Pharmacotherapy Updates in Malignant Hematology

Bispecific Antibodies & CAR T-Cell Therapy

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MLS Oncology Pharmacotherapy Conference | May 20th, 2023

Baptist Health South Florida

https://alphatauri3d.com/2019/06/14/bispecific-antibodies-for-immuno-oncology/

Objectives & Outline

Understand the mechanism of action of CAR T-cell and bispecific antibody therapy

Review recent drug approvals and clinical trial data for CAR T-cell and bispecific antibody therapy for the treatment of various hematologic malignancies including multiple myeloma and lymphoma

Discuss the pharmacotherapeutic implications, including side effects, monitoring, cost, and place in therapy of CAR T-cell and bispecific antibody therapy

FDA Approved Therapies Timeline

2017

August:
Tisa-cel R/R B-cell ALL ≥2L → ELIANA

October:
Axi-cel R/R LBCL ≥2L → Zuma-1

2018

May:
Tisa-cel R/R LBCL ≥2L → JULIET

2020

July:
Brexu-cel R/R MCL → Zuma-2

2021

February:
Liso-cel R/R LBCL R/R LBCL ≥2L → TRANSCEND NHL

March:
Axi-cel R/R FL ≥2L → Zuma-5

March:
Ide-cel RRMM ≥4L → KarMMA

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Brexu-cel Adult R/R ALL → Zuma-3

2022

February:
Cilta-cel RRMM ≥4L → CARTITUDE-1

April:
Axi-cel R/R LBCL ≥1L → Zuma-7

May:
Tisa-cel R/R FL ≥2L →ELARA

June:
Liso-cel R/R LBCL ≥1 L →TRANSFORM

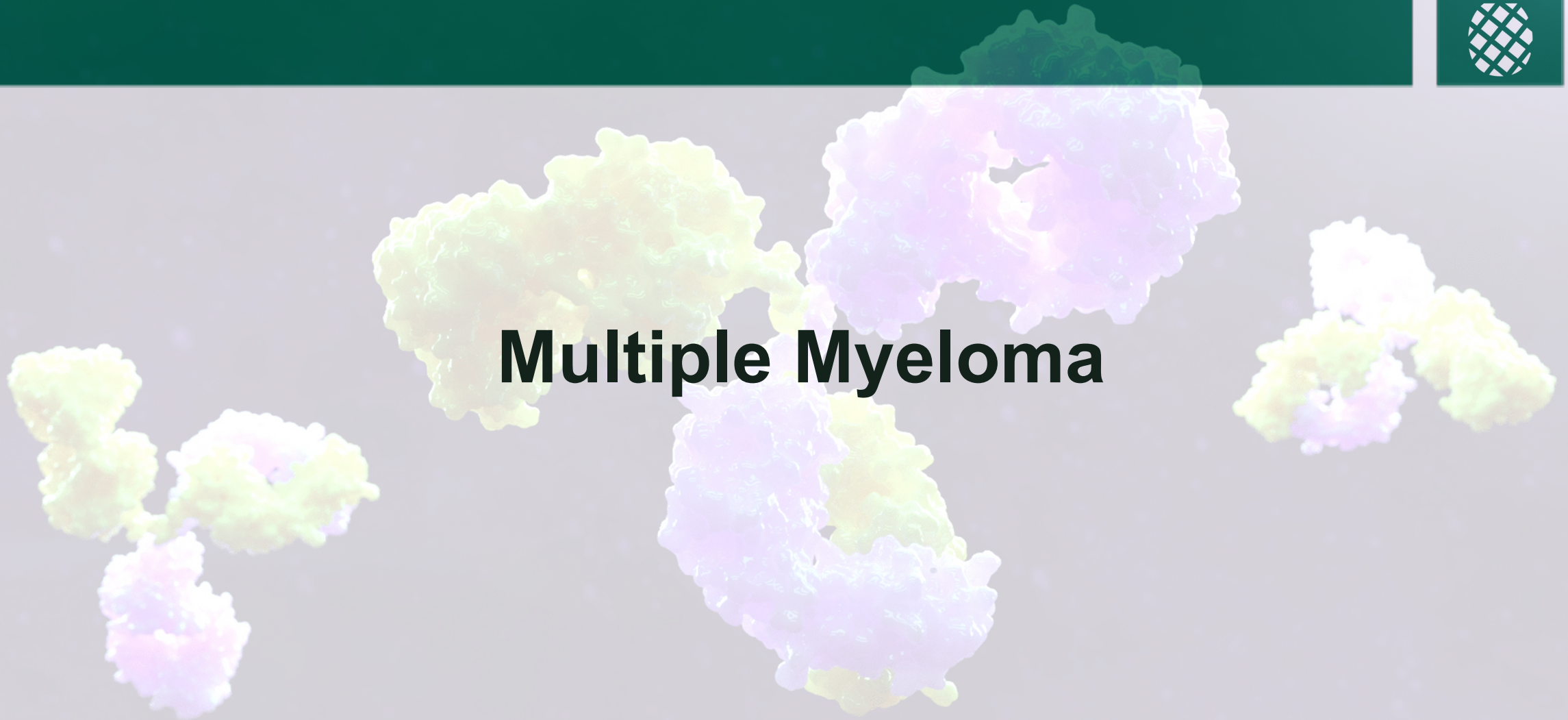
October:
Teclistamab-cqyv RR MM ≥4 L →MAJESTEC-1

October:
Mosunetuzumab-axgb R/R FL ≥2 L → GO29781

2L: two lines of therapy | FL: follicular lymphoma | RRMM: relapsed refractory multiple myeloma | LBCL: large B-Cell lymphoma | MCL: mantle cell lymphoma | ALL: acute lymphoblastic leukemia

Mosunetuzumab-axgb. Prescribing Information; December 2022.
Teclistamab-cqyv. Prescribing Information; October 2022.
Ciltacabtagene autoleucel. Prescribing Information; 2023
Axicabtagene ciloleucel. Prescribing Information; 2022
Lisocabtagene maraleucel. Prescribing Information; 2022
Tisagenlecleucel. Prescribing Information; 2022

Multiple Myeloma



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Multiple Myeloma

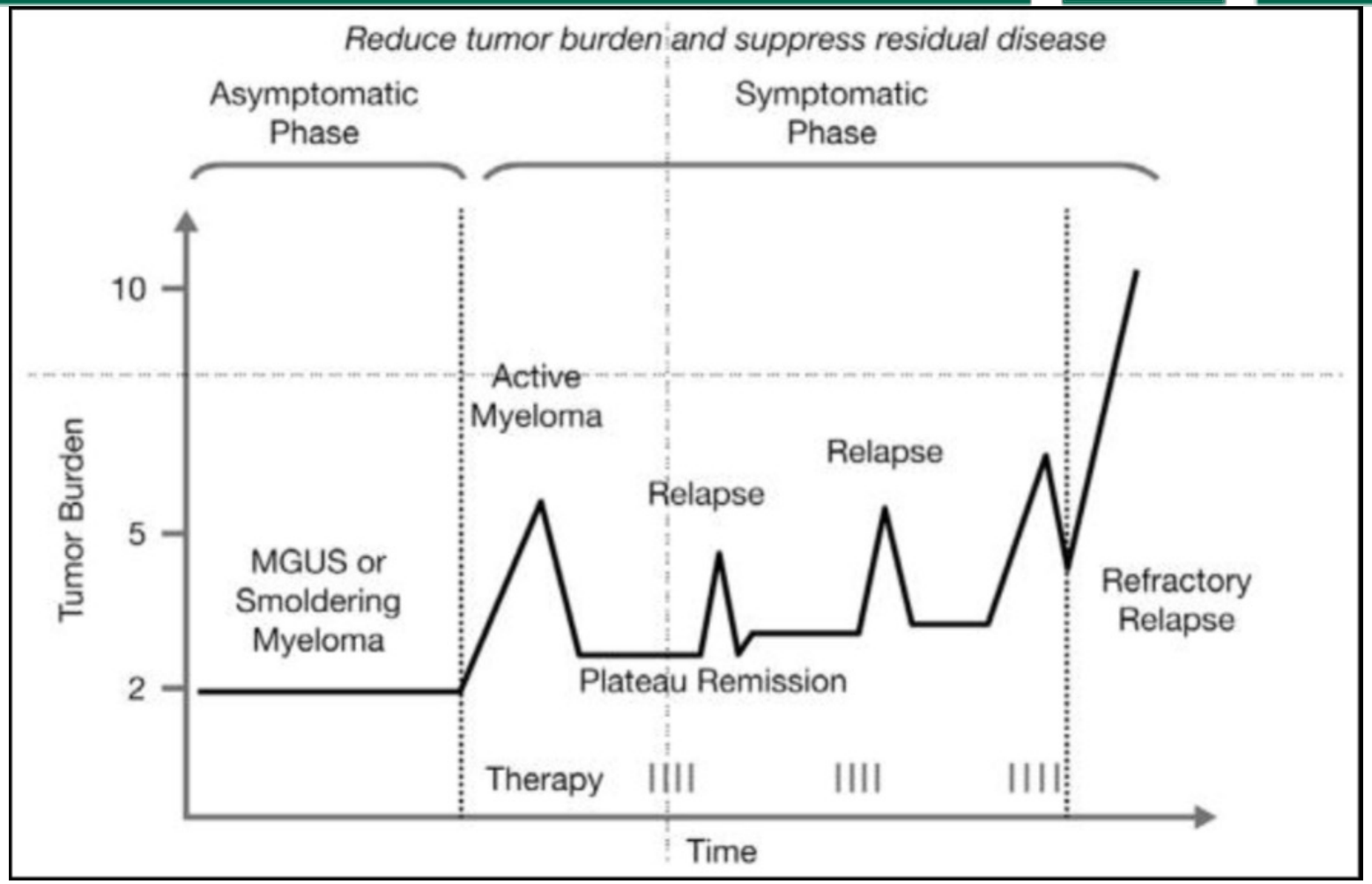
- Disease of plasma cells characterized by production of monoclonal proteins that have lost their function → proliferation of cells displaces normal cells from bone marrow
- Treatment modalities may include proteasome inhibitors, immunomodulatory drugs, anti-CD38 mAbs, and alkylating agents
- Incurable disease
- Patients who have disease that is refractory to anti-CD38 mAbs have a particularly poor prognosis:
  - Median PFS: 3.4 months
  - Median OS: 9.3 months
- Targeting BCMA
  - Antibody drug conjugates
  - CAR T-cell therapies
  - Bispecific antibodies

mAbs: monoclonal antibodies
PFS: progression free survival
OS: overall survival
BCMA: B-cell maturation antigen

Ghandi. *Leukemia*, Volume 33, (2019).

Multiple Myeloma - Incurable

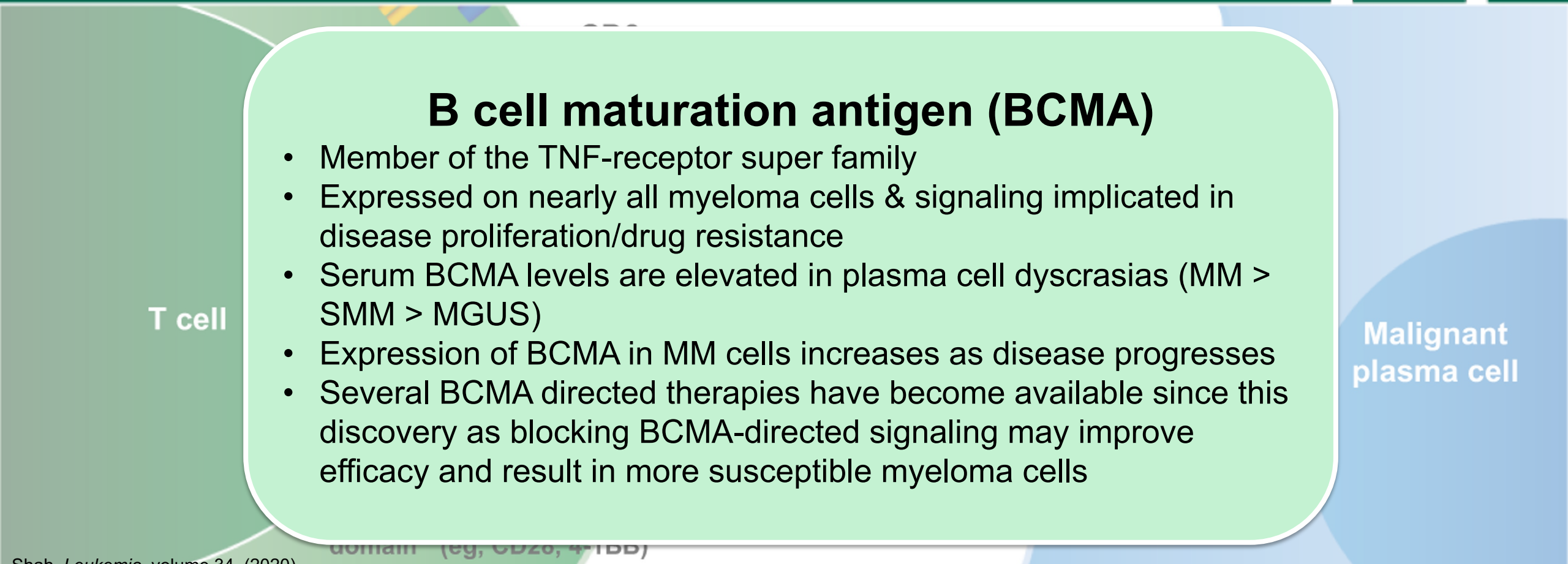
- Characteristic pattern of remission and relapse following conventional chemotherapy in multiple myeloma



Borrello. *Leuk Res*. 2012. vol. 36 Suppl 1,0 1 (2012): S3-12.

MGUS: monoclonal gammopathy of undetermined significance

Targeting BCMA on Malignant Plasma Cells



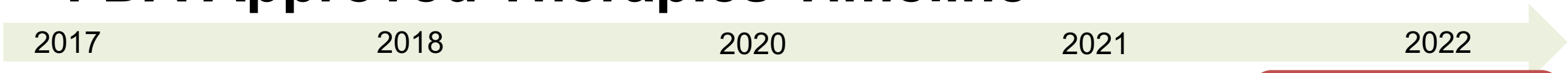
B cell maturation antigen (BCMA)

- Member of the TNF-receptor super family
- Expressed on nearly all myeloma cells & signaling implicated in disease proliferation/drug resistance
- Serum BCMA levels are elevated in plasma cell dyscrasias (MM > SMM > MGUS)
- Expression of BCMA in MM cells increases as disease progresses
- Several BCMA directed therapies have become available since this discovery as blocking BCMA-directed signaling may improve efficacy and result in more susceptible myeloma cells

Shah. *Leukemia*, volume 34, (2020).
Yang, et al. *J Hematol Oncol*. (2020)
Cho. *Front Immunol*. (2018).
Sanchez et al. *Clin Cancer Res*. 2016.
Ghermezi et al. *Haematologica.* 2017;102:785-795.

