

Immunotherapy for the Treatment of Hematologic Malignancies

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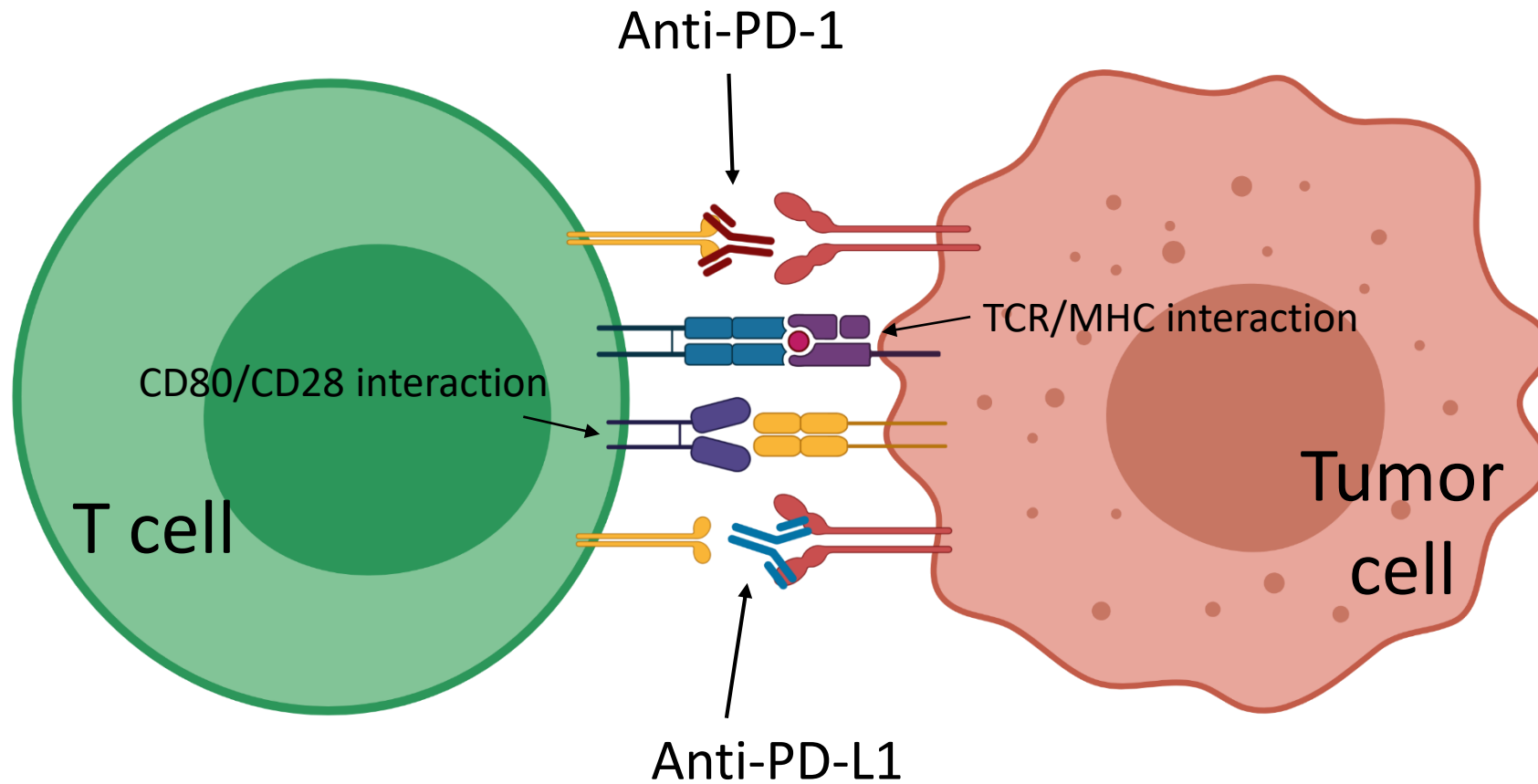
Disclosures

- No relevant financial relationships to disclose
- 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 , relapsed after HSCT and brentuximab vedotin or ≥ 3 previous therapies	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Adult relapsed/refractory classical Hodgkin lymphoma Pediatric refractory cHL or cHL relapsed after ≥ 2 lines of therapy	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 PMBCL 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%
		Brentuximab vedotin after auto-HCT cHL	68%	13%	1-year: 93%
		Brentuximab 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	PMBCL with relapse/ineligible for ASCT	48%	33%	1-year: 65%
KEYNOTE-170	Pembrolizumab	PMBCL ineligible for ASCT with progression on ≥ 2 previous therapies	45%	13%	1-year: 58%

