs 4.0 months Median DOR: 7.3 vs 4.6 months
		Chemotherapy	
NCT01207388	Adults with MRD+ B-ALL	Blinatumomab	Complete MRD response rate: 78% Median OS: 36.5 months

R/R B-ALL



MRD+ B-ALL



Dosing regimens for blinatumomab

	Cycle		Patients weighing 45 kg or more (Fixed-dose)	Patients weighing less than 45 kg (BSA-based dose)
MRD-positive B-ALL	Induction cycle 1	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Consolidation cycles 2-4	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval

	Cycle		Patients weighing 45 kg or more (Fixed-dose)	Patients weighing less than 45 kg (BSA-based dose)
R/R B-ALL	Induction cycle 1	Days 1-7	9 mcg/day	5 mcg/m^2/day (not to exceed 9 mcg/day)
		Days 8-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Induction cycle 2	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Consolidation cycles 3-5	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Continued therapy cycles 6-9	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	56-day treatment-free interval	56-day treatment-free interval

Blinatumomab prescribing information.

Dosing regimens for blinatumomab – R/R B-ALL

Induction cycle 1

7-day low-dose infusion

21-day normal dose infusion

14 days treatment-free

Induction 2, Consolidation

28-day continuous infusion

14 days treatment-free

Blinatumomab prescribing information.

Common side effects of T cell engagers

Cytokine release syndrome

- Initial flu-like symptoms→shock-like syndrome with elevation in cytokine levels
- Fever, vascular leakage, and organ dysfunction
- Variable onset and course
- Pre-treatment with dexamethasone required
- Management:
  - IL-6 and IL-6R antagonism
  - Corticosteroids
  - Other cytokine receptor antagonists

B cell aplasia

- With agents targeting CD19, which is expressed by normal and neoplastic B cells
- May result in hypogammaglobulinemia
- Increased risk of infection
- Managed through administration of intravenous immunoglobulin

Stay tuned: more information on toxicity management later in this program

Neurotoxicity

- A.K.A. "immune effector cell-associated neurotoxicity syndrome" (ICANS)
- Confusion, delirium, seizures, cerebral edema
- Largely unknown mechanisms
- ↑Incidence with ↑doses, ↑age, ↑ prior therapies
- Management:
  - Supportive care for low-grade
  - Corticosteroids for higher-grade

In development: Novel immune cell engagers in clinical trials

Trial	Indication	Treatment	Target antigens	Phase
NCT03214666	High-risk MDS, R/R AML, systemic mastocytosis	GTB-3550 (TriKE)	CD16, IL-15, CD33	1/2
NCT03516591	High-risk MDS	AMV564	CD33, CD3	1
NCT03739606	CD123+ R/R blood cancers	Flotetuzumab	CD123, CD3	2
NCT02730312	CD123+ R/R blood cancers	XmAb14045	CD123, CD3	1
NCT03888105	R/R B cell NHL	Odronextamab	CD20, CD3	2
NCT03309111	Previously treated multiple myeloma	GBR 1342	CD38, CD3	1/2
NCT03761108	R/R multiple myeloma	REGN5458	BCMA, CD3	1/2

