

# Immunotherapy for the Treatment of Hematologic Malignancies

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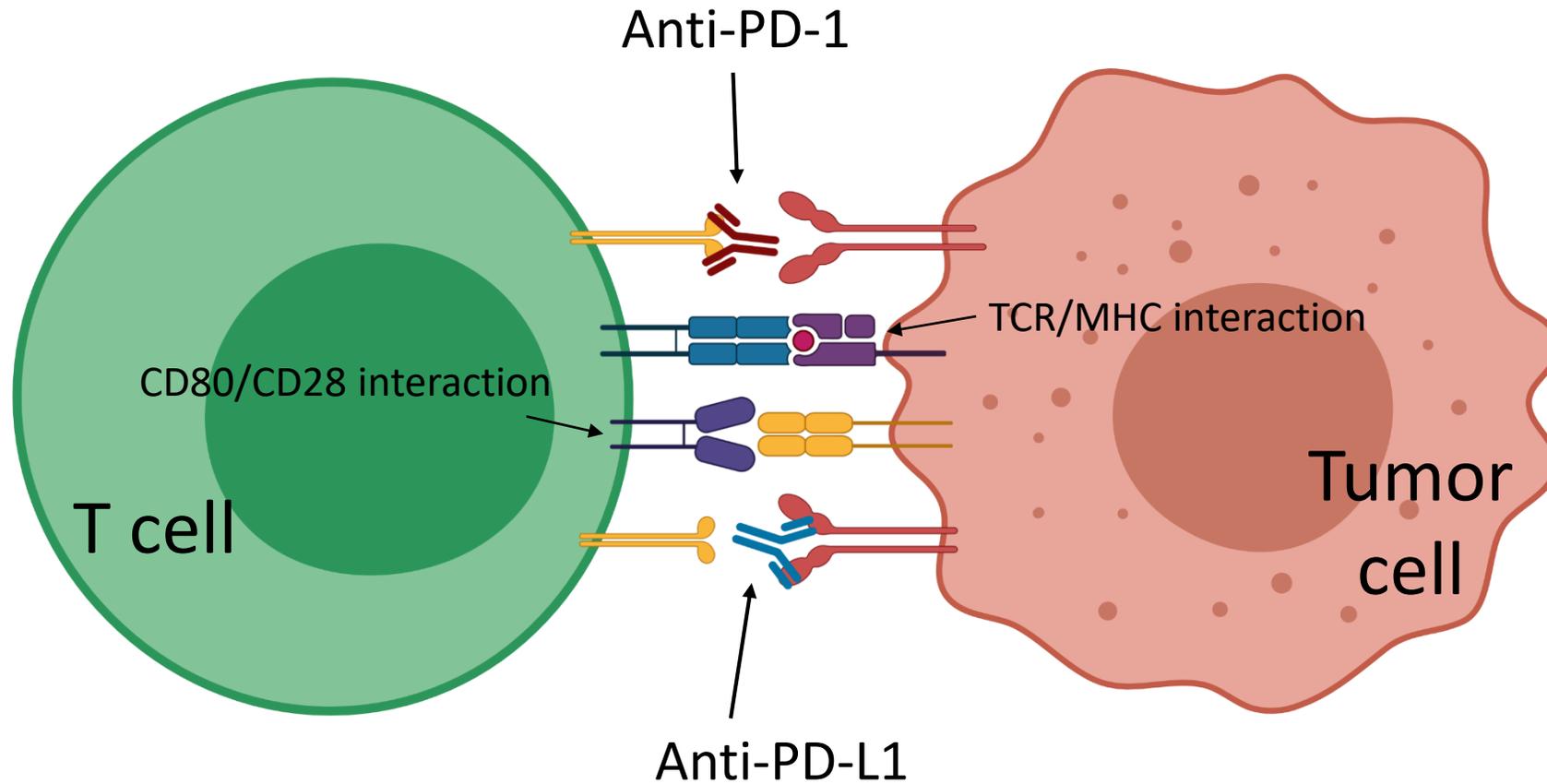
# Disclosures

- Contracted Research (Research Funding): Takeda, CTI BioPharma, Viracta, Spectrum
- 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



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# FDA-approved checkpoint inhibitors: lymphoma

Drug	Indication	Dose
Nivolumab	Classical <b>Hodgkin lymphoma</b> , relapsed after HSCT and brentuximab vedotin or $\geq 3$ previous therapies	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Adult relapsed/refractory classical <b>Hodgkin lymphoma</b>	200 mg Q3W or 400 mg Q6W adults
	Pediatric refractory <b>cHL</b> or <b>cHL</b> relapsed after $\geq 2$ lines of therapy	2 mg/kg (up to 200 mg) Q3W (pediatric)
Pembrolizumab	Adult/pediatric refractory <b>primary mediastinal large B-cell lymphoma</b> 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 <b>cHL</b>	65%	29%	1-year: 92%
		Bretuximab vedotin after auto-HCT <b>cHL</b>	68%	13%	1-year: 93%
		Bretuximab vedotin before/after auto-HCT <b>cHL</b>	73%	12%	1-year: 90%
KEYNOTE-087	Pembrolizumab	<b>cHL</b> progressed after ASCT and BV	78.3%	26%	3-year: 86.3%
		<b>cHL</b> after salvage chemo and BV, ineligible for ASCT	64.2%	26%	3-year: 85.7%
		<b>cHL</b> progressed after ASCT without BV treatment	71.7%	31.7%	3-year: 87.6%
KEYNOTE-013	Pembrolizumab	<b>PMBCL</b> with relapse/ineligible for ASCT	48%	33%	1-year: 65%
KEYNOTE-170	Pembrolizumab	<b>PMBCL</b> ineligible for ASCT with progression on $\geq 2$ previous therapies	45%	13%	1-year: 58%