MM: multiple myeloma; SMM: smoldering myeloma;
MGUS: monoclonal gammopathy of undetermined significance
TNF: tumor necrosis factor.

FDA Approved Therapies Timeline



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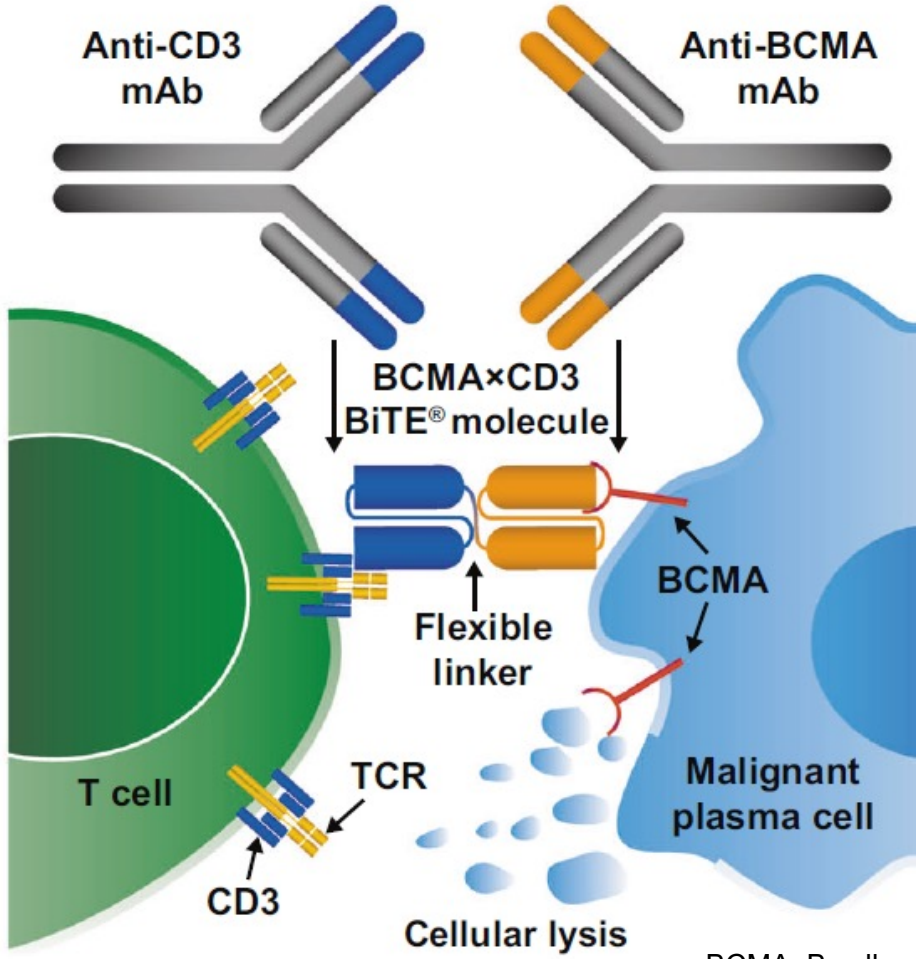
Tisagenlecleucel. Prescribing Information; 2022

Bispecific antibody - BCMA

- Human antibodies are monospecific i.e. recognize only one targeted antigen
- Bispecific antibodies simultaneously **target 2 antigens**
  - Contain 2 different antigen-binding sites in 1 molecule
- Directs immune cells to tumor cells and/or delivers drugs to tumors → activate endogenous immune cells
- T cells are the most common targets → CD3
  - Redirect autologous T lymphocytes to cell-surface antigens on cancer cells



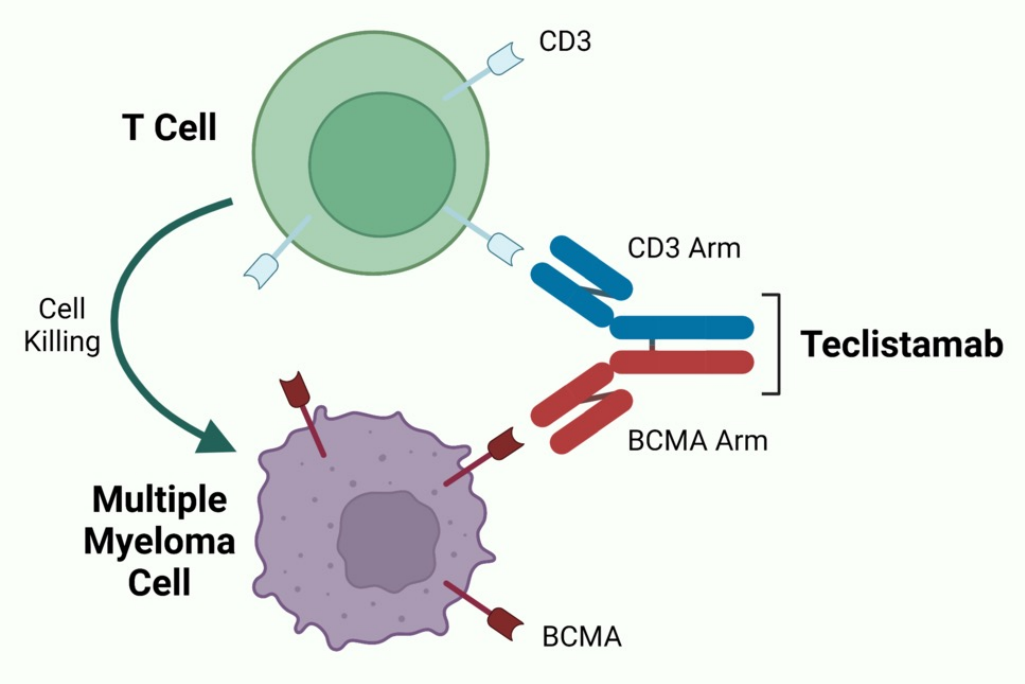
BCMA: B cell maturation antigen
TCR: T cell receptor
mAb: monoclonal antibody

Zhou et al. *Biomarker Research.* 2021; 9:38 ; Falchi L, et al. *Blood*. 2023;141(5):467-480.; Sedykh SE, et al. *Drug Des Devel Ther*. 2018;12:195-208; Shah. *Leukemia,* volume 34, (2020).

Teclistamab-cqyv

Bispecific BCMA directed T cell engager

- MOA
  - Binds CD3 and B-cell maturation antigen → actives T-cells → induces lysis of myeloma cells
  - Lysis occurs independent of tumor cell immune escape mechanisms
- Indication
  - Adult patients with RRMM after at least 4 prior lines of therapy including iMiD, PI, and anti-CD38 antibody
- First bispecific approved for MM



https://ogkologos.com/teclistamab-shows-promise-for-people-with-heavily-pretreated-multiple-myeloma/

Shah N, et al. *Leukemia*. 2020;34(4):985-1005
Teclistamab-cqyv. Prescribing Information; October 2022.

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MOA: Mechanism of action
RRMM: Relapsed/refractory multiple myeloma;
iMiD: immunomodulatory drug; PI: proteasome inhibitor;
MM: multiple myeloma; SMM: smoldering myeloma;
MGUS: monoclonal gammopathy of undetermined significance

MajestTEC-1

Phase 2 single arm, open-label, multicenter trial

- Inclusion: RRMM, previously received > 3 lines of prior therapy, progressive and measurable disease
  - Median prior lines of therapy: 5
  - 77% triple refractory; 27% penta refractory
- Previous BCMA targeted therapy excluded
- Safety:
  - CRS (all grade) in 72.1% of patients
    - Grade 3 in 0.6%
    - Grade 2 in 21.2%
    - Grade 1 in 50.3%
  - Neurotoxic events:14.5%
    - ICANS: 3%
  - Other ADRs: neutropenia, anemia, thrombocytopenia, infections

n=165

Median follow up: 14.1 months	ORR: 63%
Median DOR: 18.4 months	Median PFS: 11.3 mo OS: 18.3 mo
44 patients (27%) MRD negative	CR or better 32.7% VGPR or better: 58.8%

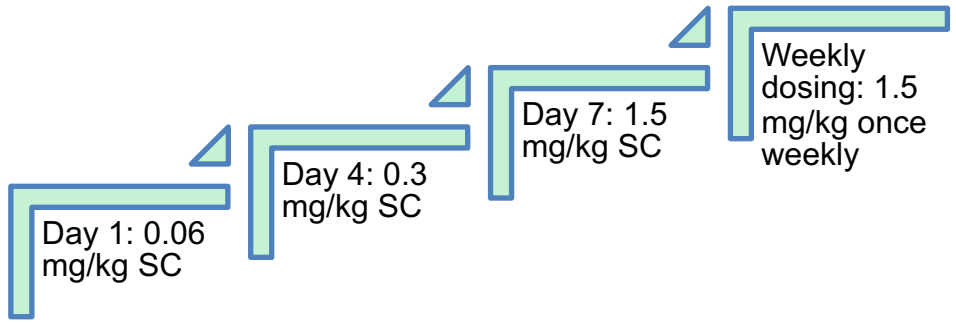
RRMM: Relapsed/refractory multiple myeloma; BCMA: B-cell maturation antigen ; CRS: Cytokine release syndrome; ICANS: Immune effector cell-associated neurotoxicity ; ORR: Overall response rate; OS: Overall survival; DOR: Duration of response; PFS: Progression-free survival; CR: Complete response; VGPR: Very good partial response; MRD: Minimal residual disease

Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505

Pharmacotherapy Considerations

Teclistamab-cqyv

- Subcutaneous administration
- Step up dosing required
  - Inpatient hospitalization required for 48 hours after all step up doses
- Pre-medication: CS, H1RA, antipyretic
  - Needed prior to all step up doses and first treatment dose
- Duration of therapy: until disease progression or unacceptable toxicity



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Teclistamab-cqyv. Prescribing Information; October 2022.

CS: Corticosteroid
H1RA: Histamine 1 receptor antagonist

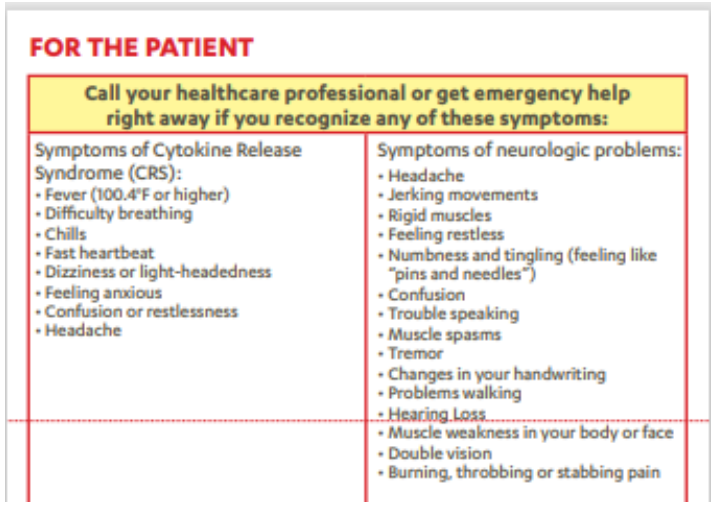
Pharmacotherapy Considerations

Teclistamab-cqyv

- **REMS** program due to CRS/neurologic toxicity
  - Prescribers: Knowledge assessment and enrollment
  - Patient counseling by prescriber is required and MUST provide wallet card to patient
  - Pharmacy/institution: Certification to dispense; must verify prescriber is certified

Black Box Warnings:

- ❑ CRS
- ❑ Neurologic toxicities



FOR THE PATIENT

Call your healthcare professional or get emergency help right away if you recognize any of these symptoms:

Symptoms of Cytokine Release Syndrome (CRS):	Symptoms of neurologic problems:
• Fever (100.4°F or higher) • Difficulty breathing • Chills • Fast heartbeat • Dizziness or light-headedness • Feeling anxious • Confusion or restlessness • Headache	• Headache • Jerking movements • Rigid muscles • Feeling restless • Numbness and tingling (feeling like "pins and needles") • Confusion • Trouble speaking • Muscle spasms • Tremor • Changes in your handwriting • Problems walking • Hearing Loss • Muscle weakness in your body or face • Double vision • Burning, throbbing or stabbing pain

Teclistamab-cqyv. Prescribing Information; October 2022.

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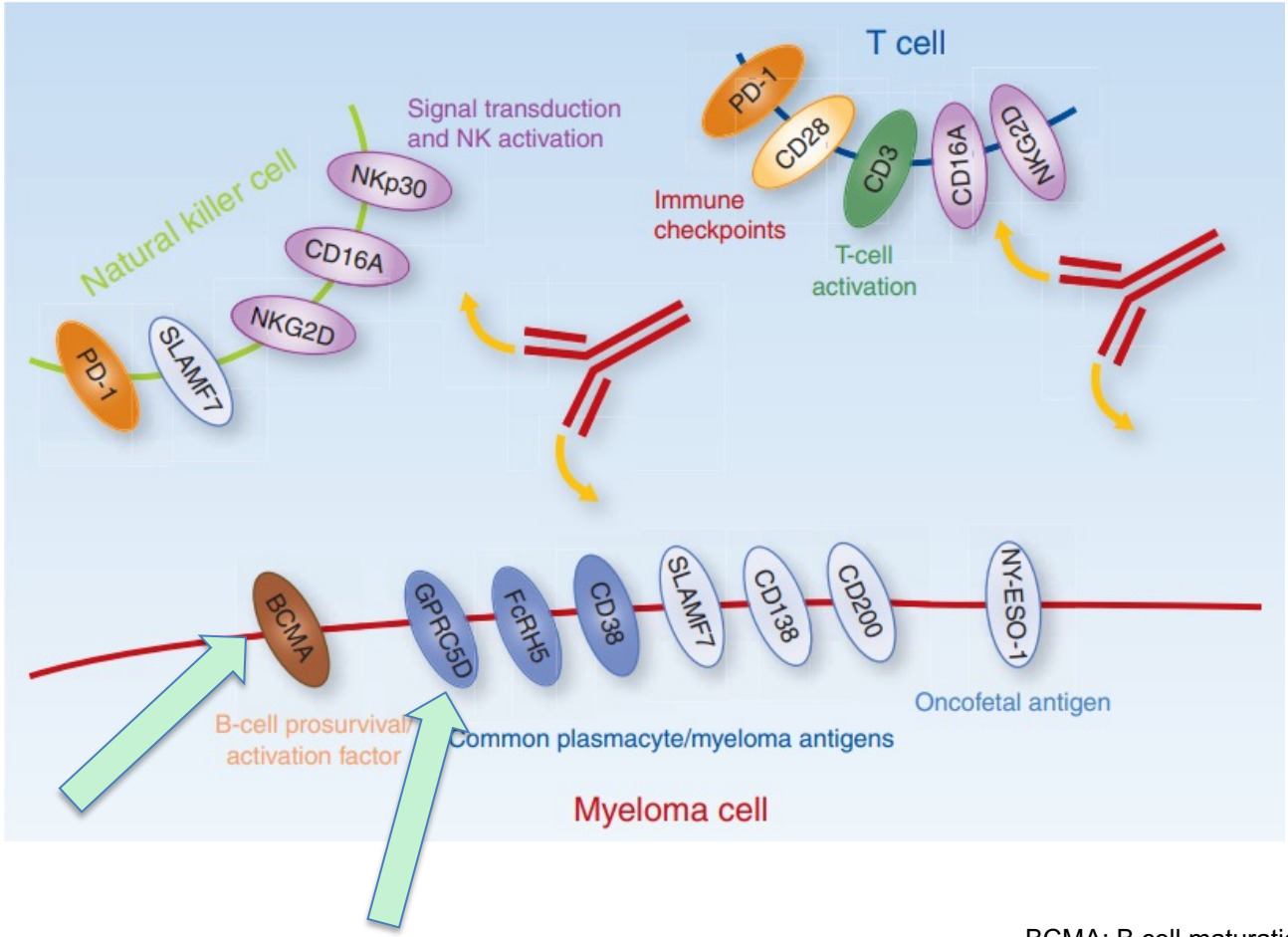
REMS: Risk Evaluation and Mitigation Strategies
CRS: Cytokine release syndrome

