
بسم الله الرحمن الرحیم

Overview of CAR T-CELL Therapy

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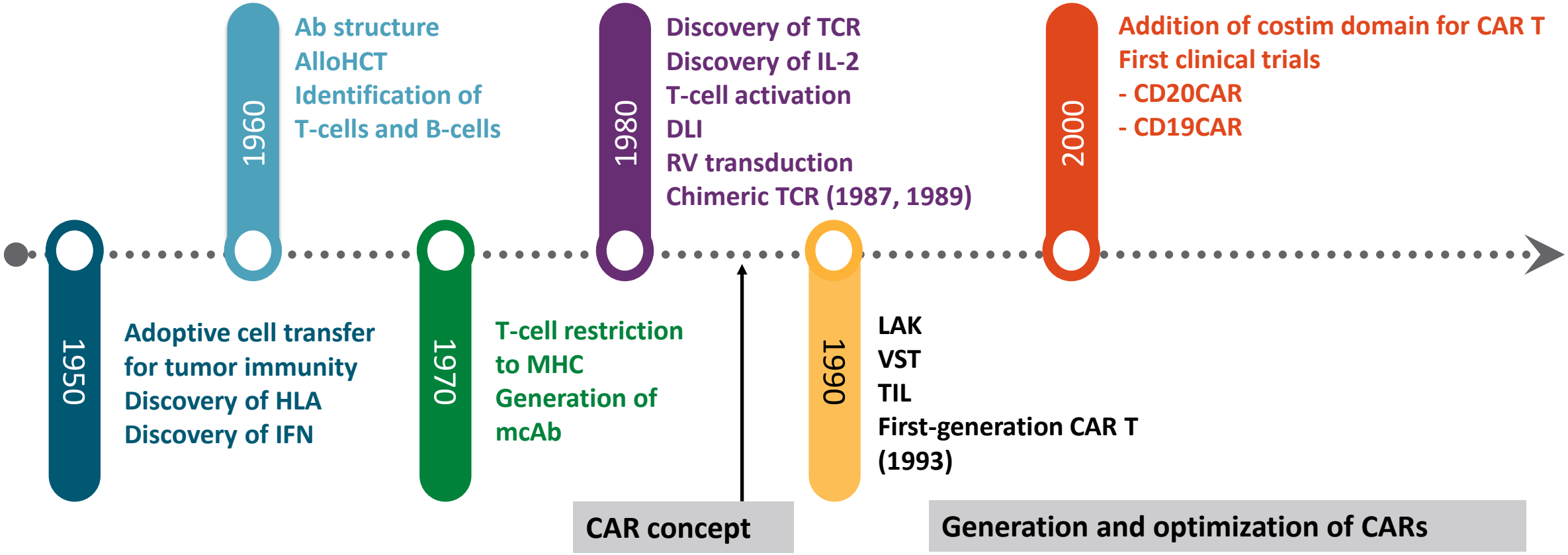
Medical Oncologist/Hematologist

CLINICAL CARE OPTIONS®
ONCOLOGY

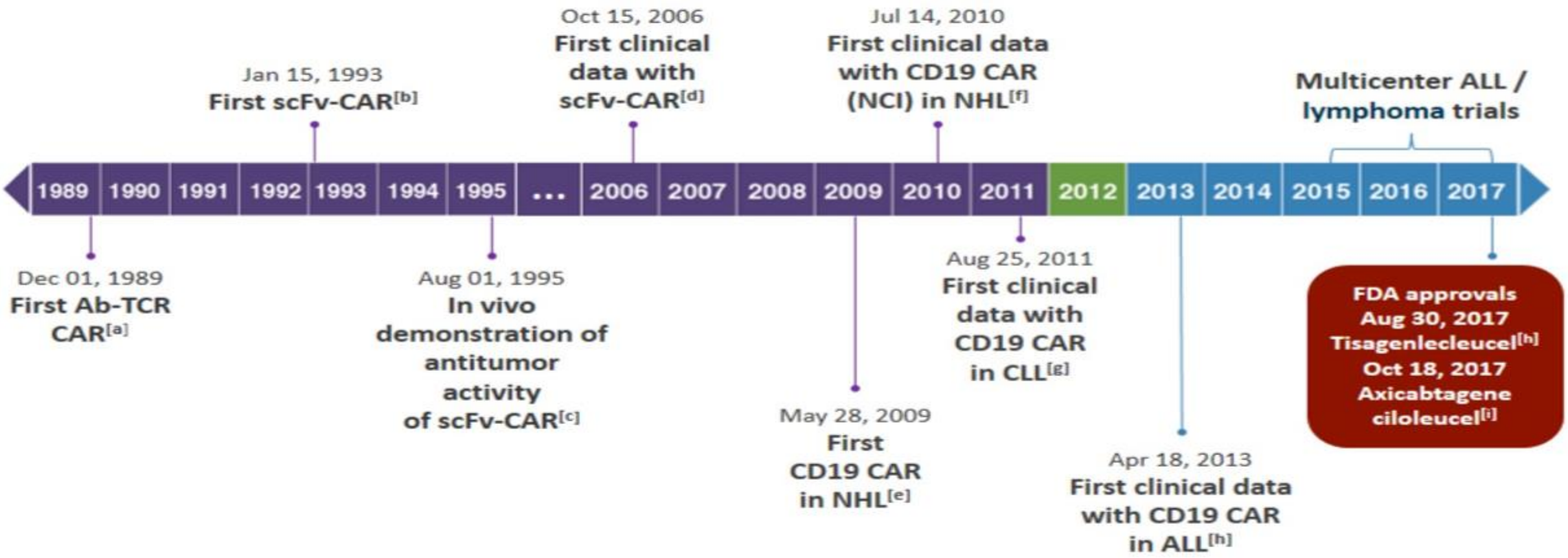
Development of Adoptive Cellular Therapy



Slide courtesy of Elizabeth Budde. Adapted from Rosenberg. Nat Rev Cancer. 2008;8:299.

Slide credit: clinicaloptions.com

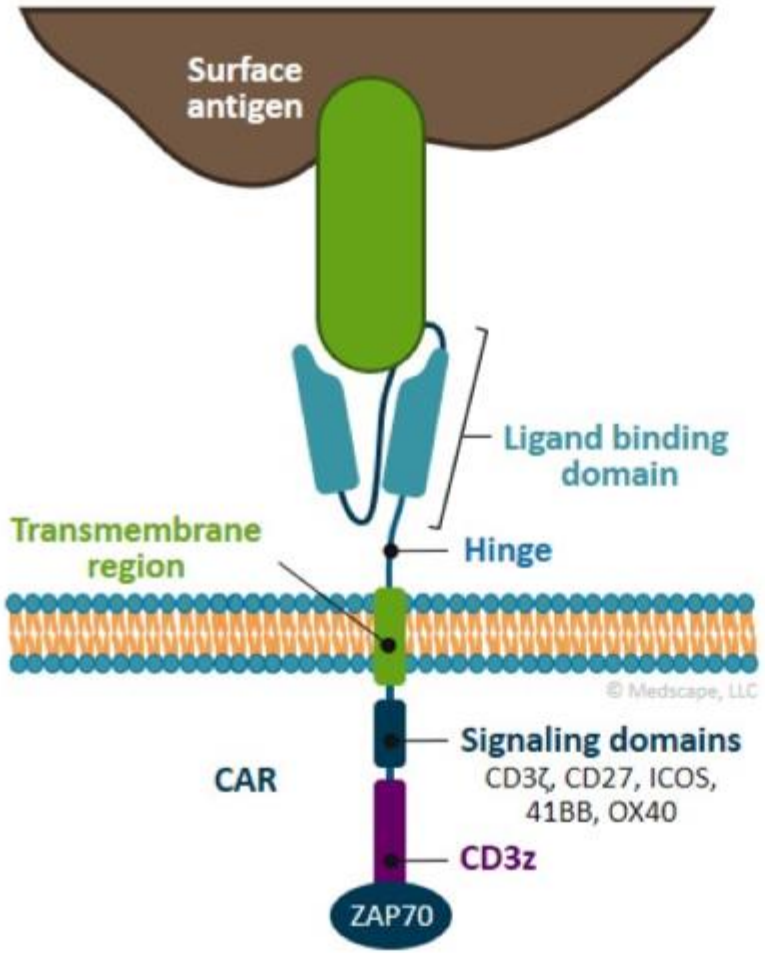
CAR T Development: From Discovery to FDA Approval Over ~25 Years



a. Gross G, et al. *Proc Natl Acad Sci U S A.* 1989;86:10024-10028; b. Eshhar Z, et al. *Proc Natl Acad Sci U S A.* 1993;90:720-724; c. Hwu P, et al. *Cancer Res.* 1995;55:3369-3373; d. Kershaw MH, et al. *Clin Cancer Res.* 2006;12:6106-6115; e. Kochenderfer JN, et al. *J Immunother.* 2009;32:689-702; f. Kochenderfer JN, et al. *Blood.* 2010;116:3875-3886; g. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73; h. Grupp SA, et al. *N Engl J Med.* 2013;368:1509-1518; i. Kymriah™ PI 2017; j. Yescarta™ PI 2017.

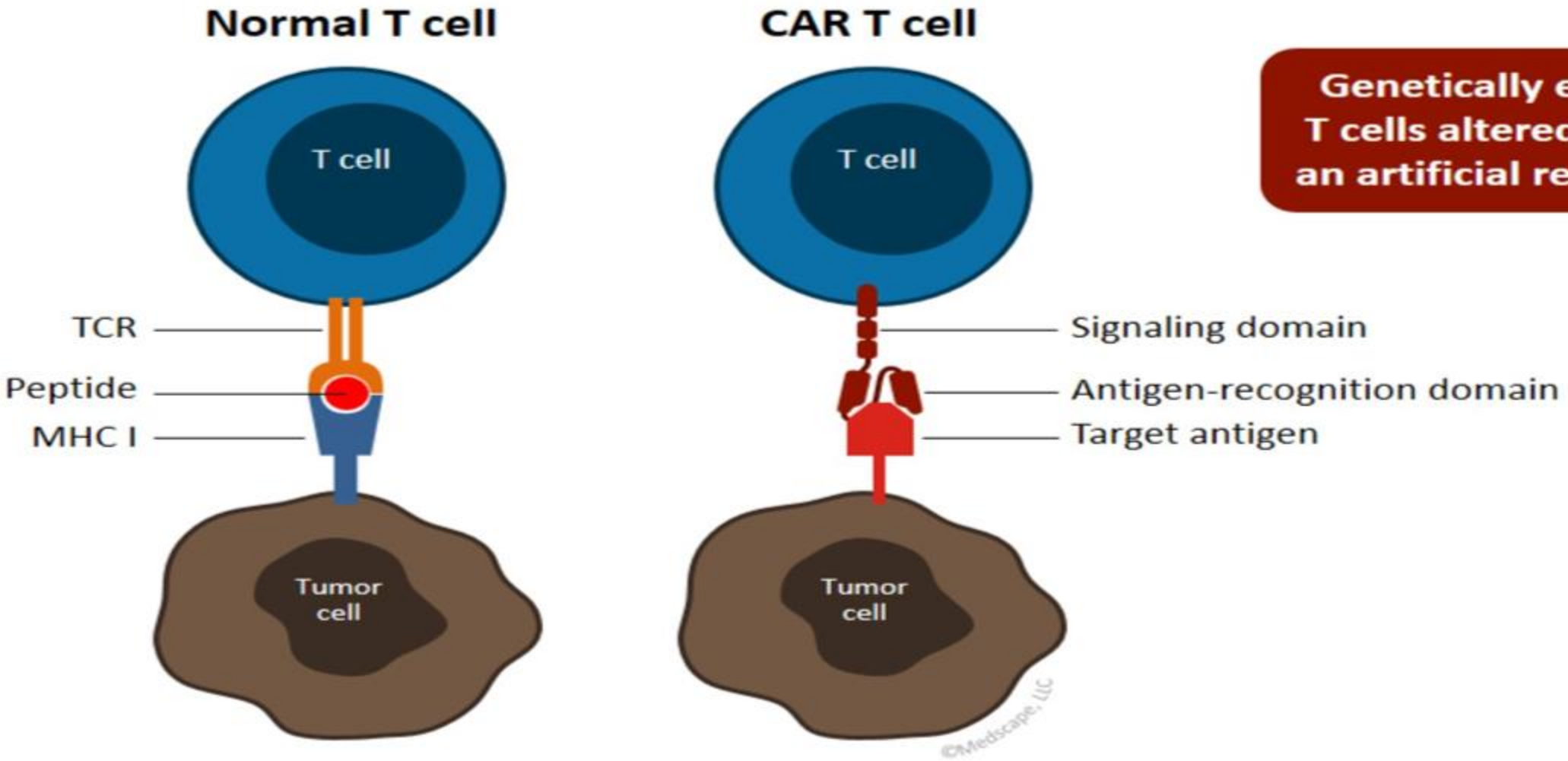
CAR T-Cell Structure

- An antigen-binding element (BCR-derived scFv) is fused to a signaling domain chain in the cell membrane with co-stimulatory proteins
- A specific domain targeting an antigen is expressed on the surface



Vu BT, et al. *Biomed Res Ther*. 2016;3:653-665.