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

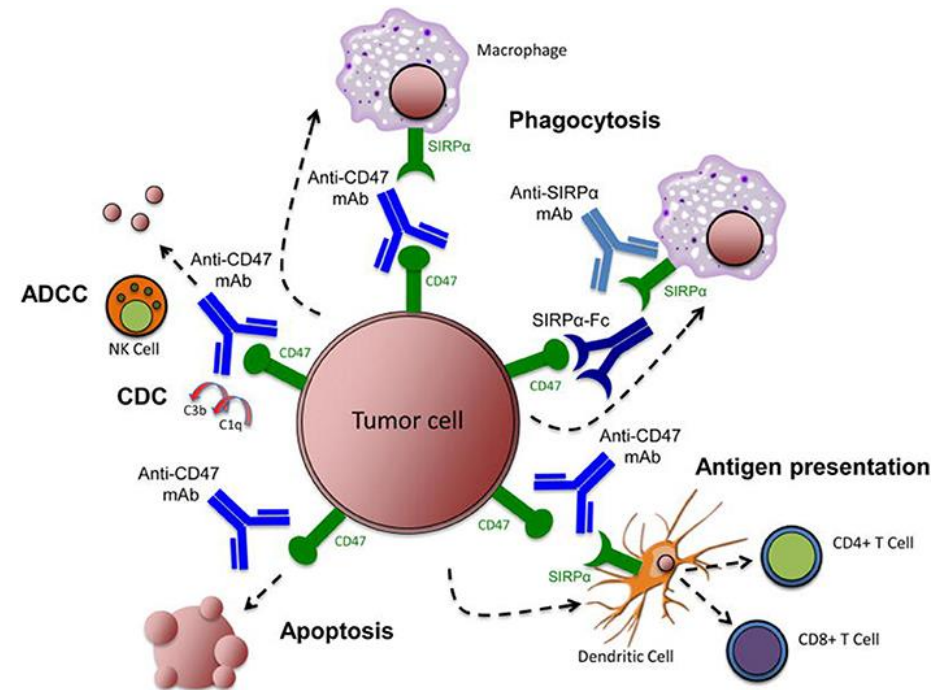
In development: Immune checkpoint inhibitors in AML

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, ≥ 65 years of age		70.5%	13.1	

In development: Macrophage checkpoint: CD47

Treatment	Populations	ORR	CRR	Median DOR
Azacitidine + magrolimab	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

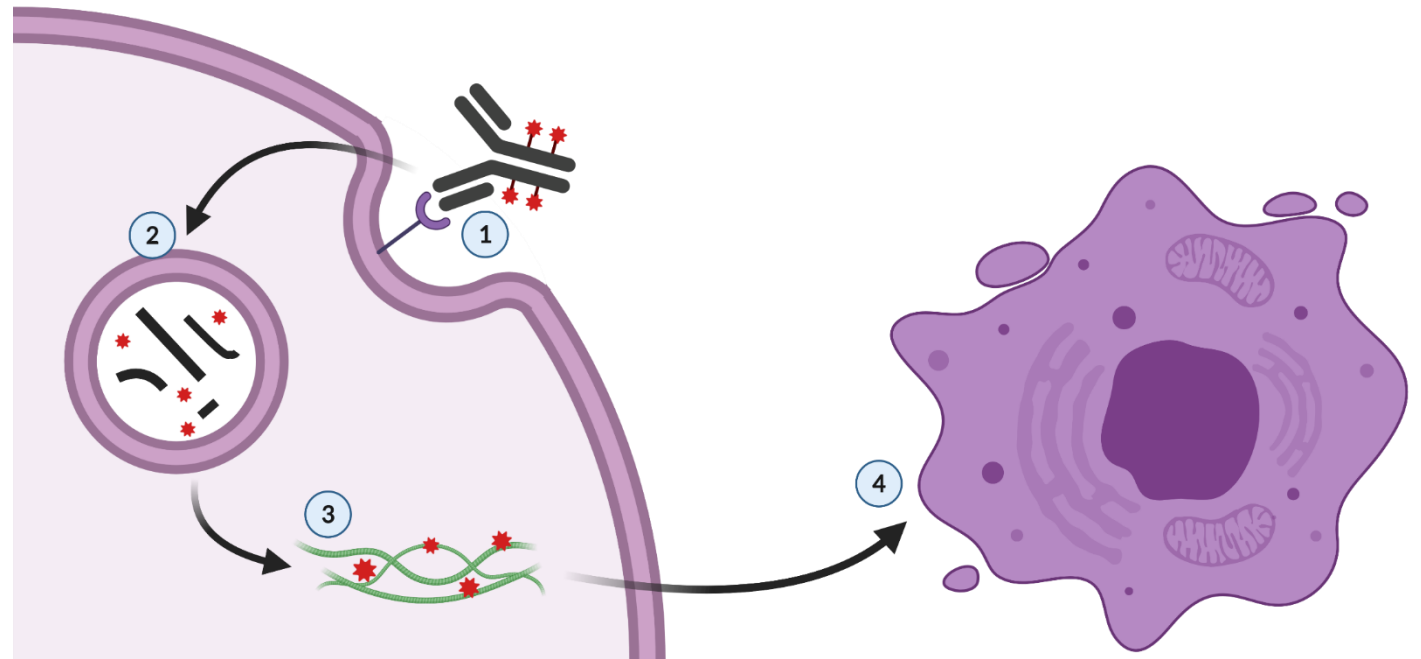


Outline

- 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	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

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 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 acute myeloid leukemia	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