Bispecifics in the Pipeline

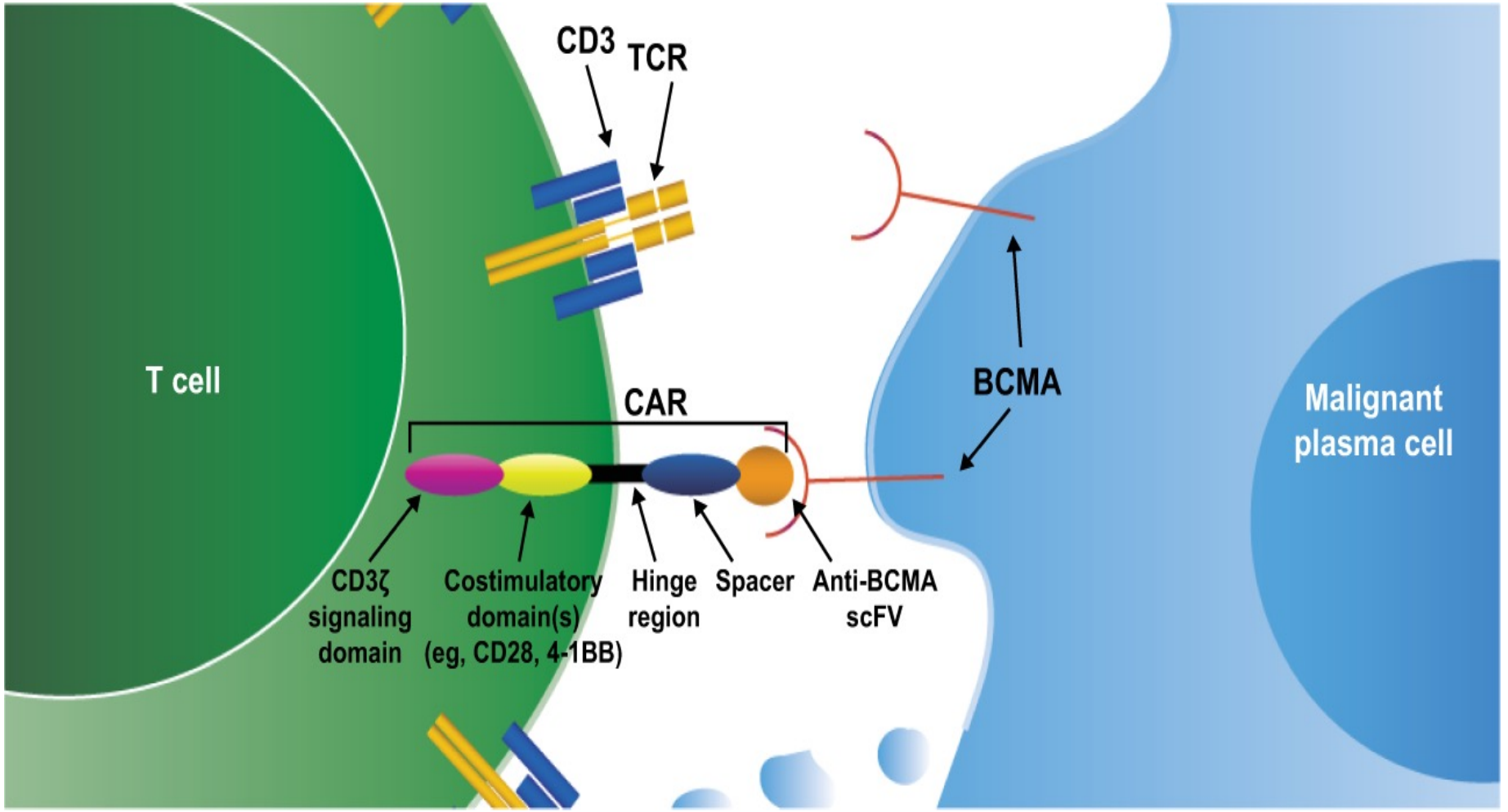
- Elranatamab – BCMA x CD3
- Linvoseltamab – BCMA x CD3
- Alnuctamab – BCMA x CD3
- Talquetamab - GPCR5D x CD3



https://clinicaltrials.gov/ct2/show/NCT05137054
https://clinicaltrials.gov/ct2/show/NCT03486067
Jakubowiak AJ et al. ASCO 2022. Abstract 8014.
Chari A, et al. *N Engl J Med* 2022; 387:2232-2244
Lancman G, et al. *Blood Cancer Discov*. 2021;2(5):423-433.

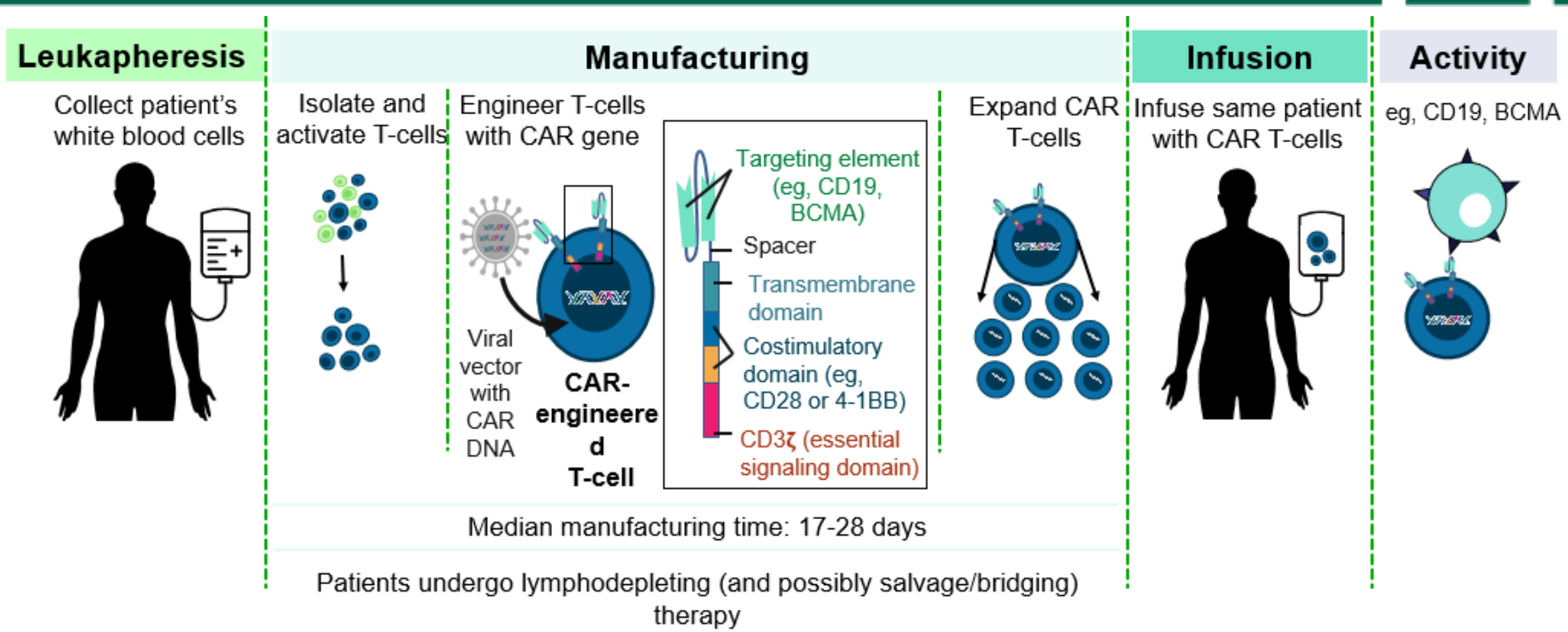
BCMA: B cell maturation antigen
GPCR5D:G protein-coupled receptor, class C group 5 member D

CAR T-cell - BCMA



Shah. *Leukemia*, volume 34, (2020).

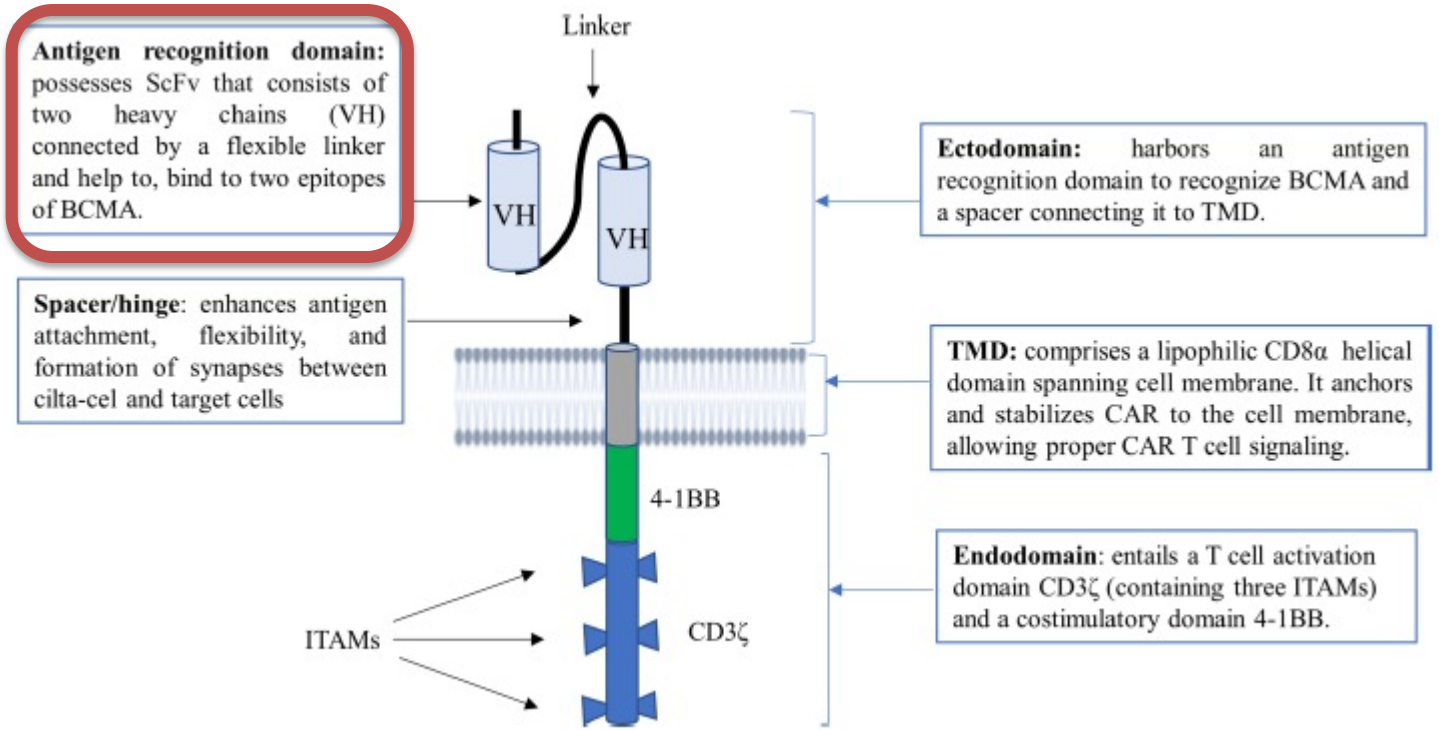
Autologous CAR T-Cell Therapy: Underlying Principles



Majors. Abstr PS1156. EHA, (2018); Lim. Cell. (2017); Sadelain. Nat Rev Cencer. (2003); Brentjens. Nat Med. (2003); Park. Abstr 682. ASH (2015); Axicabtagene ciloleucel. Prescribing Information; 2022; Tisagenlecleucel. Prescribing Information; 2022

Ciltacabtagene autoleucel (Cilta-cel)

- MOA
  - BCMA-directed genetically modified autologous T cell immunotherapy
- Indication/FDA approval
  - Adult patients with RRMM ≥ 4L, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
- LDC: Cy/Fu 300/30 mg/m² IV x 3 days
  - Infuse CAR T-cells 2-4 days after completion of LDC



Abebe et al. *Frontiers in Immunology* 13 (2022).
Ciltacabtagene autoleucel. Prescribing Information; 2023

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LDC: lymphodepleting chemotherapy

Cilta-cel → CARTITUDE -1

Phase 1b/2 multicenter, single arm, open label trial (n=113)

- Adult patients with RRMM who received ≥ 3 prior lines of therapy or were double refractory to a proteasome inhibitor and immunomodulatory drug and had received prior proteasome inhibitor, immunomodulatory drug, and anti-CD38 therapy
- Primary end point:
  - Phase Ib: Safety and confirmation of the recommended phase 2 dose
  - Phase 2: ORR
- Key secondary endpoints: duration of response and PFS