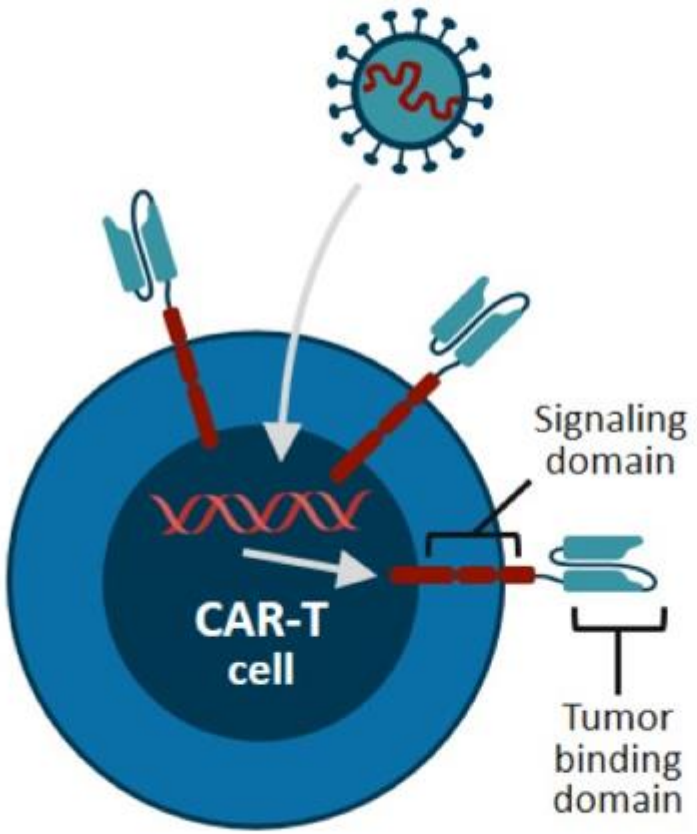
CAR-Modified T Cells

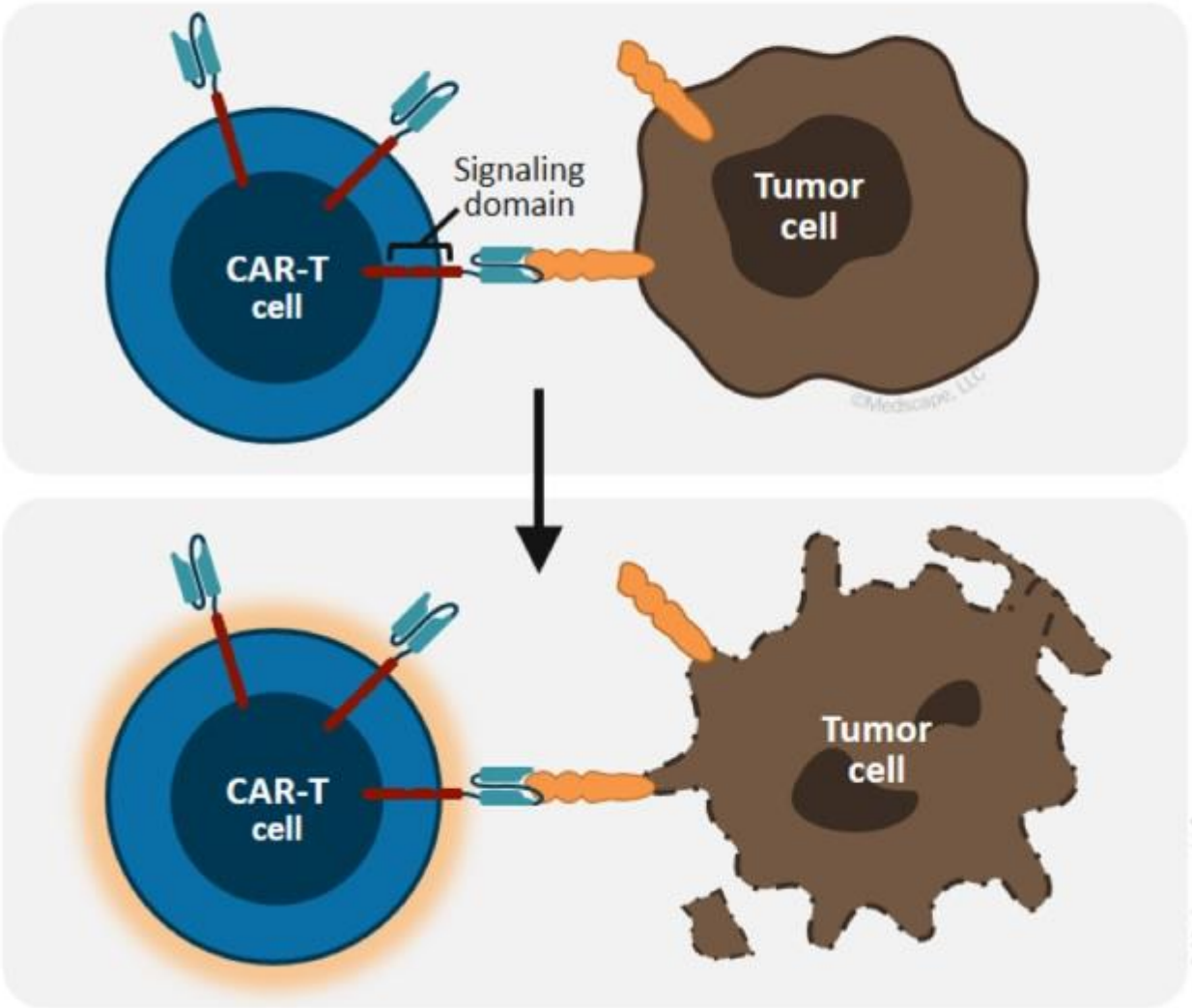


Genetically engineered T cells altered to express an artificial receptor, CAR

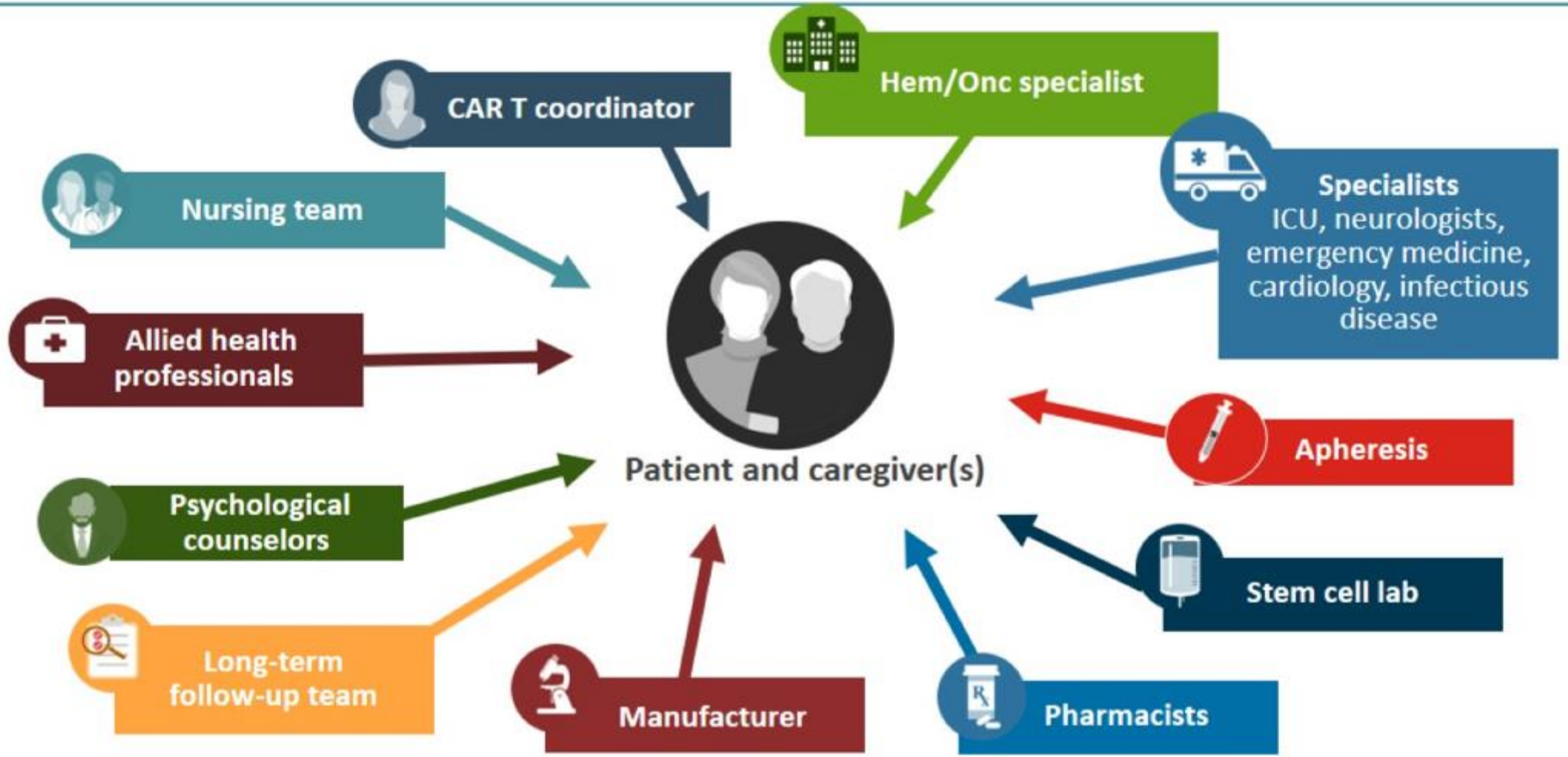
Hinrichs CS, et al. *Nat Biotechnol.* 2013;31:999-1008.

CAR T-Cell Mechanism of Action



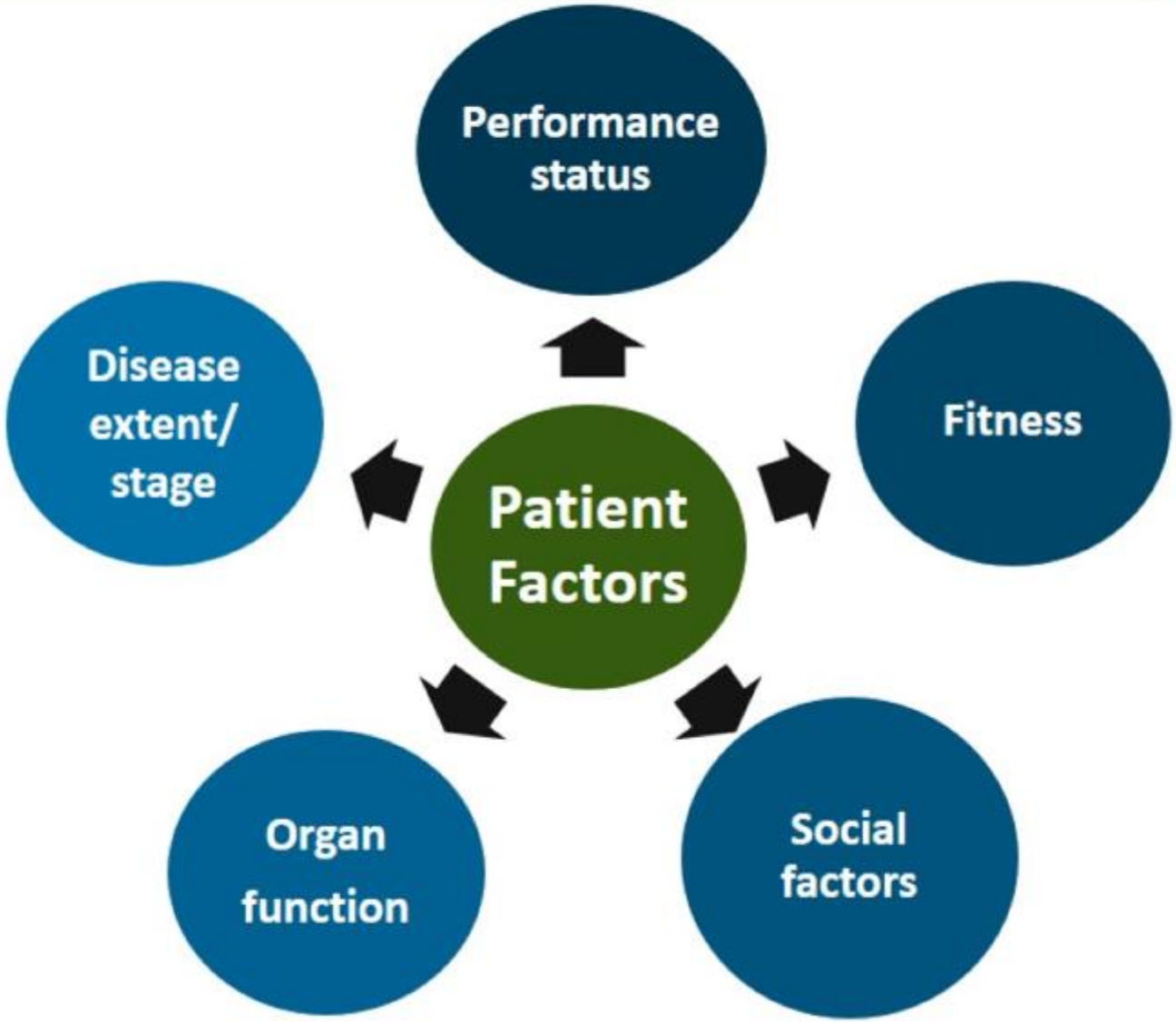


Multidisciplinary Approach to CAR T-Cell Therapy



Selecting CAR T-Cell Therapy
Patient Factors

- Can patients wait for the therapy?
  - Why? **CAR T-cell therapy must be manufactured; not available off-shelf**
    - Can take 2 to 4 weeks to develop
  - Waiting may not be possible with aggressive lymphomas
    - **Bridging therapy:** option to control disease while patient waits; may not work for refractory disease



Cahill KE, et al. *J Leuk Lymphoma*. 2020;61:799-807.

Referring Patients for CAR T-Cell Therapy

Expert Guidance

Refer early

- Refer patients for evaluation by a CAR T specialist as early as possible
- Poorly controlled disease is a common reason for CAR T ineligibility

Bridging therapy may have a role

- It may allow patients to proceed to CAR T-cell therapy
- May be administered at CAR T center or referring center

Referral at the time of relapse, or confirmation of refractory disease after first-line therapy, allows best chance for success of CAR T-cell therapy

Key Patient and Disease Factors in Determining Candidacy for CAR T-Cell Therapy

Factor	Comments
Indications	▪ Does the patient meet a current indication for an FDA-approved CAR T-cell therapy? ▪ Does the patient meet the criteria for a clinical trial?
Kinetics of disease progression	▪ Would the patient be able to go through leukapheresis (without immediate use of steroids/chemotherapy) and remain stable until the T-cell infusion (3-4 wk)? ▪ Does the patient need alternative therapy prior to CAR T-cell therapy consideration?
Immediate prior therapy	▪ How would this affect the ability to successfully manufacture CAR T-cells (ie, obtain sufficient numbers of T-cells and expand)?
Concomitant immunosuppressive therapy	▪ Can this be safely stopped prior to collection?
Active infection	▪ Higher risk of complications if patient experiences CRS
Nondisease-related comorbidities	▪ eg, severe cardiac dysfunction, active symptomatic neurologic symptoms (difficult to accurately assess neurotoxicity)

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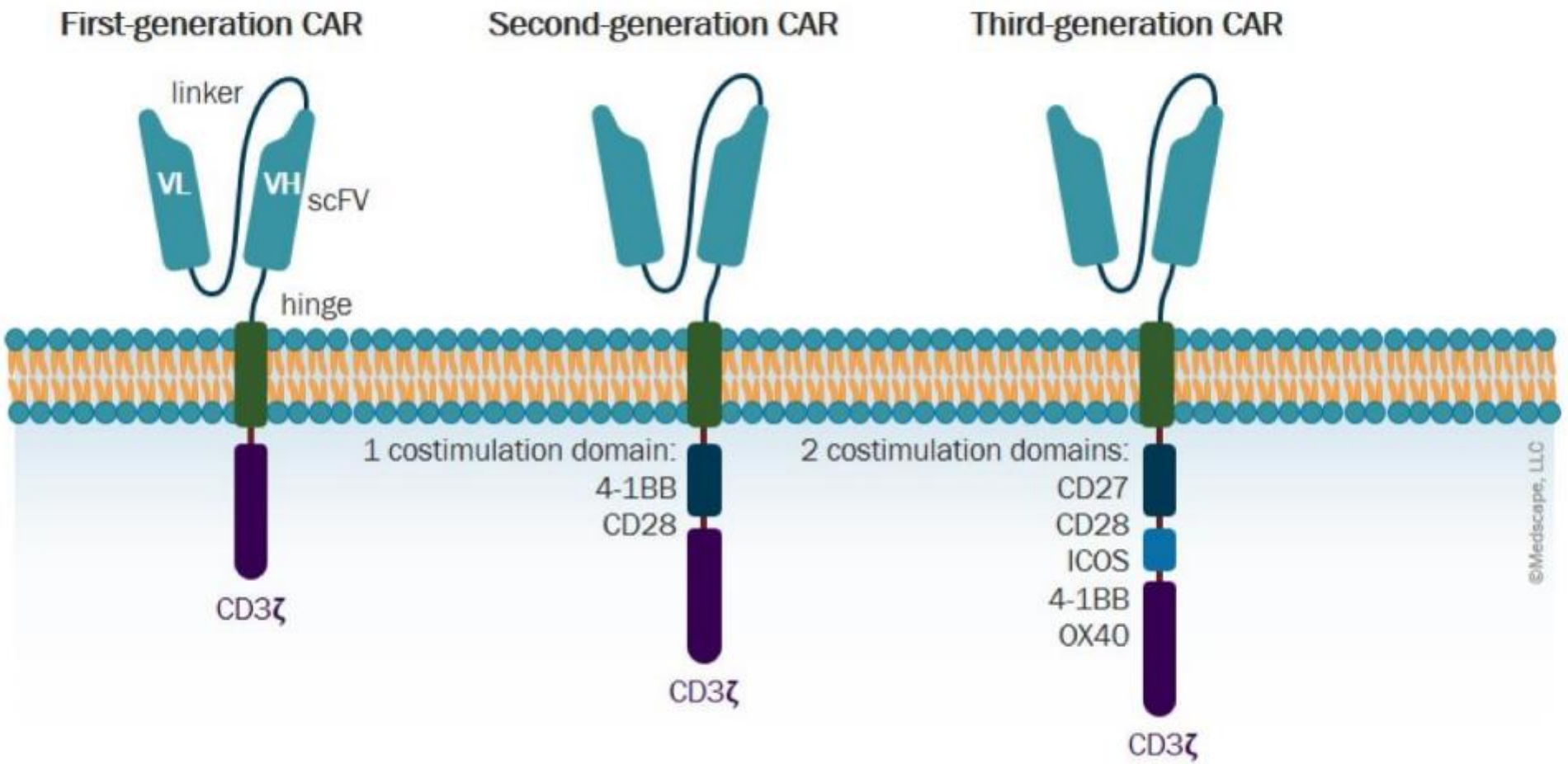
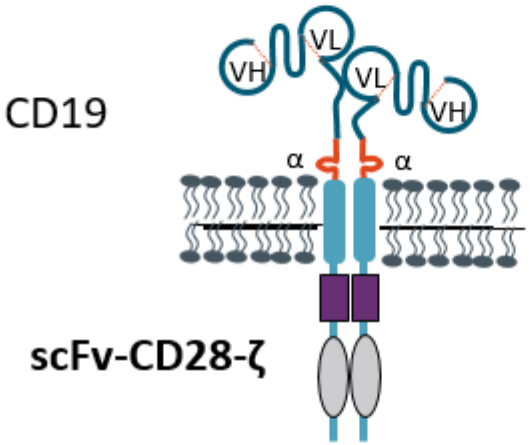
Multiple Generations of CAR T-Cell Technology



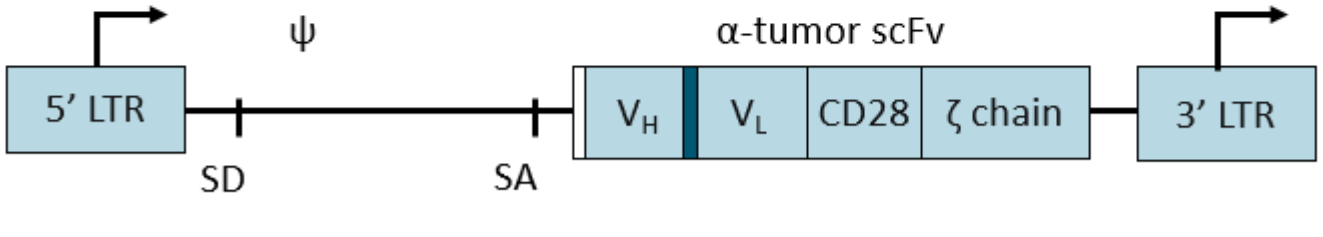
Frey NV, et al. *Am J Hematol*. 2016;91:146-150.