Outline

- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

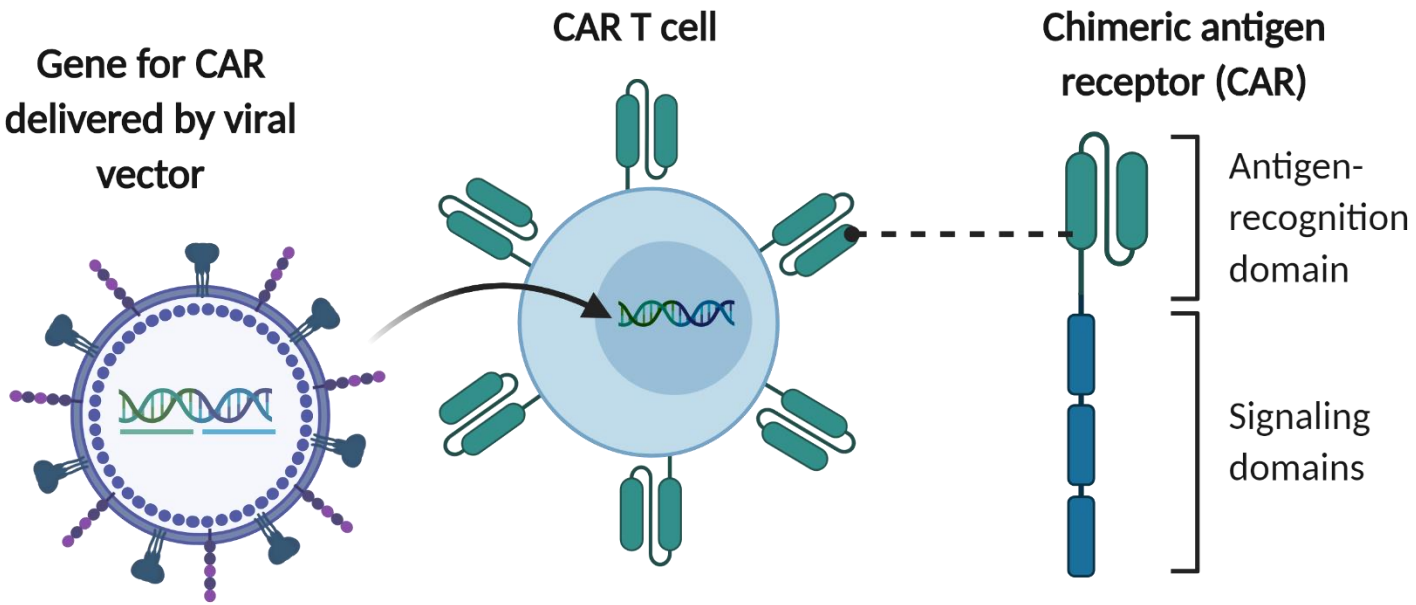
Comparing T cell engagers and CAR T therapy

	CAR T cells	T cell engagers (BiTEs)
Structure	Synthetic *gene construct* encoding an scFv against tumor antigen linked to activation/costimulatory motifs	Recombinant *protein* with two specificities: one for tumor antigen and one for T cell antigen (usually CD3)
Effector cell types	*Engineered* CD8+ and CD4+ T cells	*Endogenous* CD8+ and CD4+ T cells
Immune synapse	Atypical	Typical
Serial killing	Yes	Yes
Killing mechanisms	Perforin and granzyme B, Fas-Fas-L, or TNF/TNF-R	Perforin and granzyme B
Trafficking	Active	Passive
Clinical applications	Pre-treatment lymphodepletion followed by a single infusion	No lymphodepletion; repeat administration and continuous infusions.
Specificity	Manufactured for each patient	"Off-the-shelf"

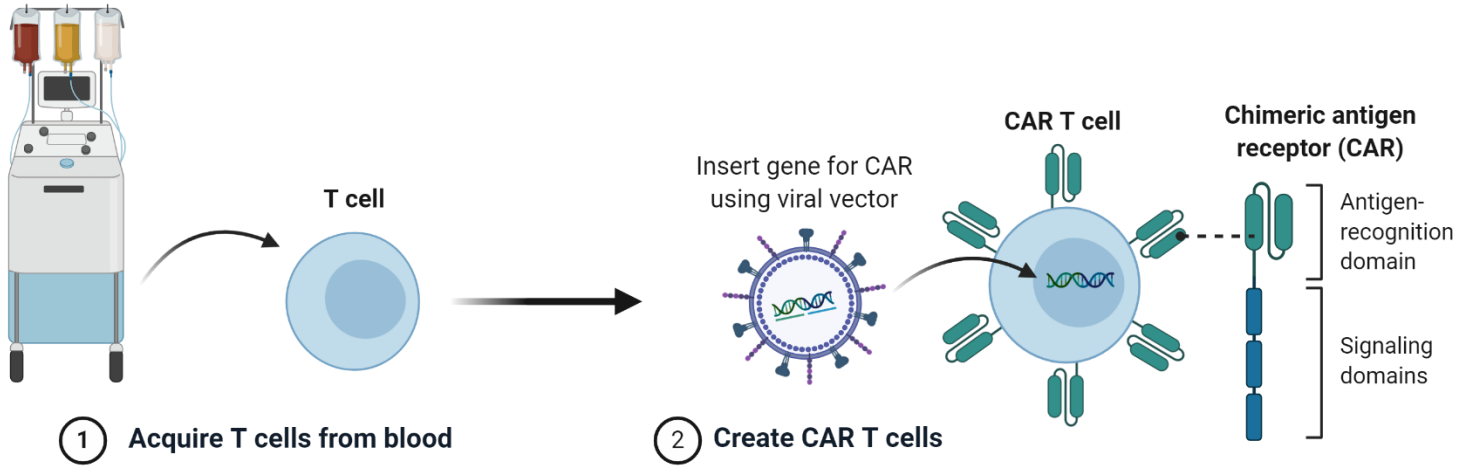
Slaney, Cancer Disc 2018.