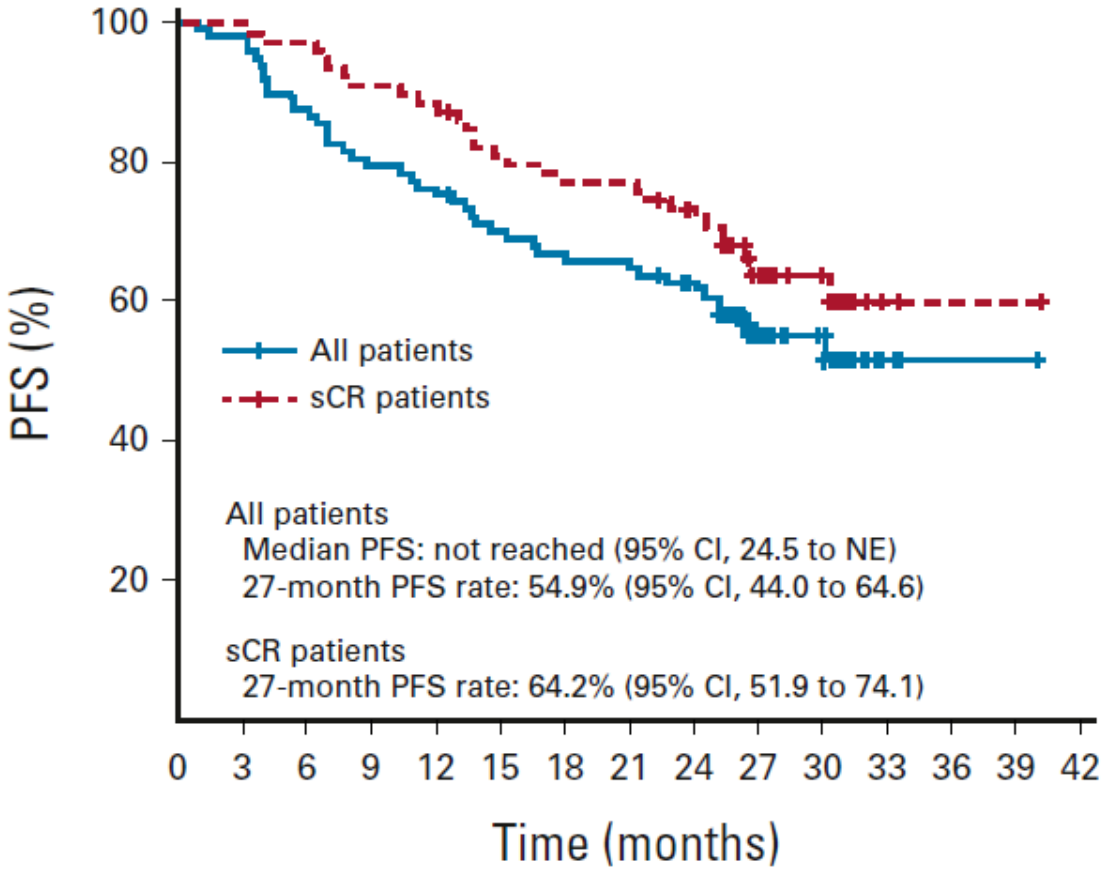
2-Yr Updated Results[2]	Ciltacabtagene Autoleucel (n = 97)
ORR, % ▪ sCR, % ▪ VGPR, % ▪ PR, %	97.9 82.5 94.9 3.1
Median PFS, mo (95% CI)	NR (24.5-NE)
27-mo PFS, %	54.9
27-mo OS, % (95% CI)	70.4% (60.1-78.6)
Median DOR	NR

VGPR: very good partial response
ORR: overall response rate
PFS: progression free survival
OS: overall survival
DOR: duration of response

1. Berdeja et al. Lancet 2021; 398: 314–24
2. Martin. J Clin Oncol 41, no. 6 (February 20, 2023) 1265-1274.

Cilta-cel → CARTITUDE -1

Phase 1b/2 multicenter, single arm, open label trial



No. at risk:

All patients	97	95	85	77	74	67	64	63	57	27	17	3	1	1	0
sCR patients	80	80	78	73	71	64	62	61	55	27	17	3	1	1	0

Martin. J Clin Oncol 41:1265-1274

ADRs of Special Interest
CARTITUDE-1

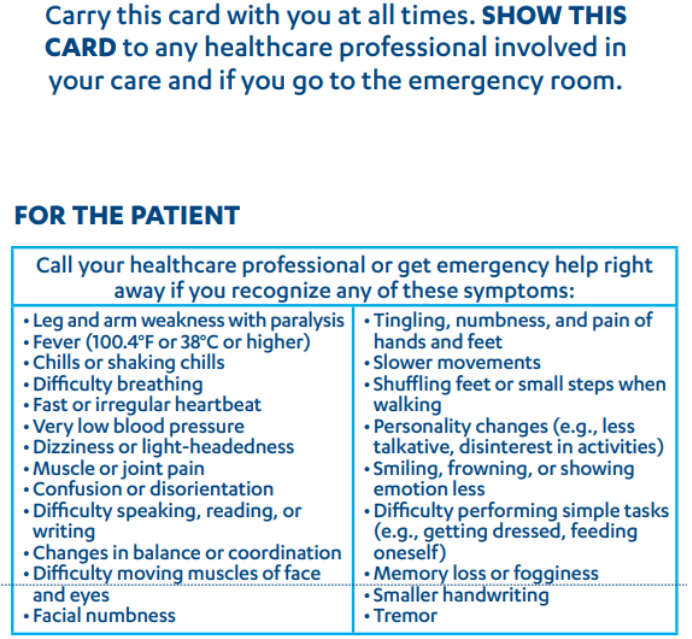
CARTITUDE-1[1,2]	Cita-cel (n= 97)
Grade ≥ 3 Any adverse event, %	94
Grade ≥ 3 CRS, %	5.1
• Time to onset in days, (range)	7 (5-8)
• Time to resolution / median duration in days	4 (3-6)
Tocilizumab use, %	69
Grade ≥ 3 NE, %	12.3
• Time to onset, (range)	8 (6-8)
• Time to resolution/median duration in days	4 (3-6.5)
Grade ≥ 3 Neutropenia, %	94.8
Grade ≥ 3 Anemia, %	68
Grade ≥ 3 Thrombocytopenia, %	59.8

1. Berdeja. Lancet. 92021);
2. Martin. J Clin Oncol 41:1265-1274

Pharmacotherapy Considerations
Cilta-cel

Black Box Warnings:

- ❑ CRS
- ❑ Neurologic toxicities
- ❑ Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome
- ❑ Prolonged cytopenias with bleeding and infection
- ❑ Must obtain agent via REMS Risk Evaluation and Mitigation Strategy
- ❑ Parkinsonism and Guillain-Barré syndrome



Carry this card with you at all times. **SHOW THIS CARD** to any healthcare professional involved in your care and if you go to the emergency room.

FOR THE PATIENT

Call your healthcare professional or get emergency help right away if you recognize any of these symptoms:

• Leg and arm weakness with paralysis • Fever (100.4°F or 38°C or higher) • Chills or shaking chills • Difficulty breathing • Fast or irregular heartbeat • Very low blood pressure • Dizziness or light-headedness • Muscle or joint pain • Confusion or disorientation • Difficulty speaking, reading, or writing • Changes in balance or coordination • Difficulty moving muscles of face and eyes • Facial numbness	• Tingling, numbness, and pain of hands and feet • Slower movements • Shuffling feet or small steps when walking • Personality changes (e.g., less talkative, disinterest in activities) • Smiling, frowning, or showing emotion less • Difficulty performing simple tasks (e.g., getting dressed, feeding oneself) • Memory loss or fogginess • Smaller handwriting • Tremor

Ciltacabtagene autoleucel. Prescribing Information; 2023

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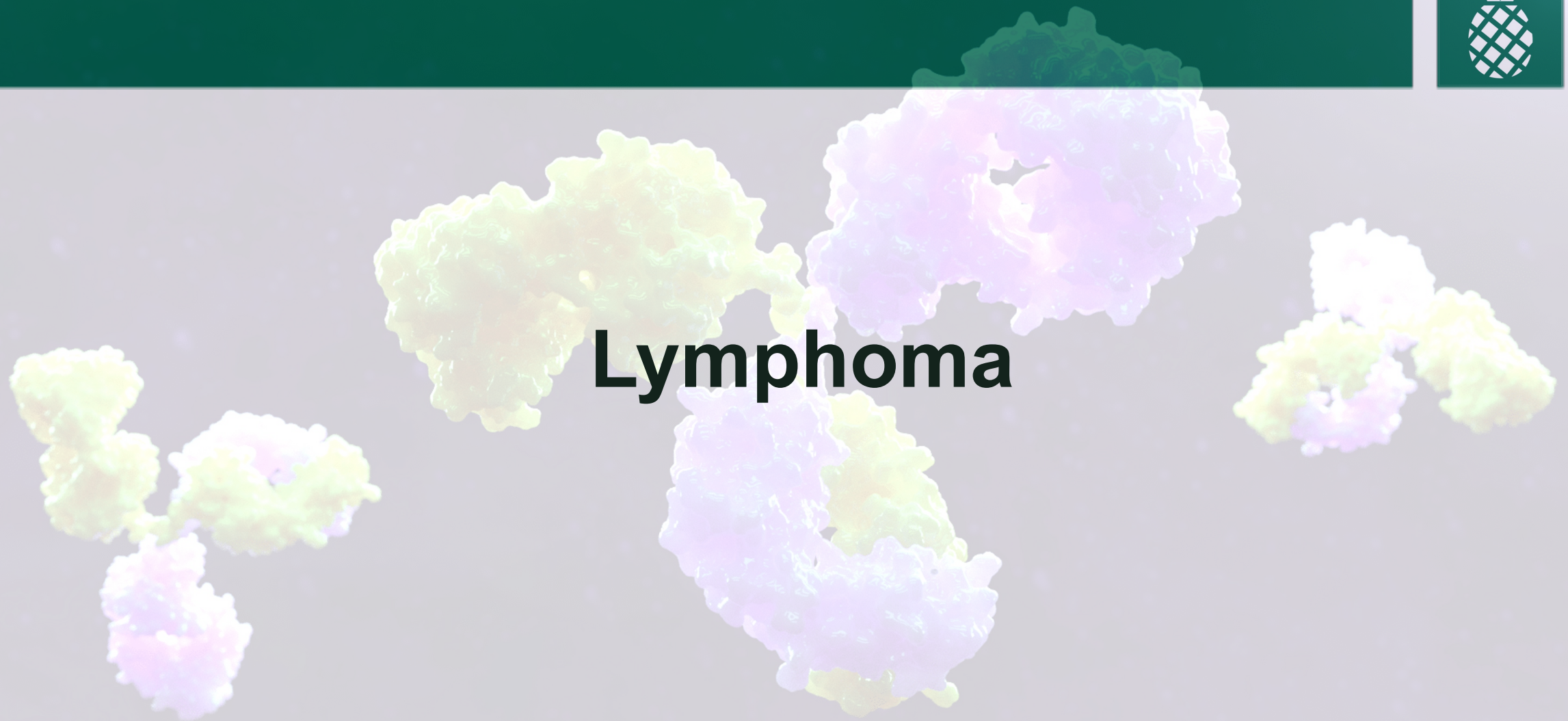

Lymphoma

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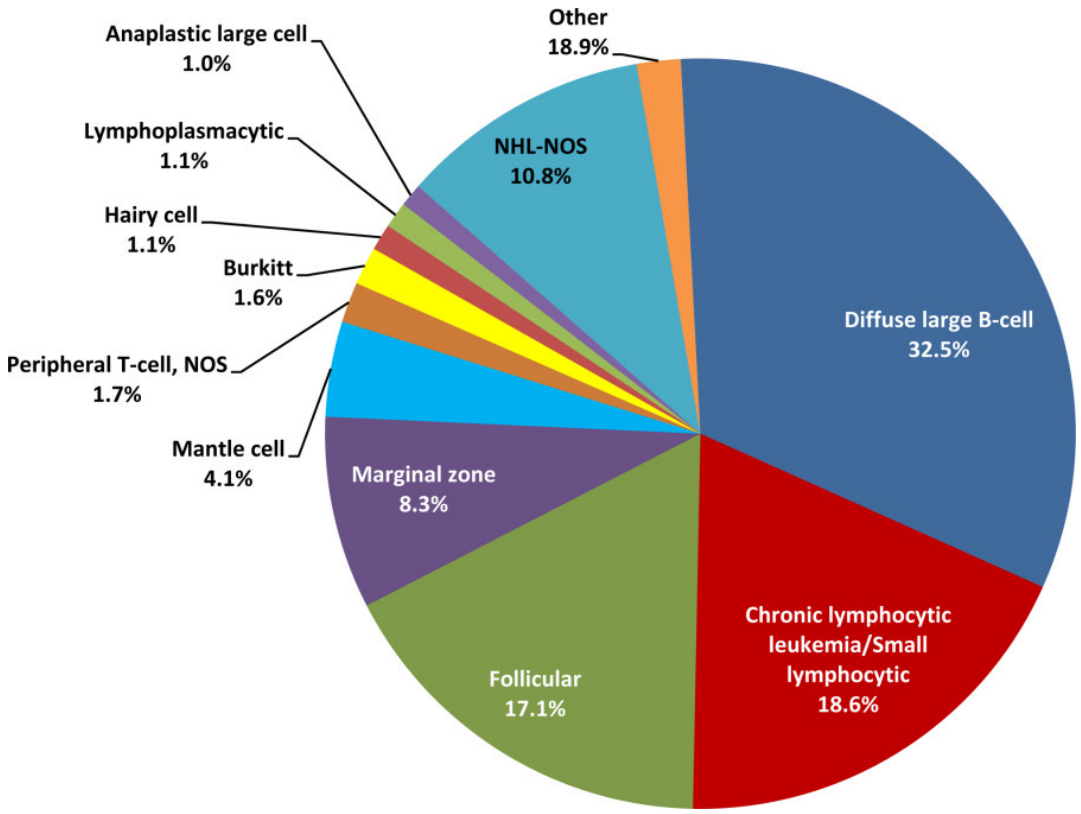
Lymphoma

- DLBCL is the most common subtype of NHL; FL is the most common indolent NHL
- Five-year survival rates in the first-line setting range from 60% to 70%, up to 50% of patients become refractory to or relapse after treatment
- SCHOLAR-1:
  - International, multicohort retrospective NHL research study
  - Largest patient-level pooled analysis to evaluate responses and OS rates in patients with
  - Patients: refractory NHL, including DLBCL-transformed follicular lymphoma and primary mediastinal B-cell lymphoma



Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011

Crump M, et al. *Blood*. 2018 Feb 1;131(5):587-588
American J Hematol, Volume: 90, Issue: 9, Pages: 790-795, First published: 10 June 2015, DOI: (10.1002/ajh.24086)

DLBCL: Diffuse large B-cell lymphoma
NHL: non-Hodgkin lymphoma

SCHOLAR-1

Pooled retrospective analysis → Rate of response to chemotherapy after refractory disease

Outcome	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)*	CORAL (n = 170)	Pooled (N = 636)
ORR, %	20	26	26	31	**26**
• CR	7	7	2	15	7
• PR	13	18	25	16	18
Response rate, %					
• Primary refractory	---	25	27	10	20
• Refractory to ≥ second-line therapy	20	21	20	40	26
• Relapse ≤ 12 mo post ASCT	19	35	---	39	34
Median OS from start of salvage therapy, mo	6.6	5.0	6.6	6.5	**6.3**