In development: Novel ADCs in clinical trials

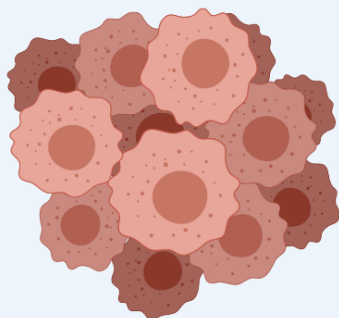
Trial	Indication	Treatment(s)	ADC target antigen	Phase
NCT03544281	R/R multiple myeloma	GSK2857916 + lenalidomide + dexamethasone	BCMA	2
		GSK2857916 + bortezomib + dexamethasone		
NCT03386513	CD123+ AML, BPDCN or ALL	IMGN632	CD123	1/2
NCT03424603	R/R B cell malignancies	STRO-001	CD74	1
NCT03682796	R/R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

Outline

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

Bispecifics in immunotherapy

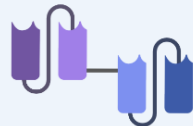
Target 1: Tumor



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

Immune cell engagers

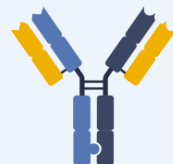
Bispecific killer
cell engagers



Bispecific T cell
engagers



Bispecific
antibodies



Nanobody-scFv

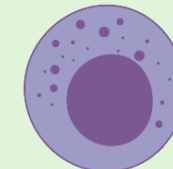


Target 2: Immune cell

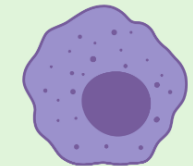
T cells



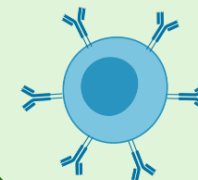
NK cells



Macrophages



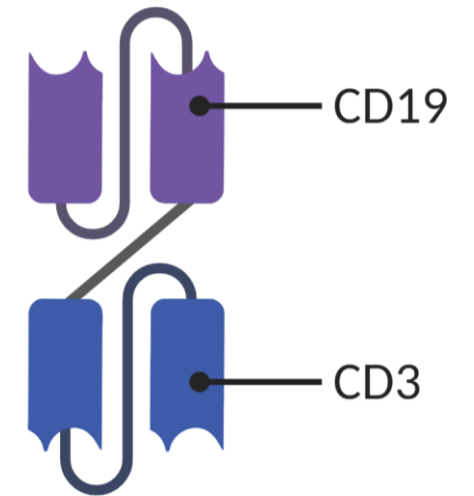
B cells



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

Clinical use of immune cell engagers

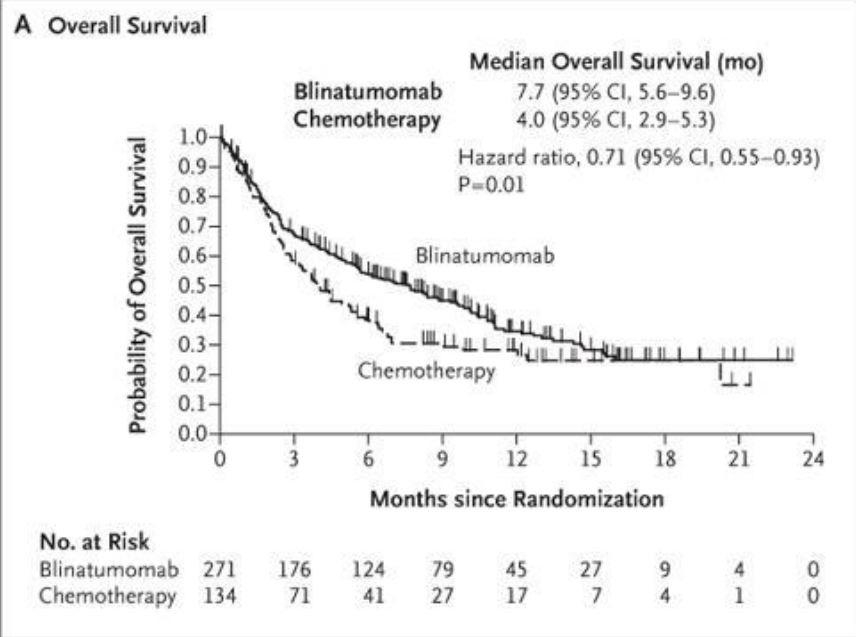
Drug	Indications
Blinatumomab	Relapsed/refractory B-ALL
	B-ALL in 1 st or 2 nd complete response with MRD \geq 0.1%