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

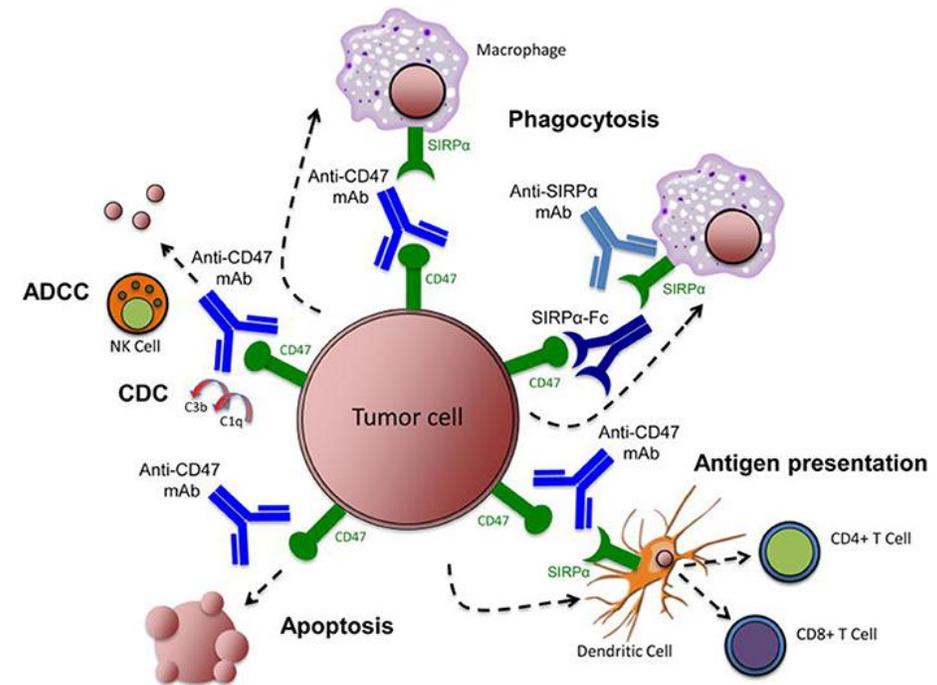
# In development: Immune checkpoint inhibitors in AML

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, $\geq 65$ years of age		70.5%	13.1	

# In development: Macrophage checkpoint: CD47

Treatment	Populations	ORR	CRR	Median DOR
Azacitidine + magrolimumab	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