***106 evaluated for response**

ASCT: autologous stem cell transplant
ORR: Objective response rate
CR: complete response
PR: partial response
OS: overall survival

Crump M, et al. *Blood*. 2018 Feb 1;131(5):587-588

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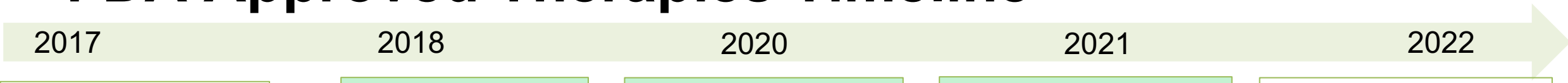

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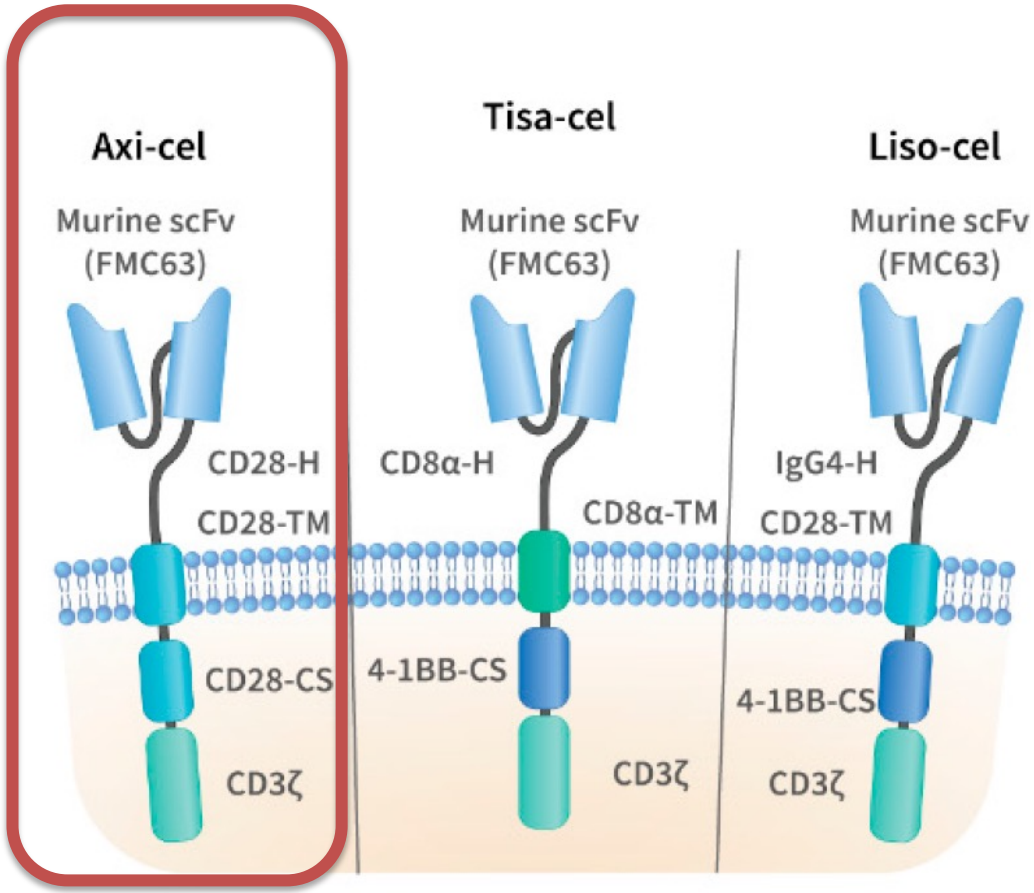
Tisagenlecleucel. Prescribing Information; 2022

Axicabtagene ciloleucel (Axi-cel)

- MOA
  - CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19-expressing cancer cells and normal B cells
- Indication/FDA approval
  - Adult patients with LBCL refractory to first-line CIT or that relapsed within 12 months of first-line CIT
  - Adult patients with R/R LBCL after ≥ 2 L
  - Adult patients with R/R FL ≥ 2 L
- LDC: Cy/flu 500/30 mg/m2 IV x 3 days on D -5, -4, -3



Maakaron et al. *BMJ*. (2020).
Roex et al. *Pharmaceutics* (2020), 12, 194
Axicabtagene ciloleucel. Prescribing Information; 2022

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MOA: Mechanism of action
R/R: Relapsed refractory
LBCL: Large B cell lymphoma
CIT: Chemoimmunotherapy

ZUMA-7

Phase 3 clinical trial
CD19 CAR T-Cell Therapy in 2L LBCL

- **Crossover:** not planned
- Patients who did not have a response to SoC could receive cellular immunotherapy outside the protocol (treatment switching)

	ZUMA-7	
Therapy	**Axi-cel (n=180)**	**SoC (n=179)**
Patient population	Adults with R/R LBCL with ≤ 12 mo 1L CIT	
ABC, %	9	5
Double/triple hit	17	14
Bridging therapy	Bridging therapy limited to corticosteroids 36%	---
Primary endpoint	EFS	
Median EFS, mo	8.3	2
2-yr EFS, %	41	16
ORR, %	83	50
CR, %	65	32
Median PFS, mo	14.7	3.7
2-yr PFS, %	46	27
Median OS. mo	NR	35.1
2-yr OS, %	61	51
Median DOR, mo	26.9	8.9

Locke. *NEJM.* (2022).

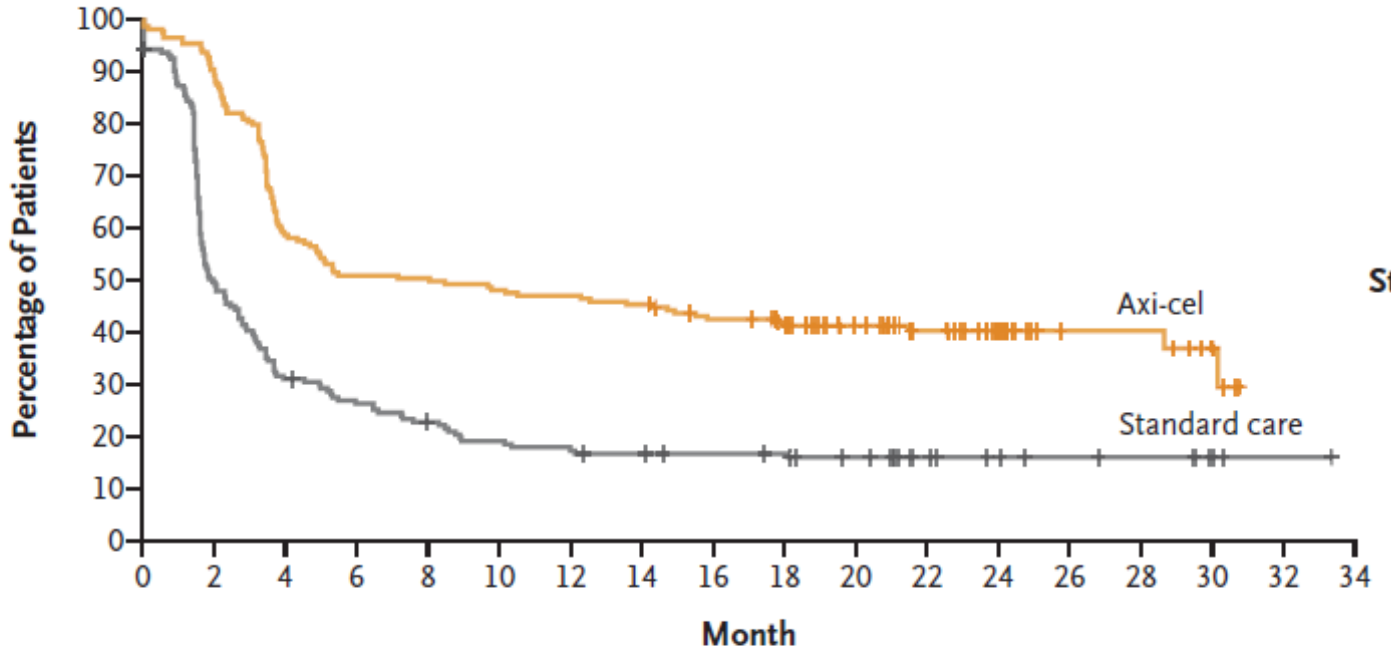
EFS: Event free survival; ORR: Overall response rate; CR: Complete response; OS: Overall survival; DOR: Duration of response

ZUMA-7

Phase 3 clinical trial

CD19 CAR T-Cell Therapy in 2L LBCL

A Event-free Survival



	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

No. at Risk

Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6		
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

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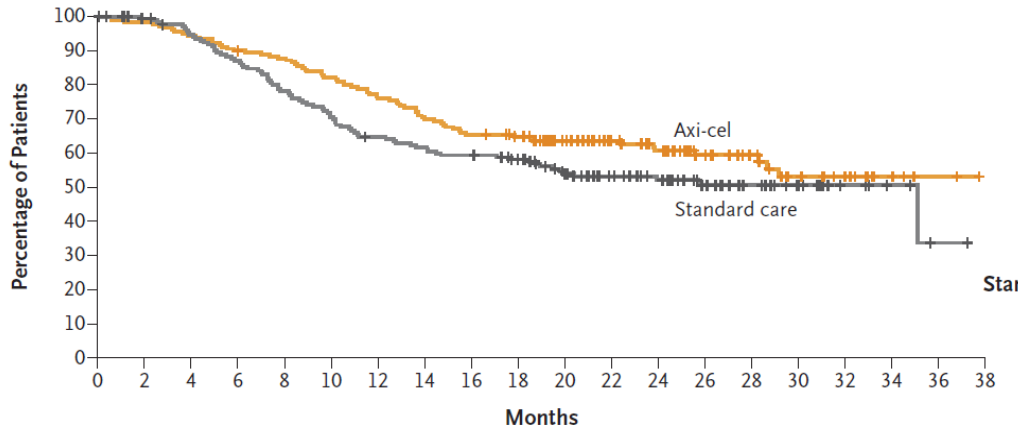
Locke. *NEJM*. (2022).

ZUMA-7
Phase 3 clinical trial
CD19 CAR T-Cell Therapy in 2L LBCL

A Overall Survival

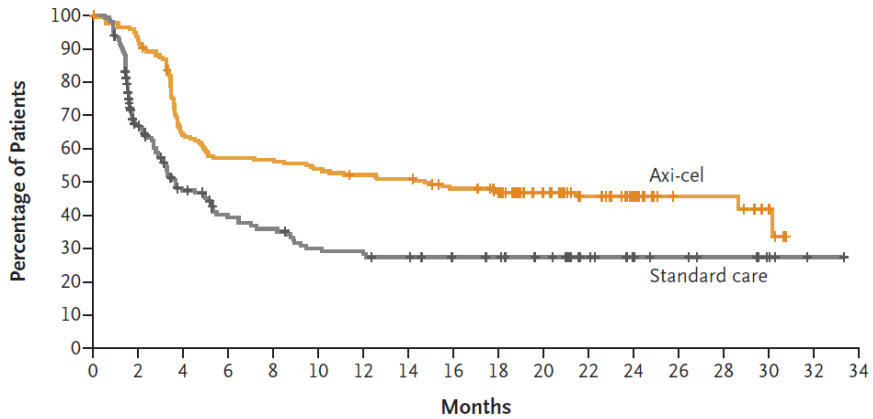


No. at Risk																			
Axi-cel	180	177	170	161	157	147	136	125	117	111	91	71	60	44	32	21	14	5	2	0
Standard care	179	171	161	148	133	120	109	104	100	91	74	58	47	33	21	14	7	4	1	0

	No. of Patients	Median Overall Survival (95% CI) *mo*
Axi-cel	180	NR (28.3–NE)
Standard Care	179	35.1 (18.5–NE)

Stratified hazard ratio for death, 0.73 (95% CI, 0.53–1.01)

B Progression-free Survival



No. at Risk																		
Axi-cel	180	166	112	100	99	94	90	88	80	73	56	43	28	12	12	6		
Standard care	179	94	61	47	43	35	33	31	28	27	24	15	11	9	7	4	1	0

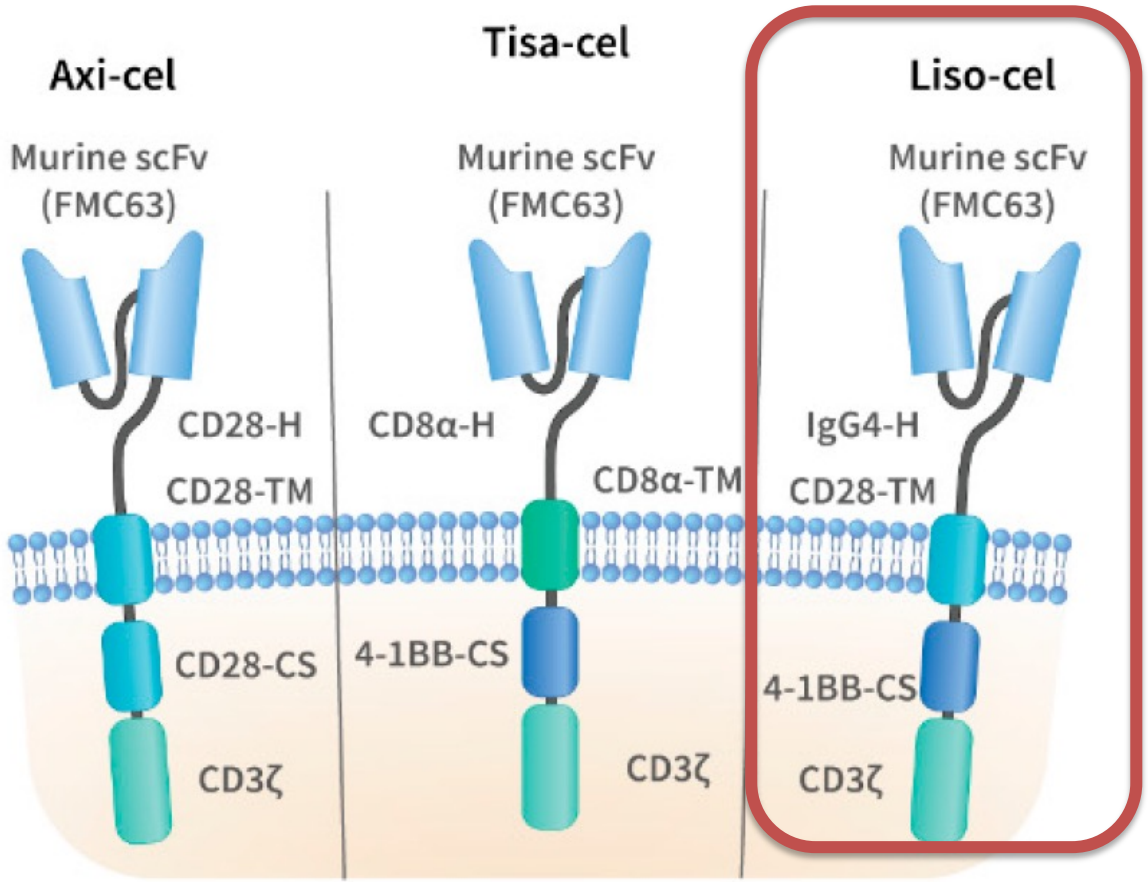
	No. of Patients	Median Progression-free Survival (95% CI) *mo*
Axi-cel	180	14.7 (5.4–NE)
Standard Care	179	3.7 (2.9–5.3)

Stratified hazard ratio for disease progression or death, 0.49 (95% CI, 0.37–0.65)

Locke. *NEJM*. (2022).