Generation of TAA-Targeted CAR T-Cells for Treatment of Cancer

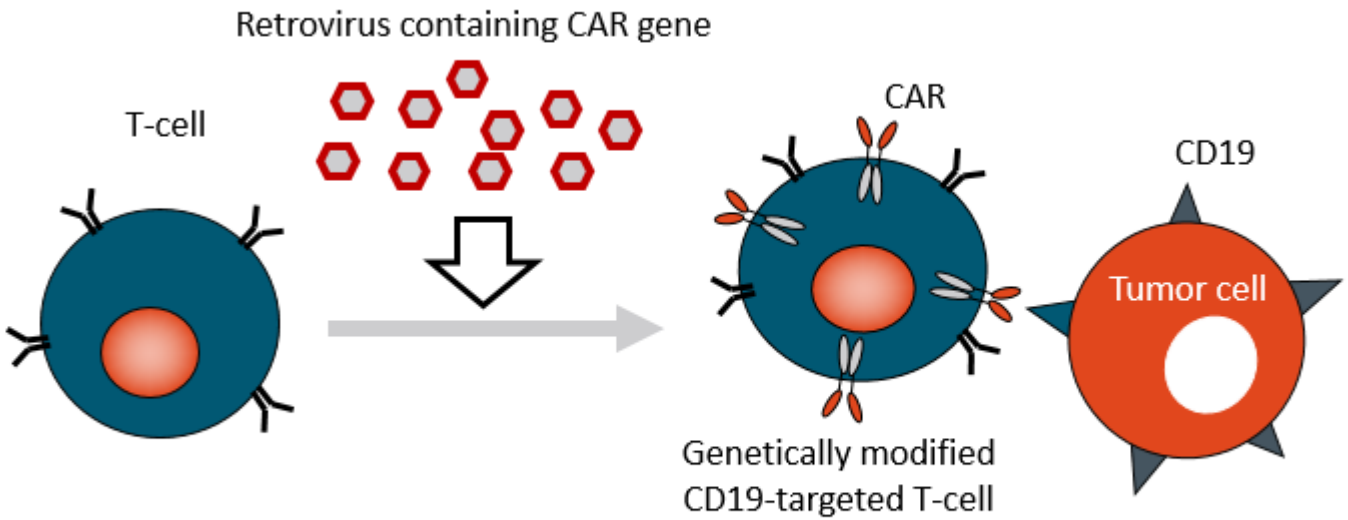
1. Construct a CAR gene



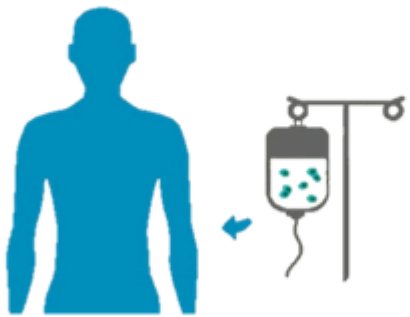
2. Insert CAR gene into a retrovirus vector



3. Transduce and expand patient T-cells ex vivo



4. Infuse CAR T-cells into patient



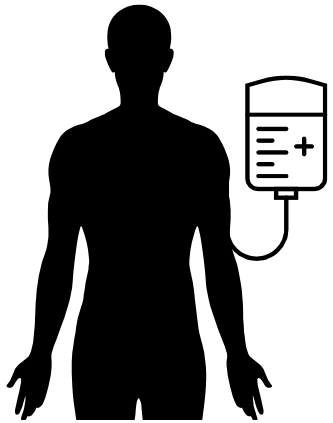
Sadelain. Nat Rev Cancer. 2003;3:35. Brentjens. Nat Med. 2003;9:279. Park. NEJM. 2018;378:449.

Slide credit: clinicaloptions.com

Autologous CAR T-Cell Therapy: Underlying Principles

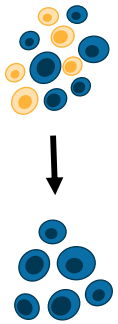
Leukapheresis

Collect patient's white blood cells

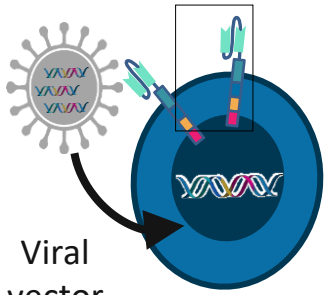


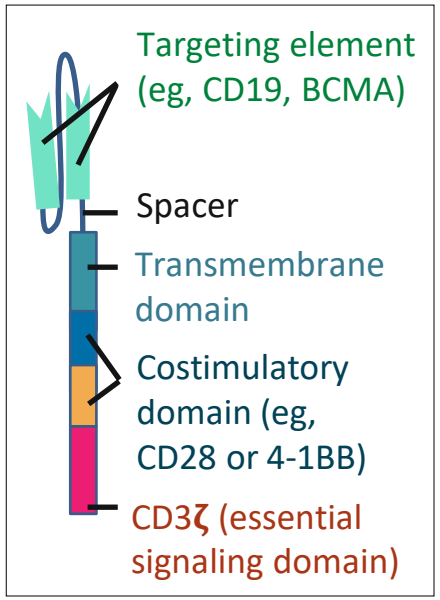
Manufacturing

Isolate and activate T-cells

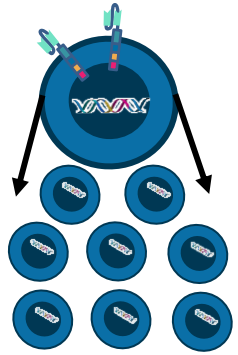


Engineer T-cells with CAR gene





Expand CAR T-cells

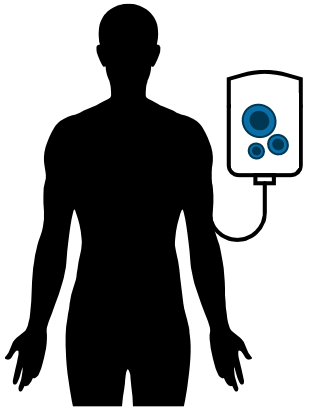


Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

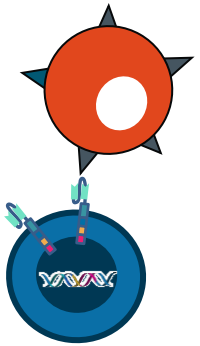
Infusion

Infuse same patient with CAR T-cells



Activity

eg, CD19, BCMA

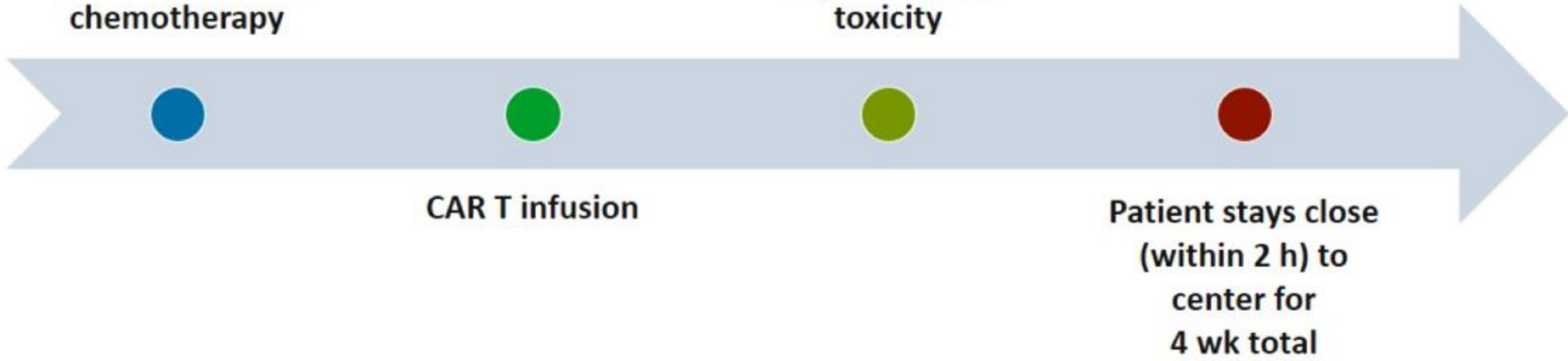


Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

Key Steps in CAR T-Cell Therapy

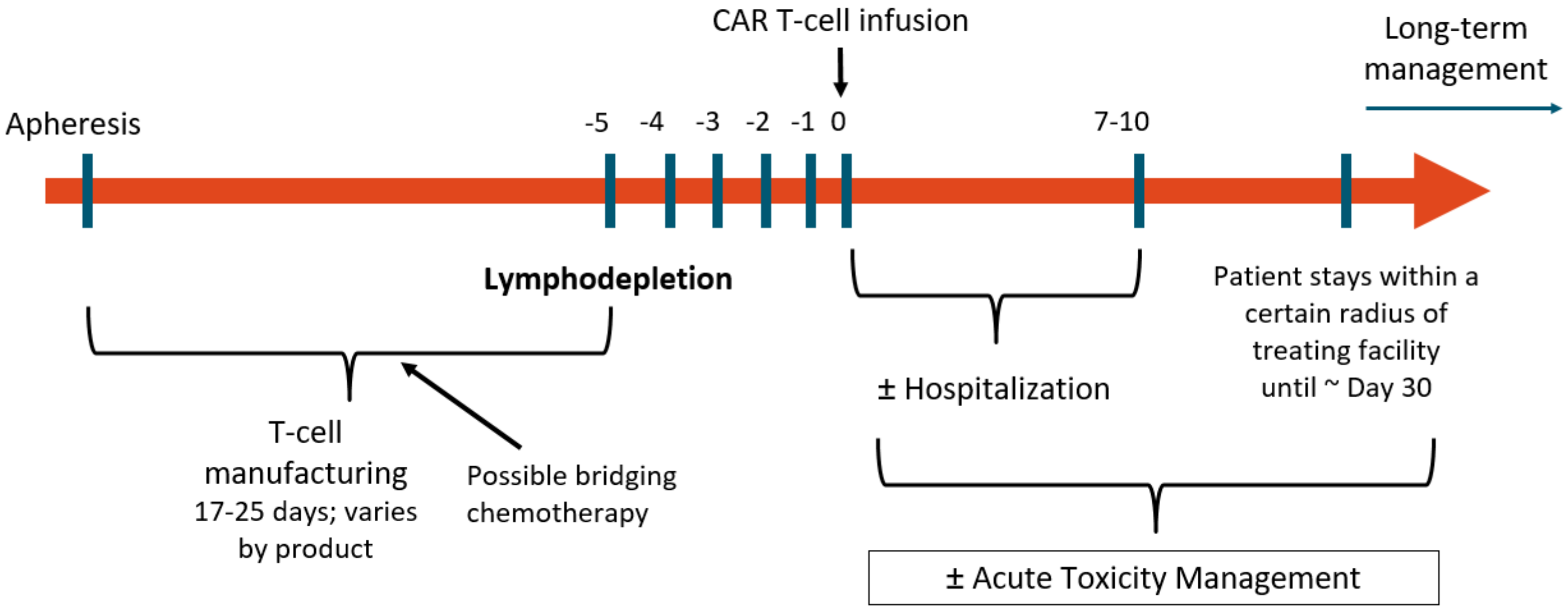
Typical Timeline[a,b]



T-cell manufacturing is successful for up to 99% of patients[c]

a. Hay KA, et al. *Drugs*. 2017;77:237-245; b. Pfefferle A, et al. *Cancers*. 2020;12:1-23; c. Itzhaki O, et al. *J Immunother Cancer*. 2020;8:e000148.

CAR T-Cell Treatment Schema



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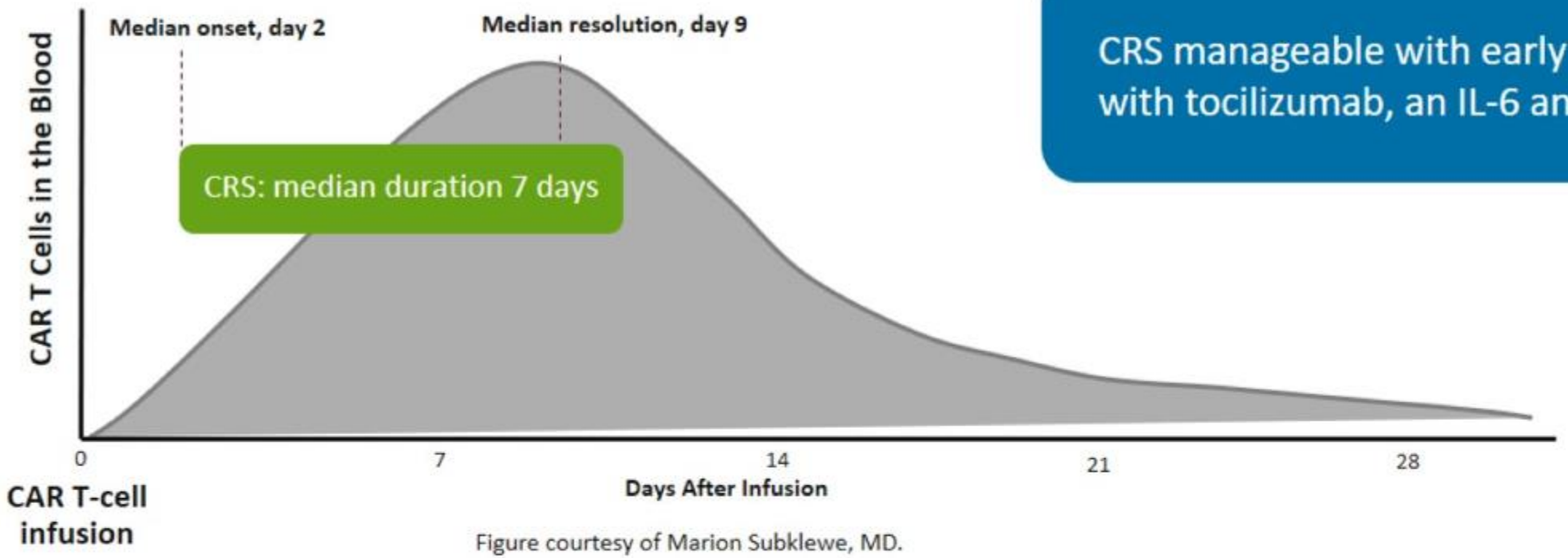
CAR T Cell-Associated Toxicities

CRS and ICANS

CRS coincides with maximal T-cell expansion[a]
CRS may occur within minutes,
but more typically within days[a,b]



CRS manageable with early treatment with tocilizumab, an IL-6 antibody[c]

Figure courtesy of Marion Subklewe, MD.

a. Lee DW, et al. *Blood.* 2014;124:188-195; b. YESCARTA® (axicabtagene ciloleucel) PI 2019; c. Kotch C, et al. *Expert Rev Clin Immunol.* 2019;15:813-822.

Transition of Care to Local Oncologist

CAR T center will provide guidance, and remain in communication with referring providers, regarding monitoring and management of potential prolonged or late toxicities, including

- B-cell aplasia
- Neutropenia -- may require growth factor support
- Opportunistic infections
- Secondary malignancies
- Late neurotoxicity

CAR T specialists encourage open communication with local oncologists and patients

Monitoring Response to CAR T-Cell Therapy

Expert Recommendations

1 month postinfusion: first PET scan done at CAR T center

- Maximal response often observed at this point

1 to 3 months postinfusion: follow-up visits as needed

- Frequency of visits depends on degree of cytopenias and requirements for supportive care

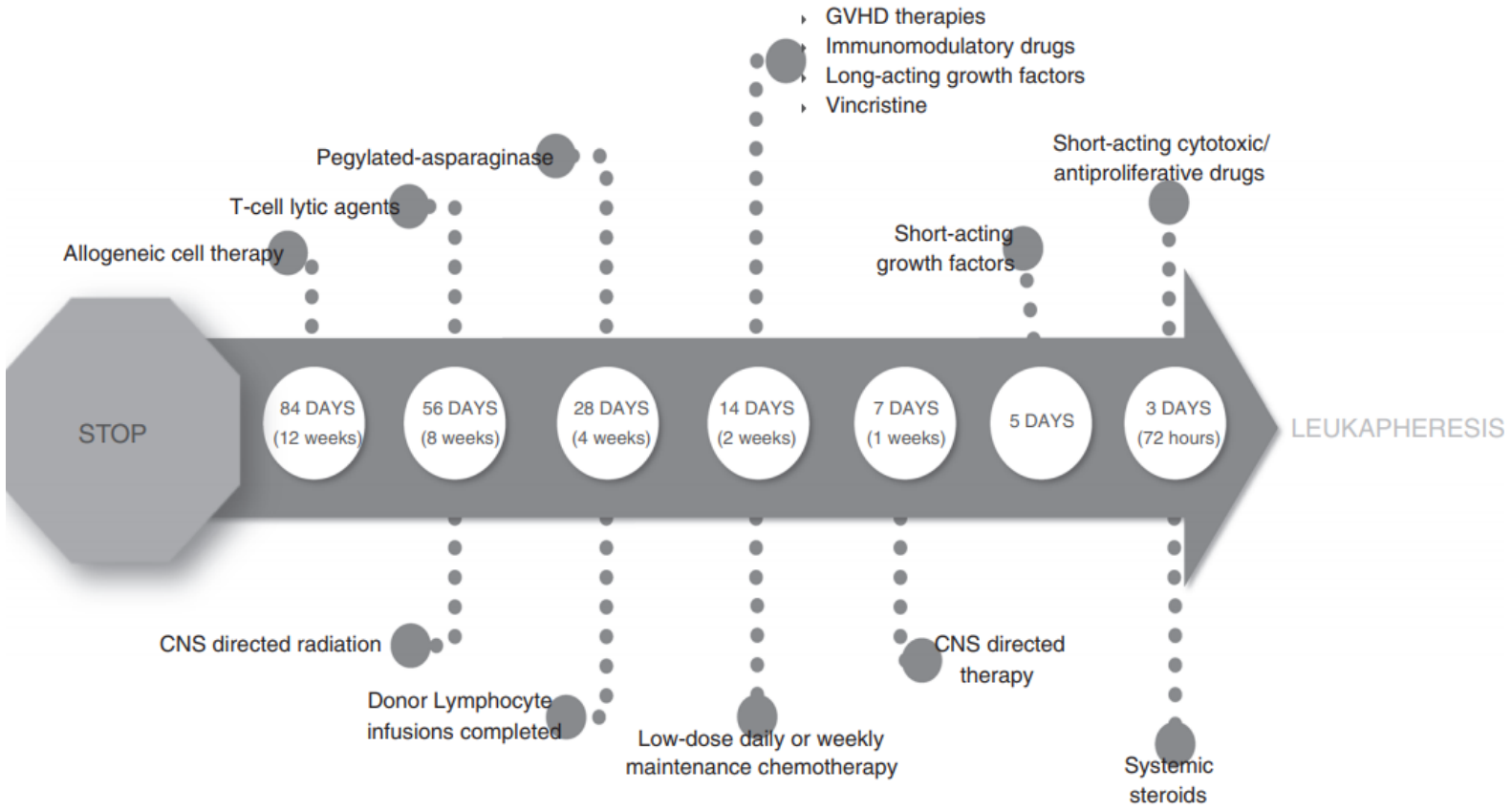
3 months postinfusion: repeat PET scan

- A proportion of PRs will deepen over time[a]

a. Chavez JC, et al. *Ther Adv Hematol*. 2019;10:1-20.