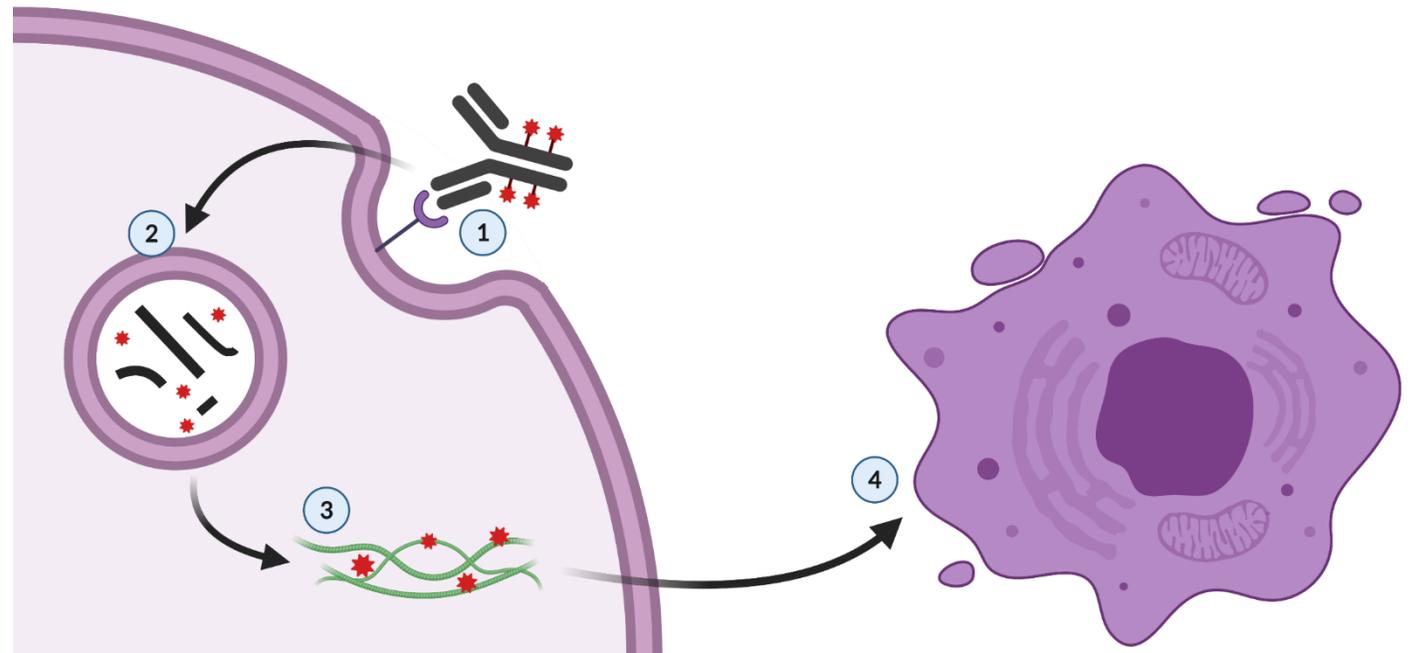


# Outline

- 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	<b>Classical Hodgkin lymphoma</b> , relapsed after HSCT or $\geq 2$ previous therapies
		<b>Cutaneous anaplastic large cell lymphoma</b> or <b>CD30+ mycosis fungoides</b> $\geq 1$ previous therapies
		<b>Classical Hodgkin lymphoma</b> - first line with combination chemo
		<b>Classical Hodgkin lymphoma</b> consolidation after auto-HSCT
Inotuzumab ozogamicin	CD22	Relapsed/refractory/MRD+ <b>B-cell ALL</b>
Polatuzumab vedotin (w/ bendamustine & rituximab)	CD79b	<b>DLBCL</b> $\geq 2$ previous therapies
Gemtuzumab ozogamicin	CD33	<b>R/R or newly-diagnosed CD33+ AML</b> in adults or pediatric patients
Belantamab mafodotin	BCMA	<b>R/R multiple myeloma</b> after $\geq 4$ prior therapies
Loncastuximab tesirine	CD19	<b>R/R large B-cell lymphoma</b> after 2+ therapies, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma

# Efficacy of approved ADCs – brentuximab vedotin

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

# Efficacy of approved ADCs

Study	Treatment(s)	Patient population	Key outcomes
INO-VATE	Inotuzumab ozogamicin	Relapsed/refractory <b>B cell precursor ALL</b>	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 <b>DLBCL</b>	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 acute <b>myeloid leukemia</b>	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 <b>multiple myeloma</b> after IMiD, PI, and anti-CD38	ORR: 31% Median PFS: 2.9 months
LOTIS-2	Loncastuximab tesirine	R/R <b>DLBCL</b> or high-grade <b>B cell lymphoma</b> after 2 treatments	ORR: 48.3% Median DOR: 10.3 months

# In development: Novel ADCs in clinical trials

Trial	Indication	Treatment(s)	ADC target antigen	Phase
NCT03544281	R/R multiple myeloma	GSK2857916 + lenalidomide + 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

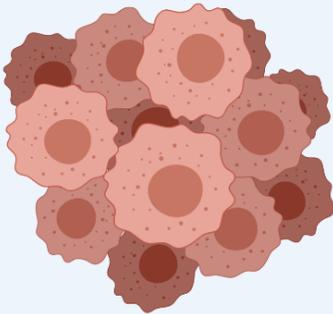
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# Outline

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

# Bispecifics in immunotherapy

## Target 1: Tumor



Explored targets include:  
 CD19, CD20, EGFR, BCMA,  
 CEA, FAP, EpCAM, CD123

...