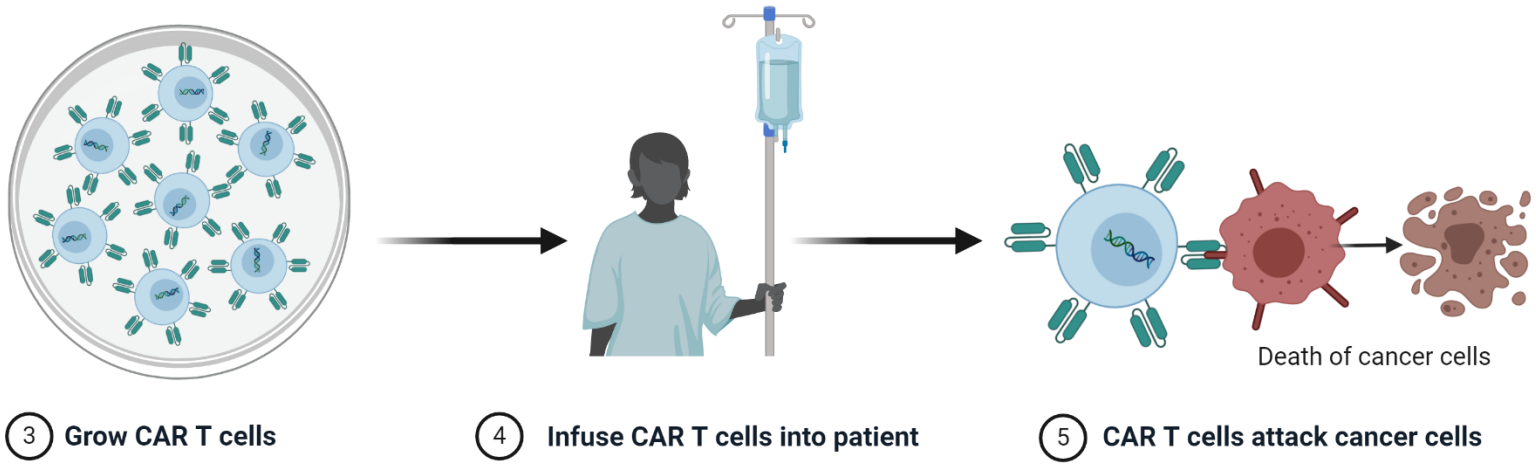
Chimeric antigen receptors

- Overcome immune tolerance
- Targets surface molecules in native conformation
- Independent of antigen presenting cell and MHC complex



CAR T manufacturing and administration





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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 **DLBCL**, **PMBL**, **high-grade B-cell lymphoma (HGBL)**, and DLBCL **arising from follicular lymphoma (tFL)**	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 ALL** 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**, **HGBL, tFL**	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)

Comparing clinical trials of CAR T therapies

Trial	Indication	Treatment(s)	ORR	Landmark OS	Grade 3+ toxicity rates
ZUMA-2	R/R MCL	Brexucabtagene autoleucel (KTE-X19)	86% CRR: 57%	1-year: 86%	CRS: 18% NE: 46%
ZUMA-1	Refractory large B cell lymphoma	Axicabtagene ciloleucel	83% CRR: 58%	2-year: 50%	CRS: 11% NE: 32%
JULIET	R/R DLBCL	Tisagenlecleucel	52% CRR: 40%	1-year: 49%	CRS: 22% NE: 12%
ELIANA	R/R B-cell ALL	Tisagenlecleucel	82% CRR: 62%	18-month: 70%	CRS: 48% NE: 13%

Wang, ASH 2019; Locke, Lancet Oncol 2019; Schuster, N Engl J Med 2019; Grupp, Biol Blood Mar Trans 2019.