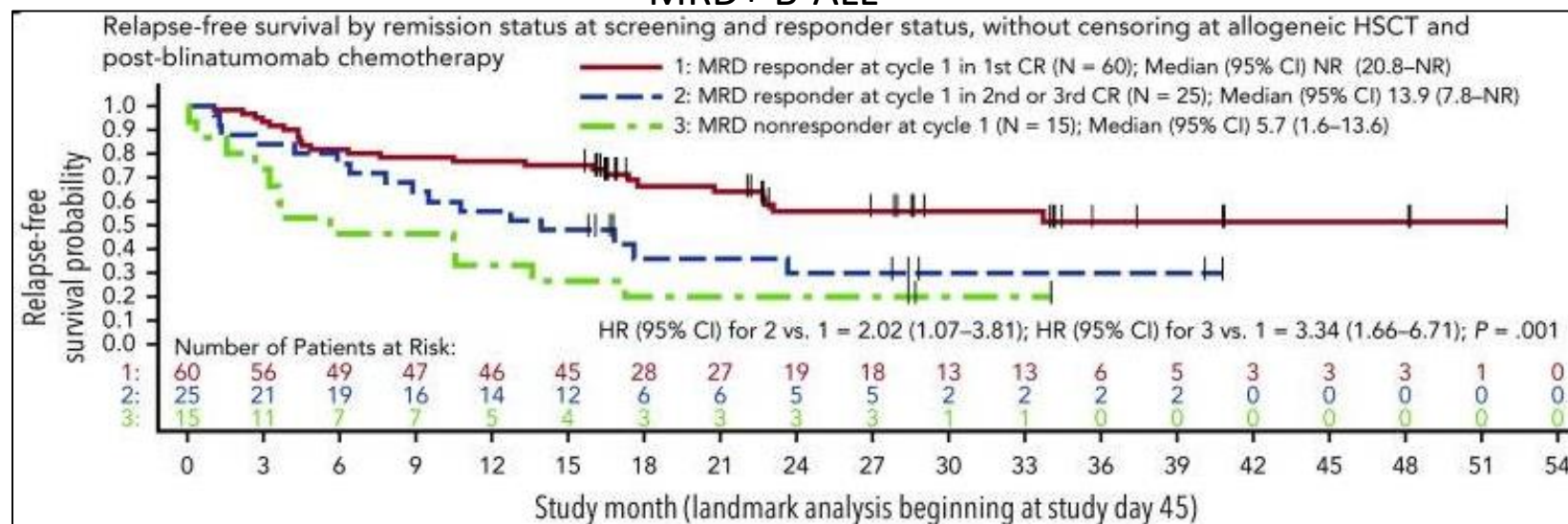
Blinatumomab in R/R B-ALL

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

R/R B-ALL



MRD+ B-ALL

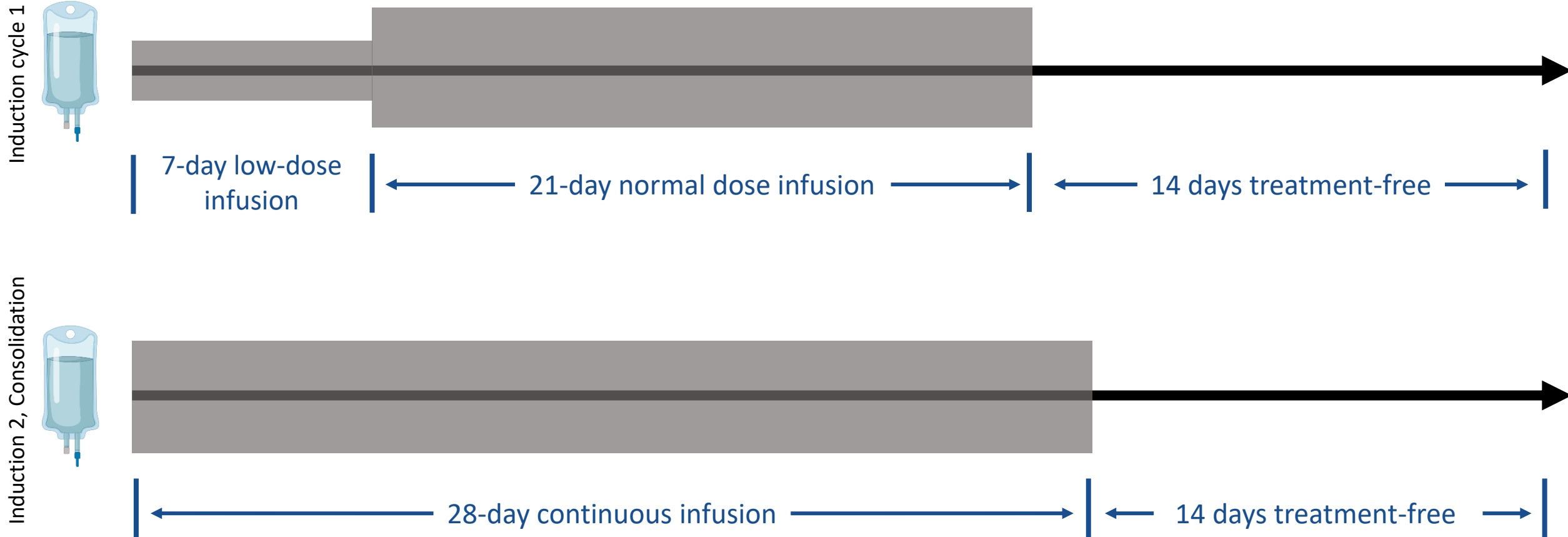


Dosing regimens for blinatumomab

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 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

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 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