## Immune cell engagers

Bispecific killer  
cell engagers



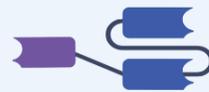
Bispecific T cell  
engagers



Bispecific  
antibodies

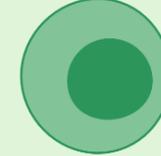


Nanobody-scFv

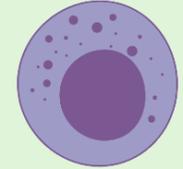


## Target 2: Immune cell

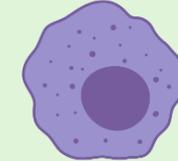
T cells



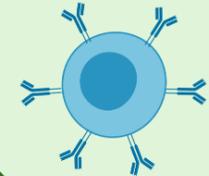
NK cells



Macrophages



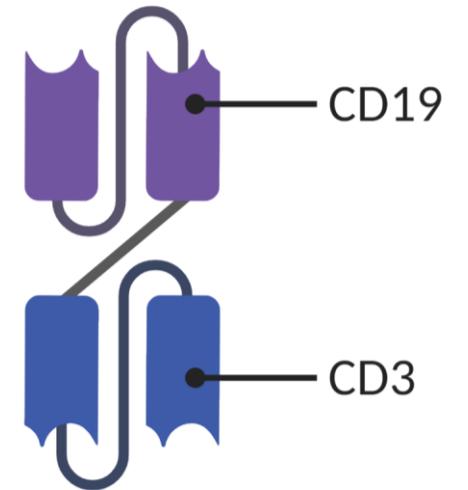
B cells



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

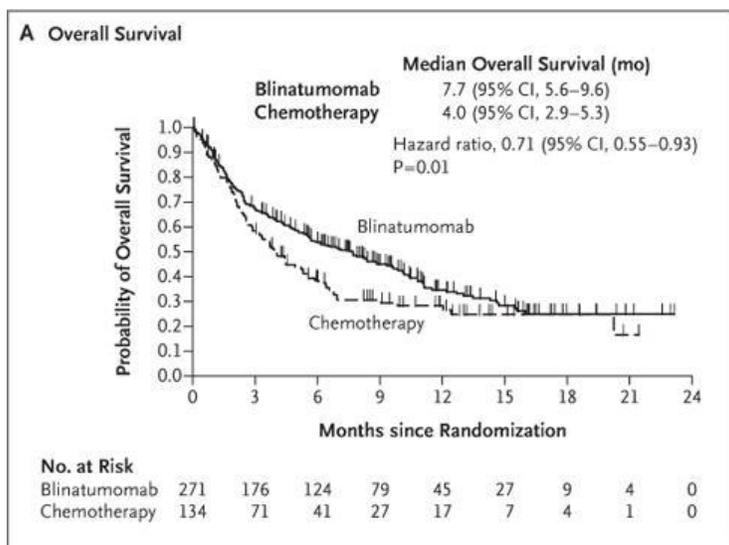
# Clinical use of immune cell engagers

Drug	Indications
Blinatumomab	Relapsed/refractory B-ALL
	B-ALL in 1 <sup>st</sup> or 2 <sup>nd</sup> complete response with MRD $\geq$ 0.1%



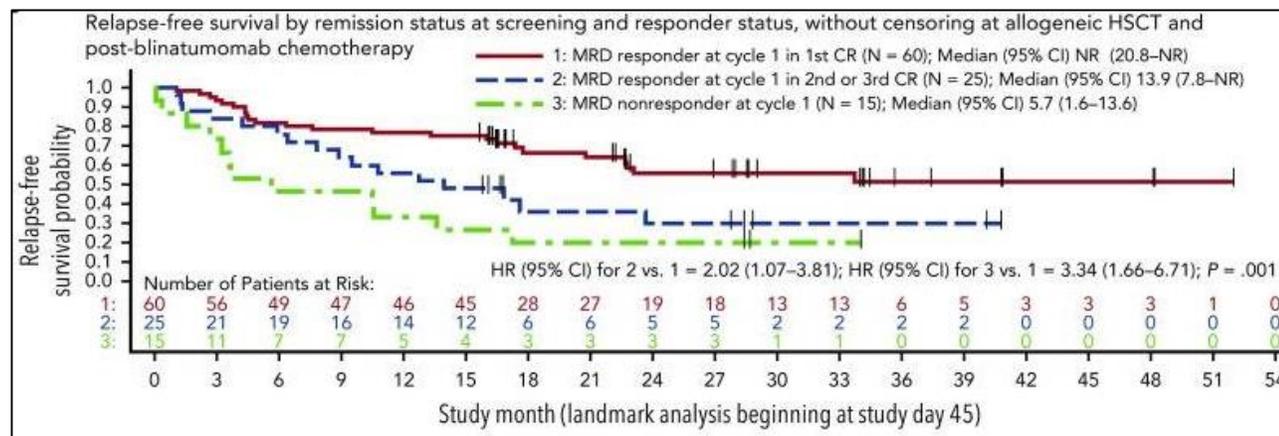
# Blinatumomab in R/R B-ALL

## 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

## MRD+ B-ALL



# Dosing regimens for blinatumomab

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

R/R B- ALL	Cycle		Patients weighing 45 kg or more (Fixed-dose)	Patients weighing less than 45 kg (BSA-based dose)
	Induction cycle 1	Days 1-7	9 mcg/day	5 mcg/m <sup>2</sup> /day (not to exceed 9 mcg/day)
		Days 8-28	28 mcg/day	15 mcg/m <sup>2</sup> /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 <sup>2</sup> /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 <sup>2</sup> /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 <sup>2</sup> /day (not to exceed 28 mcg/day)
		Days 29-42	56-day treatment-free interval	56-day treatment-free interval

# Dosing regimens for blinatumomab – R/R B-ALL

Induction cycle 1



Induction 2, Consolidation



# Common side effects of T cell engagers

## Cytokine release syndrome

- Characterized by initial flu-like symptoms, which progress into a shock-like syndrome with elevation in cytokine levels
- Patients display 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

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

## Neurotoxicity

- Also known as “immune effector cell-associated neurotoxicity syndrome” (ICANS)
- Manifests as confusion, delirium, seizures, cerebral edema
- Largely unknown mechanisms
- Incidence increases with more doses, increased age, more prior therapies
- Management:
  - Supportive care for low-grade
  - Corticosteroids for higher-grade

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

# In development: Novel immune cell engagers in clinical trials

Trial	Indication	Treatment	Target antigens	Phase
NCT03214666	HR myelodysplastic syndromes, R/R AML, systemic mastocytosis	GTB-3550 (TriKE)	CD16, IL-15, CD33	1/2
NCT03516591	High-risk myelodysplastic syndromes	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