CAR T side effects

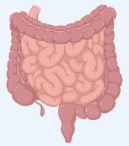
- Cytokine Release Syndrome (CRS)
- Neurotoxicity
  - ICANS: Immune effector cell-associated neurotoxicity syndrome
  - NE: Neurologic events
- B cell aplasia
- Macrophage Activation Syndrome (MAS)/HLH

Stay tuned: more information on toxicity management later in this program

CAR T side effects - CRS

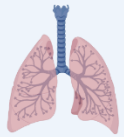
Cytokine Release Syndrome symptoms

Gastrointestinal
- Nausea/vomiting
- Diarrhea
- Anorexia



Skin
- Rash

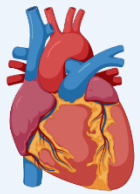
Respiratory
- Tachypnea
- Hypoxia
- Pulmonary edema



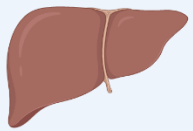
Constitutional
- Fever +/- rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

Coagulation
- Elevated D-dimer
- Hypofibrinogenemia +/- bleeding

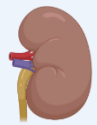
Cardiovascular
- Tachycardia
- Hypotension
- Capillary leak
- Widened pulse presssure
- Increased cardiac output (early)
- Potentially diminished cardiac output (late)



Hepatic dysfunction
- Transaminitis
- Hyperbilirubinemia



Renal function
- Azotemia



Symptoms often mimic sepsis, but treatment of CRS is quite different

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
  - Availability of tocilizumab for CRS management

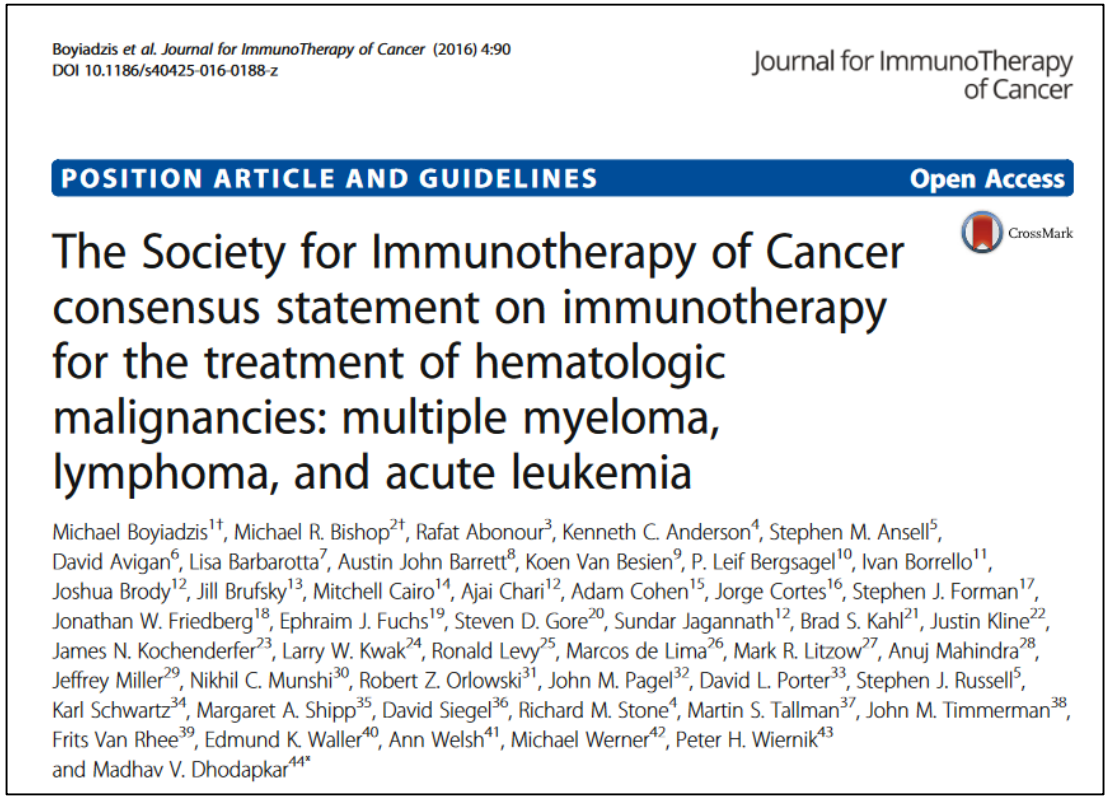
In development: Novel CAR T therapies in clinical trials

Trial	Indication	Treatment	Target antigen	Phase
NCT03651128	R/R multiple myeloma	bb2121	BCMA	3
NCT03971799	R/R pediatric AML	CD33CART	CD33	1/2
NCT04186520	R/R B cell malignancies	CAR-20/19 T cells	CD19, CD20	1/2
NCT04109482	R/R BPDCN, AML, HR MDS	MB-102	CD123	1/2
NCT03287817	Diffuse large B cell lymphoma	AUTO3	CD19, CD22	1/2
NCT02690545	R/R HL and NHL	ATLCAR.CD30	CD30	1/2