Dosing regimens for blinatumomab – R/R B-ALL



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

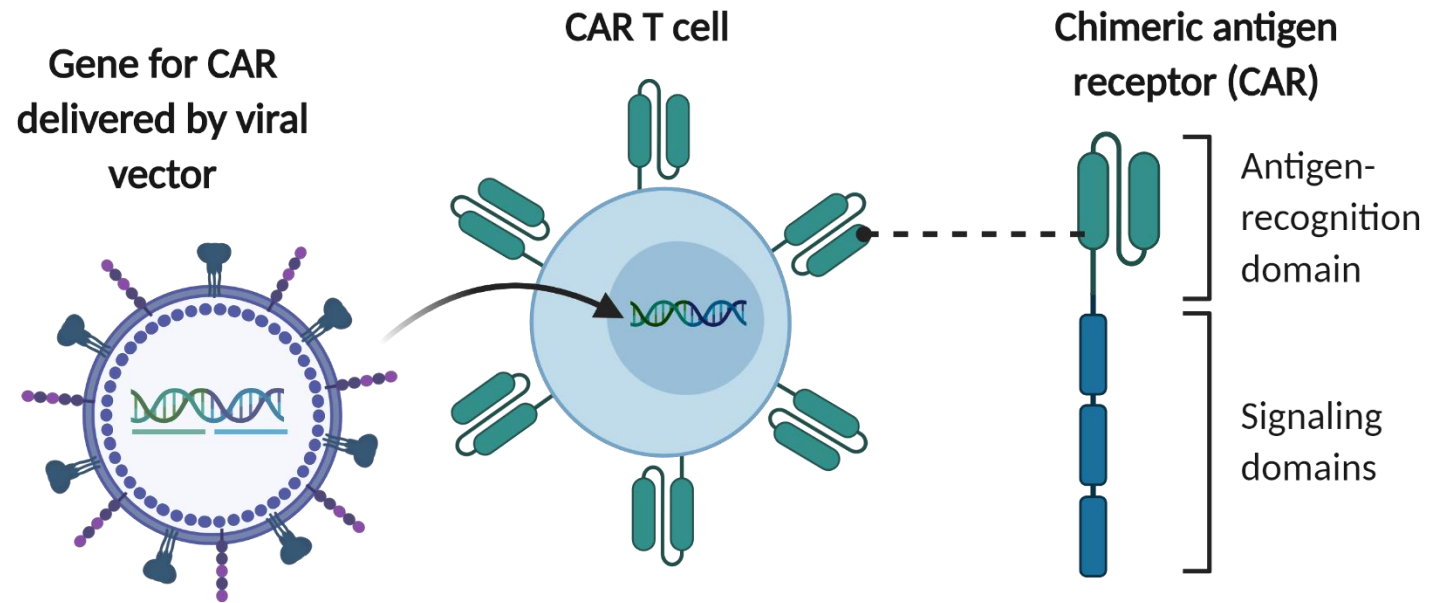
- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Comparing T cell engagers and CAR T therapy

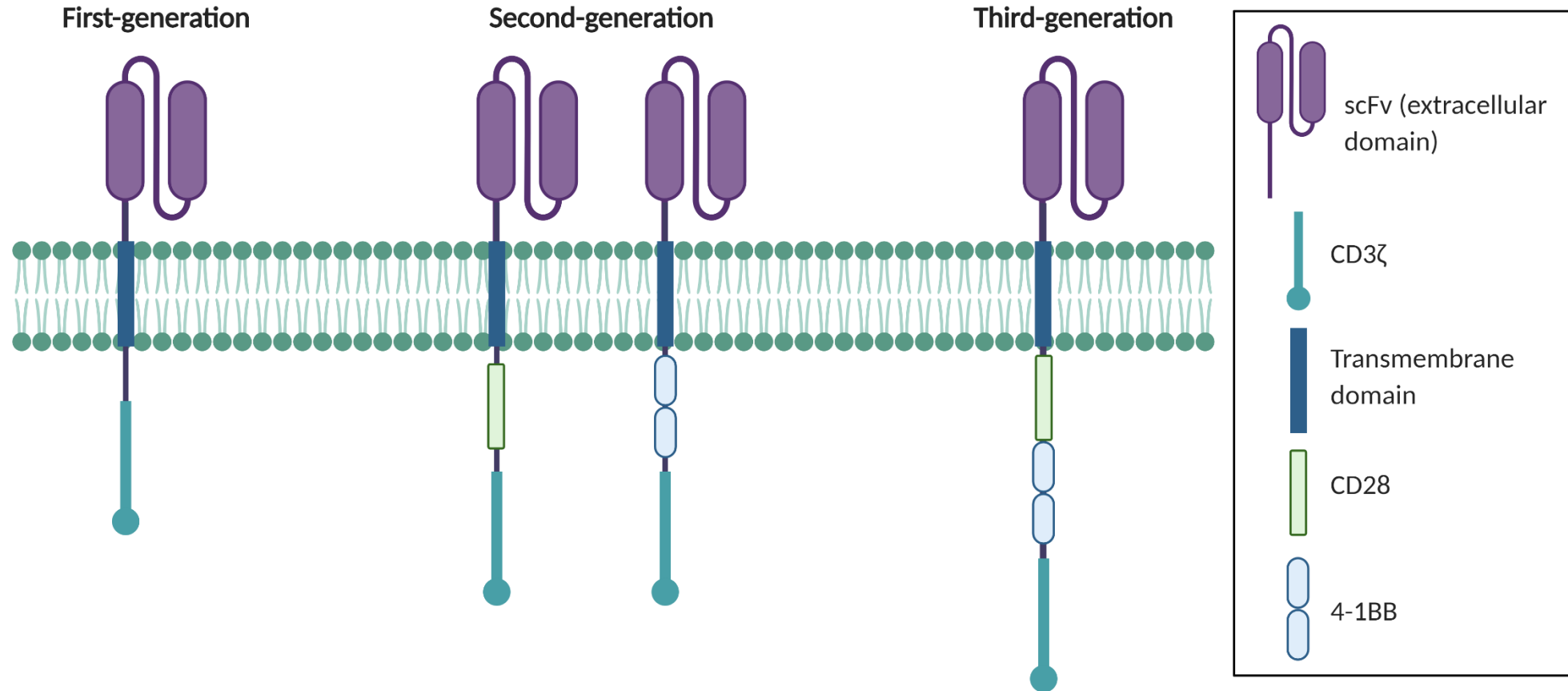
	CAR T cells	T cell engagers (BiTEs)
Structure	Synthetic gene construct encoding an scFv against tumor antigen linked to activation/costimulatory motifs	Recombinant protein with two specificities: one for tumor antigen and one for T cell antigen (usually CD3)
Effector cell types	Engineered CD8+ and CD4+ 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”