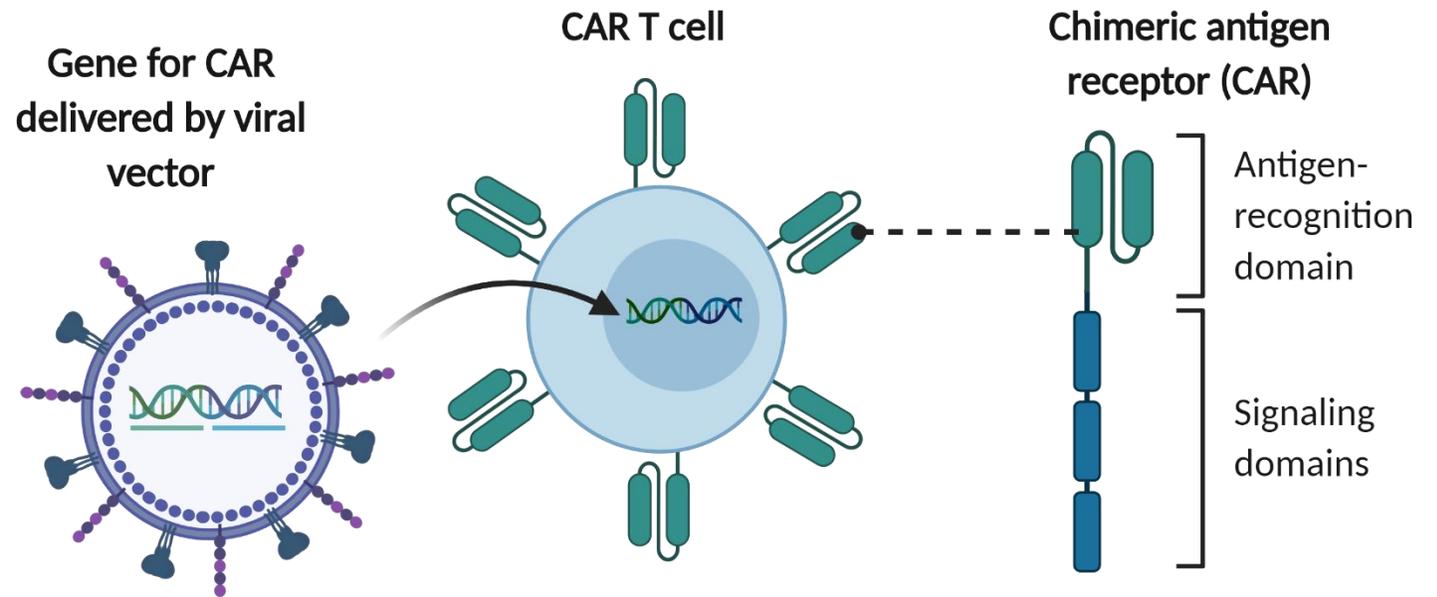
- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

# Comparing T cell engagers and CAR T therapy

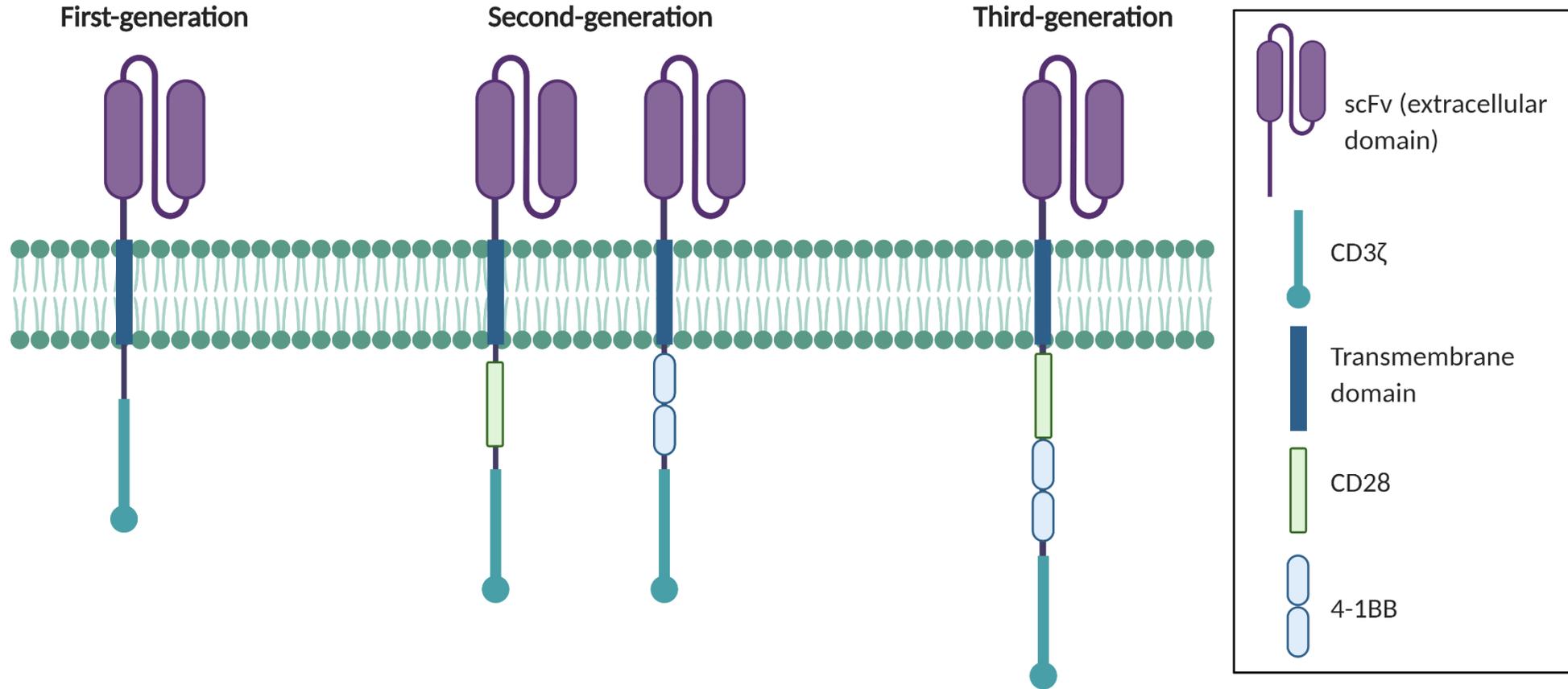
	CAR T cells	T cell engagers (BiTEs)
<b>Structure</b>	Synthetic gene construct encoding an scFv against tumor antigen linked to activation/costimulatory motifs	Recombinant protein with two specificities: one for tumor antigen and one for T cell antigen (usually CD3)
<b>Effector cell types</b>	Engineered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