Lisocabtagene maraleucel (Liso-cel)

- MOA
  - CD19-directed genetically modified autologous cell immunotherapy
- Indication/FDA approval
  - Adult patients with LBCL and FL grade 3B, who have:
    - Refractory disease to first-line CIT or relapse within 12 months of first-line CIT
    - Refractory disease to first-line CIT or relapse after first line CIT and are not eligible for HSCT due to comorbidities or age
    - R/R disease after ≥ 2 L of systemic therapy
- LDC: Cy/Fu 300/30 mg/m² IV x 3 days
  - Infuse CAR T-cells 2-7 days after completion of LDC



MOA: Mechanism of action ; R/R: Relapsed refractory
LBCL: Large B cell lymphoma; FL: Follicular lymphoma
HSCT: Hematopoietic stem cell transplant
CIT: Chemoimmunotherapy

Maakaron et al. *BMJ*. (2020);
Roex et al. *Pharmaceutics* (2020), 12, 194;
Lisocabtagene maraleucel. Prescribing Information; 2022.

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TRANSFORM

Phase 3 clinical trial

CD19 CAR T-Cell Therapy in 2L LBCL

- **Crossover:** 50 patients in the SoC group were approved for crossover, with 40 (80%) patients crossing over during salvage CIT and 10 (20%) after high-dose chemotherapy or autologous HSCT

	TRANSFORM Phase III Trial	
Therapy	**Liso-cel (n=92)**	**SoC (n=92)**
Patient population	Adults with R/R LBCL with ≤ 12 mo 1L CIT	
ABC, %	23	32
Double/triple hit	24	23
Bridging therapy, %	Bridging therapy allowed 83%	---
Primary endpoint	EFS	
Median EFS, mo	10.1	2.3
1-yr EFS, %	44.5	23.7
ORR, %	86	48
CR, %	66	39
Median PFS, mo	14.8	5.7
1-yr PFS, %	52.3	33.9
Median OS. mo	NR	16.4
1-yr OS, %	79.1	64.2
Median DOR, mo	NR	14.5

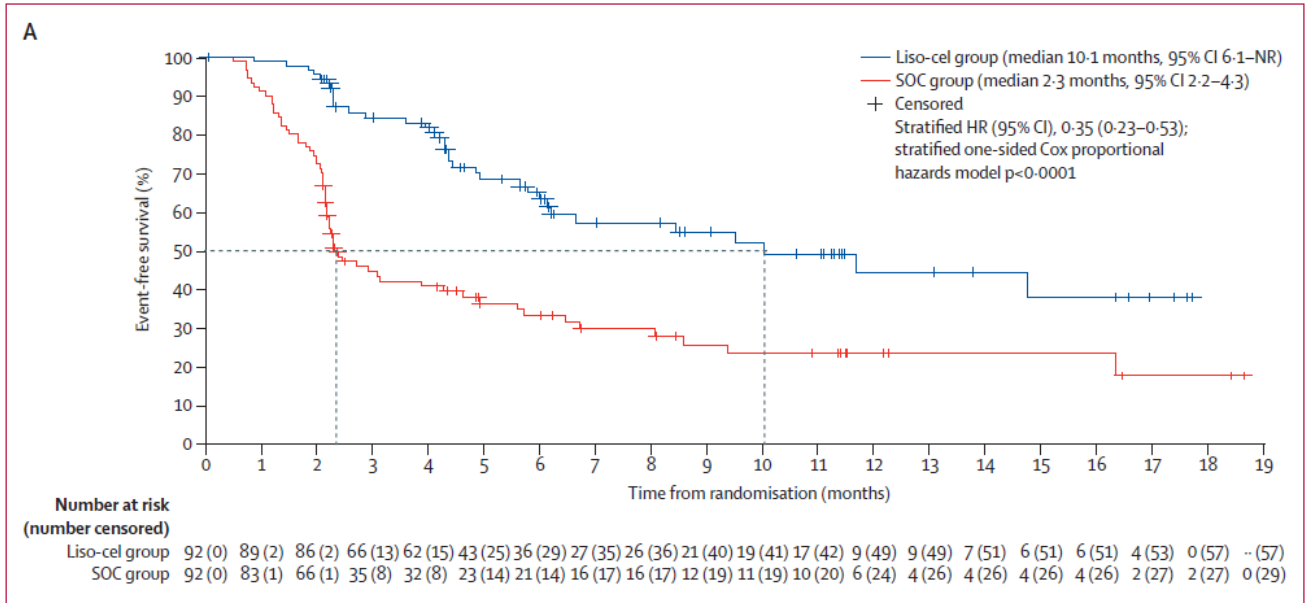
Kamdar. *Lancet.* (2022).

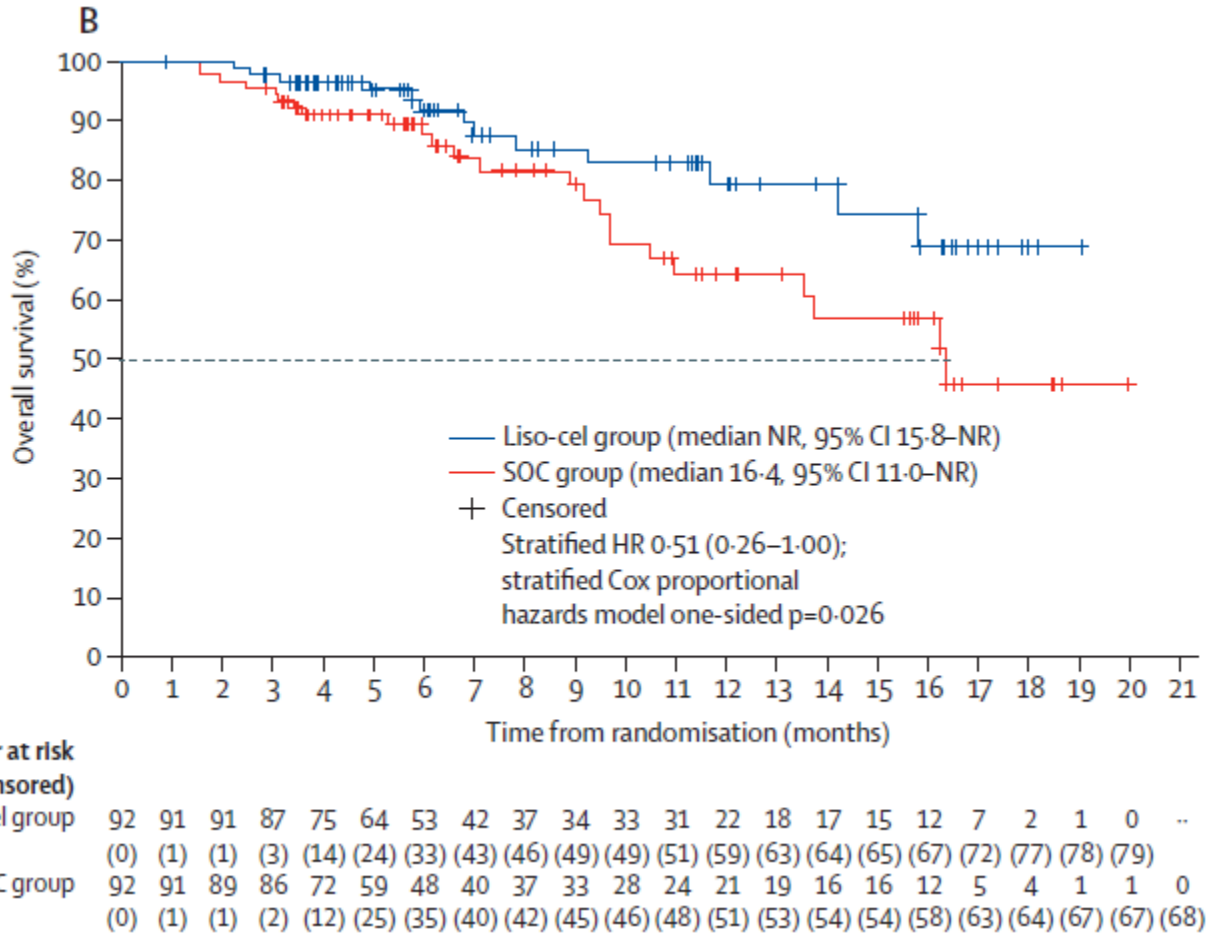
EFS: Event free survival; ORR: Overall response rate; CR: Complete response; OS: Overall survival; DOR: Duration of response

TRANSFORM

Phase 3 clinical trial

CD19 CAR T-Cell Therapy in 2L LBCL





65% reduction in risk of EFS events

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Kamdar. *Lancet*. (2022).

ADRs of Special Interest
ZUMA-7 & TRANSFORM

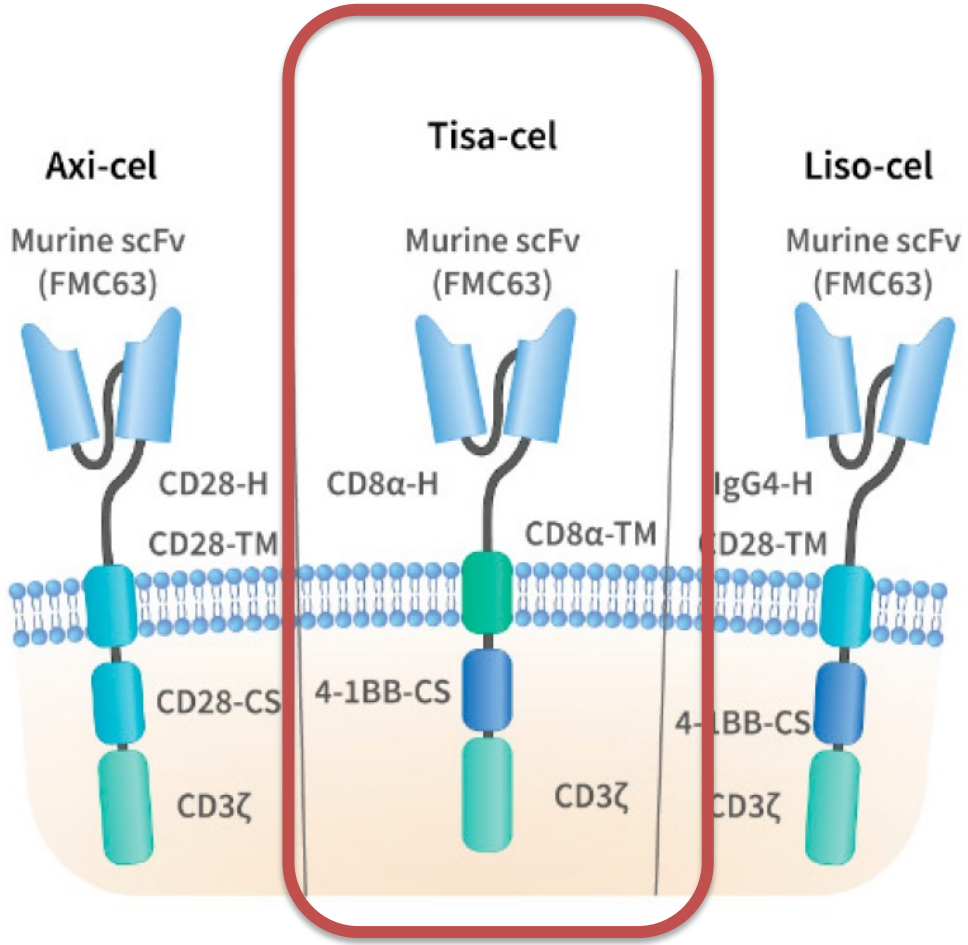
	ZUMA-7[1] Axi-cel (n=170)	TRANSFORM[2] (Liso-cel n=92)
Grade ≥ 3 Any adverse event, %	91	92
Grade ≥ 3 CRS, %	6	1
• Time to onset in days, (range)	3, (1-10)	5, (3-8)
• Time to resolution / median duration in days	7, (2-43)	4, (2-5)
Tocilizumab use, %	65	24
Grade ≥ 3 NE, %	21	4
• Time to onset, (range)	7	11, (10-17)
• Time to resolution / median duration in days	9	6, (2-19)
Grade ≥ 3 Neutropenia, %	69	80
Grade ≥ 3 Thrombocytopenia, %	15	49

1. Locke. *NEJM.* (2022);
2. Kamdar. *Lancet.* (2022).

CRS: cytokine release syndrome; NE: neurologic events

Tisagenlecleucel (Tisa-cel)

- MOA
  - CD19-directed genetically modified autologous T cell immunotherapy
- Indication/FDA approval
  - Patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse
  - Adult patients with R/R LBCL large B-cell lymphoma after ≥ 2 L
  - Adult patients with R/R FL after ≥ 2 L
- LDC: Cy/Flu 250/25 mg/m2 IV daily x3 days OR Bendamustine 90 mg/m2 IV daily x 2 days
  - Infuse CAR T cells: 2-11 for DLBCL and 2-6 days for FL days after completion of LDC



Maakaron et al. *BMJ*. (2020)
Roex et al. *Pharmaceutics* (2020), 12, 194
Tisagenlecleucel. Prescribing Information; 2022

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MOA: Mechanism of action ; R/R: Relapsed refractory
LBCL: Large B cell lymphoma; FL: Follicular lymphoma

ELARA
Phase 2 multicenter clinical trial

- R/R FL after ≥ 2L or who relapsed after ASCT
- Primary endpoint: CR
- Secondary endpoint: ORR, DOR, PFS, OS, pharmacokinetics and safety
- Median follow up: 16.59 mo
- DOR, PFS, OS not reached
- Among patients who achieved CR
  - Estimated DOR rate at 9 months was 86.5% (95% CI, 74.7–93.1)
  - Estimated PFS rate at 12 months was 85.5% (95% CI, 74.0–92.2)
  - PFS rate for the overall population at 12 months was 67% (95% CI, 56–76)