Chimeric antigen receptors

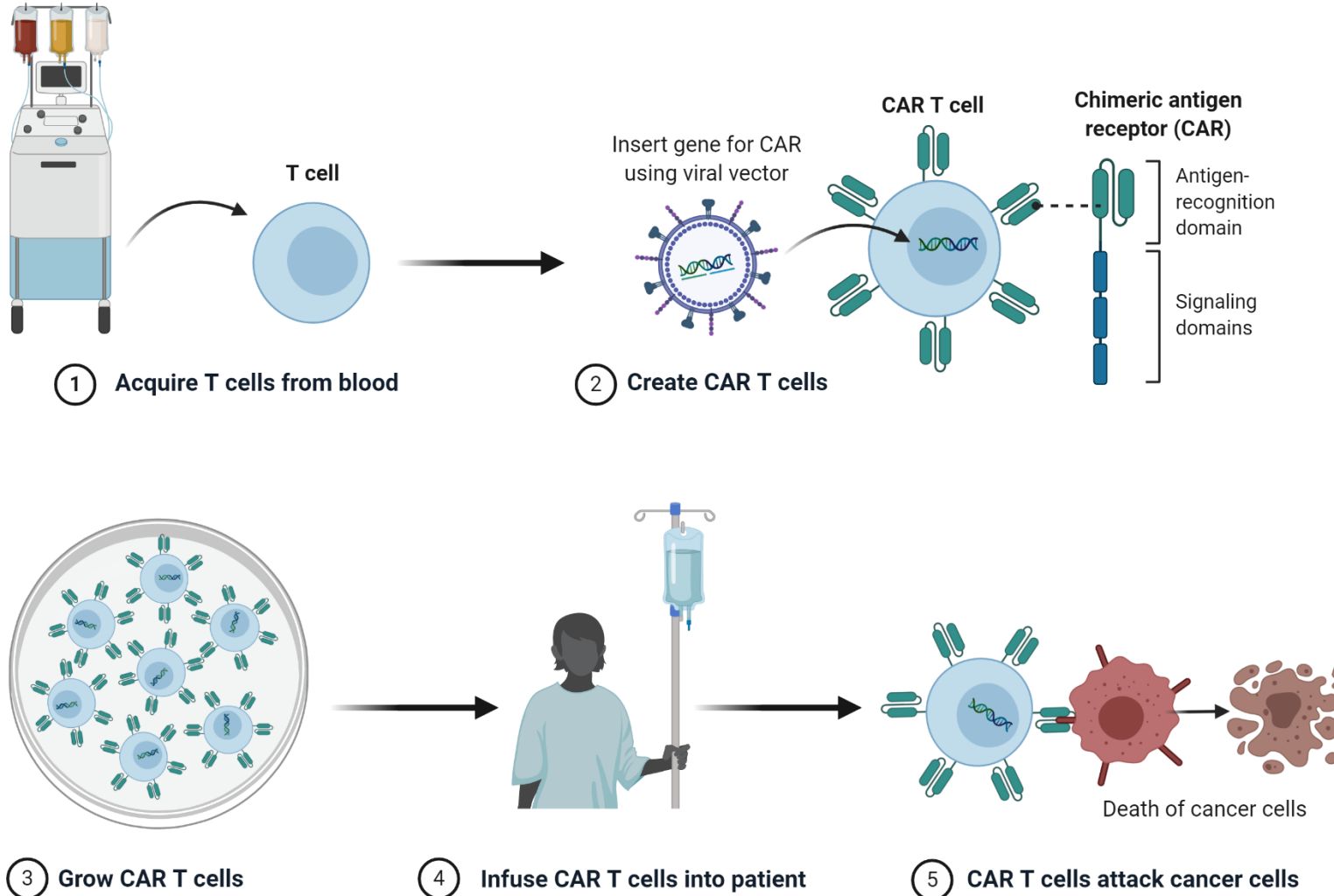
- Overcome immune tolerance
- Targets surface molecules in native conformation
- Independent of antigen presenting cell and MHC complex