# Chimeric antigen receptors

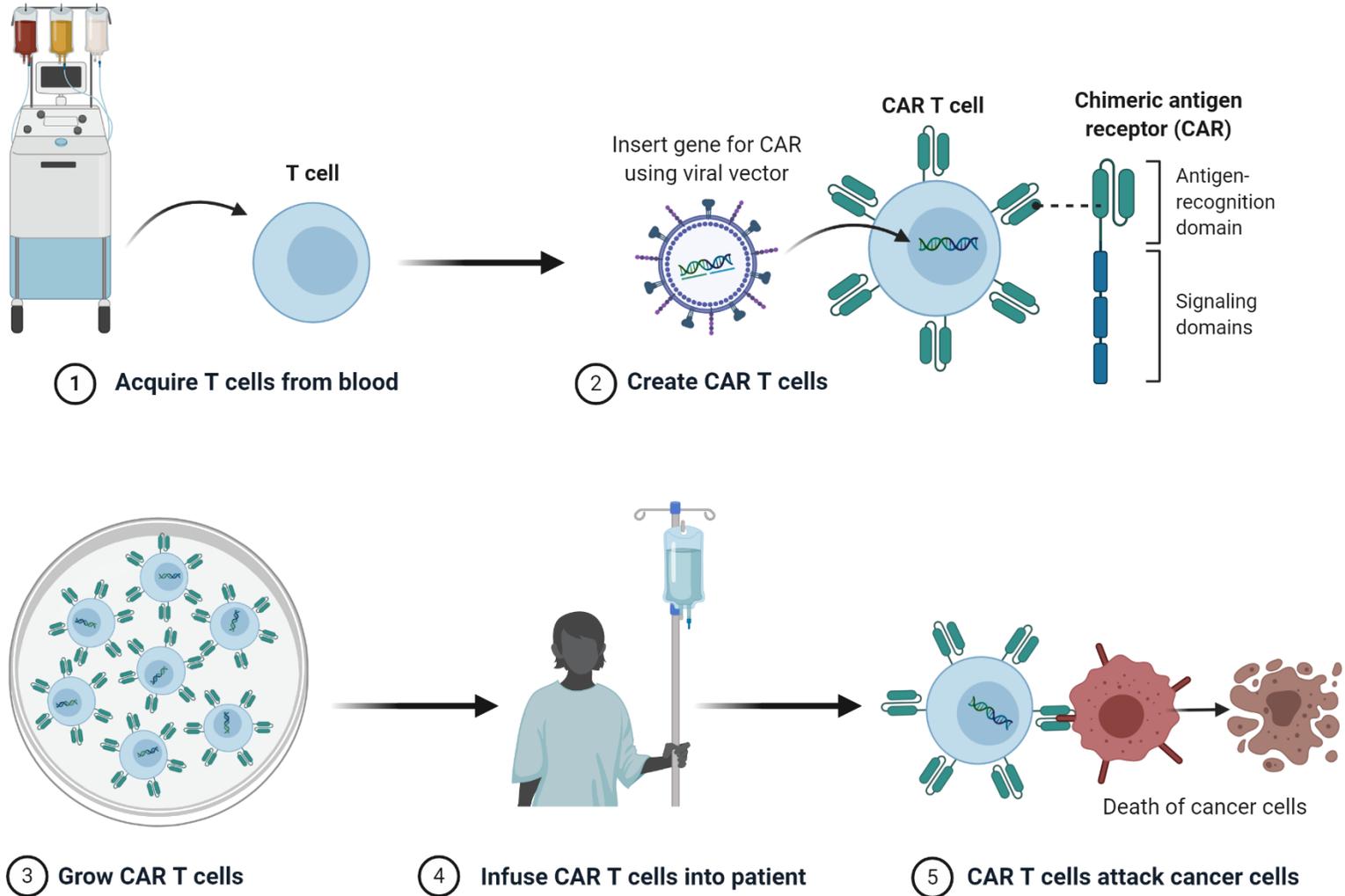
- Overcome immune tolerance
- Targets surface molecules in native conformation
- Independent of antigen presenting cell and MHC complex