Ready for Leukapheresis?

- Minimum ALC in trials:
  - ZUMA-1: >100/µL[1]
  - JULIET: >300/µL[2]
  - TRANSCEND NHL 001: no minimum[3]
- Limit/space lymphotoxic therapies to enable successful collection[4,5]



1. Neelapu. NEJM. 2017;377:2531. 2. Schuster. NEJM. 2019;380:45. 3. Abramson. Lancet. 2020;396:839.
4. Kansagra. Bone Marrow Transplant. 2019;54:1868. 5. Jain. Biol Blood Marrow Transplant. 201925:2305.

Slide credit: clinicaloptions.com

Do I Need to Consider Bridging Therapy?

- Timing: between leukapheresis and lymphodepletion; not permitted in all trials
- Aim: to reduce/control tumor during CAR T-cell manufacturing
- Key concepts:
  - Limit CRS/ICANS severity
  - Potential impact on CAR T-cell therapy efficacy
  - Stop bridging and allow hematologic recovery prior to lymphodepletion
  - Real-life time from pheresis to infusion often >30 days
  - Some patients may obtain CR with bridging alone

What Lymphodepletion Should I Use?

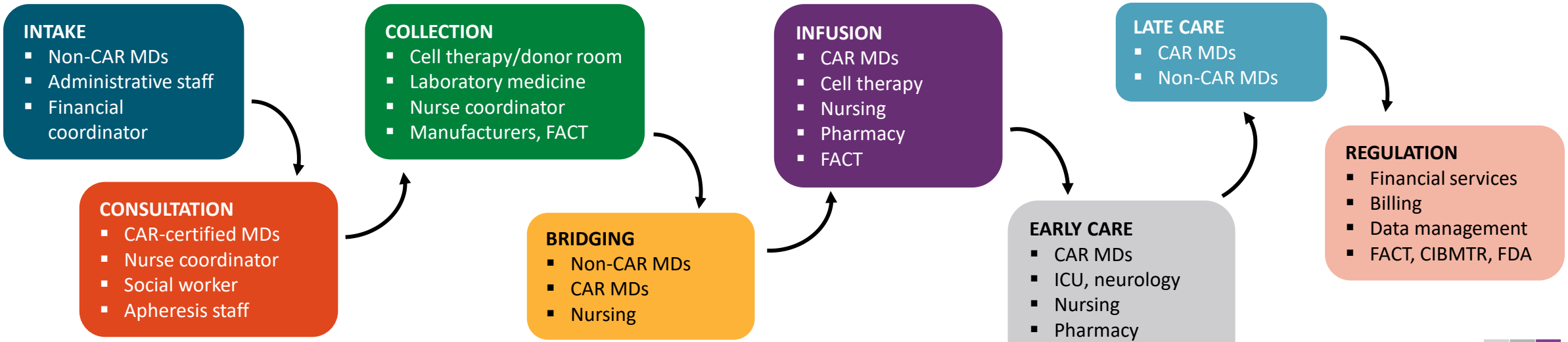
- Is Flu/Cy right for everyone? What if fludarabine is not available?[1,2]
  - Consider prior cyclophosphamide exposure/response/cross-resistance
  - Consider cytopenias (preexisting and tolerance for additional cytopenias)
  - Fludarabine shortage in 2020-2021; transition to bendamustine for lymphoma CAR T-cell therapies[3]
- JULIET: lymphodepletion left to investigator's choice of Flu/Cy, bendamustine, or none[4]
  - Flu/Cy in 73%, bendamustine in 20%, none in 7%
- Bendamustine with commercial tisa-cel (N = 28)[1]
  - 3-mo ORR, 46%; 3-mo CR, 38%; 3-mo PFS rate, 52%; grade ≥3 CRS, 0%; grade 3 neurotoxicity, 4%
  - Day 28: grade ≥3 neutropenia, 11%; grade ≥3 thrombocytopenia, 11%
  - 93% received tisa-cel outpatient
- Lymphodepletion may be omitted if WBC <1000/µL within 7 days of CAR T-cell therapy[2,4]

1. Svoboda. ASH 2019. Abstr 1606. 2. Jain. Biol Blood Marrow Transplant. 201925:2305.
3. https://www.ashp.org/Drug-Shortages. 4. Schuster. NEJM. 2019;380:45.

Multidisciplinary Team Roles in Delivering CAR T-Cell Therapies

- All physicians, pharmacists, nurses, and other advanced practice providers interacting with patients receiving CAR T-cell therapy must have FDA-mandated training in management of CRS and neurologic toxicities
- Pharmacists and nurses have vital roles in patient and caregiver education and in prevention, identification, and management of CAR T-cell–associated toxicities

Essential Steps and Required Personnel



Perica. Biol Blood Marrow Transplant. 2018;24:1135. Axicabtagene ciloleucel PI. Brexucabtagene autoleucel PI. Idecabtagene vicleucel PI. Lisocabtagene maraleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

Clinical Trial and Real-World Data for Currently Approved Agents

CD19 = Good CAR T-Cell Tumor Antigen

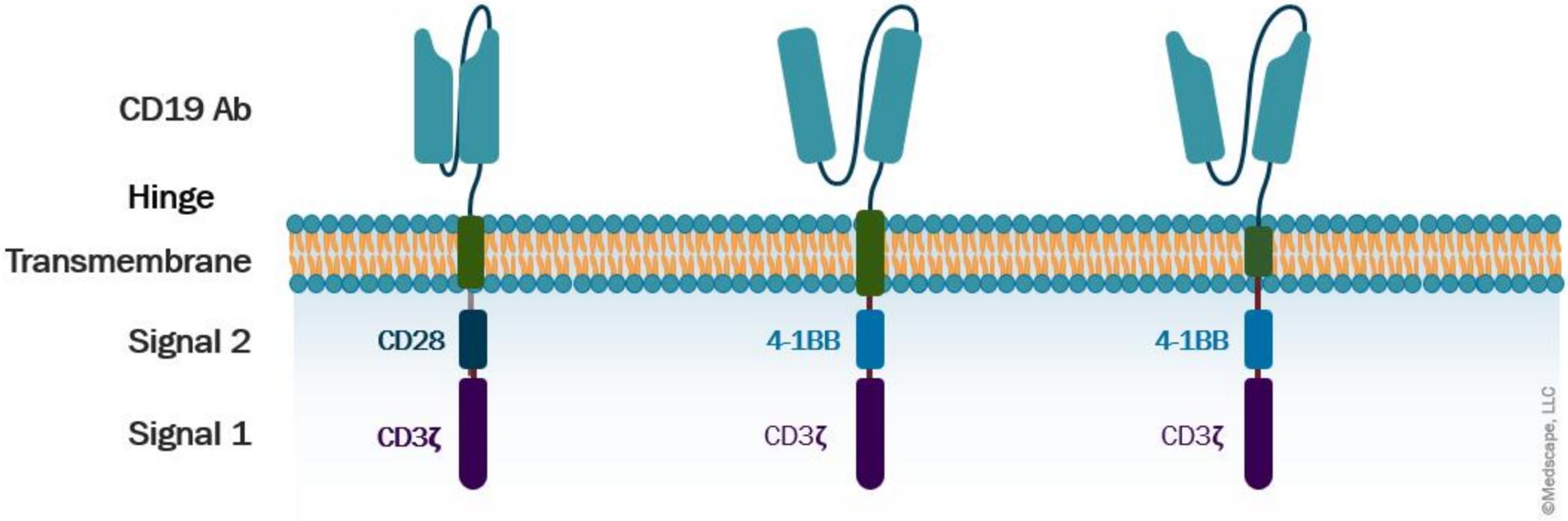
University of Pennsylvania → Tisagenecleucel
- Costumulatory molecule: 4-1BB

National Cancer Institute → Axicabtagene ciloleucel
- Costumulatory molecule: CD28

Memorial Sloan Kettering → CD28: JCAR015
- Costumulatory molecule: CD28

Fred Hutchinson Cancer Research Center → 4-1BB: lisocabtagene ciloleucel (JCAR017)
- Costumulatory molecule: 4-1BB

CD19 CAR T Products in Pivotal Trials in ALL and/or NHL



Gene transfer	Retrovirus	Lentivirus	Lentivirus
	↓	↓	↓
	Axicabtagene ciloleucel	**Tisagenlecleucel**	**Lisocabtagene maraleucel (JCAR017) CD4:CD8 = 1.1**

van der Stegen SJ, et al. *Nat Rev Drug Discov*. 2015;14(7):499-508.

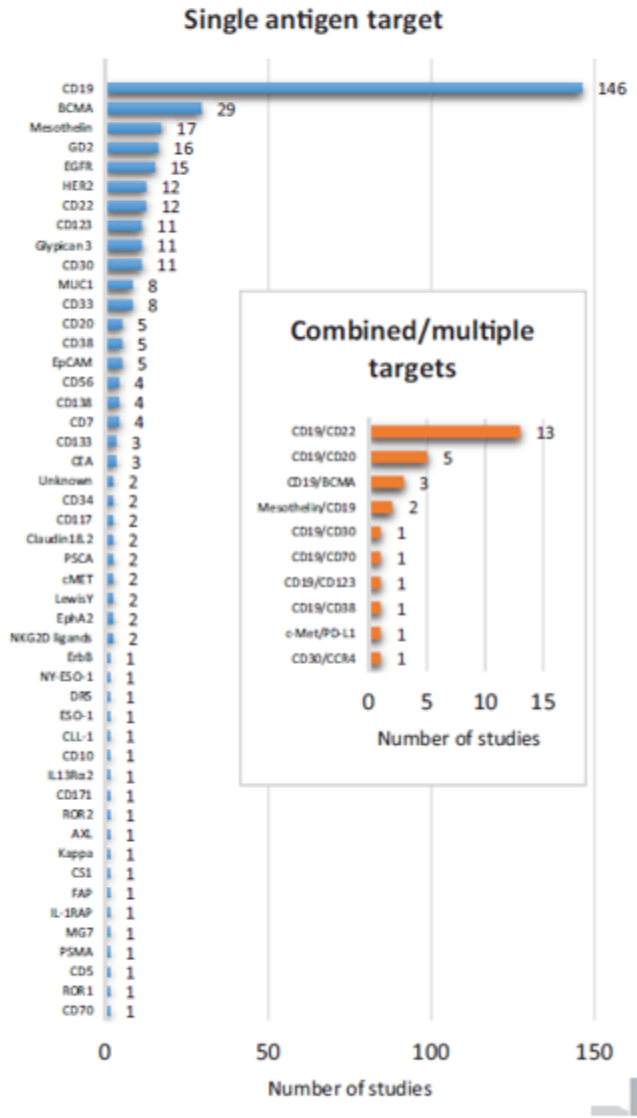
Other Engineered T-Cell Tumor Antigens

MM	BCMA
HL	CD30
AML	CD123
Synovial Cell Carcinoma	NY ESO-1

Brudno JN, et al. *J Clin Oncol*. 2018;36:2267-2280.
Wang C-M, et a.l *Clin Cancer Res*. 2017;23:1156-1166.
Gill S, et al. *Blood*. 2014;123:2343
Robbins PF, et al. *JCO*. 2011;29:917

CAR T-cell Targets for the Treatment of Hematologic Malignancies

Antigen Target	CAR structure	Malignancy
CD19	CD3ζ and CD28 or CD3ζ and 4-1BB	B-ALL, CLL, DLBCL, FL, MCL
CD22	CD3ζ and CD28	B-ALL, DLBCL, FL, NHL
CD20	CD3ζ or and CD3ζ and 4-1BB	CD20-positive malignancies
ROR1	CD3ζ and 4-1BB	CLL, SLL
Igk	CD3ζ and CD28	CLL, low-grade malignancies
CD30	CD3ζ and CD28	HL, NHL
CD123	CD3ζ and CD28	AML
CD33	CD3ζ and 4-1BB	AML
LeY	CD3ζ and CD28	AML
BCMA	CD3ζ and 4-1BB	MM
CD138	CD3ζ and 4-1BB	MM



Jackson. Nat Rev Clin Oncol. 2016;13:370. Charrot. Hemasphere. 2019;3:e188.

Slide credit: clinicaloptions.com

FDA-Approved CAR T-Cell Therapies

Therapy	Indications	Cost*
CD19-Targeting Therapies		
Axicabtagene ciloleucel	▪ **Adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy,** including DLBCL NOS, DLBCL arising from follicular lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma ▪ **Adults with R/R follicular lymphoma after ≥2 lines of systemic therapy**	$373,000
Brexucabtagene autoleucel	▪ **Adults with R/R MCL**	$373,000
Lisocabtagene maraleucel	▪ **Adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy**, including DLBCL NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B	$410,300
Tisagenlecleucel	▪ **Patients aged up to 25 yr with B-cell precursor ALL that is refractory or in second/later relapse** ▪ **Adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy**, including DLBCL NOS, DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma	DLBCL: $373,000 ALL: $475,000
BCMA-Targeted Therapy		
Idecabtagene vicleucel	▪ **Adults with R/R multiple myeloma after ≥4 prior lines of therapy**, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab	$419,500

*Wholesale acquisition cost (USD).

Axicabtagene ciloleucel PI. Brexucabtagene autoleucel PI. Idecabtagene vicleucel PI. Lisocabtagene maraleucel PI. Tisagenlecleucel PI. Geethakumari. Curr Hematol Malig Rep. 2021(Jun 5):1.