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-cell lymphoma , 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	2×10^6 CAR-positive, viable T cells per kg bodyweight (up to 2×10^8)
Tisagenlecleucel	CD19/4-1BB	Patients ≤ 25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse	$0.2\text{--}0.5 \times 10^6$ CAR-positive, viable T cells per kg if under 50 kg $0.1\text{--}2.5 \times 10^8$ 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	$0.6\text{--}6.0 \times 10^8$ 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	2×10^6 CAR-positive, viable T cells per kg bodyweight (up to 2×10^8)
Lisocabtagene maraleucel	CD19/4-1BB	Adults with R/R large B-cell lymphoma after at least 2 prior therapies	$50\text{--}110 \times 10^6$ CAR-positive viable T cells (1:1 CD4:CD8)
Idecabtagene vicleucel	BCMA/4-1BB	Adults with R/R multiple myeloma after 4+ prior therapies	$300\text{--}460 \times 10^6$ 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%
TRANSCEND NHL 001	R/R B cell lymphoma	Lisocabtagene maraleucel	73% CRR: 53%	1-year: 58%	CRS: 2% NE: 10%
KarMMA	R/R multiple myeloma	Idecabtagene vicleucel	72% CRR: 28%	1-year: 78%	CRS: 9% NE: 4%

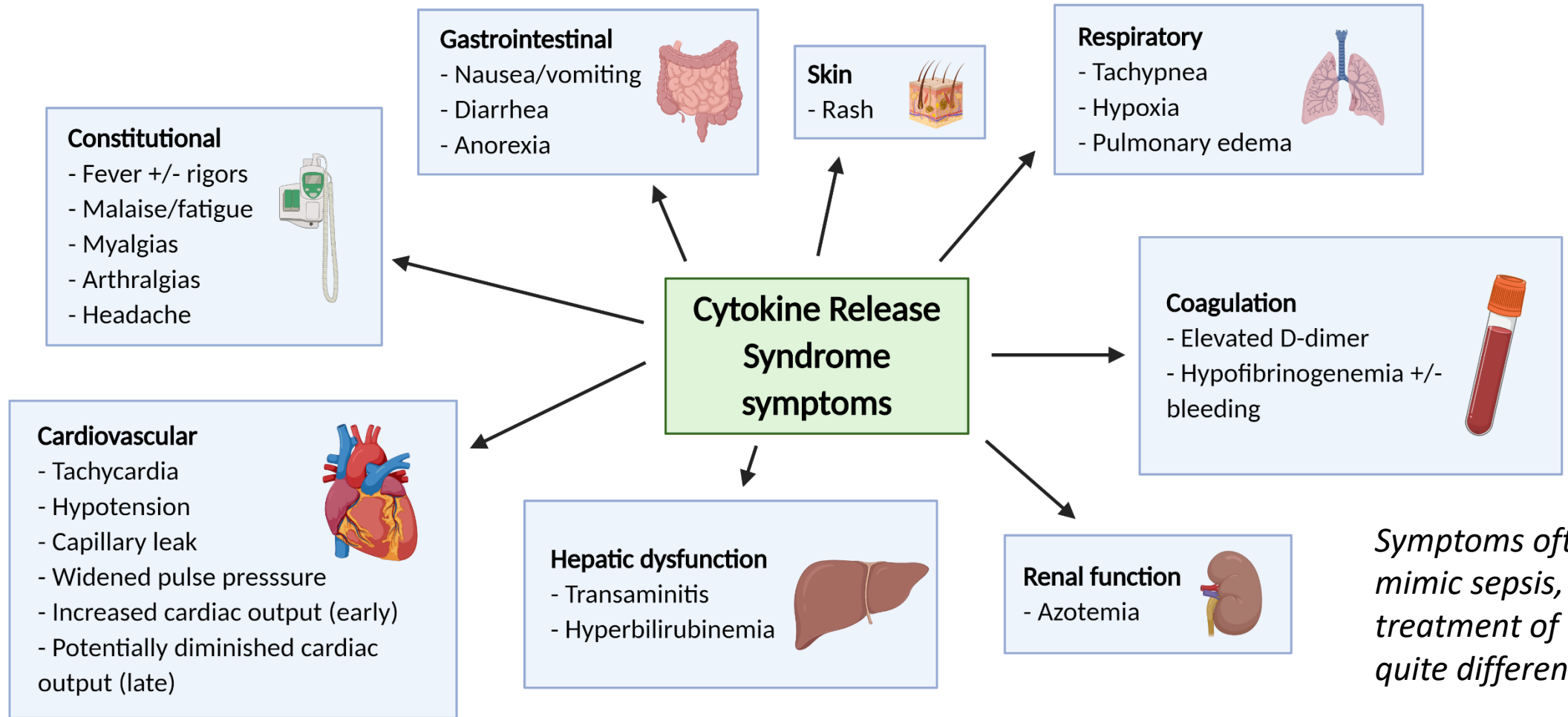
Wang, ASH 2019; Locke, Lancet Oncol 2019; Schuster, N Engl J Med 2019; Grupp, Biol Blood Mar Trans 2019; Abranson, Lancet 2020; Munshi N Engl J Med 2021.