# Evolution of CAR constructs



# CAR T manufacturing and administration



# FDA-approved CAR T cell therapies

Drug	Target/co-stimulatory domain	Indication	Dose
Axicabtagene ciloleucel	CD19/CD28	Adults with r/r large <b>B-cell lymphoma</b> , including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma, and R/R follicular lymphoma	2 x 10 <sup>6</sup> CAR-positive, viable T cells per kg bodyweight (up to 2x10 <sup>8</sup> )
Tisagenlecleucel	CD19/4-1BB	Patients ≤25 yr with refractory <b>B-cell acute lymphoblastic leukemia</b> or in 2+ relapse	0.2-0.5x10 <sup>6</sup> CAR-positive, viable T cells per kg if under 50 kg 0.1-2.5x10 <sup>8</sup> CAR-positive, viable T-cells if over 50 kg
Tisagenlecleucel	CD19/4-1BB	Adults with r/r large <b>B-cell lymphoma</b> after 2+ therapies including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma	0.6-6.0 x 10 <sup>8</sup> CAR-positive, viable T cells
Brexucabtagene autoleucel	CD19/CD28	Adults with <b>mantle cell lymphoma (MCL)</b> who have not responded to or who have relapsed following other treatments	2 x 10 <sup>6</sup> CAR-positive, viable T cells per kg bodyweight (up to 2x10 <sup>8</sup> )
Lisocabtagene maraleucel	CD19/4-1BB	Adults with R/R large <b>B-cell lymphoma</b> after at least 2 prior therapies	50-110 x 10 <sup>6</sup> CAR-positive viable T cells (1:1 CD4:CD8)
Idecabtagene vicleucel	BCMA/4-1BB	Adults with R/R <b>multiple myeloma</b> after 4+ prior therapies	300-460x10 <sup>6</sup> CAR-positive T cells

# Comparing clinical trials of CD19 CAR T therapies

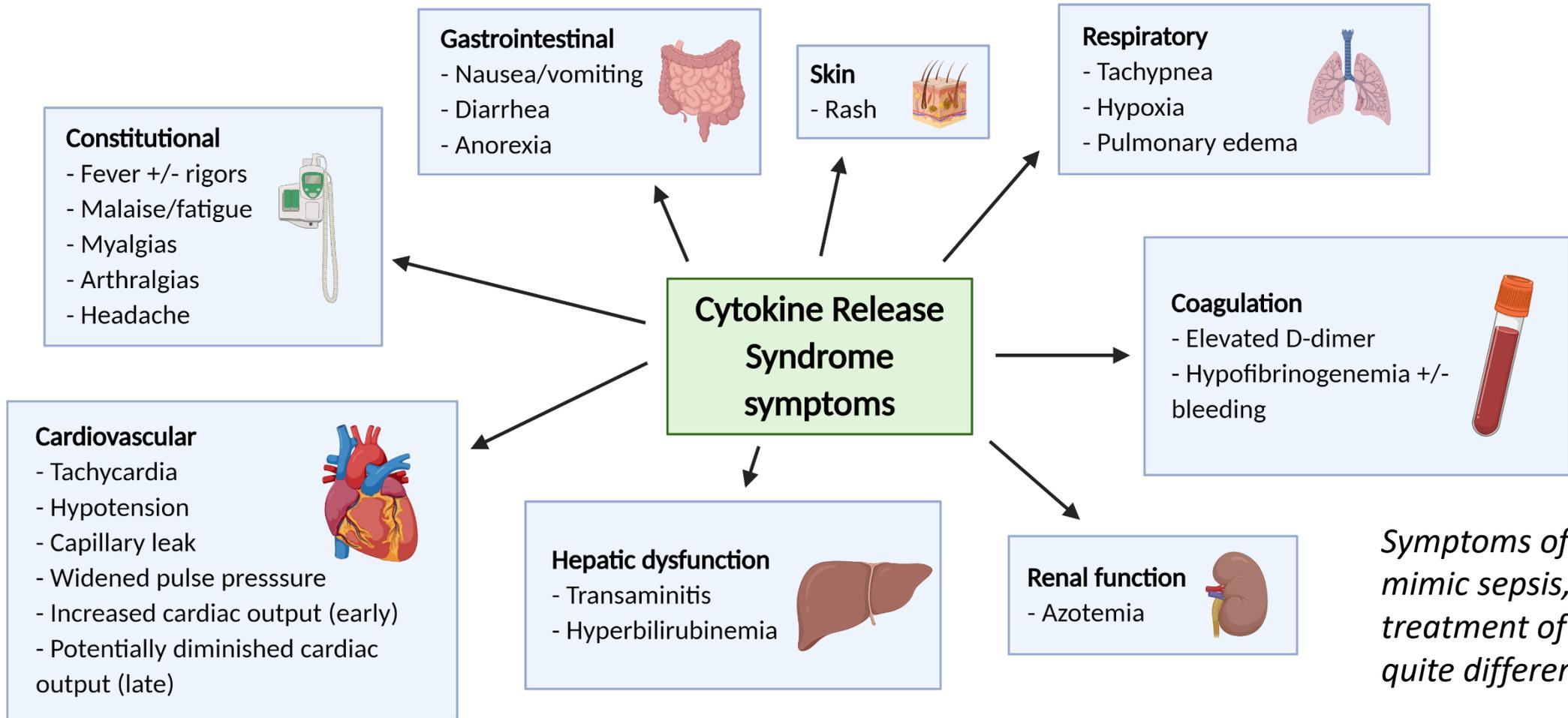
Trial	Indication	Treatment(s)	ORR	Landmark OS	Grade 3+ toxicity rates
ZUMA-2	R/R mantle cell lymphoma	Brexucabtagene autoleucel (KTE-X19)	86% CRR: 57%	1-year: 86%	CRS: 18% NE: 46%
ZUMA-1	Refractory large B cell lymphoma	Axicabtagene ciloleucel	83% CRR: 58%	2-year: 50%	CRS: 11% NE: 32%
JULIET	R/R diffuse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