Slide credit: clinicaloptions.com

CLINICAL CARE OPTIONS®
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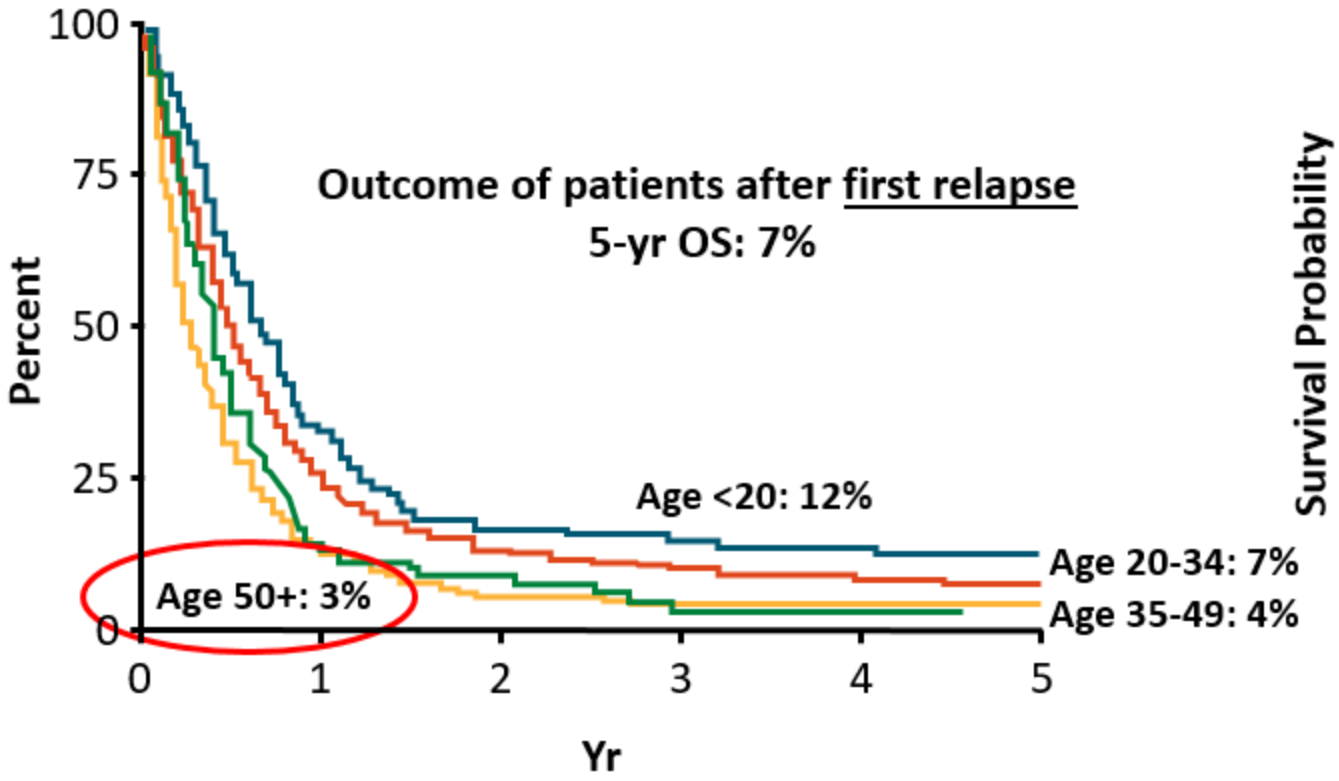
CAR T-Cell Therapies for ALL

Jae H. Park, MD
Associate Member
Leukemia Service and Cellular Therapeutics Center
Memorial Sloan Kettering Cancer Center
New York, New York

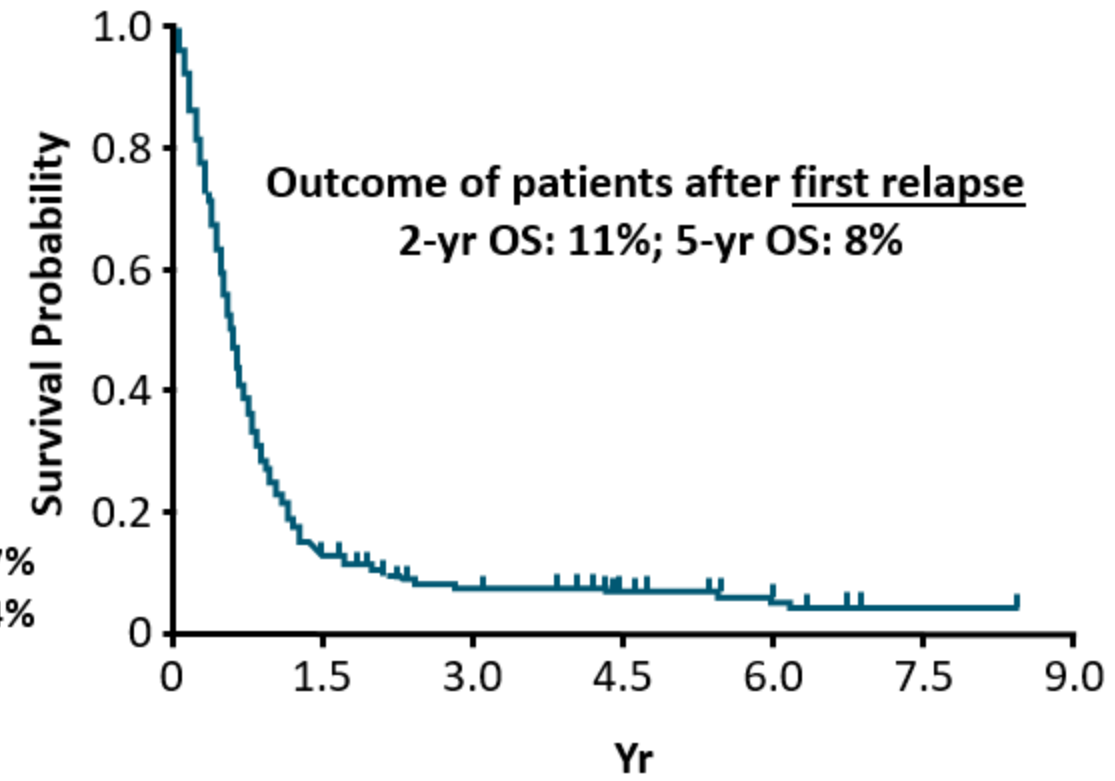
Supported by an educational grant from Bristol-Myers Squibb.

Poor Prognosis of Relapsed ALL in Adults

MRC UKALL2/ ECOG2993 Study (N = 609)[1]



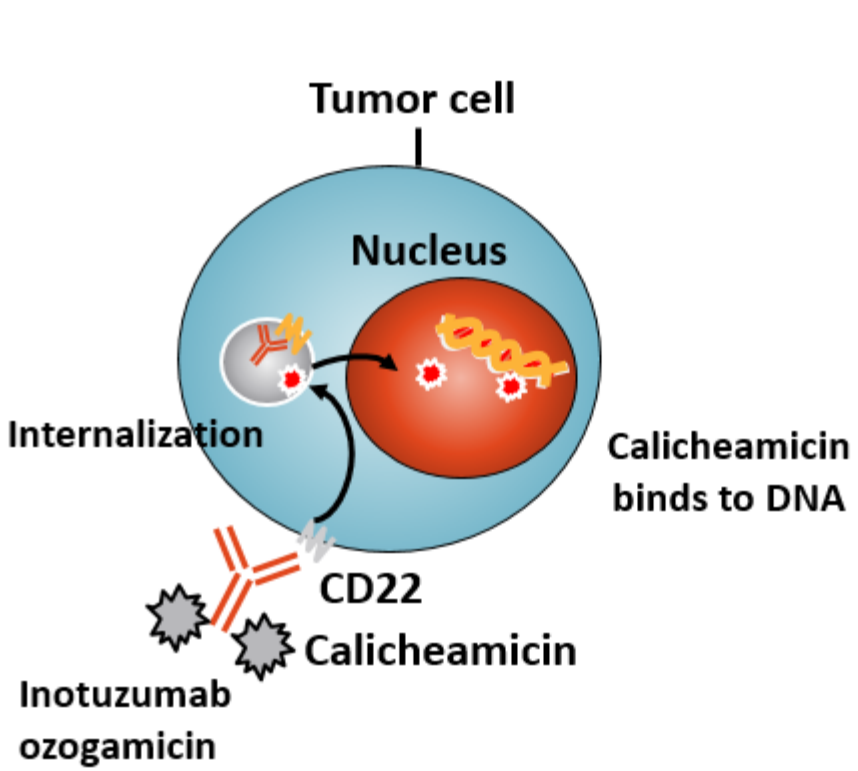
LALA-94 Study (n=421)[2]

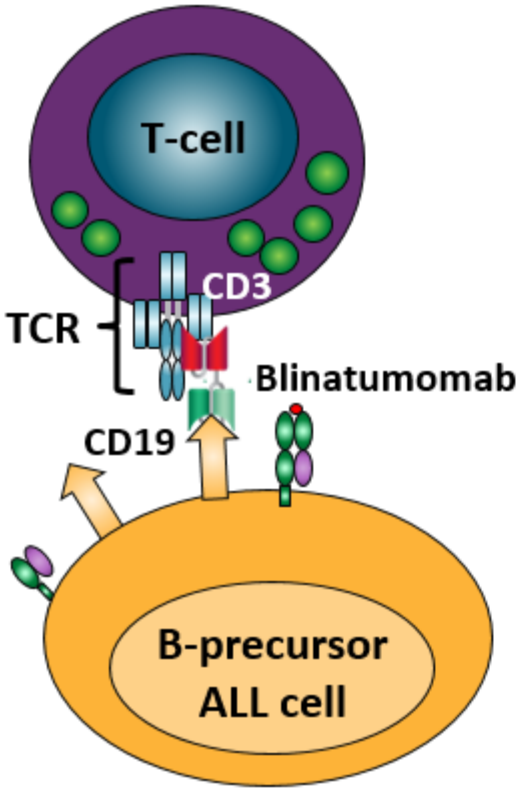


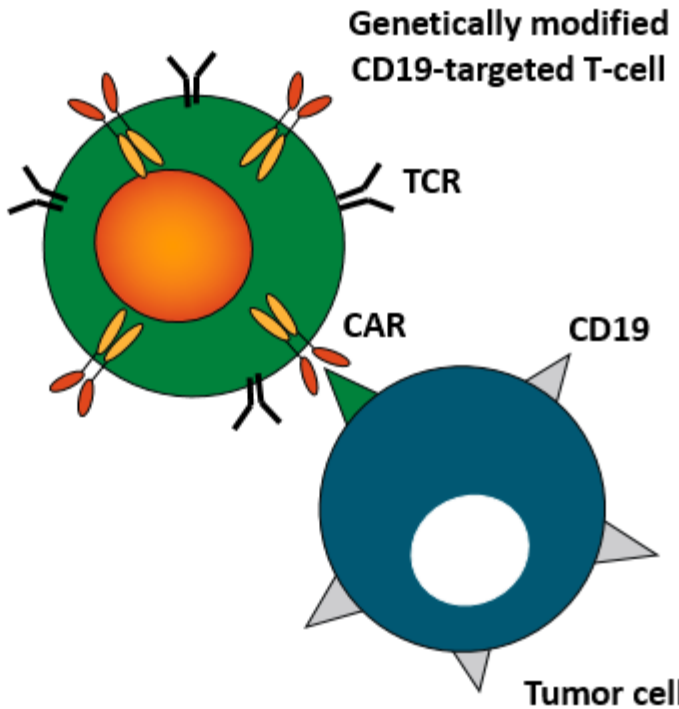
1. Fielding. Blood. 2007;109:944. 2. Tavernier. Leukemia. 2007;21:1907.

Slide credit: clinicaloptions.com

Current Immunotherapy Targets in Adult Relapsed/Refractory ALL







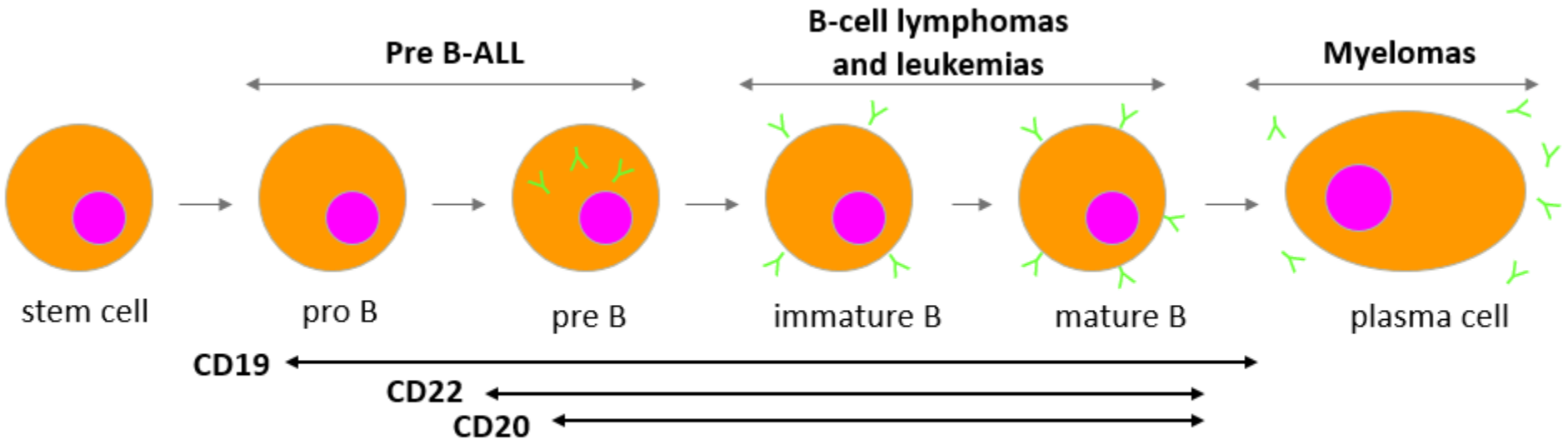
BiTE and CAR T-cell therapies engage the immune system to fight ALL

Maino. Exp Rev Hema. 2016;9:563.

Slide credit: clinicaloptions.com

CD19

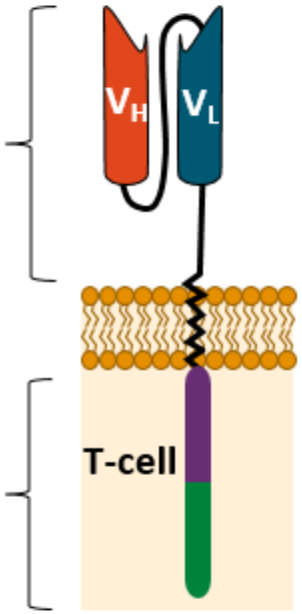
- CD19 expression is restricted to B-cells and possibly follicular dendritic cells
- CD19 is not expressed on pluripotent bone marrow stem cells
- CD19 is expressed on the surface of most B-cell malignancies
- Antibodies against CD19 inhibit growth of tumor cells



Mostolizadeh. Numer Algebra Control Optim. 2018;8:63. Wang. Exp Hematol Oncol. 2012;1:36.

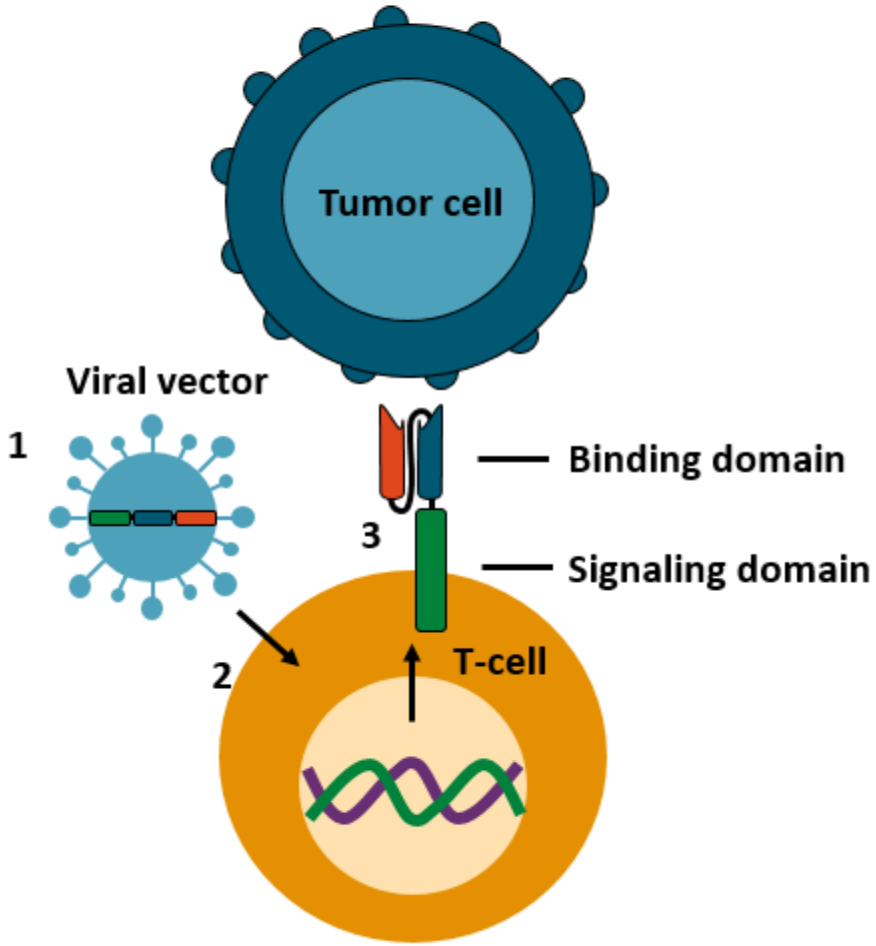
Slide credit: clinicaloptions.com

CD19-Directed CAR T-Cell



Fusion protein

- T-cell costimulatory receptor signaling domain
- TCRζ activation domain



CD19-directed CAR T-cell

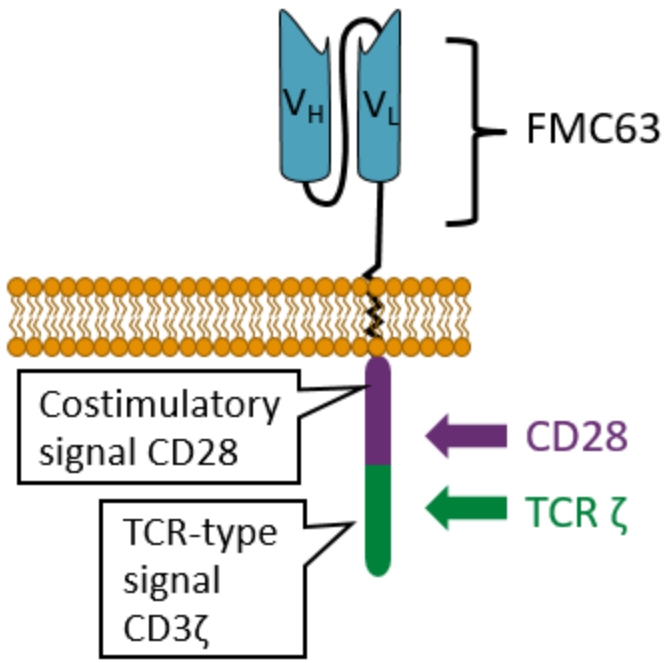
- Comprising a CD19 antigen–binding domain, a costimulatory domain (generally CD28 or 4-1BB), and CD3-ζ signaling domain