Conclusions

- Many immunotherapy options for hematological malignancies
- Checkpoint inhibitors for cHL and PMBL – 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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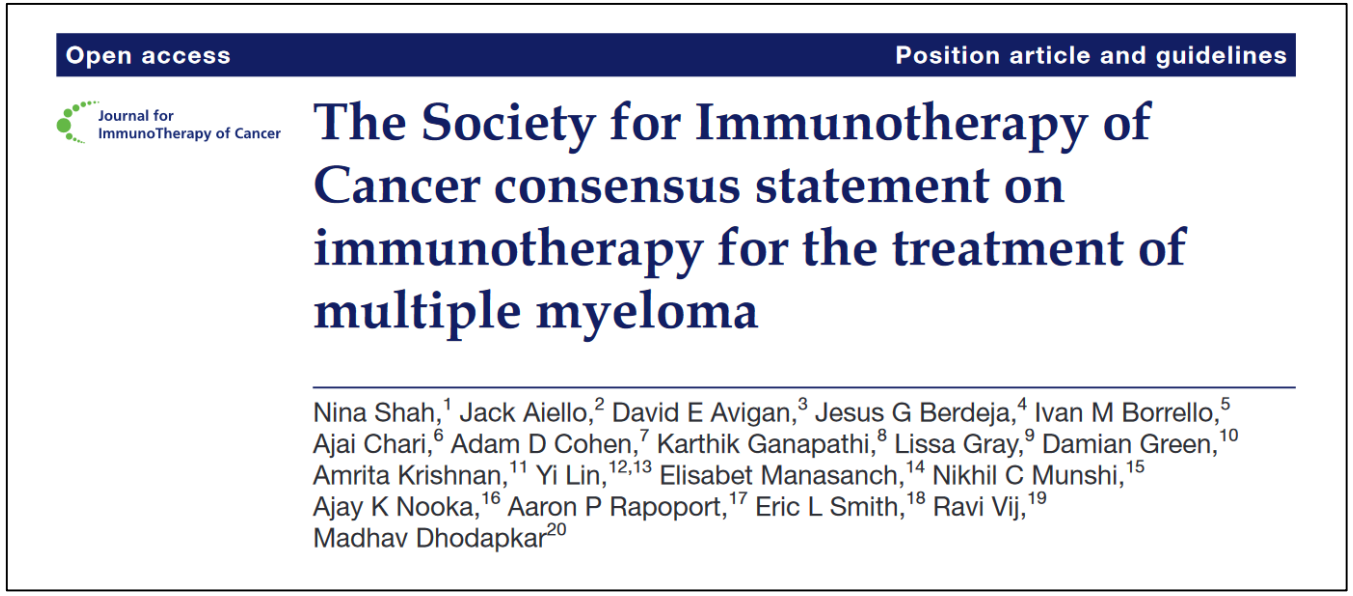

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The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of multiple myeloma

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Case Study

75-year-old woman with stage IV DLBCL with bone marrow involvement was initially treated with R-CHOP × 6 cycles and achieved a CR.

Her disease relapsed within 12 months and was treated with 2nd-line R-ICE, achieving SD.

What treatment option(s) are now appropriate for this patient?

What treatment option(s) are now appropriate to consider for this patient?

A. Bendamustine-rituximab + polatuzumab vedotin
B. CAR-T therapy
C. Consolidation with allogeneic stem cell transplant
D. Brentuximab vedotin

Patient undergoes T cell apheresis, with successful manufacture of CAR-T cells. She is admitted for lymphodepleting chemotherapy with fludarabine and cyclophosphamide, and undergoes CAR-T infusion.

Which of the following would be an indication to start corticosteroids after her CAR-T infusion?

A. She spikes a fever to 39.4°C 2 days after infusion.
B. She develops hypotension that is responsive to IV fluids 2 days after infusion.
C. Four days after infusion, she exhibits a decreased level of consciousness, but is arousable to voice.
D. Both (B) and (C).
E. All of the above.

Patient is monitored inpatient for a total of 7 days after her CAR-T infusion, at which time she has no evidence of CRS or neurotoxicity and is discharged home with close follow-up in clinic.

Although her 3-month restaging scans showed CR, at 9 months she develops progressive LAD consistent with PD.

She is started on bendamustine-rituximab with polatuzumab and achieves a PR after cycle 3, with a CR after cycle 6.