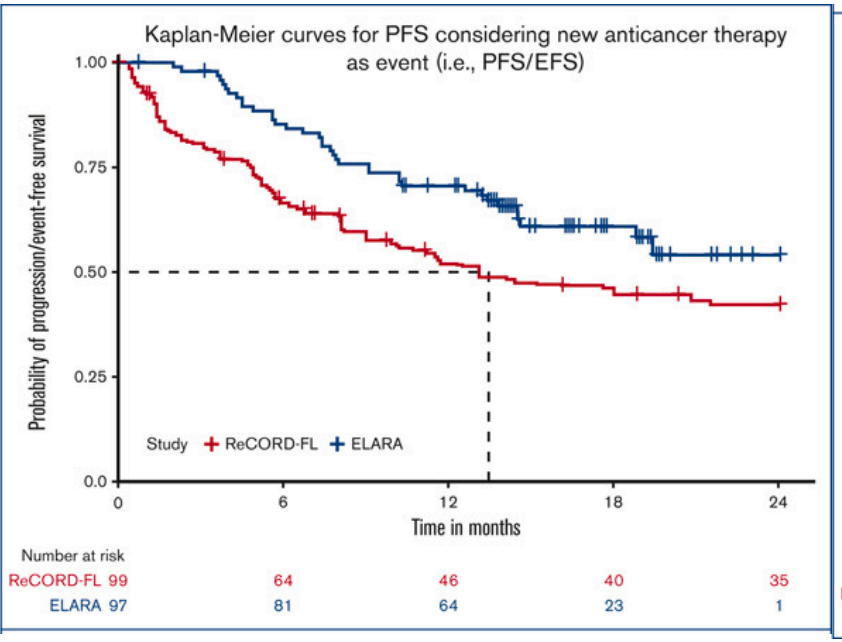
Efficacy	N = 94
ORR, %	86.2
CR, %	69.1

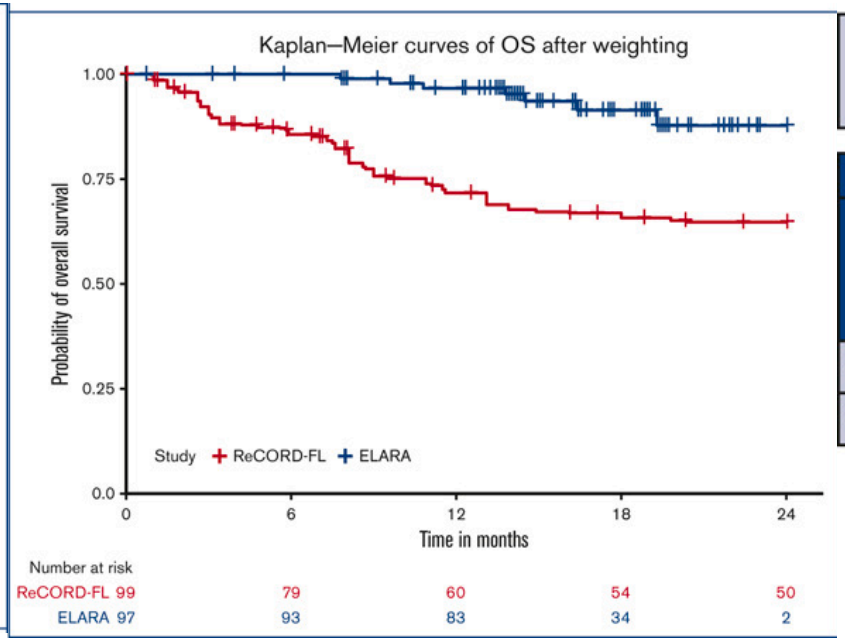
Safety	N = 94
Grade ≥ 3 CRS, %	0
Tocilizumab, %	34
Grade ≥ 3 NE, %	3

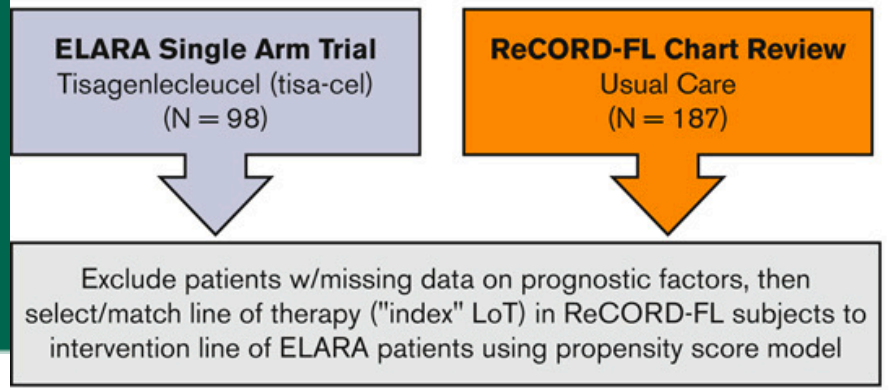
Fowler. *Nature Medicine* volume 28, (2022)
Salles. *Blood Adv* (2022).

ASCT: autologous stem cell transplant

ELARA
Phase 2 multicenter clinical trial







Weighted Indirect Treatment Comparison (ITC) Analysis

Tisa-Cel (N = 97)	Usual Care (Weighted N = 99)

Best Response to Therapy

	ELARA (Tisa-Cel)	ReCORD-FL (Usual Care)
	N = 97	Weighted N = 99
CRR (95% CI)	69.1% (59.8-78.3%)	37.3% (26.4-48.3%)
ORR (95% CI)	85.6% (78.7-92.5%)	63.6% (52.5-74.7%)

After LoT selection/matching and weighted adjustment of prognostic factors, tisa-cel was associated with:

- 1.9-fold higher complete response rate (CRR)
- 80% reduction in death risk (hazard ratio [95% CI]: 0.20 [0.02, 0.38])
- 40% reduction in risk of progression (hazard ratio [95% CI]: 0.60 [0.34, 0.86])

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Salles. *Blood Adv*. (2022).

Pharmacotherapy Considerations

Black Box Warnings for all CD19 CAR T products:

- ❑ CRS
- ❑ Neurologic toxicities
- ❑ Must obtain agent via **REMS** Risk Evaluation and mitigation Strategy

Call your oncologist or go to the emergency room if these signs appear.

SIGNS AND SYMPTOMS MAY INCLUDE:

- Difficulty breathing
- Fever (100.4°F/38°C or higher)
- Chills/shaking chills
- Confusion
- Severe nausea, vomiting, diarrhea
- Severe muscle or joint pain
- Very low blood pressure
- Dizziness/lightheadedness
- Headache

PATIENT WALLET CARD

Have This Card With You At All Times
Show It To Any Doctor That Sees You And When You Go To The Hospital

Call or see your oncologist or get emergency help **RIGHT AWAY** if you have any of **these symptoms**:

- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heartbeat
- Severe fatigue or weakness

Carry this card with you at all times. SHOW THIS CARD if you go to the emergency room or see any physician.

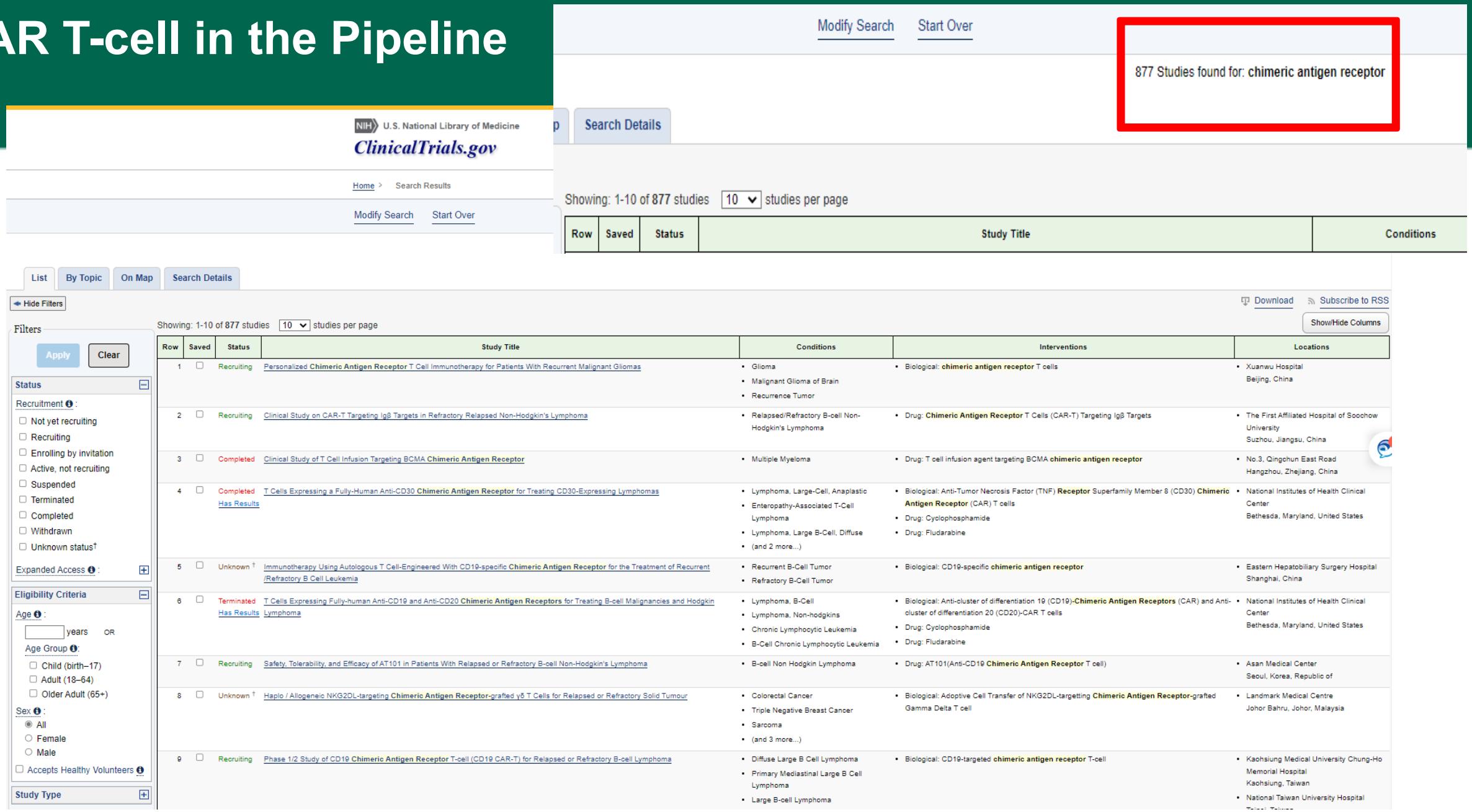
Call your oncologist or go to the emergency room right away if the following symptoms appear:

- Fever (100.4˚F/38˚C or higher)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heart rate
- Severe fatigue or weakness

Have this card with you at all times. Show it to any doctor who sees you and when you go to the hospital.

Axicabtagene ciloleucel. Prescribing Information; 2022
Lisocabtagene maraleucel. Prescribing Information; 2022
Tisagenlecleucel. Prescribing Information; 2022

CAR T-cell in the Pipeline



NIH U.S. National Library of Medicine
ClinicalTrials.gov

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877 Studies found for: chimeric antigen receptor

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Status

Recruitment :
- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated
- Completed
- Withdrawn
- Unknown status†

Expanded Access :

Eligibility Criteria

Age : years OR

Age Group :
- Child (birth–17)
- Adult (18–64)
- Older Adult (65+)

Sex :
- All
- Female
- Male

Accepts Healthy Volunteers

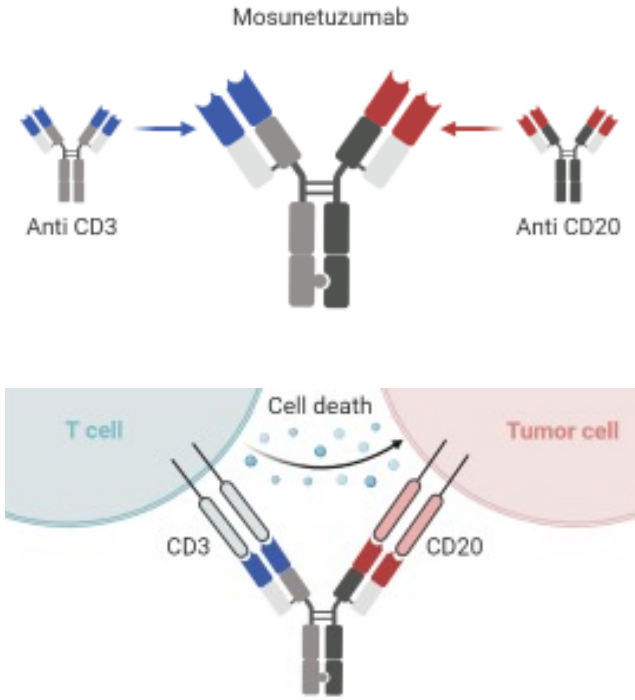
Study Type

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Recruiting	Personalized **Chimeric Antigen Receptor** T Cell Immunotherapy for Patients With Recurrent Malignant Gliomas	• Glioma • Malignant Glioma of Brain • Recurrence Tumor	• Biological: **chimeric antigen receptor** T cells	• Xuanwu Hospital Beijing, China
2		Recruiting	Clinical Study on CAR-T Targeting IgB Targets in Refractory Relapsed Non-Hodgkin's Lymphoma	• Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma	• Drug: **Chimeric Antigen Receptor** T Cells (CAR-T) Targeting IgB Targets	• The First Affiliated Hospital of Soochow University Suzhou, Jiangsu, China
3		Completed	Clinical Study of T Cell Infusion Targeting BCMA **Chimeric Antigen Receptor**	• Multiple Myeloma	• Drug: T cell infusion agent targeting BCMA **chimeric antigen receptor**	• No.3, Qingchun East Road Hangzhou, Zhejiang, China
4		Completed Has Results	T Cells Expressing a Fully-Human Anti-CD30 **Chimeric Antigen Receptor** for Treating CD30-Expressing Lymphomas	• Lymphoma, Large-Cell, Anaplastic • Enteropathy-Associated T-Cell Lymphoma • Lymphoma, Large B-Cell, Diffuse • (and 2 more...)	• Biological: Anti-Tumor Necrosis Factor (TNF) **Receptor** Superfamily Member 8 (CD30) **Chimeric Antigen Receptor** (CAR) T cells • Drug: Cyclophosphamide • Drug: Fludarabine	• National Institutes of Health Clinical Center Bethesda, Maryland, United States
5		Unknown †	Immunotherapy Using Autologous T Cell-Engineered With CD19-specific **Chimeric Antigen Receptor** for the Treatment of Recurrent /Refractory B Cell Leukemia	• Recurrent B-Cell Tumor • Refractory B-Cell Tumor	• Biological: CD19-specific **chimeric antigen receptor**	• Eastern Hepatobiliary Surgery Hospital Shanghai, China
6		Terminated Has Results	T Cells Expressing Fully-human Anti-CD19 and Anti-CD20 **Chimeric Antigen Receptors** for Treating B-cell Malignancies and Hodgkin Lymphoma	• Lymphoma, B-Cell • Lymphoma, Non-hodgkins • Chronic Lymphocytic Leukemia • B-Cell Chronic Lymphocytic Leukemia	• Biological: Anti-cluster of differentiation 19 (CD19)-**Chimeric Antigen Receptors** (CAR) and Anti-cluster of differentiation 20 (CD20)-CAR T cells • Drug: Cyclophosphamide • Drug: Fludarabine	• National Institutes of Health Clinical Center Bethesda, Maryland, United States
7		Recruiting	Safety, Tolerability, and Efficacy of AT101 in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma	• B-cell Non Hodgkin Lymphoma	• Drug: AT101(Anti-CD19 **Chimeric Antigen Receptor** T cell)	• Asan Medical Center Seoul, Korea, Republic of
8		Unknown †	Haplo / Allogeneic NKG2DL-targeting **Chimeric Antigen Receptor**-grafted γδ T Cells for Relapsed or Refractory Solid Tumour	• Colorectal Cancer • Triple Negative Breast Cancer • Sarcoma • (and 3 more...)	• Biological: Adoptive Cell Transfer of NKG2DL-targetting **Chimeric Antigen Receptor**-grafted Gamma Delta T cell	• Landmark Medical Centre Johor Bahru, Johor, Malaysia
9		Recruiting	Phase 1/2 Study of CD19 **Chimeric Antigen Receptor** T-cell (CD19 CAR-T) for Relapsed or Refractory B-cell Lymphoma	• Diffuse Large B Cell Lymphoma • Primary Mediastinal Large B Cell Lymphoma • Large B-cell Lymphoma	• Biological: CD19-targeted **chimeric antigen receptor** T-cell	• Kaohsiung Medical University Chung-Ho Memorial Hospital Kaohsiung, Taiwan • National Taiwan University Hospital