Slide credit: clinicaloptions.com

CD19-Directed CAR T-Cell Products

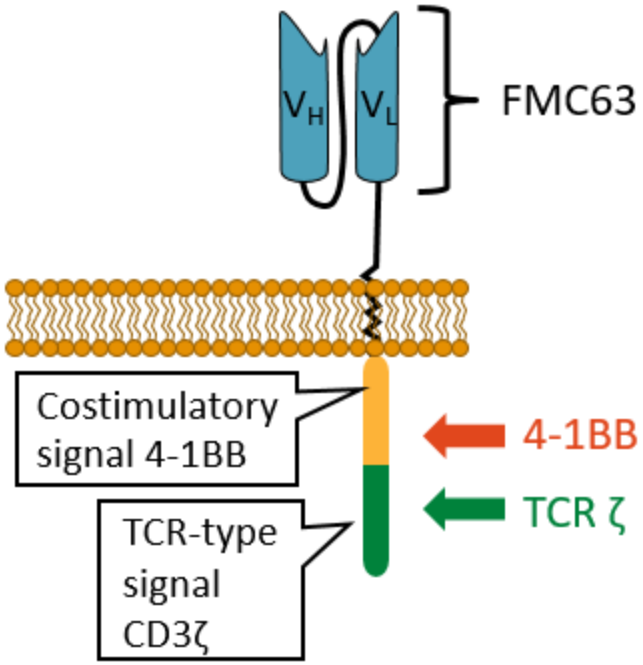
Axicabtagene ciloleucel (Axi-cel)
Brexucabtagene autoleucel

- CD28 costimulation
- Second generation



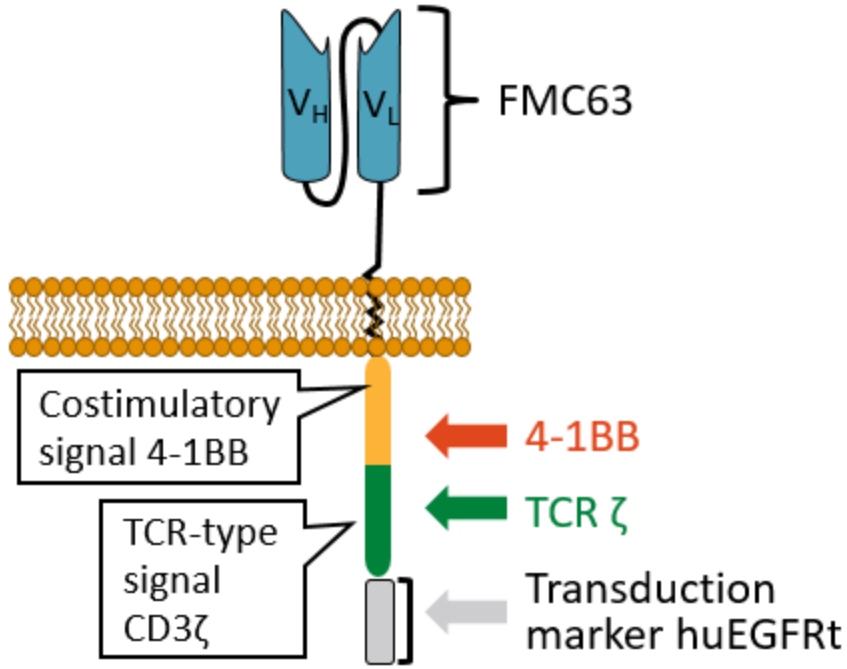
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



van der Stegen. Nat Rev Drug Discov. 2015;14:499.

Slide credit: clinicaloptions.com

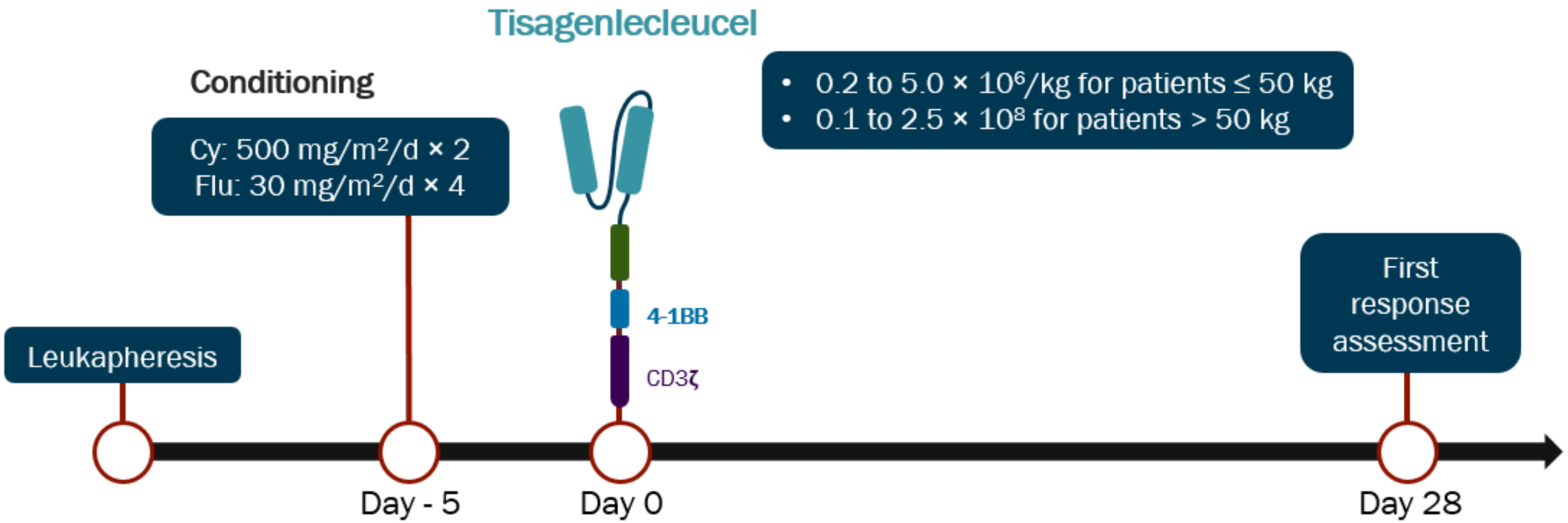
Anti-CD19 CAR T Cell Products for Aggressive B-Cell NHL

	Axicabtagene Ciloleucel (axi-cel)	Tisagenlecleucel (tisa-cel)	Lisocabtagene Maraleucel[e] (liso-cel)
Construct	anti-CD19-CD28-CD3ζ[a]	anti-CD19-41BB-CD3ζ[c]	anti-CD19-41BB-CD3ζ
Vector	Retrovirus[a]	Lentivirus[c]	Lentivirus
T-cell manufacturing	Bulk[b]	Bulk[c]	Defined doses CD4, CD8
Dose	2×10^6/kg (max 2×10^8)[b]	0.1 to 6.0×10^8[d]	DL1: 0.5×10^7 DL2: 1.0×10^8 DL3: 1.5×10^8
Treated / enrolled, n/n (%)	101/119 (91)	111/165 (67)[d]	256/344 (74)
Bridging therapy	None allowed in pivotal trial but often used in standard practice	92%[d]	72%
Lymphodepletion	Flu/Cy 30/500 mg/m^2 × 3 d	Flu/Cy 25/250 mg/m^2 × 3 d, or Benda 90 mg × 2 d[d]	Flu/Cy 30/300 mg/m^2 × 3 d
Approval status	FDA/EMA approved for DLBCL, high grade B-cell lymphoma, transformed FL, PMBCL	FDA/EMA approved for pediatric B-ALL, DLBCL, high grade B-cell lymphoma, transformed FL[c]	FDA approved for R/R large B-cell lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B[f]*

*The FDA approved liso-cel on February 5, 2021, after the taping of this video.

a. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42; b. YESCARTA™ (axicabtagene ciloleucel) [PI]. 2017; c. KYMRIAH™ (tisagenlecleucel)[PI]. 2017; d. Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56; e. Abramson J, et al. *Lancet*. 2020;396:839-852; f. FDA. News release. February 5, 2021.

ELIANA: First Multicenter Trial of CTL019 in Relapsed/Refractory Pediatric and Young Adult ALL



Eligibility

- R/R B-cell ALL with ≥ 5% lymphoblasts in BM
- Ages 3 to 23 years at screening, median: 11 years

Endpoints

- Primary: ORR within 3 months
- Secondary: MRD status within 3 months, DOR, OS

Grupp SA, et al. ASH 2016. Abstract 221.

ELIANA: Efficacy of Tisagenlecleucel in R/R B-ALL

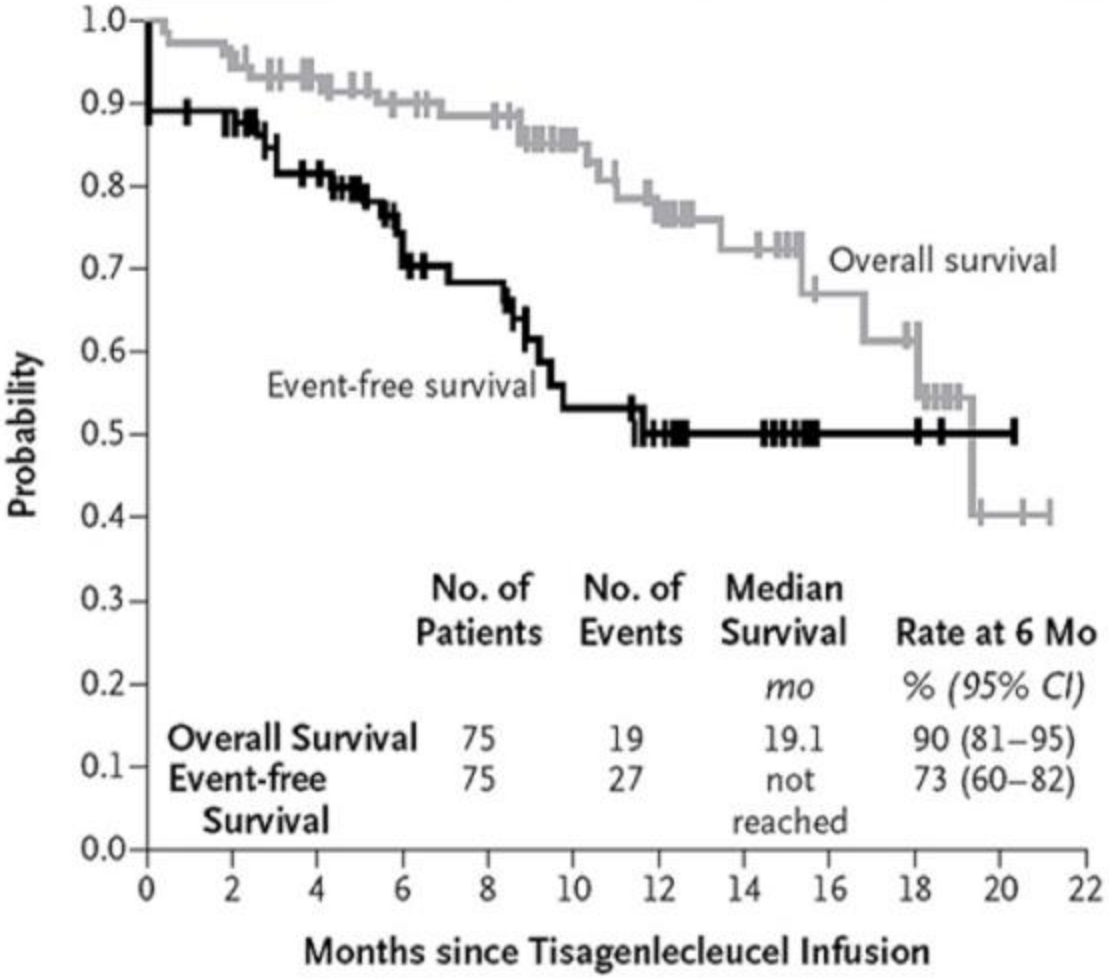
Response, N = 63	n, %
ORR (CR plus CRi) within 3 mo	52 (83)*
CR	40 (63)
CRi	12 (19)
Day 28 response	53 (84)
CR or CRi with MRD-negative bone marrow	52 (83)*

- MRD-negative = flow cytometry of < 0.01%

*P <.0001.

Grupp SA, et al. ASH 2016. Abstract 221.
FDA Oncologic Drugs Advisory Committee website. CTL019 (tisagenlecleucel).

ELIANA: EFS and OS

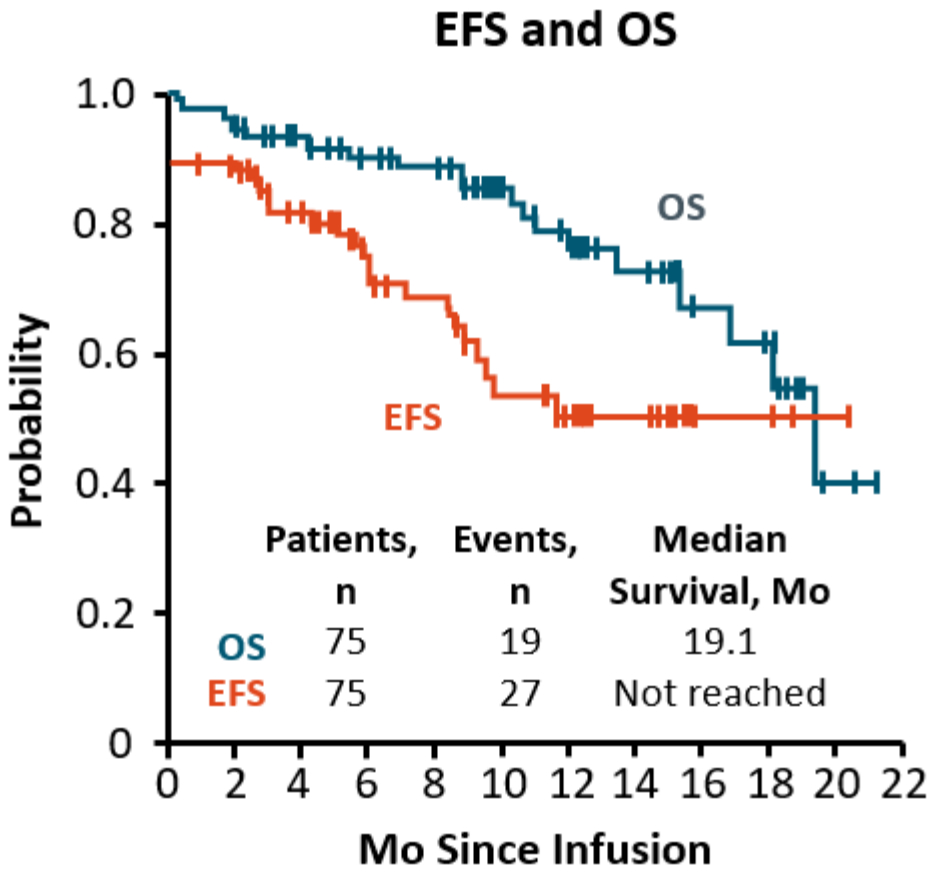


	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

- Median duration of EFS not reached
  - 75% relapse-free at 6 months after onset of remission
- Median OS: 16.6 months
  - Probability of 6-month and 12-month OS 89% and 79%
- FDA approved tisagenlecleucel on August 30, 2017

Maude SL, et al. *N Engl J Med.* 2018;378(5):439-448.