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, including multiple myeloma; patient selection and toxicity management still concerns

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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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Position article and guidelines



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

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- Some figures created using Biorender.com

Case Studies

Case 1

64M presented with B symptoms and was found to have a rectal mass consistent with Stage IVB DLBCL (EBV+, CD30+) in late 2018. He completed 6 cycles of R-CHOP in May 2019. Follow up PET CT showed enlarging inguinal nodes and enlarging rectal mass. He received ICE chemotherapy x 2 cycles as a bridge to CAR-T (axi-cel). He receives conditioning with fludarabine and cyclophosphamide. On Day 2, he develops fatigue, cough, and mild dyspnea and his SaO2 is 89% which improves with supplemental oxygen. He is pancultured, including a respiratory viral panel and empirically started on broad spectrum antibiotics. CT chest shows no obvious pathology. On Day 4, his vitals are: 101.4F, HR: 115bpm, BP: 75/50mmHg, SaO2: 85% on 2L by NC.

He receives IVF resuscitation with minimal improvement in his pressure. Infectious work up remains negative. His antibiotic coverage is broadened, and he is admitted to the ICU for pressor support. On physical exam, he remains fully alert and oriented, without evidence of neurologic deficits. Labs show normal kidney and liver function.

What should be the next step in management?

- A. Etoposide
- B. Etoposide and Dexamethasone
- C. Tocilizumab
- D. Dexamethasone and Tocilizumab
- E. Dexamethasone

Case 1: C. Tocilizumab

- This patient is exhibiting symptoms of CRS due to high level immune activation.
- Symptom onset can be on day 2 and can occur up to 2 weeks after CAR-T infusion
- Treatment is based on grading of CRS:
 - Grade 1: Non–life-threatening and requires symptomatic treatment only. These include fever, nausea, fatigue, headache, myalgias, and malaise. Patients should be assessed and empirically treated for infections, along with aggressive supportive care.
 - Grade 2: Symptoms require and respond to moderate supportive interventions. These include oxygen requirement lower than 40 percent PaO2 or hypotension responsive to fluids or low dose of one vasopressor or grade 2 organ toxicity.
 - **Grade 3:** Symptoms require and respond to aggressive intervention. These include oxygen requirement higher than 40 percent PaO2 or hypotension requiring high dose or multiple vasopressors, or higher than grade 2 organ toxicity. Patients should receive tocilizumab (humanized, immunoglobulin G1 (IgG1) anti-human IL-6 receptor monoclonal antibody that prevents IL-6 binding to both cell-associated and soluble IL-6 receptors).
 - Grade 4: Life-threatening symptoms, requirement for ventilator support, or grade 4 organ toxicity (excluding transaminitis). Patients should receive tocilizumab and dexamethasone.

In this case, the patient has grade 3 CRS, and treatment with tocilizumab alone is warranted. Addition of steroids to tocilizumab (answer choice D) would be appropriate in a patient with grade 4 CRS. Treatment with etoposide, with or without steroids (answer choices A and B), would be reasonable in a patient with HLH — a distinct, but related, hyperinflammatory syndrome, which likely exists on a continuum with CRS and shares many of the same clinical and laboratory features. Dexamethasone alone (answer choice E) would not be optimal to control severe CRS.

Case 2

- After receiving 2 doses of tocilizumab, the patient's blood pressure stabilized, and he was taken off pressors and transferred back to the floors.
- On Day +8, he was noted to be confused and was oriented only to himself. He is unable to follow simple commands, write a sentence, or count backwards from 100.
- What is the most likely explanation for his symptoms?

Case 2

- A. CNS hemorrhage
- B. Stroke
- C. Neurotoxicity from CAR-T
- D. Seizure

C. CAR-T neurotoxicity

- The neurological toxicity is also referred to as Cell-Associated Neurotoxicity Syndrome (ICANS)
- This is the second most common adverse event post-CAR T-cell infusion and its incidence varies from 12-55% in literature.
- Time to onset is ~6 days after CAR-T infusion; however later presentations can sometimes occur
- The duration of symptoms is generally between 2 to 9 days; however prolonged presentations of ICANS sometimes occur.
- It may develop at the same time or following resolution of CRS but may occur without preceding CRS.

What would you do next?

- A. Order head imaging
- B. Obtain neurology consultation
- C. Evaluate for a seizure with an EEG
- D. Start Dexamethasone
- E. All of the above

E. All of the above

- Rapid recognition of neurotoxicity is important as is access to neurology expertise.
- Cross-sectional imaging should be obtained to rule out acute pathology including hemorrhage, stroke, etc.
- EEG should also be obtained to evaluate for seizures.
- Depending on the ICANS score , the patient should be started on dexamethasone
- ICE Score: 0=unarousable, 0-2: Grade 3 ICANS, 3-6: Grade 2 ICANS, 7-9: Grade 1 ICANS, 10: No impairment
 - Orientation: year, month, city, hospital (1 point each)
 - Naming: 3 objects (1 point each)
 - Following simple commands (1 point)
 - Writing: Ability to write a standard sentence (1 point)
 - Attention: Count backwards from 100 by 10 (1 point)