Mosunetuzumab-axgb

Bispecific CD20-directed T cell engager

- MOA
  - IgG1 bispecific antibody
  - Targets CD20 and CD3 → activates T-cells → causes release of proinflammatory cytokines → induces lysis of B-cells
  - Lysis occurs independent of tumor cell immune escape mechanisms
- Indication
  - Adult patients with R/R FL after 2 or more lines of systemic therapy



https://www.genscript.com/antibody-news/therapeutic-antibodies-advancing-toward-approval-for-clinical-use.html

Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065
Mosunetuzumab-axgb. Prescribing Information; December 2022.

Baptist Health South Florida

MOA: Mechanism of action
FL: Follicular lymphoma

GO29781 Clinical Trial

Phase 2 single arm, multicenter trial

- Inclusion criteria: Grade 1-3A FL, ECOG 0-1, R/R FL to 2 or more previous lines of treatment including anti-CD20 and alkylating agent
  - Median prior lines of therapy: 3
  - 69% refractory to their last previous therapy, 79% refractory to any previous anti-CD20 therapy, 53% were double refractory to both previous anti-CD20 therapy and a previous alkylating agent
- Safety:
  - CRS in Cycle 1
    - Median time to CRS onset: 5 hours after C1D1 infusion
    - Cycle 1 day 1 (23%) & Cycle 1 day 15 (36%)
  - CRS (all grade) in 44% of patients
    - Grade 1 in 26%
    - Grade 2 in 17%
    - Grade 3 in 1% (one patient)
    - Grade 4 in 1% (one patient)
  - Other ADRs: Fatigue, neutropenia, headache, hypophosphatemia, anemia

n=90

Median follow up: 18.3 mo	ORR: 80%
CR: 60%	Median DOR: 22.8 mo
12-month event free rate: 61.8% 18-month event free rate: 56.9%	Time to first response: 1.4 mo Time to CR: 3 mo

Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065

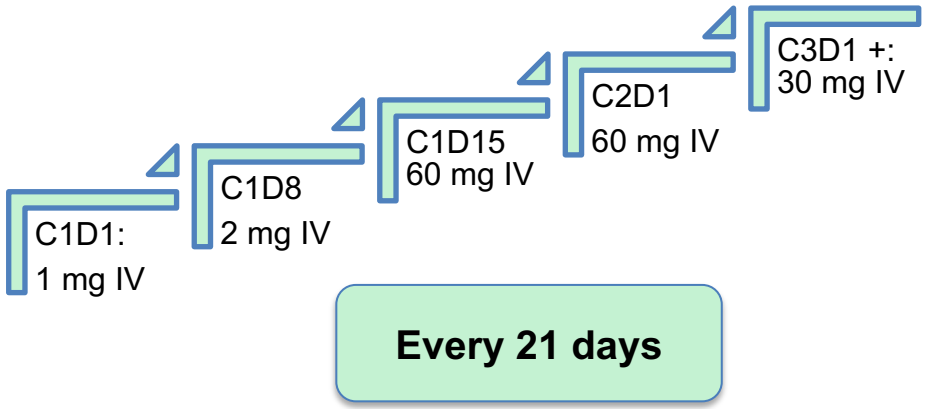
ECOG: Eastern cooperative oncology group; CRS: Cytokine release syndrome; ADR: Adverse drug reactions; ORR: Overall response rate; CR: Complete response; DOR: Duration of response

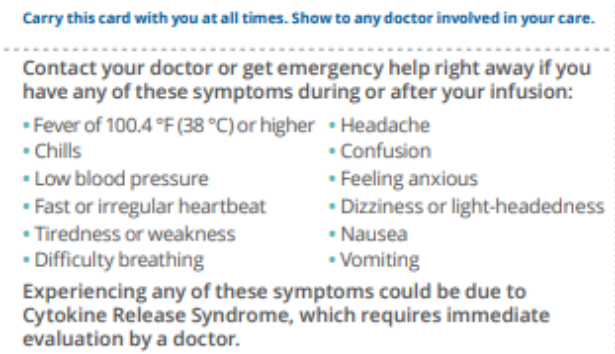
Pharmacotherapy Considerations
Mosunetuzumab-axgb

- Intravenous administration
  - Administered over 4 hours in C1 and 2 hours in C2+ if tolerated
- Step up dosing
  - Outpatient administration for all doses; consider inpatient if previous CRS

Mosunetuzumab-axgb. Prescribing Information; December 2022.

- Pre-medications: CS, H1RA, antipyretic
  - Recommended prior to each dose in C1 and C2; may administer in C3+ if patient experienced CRS
- Duration of therapy: 8 cycles
  - If partial response (PR) or stable disease (SD) after 8 cycles, then treatment continues up to 17 cycles
- No REMS program
  - Wallet card available




Carry this card with you at all times. Show to any doctor involved in your care.

Contact your doctor or get emergency help right away if you have any of these symptoms during or after your infusion:

- Fever of 100.4 °F (38 °C) or higher
- Chills
- Low blood pressure
- Fast or irregular heartbeat
- Tiredness or weakness
- Difficulty breathing
- Headache
- Confusion
- Feeling anxious
- Dizziness or light-headedness
- Nausea
- Vomiting

Experiencing any of these symptoms could be due to Cytokine Release Syndrome, which requires immediate evaluation by a doctor.

Mosunetuzumab-axgb. Prescribing Information; December 2022.

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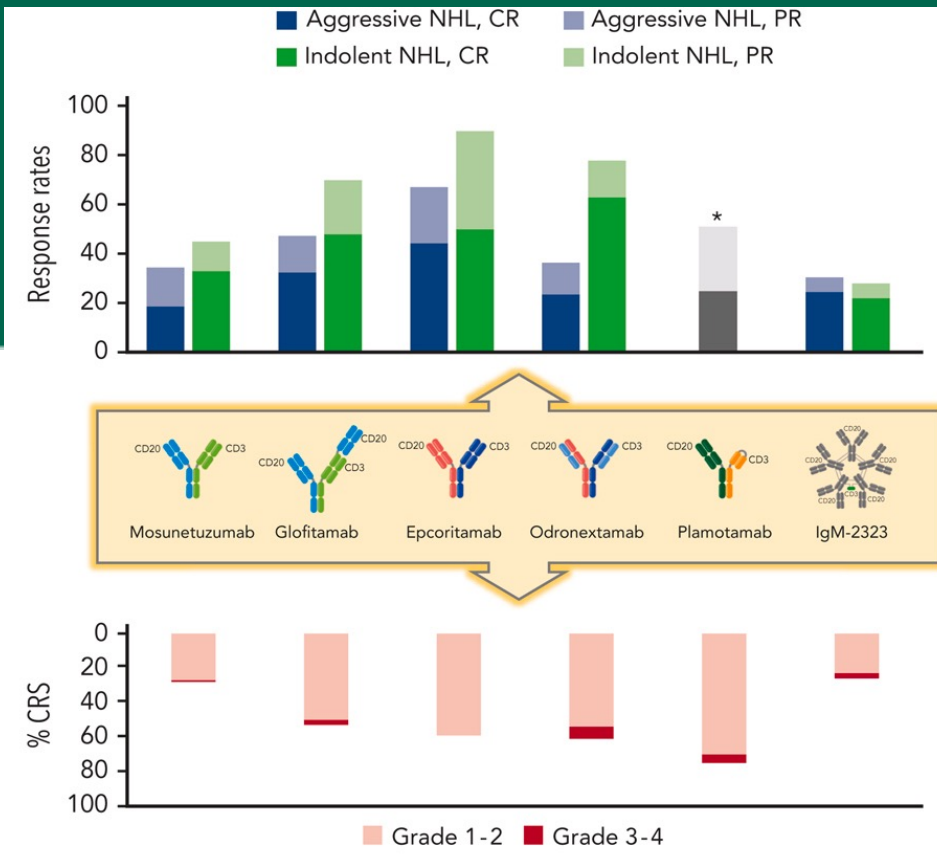
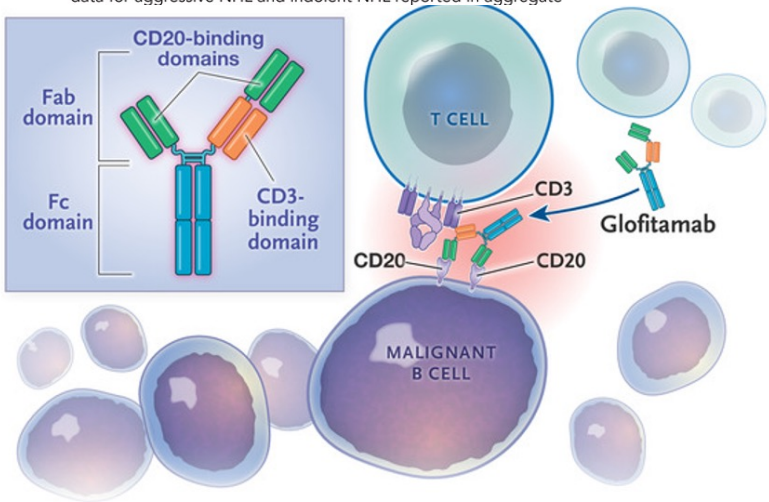
CS: Corticosteroid
H1RA: Histamine 1 receptor antagonist
REMS: Risk Evaluation and Mitigation Strategies

Bispecifics in the Pipeline

- Giofitamab – CD3xCD20 bsAb
- Epcoritamab – CD3xCD20 bsAb
- Odronextamab – CD3xCD20 bsAb
- Plamotamab – CD3xCD20 bsAb



• Other common adverse events (AE): Neutropenia, diarrhea, fatigue, anemia;
• ICANS-like syndrome, TLS, HLH: rare (<5%)
* data for aggressive NHL and indolent NHL reported in aggregate



Falchi. *Blood* (2023) 141 (5): 467–480
Dickinson MJ et al. *N Engl J Med* 2022; 387:2220-2231
Thieblemont C, et al. *J Clin Oncol.* 2023 Apr 20;41(12):2238-2247
Bannerji R, et al. *Lancet Haematol.* 2022 May;9(5):e327-e339.
Patel K, et al. *Blood* (2022) 140 (Supplement 1): 9470–9472.
www.clinicaltrials.gov

Cytokine Release Syndrome & Neurotoxicity

- Both CAR T and bispecific antibody therapy are associated with ADRs due to **T-cell overactivation**

- Most common manifestations are:
  - Cytokine Release Syndrome (CRS)
    - Cytokine mediated systemic inflammatory response
    - Chills, fevers, skin rash, hypotension, hypoxia, confusion
  - Immune Effector Cell-associated Neurotoxicity (ICANS)
    - Characterized by immune-mediated inflammation in the central nervous system
    - Aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema

CAR T- cell	Bispecific
CRS, ICANS	CRS >> ICANS
High grade CRS more common	Low grade CRS more common
Graded the same (ASTCT criteria)	
CRS management*: Anti IL-6 therapy (tocilizumab), corticosteroids, fluids, supportive care Ensure symptom resolutions for at least 72 hours prior to next dose (Bispecifics)	
Mandatory 2 doses tocilizumab in stock per patient	Tocilizumab stock encouraged

*differs slightly between management depending on product (see package insert) and institution

Falchi. *Blood* (2023) 141 (5): 467–480.
Murthy H, et al. *Immunotargets Ther* 2019;8:43 52.
Lee et al. *Biol Blood Marrow Transplant*, Dec 2018

CAR T-cell therapy vs. Bispecific antibodies

CAR T-cell	Bispecifics
Inpatient or Outpatient (product/institution specific)	Inpatient or Outpatient (product/institution specific)
Engineered for individual patient	Off the shelf
Delayed availability, more insurance barriers 4-8 weeks	Immediate availability, less insurance barriers 3-7 days
$$$	$$ | Variable insurance coverage
Cells infused IV; may also need lymphodepleting chemo prior	IV or SC Long administration times initially
Higher rates/grades of CRS/ICANS	Mostly low-grade CRS/ICANS
One time	Repeated dosing / cycles
REMS	+/- REMS depending on product
Generally later line; some 2nd line	Generally later line of therapy; 3rd or greater

Subklewe M. *Blood Adv* (2021) 5 (2): 607–612.
Falchi. *Blood* (2023) 141 (5): 467–480.

Future Directions

- Earlier use of CAR T-cell and bispecific antibody therapy
  - May benefit certain high risk populations
- Combinations with other agents
- Cost analysis
- Toxicity management – identifying risk factors, optimizing prevention and education
- Increasing accessibility

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Subklewe M. *Blood Adv* (2021) 5 (2): 607–612..

Pharmacotherapy Updates in Malignant Hematology

Bispecific Antibodies & CAR T-Cell Therapy

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https://alphatauri3d.com/2019/06/14/bispecific-antibodies-for-immuno-oncology/