ELIANA: Efficacy



Outcome, %	Mo 6	Mo 12
OS	90	76
Event-free survival	73	50

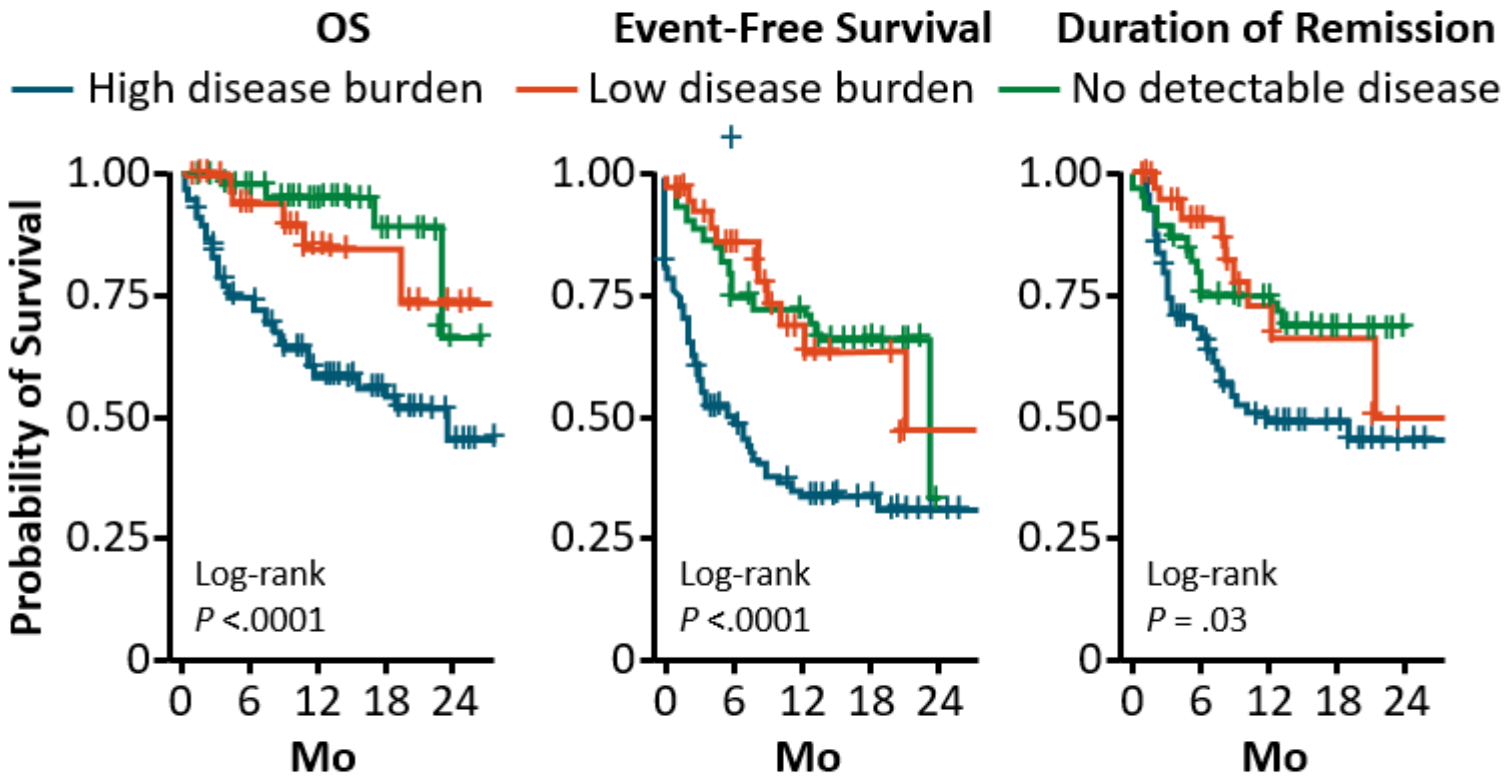
- ORR at 3 mo: 81%
- Tisagenlecleucel FDA approved for patients aged up to 25 yr with B-cell precursor ALL that is refractory or in second or later relapse

Maude. NEJM. 2018;378:439.

Slide credit: clinicaloptions.com

Real World Outcomes With Tisagenlecleucel in Pediatric R/R B-ALL

- Aim: assess real-world clinical outcomes among pediatric patients with R/R B-ALL receiving tisagenlecleucel
- Design: retrospective analysis of data collected from 15 institutions in Pediatric Real World CAR Consortium (PRWCC) (N = 184)



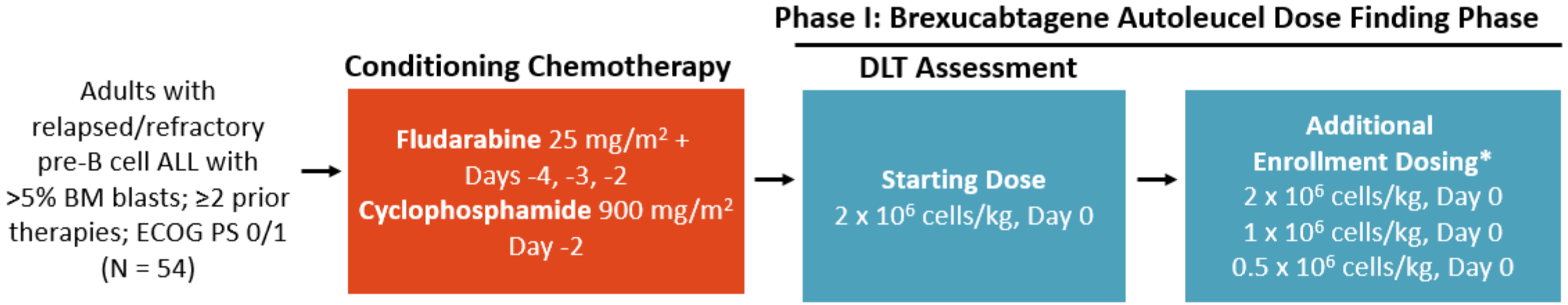
- High disease burden associated with poorer outcomes

Schultz. ASH 2020. Abstr 468.

Slide credit: clinicaloptions.com

ZUMA-3: Brexucabtagene Autoleucel (KTE-X19) for Adult Patients With Relapsed/Refractory ALL

- Multicenter, open-label phase I/II trial

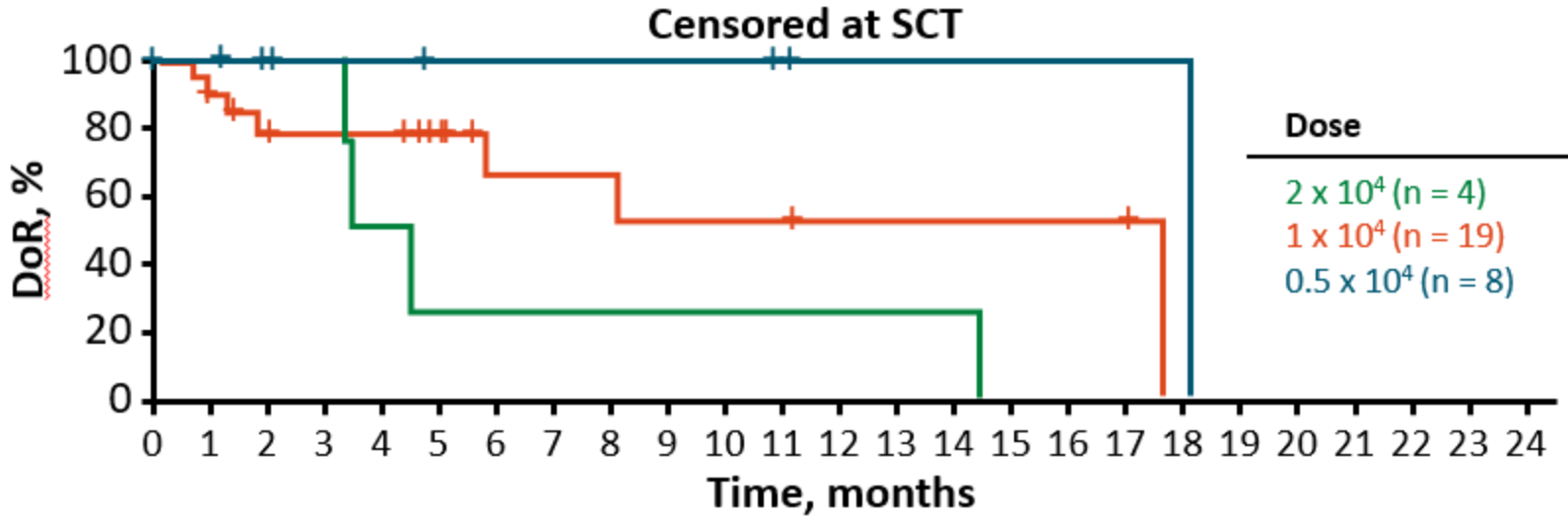


- Phase I primary endpoints: DLTs,† safety; phase I secondary endpoints: ORR, DoR, RFS, OS, MRD-negativity, safety, CAR T-cell levels

*Potential to enroll additional patients at lower doses based on safety assessment. †Grade 3 nonhematologic AEs persisting >7 days, all grade 4 nonhematologic AEs within 28 days of infusion except prespecified expected events, or grade 4 hematologic AEs persisting >30 days except lymphopenia.

Shah. Blood. 2021;[Epub].

ZUMA-3: Phase I Updated Response



Dose	Median DoR (95% CI), mo
2 x 10^4 (n = 4)	4.0 (3.4, 14.5)
1 x 10^4 (n = 19)	17.6 (5.8, 17.6)
0.5 x 10^4 (n = 8)	18.1 (NE, NE)

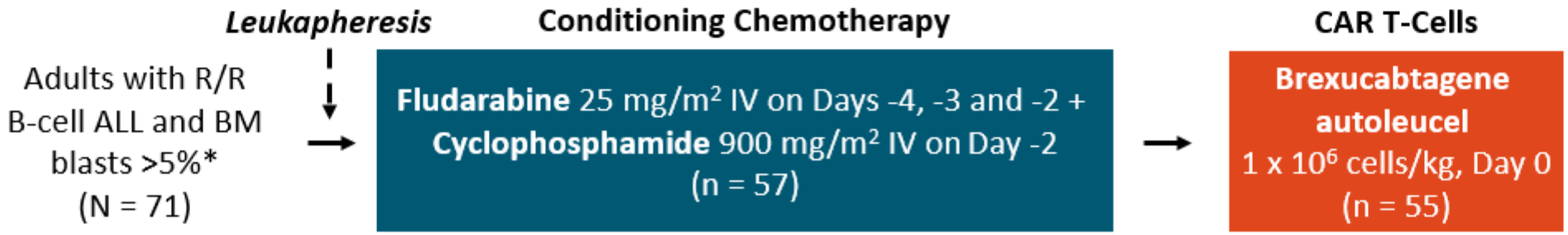
Response, n (%)*	2 x 10^6 Dose (n = 6)	1 x 10^6 Dose (n = 23)	0.5 x 10^6 Dose (n = 16)	Overall (n = 45)
CR + CRi	4 (67)	**19 (83)**	8 (50)	31 (69)
▪ CR	3 (50)	**15 (65)**	6 (38)	24 (53)
▪ CRi	1 (17)	**4 (17)**	2 (13)	7 (16)
Blast-free hypo/aplastic BM	0	**1 (4)**	1 (6)	2 (4)
PR	0	**1 (4)**	0	1 (2)
PD	1 (17)	**2 (9)**	6 (38)	8 (18)

Shah. Blood. 2021;[Epub ahead of print].

Slide credit: clinicaloptions.com

ZUMA-3: Phase II Study Design

- Multicenter, open-label phase I/II trial



*Prior blinatumomab permitted.

- Primary endpoint: CR/CRi by central assessment
- Secondary endpoints: MRD negativity, DoR, RFS, OS, safety, CAR T-cell levels in blood and cytokines in serum
- Median follow-up: 16.4 mo (range: 10.3-22.1)
- Brexucabtagene autoleucel successfully manufactured in 65 of 71 (92%) of patients; median time from leukapheresis to CAR T-cell delivery was 13 days in US and 14.5 days in Europe

Shah. ASCO 2021. Abstr 7002.

Slide credit: clinicaloptions.com

ZUMA-3: Response

Response, n (%)	Treated Patients (N = 55)
CR/CRi	39 (70.9)
▪ CR	31 (56.4)
▪ CRi	8 (14.5)
BFBM*	4 (7.3)
No response	9 (16.4)
Unknown/NE	3 (5.5)

*≤5% blasts by morphology in BM and any ANC or platelet count that does not meet criteria for CR, CRi, or CR with partial hematologic recovery.

Outcome, Mo (95% CI)	Treated Patients (N = 55)	Patients With CR/CRi (n = 39)	Patients Without CR/CRi (n = 16)
Median OS	18.2 (15.9-NE)	NR (16.2-NE)	2.4 (0.7-NE)
Median RFS	11.6 (2.7-15.5)	14.2 (11.6-NE)	0 (NE-NE)

- CRS: all grade, 89%; grade ≥3, 24%; ICANS: all grade, 60%; grade ≥3, 25%

Shah. ASCO 2021. Abstr 7002. Shah. Lancet. 2021;[Epub].

Slide credit: clinicaloptions.com

Select Ongoing Trials With Autologous CAR T-Cell Therapy for CLL and ALL

Trial	Phase	Treatment	Population
Lymphomas/CLL			
ZUMA-8 (NCT03624036)	I/II	Brexucabtagene autoleucel	Relapsed/refractory CLL
ALL			
OBERON (NCT03628053)	III	Tisagenlecleucel vs blinatumomab or inotuzumab ozogamicin	Adults with B-ALL; R/R after 1-2 lines of therapy or ASCT
CASSIOPEIA (NCT03876769)	II	Tisagenlecleucel	Pediatric/young adult high-risk B-cell ALL; MRD+ after 1L
ZUMA-4 (NCT02625480)	I/II	Axicabtagene ciloleucel	Pediatric/adolescent pts with R/R B-ALL or B-NHL

Slide credit: clinicaloptions.com

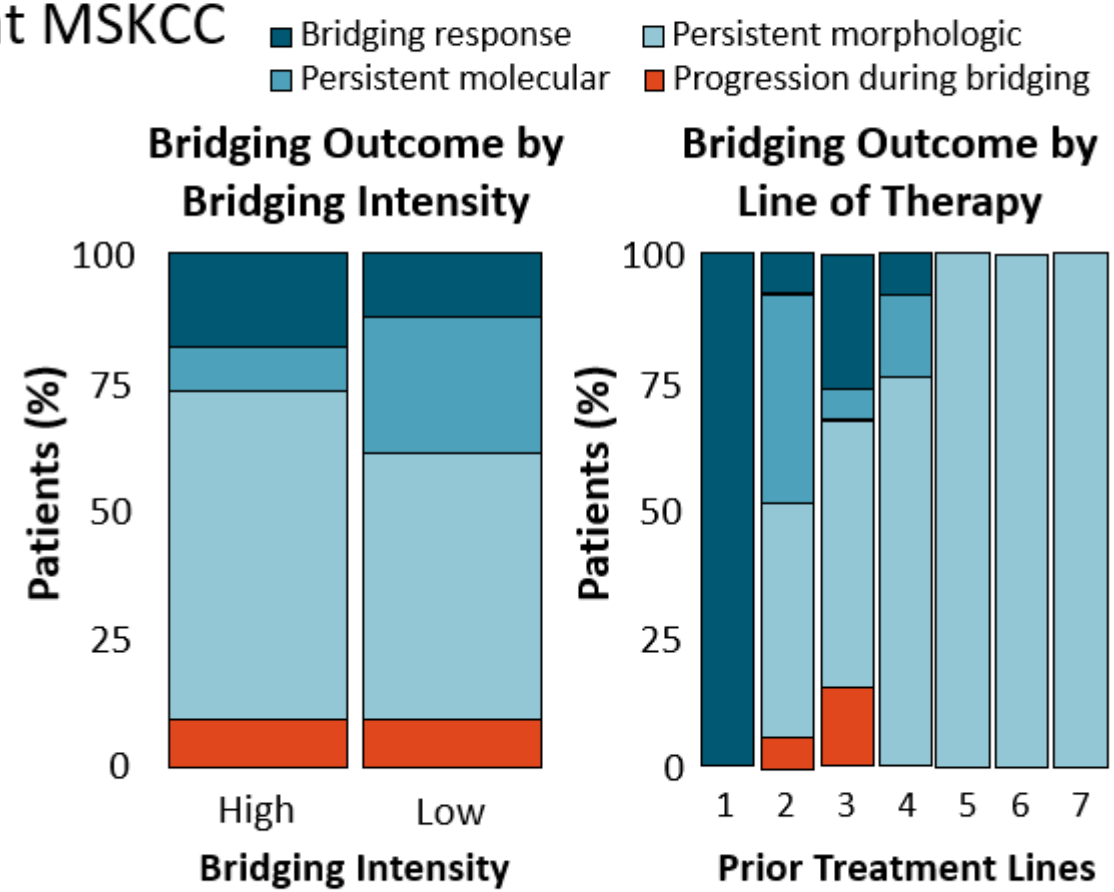
Bridging Therapy Consideration in B-ALL

- **Indications**
  - Rapidly proliferative disease
  - Cytoreduction
- **Regimen selection** depends on prior therapies, regimen-related toxicities, site(s) of disease, comorbidities, blood counts, simplicity of administration
- **Regimens**
  - Low intensity: steroids, vincristine, cyclophosphamide, inotuzumab
  - High intensity: HyperCVAD, HiDAC, FLAG

Use of Bridging Chemotherapy in Adult ALL CAR T-Cell Therapy Trial

- Retrospective review of bridging therapy strategies in adult patients with R/R ALL who received 19-28z CAR T-cell therapy at MSKCC