# 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



# 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
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 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

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<sup>1†</sup>, Michael R. Bishop<sup>2†</sup>, Rafat Abonour<sup>3</sup>, Kenneth C. Anderson<sup>4</sup>, Stephen M. Ansell<sup>5</sup>, David Avigan<sup>6</sup>, Lisa Barbarotta<sup>7</sup>, Austin John Barrett<sup>8</sup>, Koen Van Besien<sup>9</sup>, P. Leif Bergsagel<sup>10</sup>, Ivan Borrello<sup>11</sup>, Joshua Brody<sup>12</sup>, Jill Brufsky<sup>13</sup>, Mitchell Cairo<sup>14</sup>, Ajai Chari<sup>12</sup>, Adam Cohen<sup>15</sup>, Jorge Cortes<sup>16</sup>, Stephen J. Forman<sup>17</sup>, Jonathan W. Friedberg<sup>18</sup>, Ephraim J. Fuchs<sup>19</sup>, Steven D. Gore<sup>20</sup>, Sundar Jagannath<sup>12</sup>, Brad S. Kahl<sup>21</sup>, Justin Kline<sup>22</sup>, James N. Kochenderfer<sup>23</sup>, Larry W. Kwak<sup>24</sup>, Ronald Levy<sup>25</sup>, Marcos de Lima<sup>26</sup>, Mark R. Litzow<sup>27</sup>, Anuj Mahindra<sup>28</sup>, Jeffrey Miller<sup>29</sup>, Nikhil C. Munshi<sup>30</sup>, Robert Z. Orlowski<sup>31</sup>, John M. Pagel<sup>32</sup>, David L. Porter<sup>33</sup>, Stephen J. Russell<sup>5</sup>, Karl Schwartz<sup>34</sup>, Margaret A. Shipp<sup>35</sup>, David Siegel<sup>36</sup>, Richard M. Stone<sup>4</sup>, Martin S. Tallman<sup>37</sup>, John M. Timmerman<sup>38</sup>, Frits Van Rhee<sup>39</sup>, Edmund K. Waller<sup>40</sup>, Ann Welsh<sup>41</sup>, Michael Werner<sup>42</sup>, Peter H. Wiernik<sup>43</sup> and Madhav V. Dhodapkar<sup>44\*</sup>

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**Position article and guidelines**



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

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

# Acknowledgements

- Some figures created using Biorender.com

# Case Study

# Case Study

KC is a 20 year old female diagnosed with Ph-negative B acute lymphoblastic leukemia. The CD34+ blasts population is positive for CD19 and CD22. She underwent induction chemotherapy with hyperCVAD induction chemotherapy and achieved morphologic remission. Measurable residual disease testing revealed 1.74% B-ALL. Her weight is 68 kg. What would be a reasonable treatment plan for KC?

- A. Option 1 (recommend blinatumomab 28 mcg/kg continuous infusion for 28 days)
- B. Option 2 (recommend blinatumomab 9 mcg/kg Day 1-7 followed by 28 mcg/kg for Day 8-28)
- C. Option 3 (recommend CD19 directed CAR T cell therapy)

# Case Study continued

KC, the 20 year old female with MRD positive disease, proceeds with blinatumomab with MRD dosing. After Cycle 1, she reports neck lymphadenopathy and axillary LAD which was biopsied showing recurrent/persistent B cell ALL. Flow cytometry showed a population of blasts expressing CD10, CD19, CD20, partial CD34, CD38, HLA-DR and TdT. What would you consider for her next treatment option?

- A. continue with blinatumomab for a second cycle
- B. plan for bridging chemotherapy and proceed with CD19 directed CAR T cell therapy
- C. proceed with allogeneic stem cell transplant
- D. proceed with inotuzumab therapy