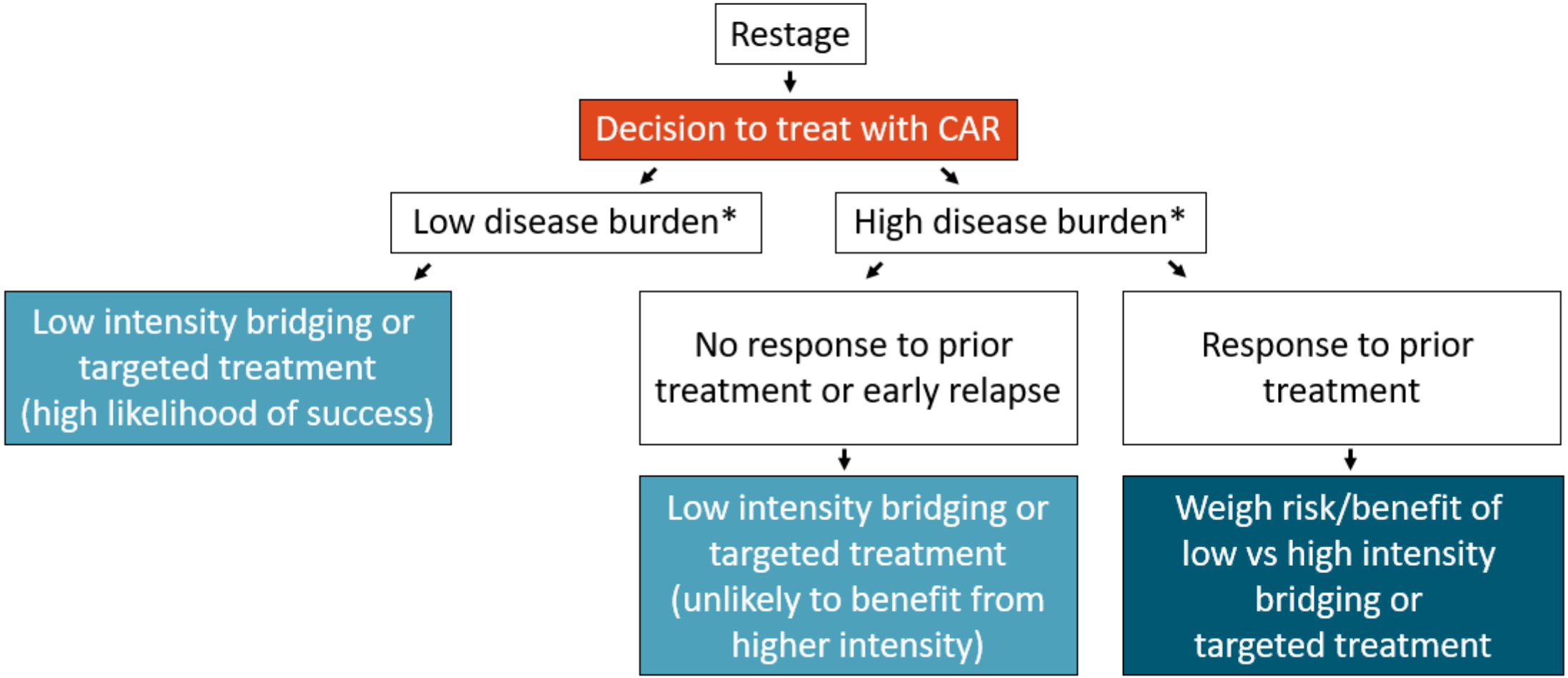
Baseline Characteristic	Bridging Therapy Intensity		*P*
	High	Low or None	
Patients, n (%)	33 (41)	48 (59)	
Age, yr	46 (22-73)	42 (22-74)	.5
Ph+ disease, n (%)	6 (18)	14 (29)	.3
Median no. prior tx lines	3 (1-7)	3 (2-7)	.2
Prior blinatumomab, n (%)	9 (28)	14 (29)	>.9
Prior HSCT, n (%)	12 (36)	17 (35)	>.9
MRD+ disease, n (%)	5 (15)	13 (27)	.2
Median BM blasts	52 (0-99)	35 (0-95)	.2
EMD, n (%)	6 (18)	4 (8.3)	.3



Perica. Leukemia. 2021;[Epub].

Slide credit: clinicaloptions.com

Proposed Schema for Patient-Specific Selection of Bridging Therapy



*Low (eg), BM blasts <5%, no EMD; high (eg), BM blasts ≥5%, no EMD.

Perica. Leukemia. 2021;[Epub].

Slide credit: clinicaloptions.com

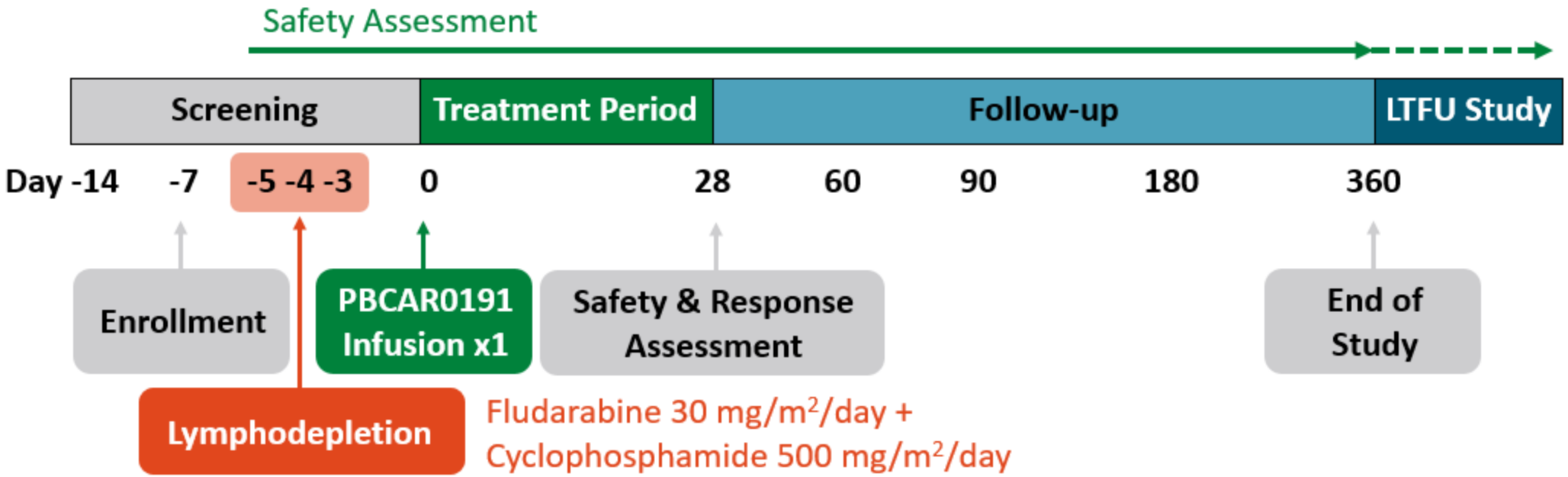
Allogeneic CAR T-Cell Therapy: Rationale and Recent Key Data

- "Off-the-shelf" CAR T-cells manufactured using cells from healthy donors
- Potential advantages: more rapid treatment with preproduced products, decreased cost; potential concerns: GVHD, rapid CAR T-cell elimination[1]

Recent Key Clinical Study Reports		
Trial	**CAR T-Cell Therapy/Malignancy**	**Key Findings**
UNIVERSAL[2]	ALLO-715 (anti-BCMA CAR T) and ALLO-647 (anti-CD52 Ab) for R/R MM	▪ Up to 75% ORR dep. on dose; no GVHD (N = 35)
Multitrial analysis[3]	Anti-CD19 CAR T-cells for R/R B-ALL	▪ 96% CR if prior allo-HSCT; 8% overall GVHD (N = 37)
ALPHA[4]	ALLO-501 (anti-CD19 CAR T) and ALLO-647 (anti-CD52 Ab) for R/R lymphoma	▪ 63% ORR, 37% CR; no GVHD

1. Depil. Nat Rev Drug Discov. 2020;19:185. 2. Mailankody. ASH 2020. Abstr 129.
3. Zhang. ASH 2020. Abstr 161. 4. Neelapu. ASCO 2020. Abstr 8002.

Initial Findings of the Phase I Trial of PBCAR0191, a CD19-Targeted Allogeneic CAR T-Cell Therapy



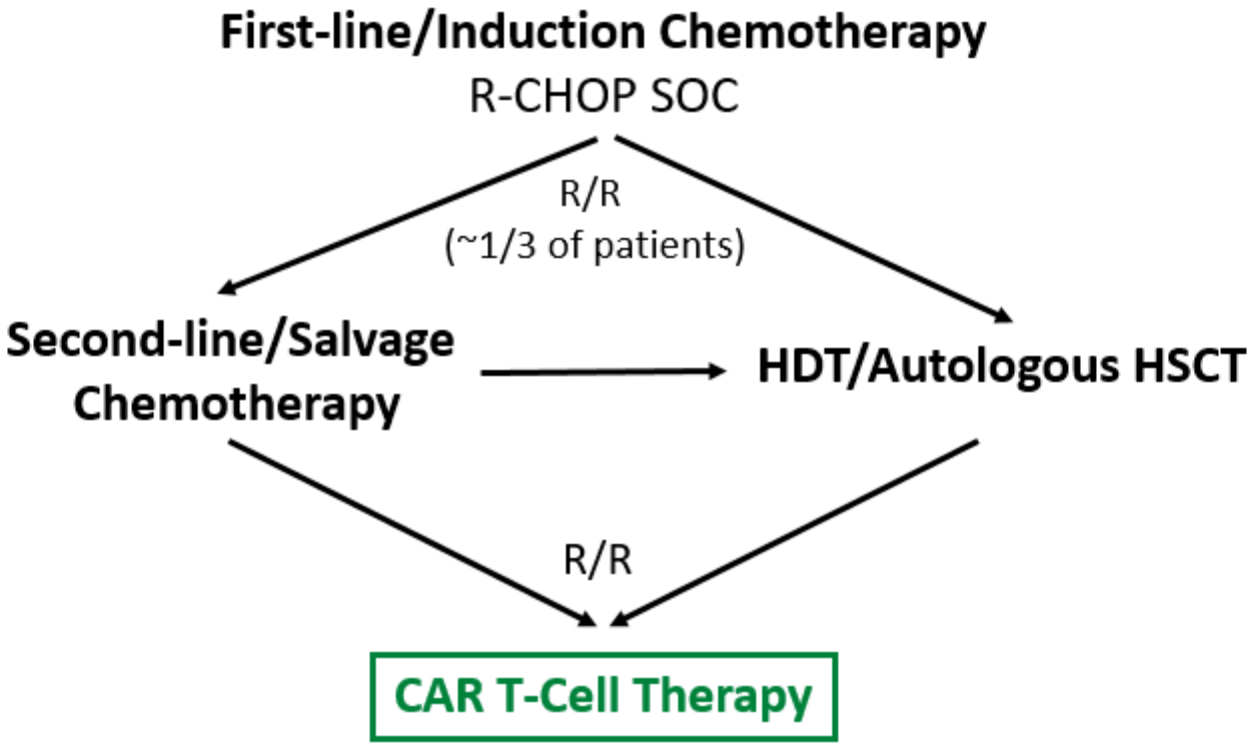
Summary of Objective Responses	NHL/DL1 (n = 3)	NHL/DL2 (n = 3)	NHL/Total (n = 6)
Response at Day ≥28	2 (66%)	2 (66%)	4 (66%)
Progressive disease Day < 28	1 (33%)	1 (33%)	2 (33%)

Jacobson. ASH 2019. Abstr 4107.

Slide credit: clinicaloptions.com

CAR T-Cell Therapy in Lymphoma

Fitting CAR T-Cell Therapy Into Current Treatment Paradigms for DLBCL



Tilly. Ann Oncol. 2015;26 Suppl 5:v116. Hoelzer. Ann Oncol. 2016;27 Suppl 5:v69. MDACC. ALL adult guidelines. Approved February 26, 2019. Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Lisocabtagene maraleucel

Slide credit: clinicaloptions.com

CD19-Directed CAR T-Cell Products for NHL

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]	Brexucabtagene Autoleucel[4]
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z
Dose	2 x 10^6/kg (max 2 x 10^8)	0.6 to 6.0 x 10^8/kg	50 to 150 x 10^6	2 x 10^6/kg (max 2 x 10^8)
Lymphodepletion	Flu/Cy 30/500 x 3 days	Flu/Cy 25/250 x 3 days, or bendamustine x 2 days	Flu/Cy 30/300 x 3 days	Flu/Cy 30/500 x 3 days
FDA approval status	**R/R DLBCL,* HGBCL, primary mediastinal B-cell lymphoma, FL**	**R/R pediatric ALL, R/R DLBCL,* HGBCL**	**R/R DLBCL,† HGBCL, FL grade 3B, primary mediastinal B-cell lymphoma**	**R/R MCL**

*DLBCL NOS, including DLBCL arising from follicular lymphoma. †DLBCL NOS, including DLBCL arising from indolent lymphoma.

1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. 3. Lisocabtagene maraleucel PI. 4. Brexucabtagene autoleucel PI.

Slide credit: clinicaloptions.com

Multicenter CAR T NHL Trials: Study Design

Study Agent	ZUMA1[a] Axicabtagene Ciloleucel	JULIET[b] Tisagenlecleucel	TRANSCEND[c] JCAR017
CAR T design	CD19/CD3z/CD28	CD19/CD3z/4-1BB	CD19/CD3z/4-1BB
CAR T dose	2 x 10^6/kg	Up to 1 to 6 x 10^8	1 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL/PMBCL/TFL	DLBCL	DLBCL/TFL
Sample size	101	51	54
Disease status	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT, %	21	51	44
Bridging therapy	None	Allowed	Allowed
Manufacturing success, %	99	94	98

a. Neelapu SS, et al. ICML 2017. Abstract 8; b. Schuster SJ, et al. ICML 2017. Abstract 7; c. Abramson J, et al. ICML 2017. Abstract 128.

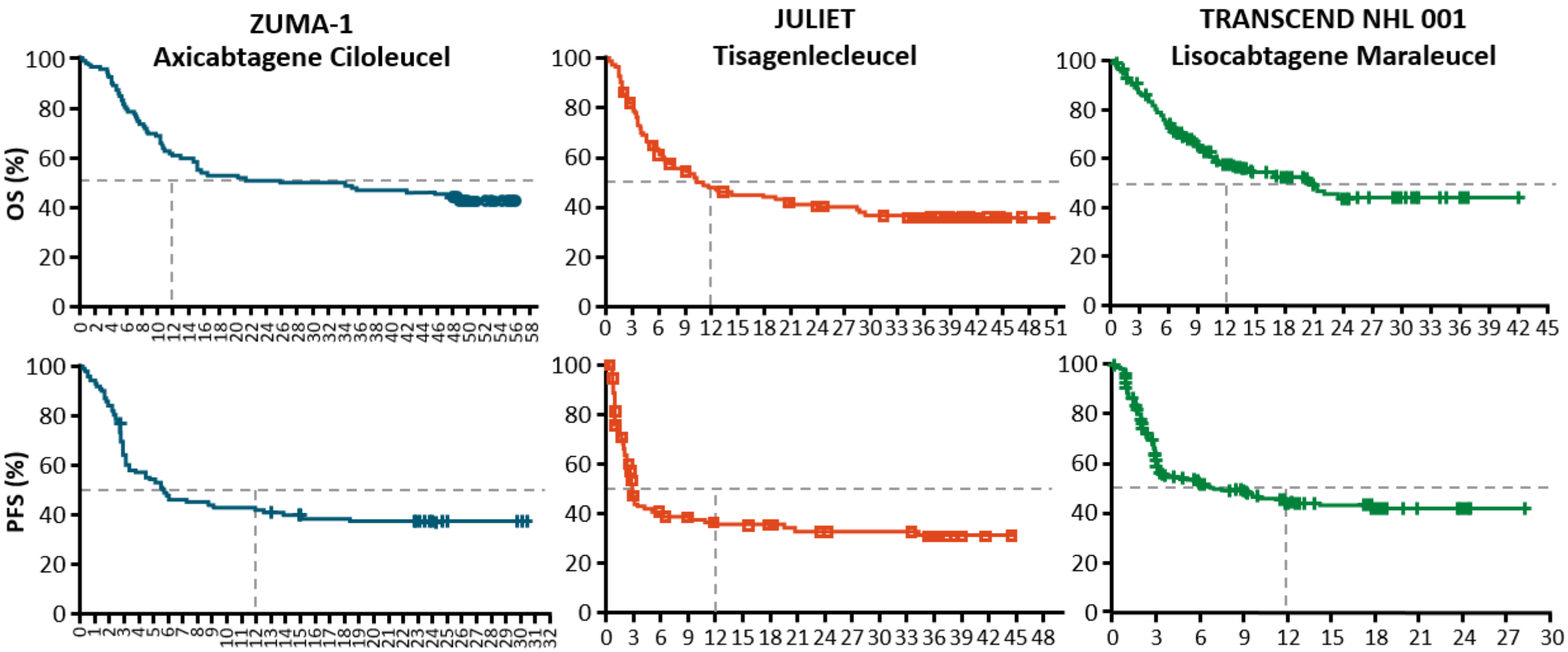
Multicenter CAR T NHL Trials: Efficacy and Safety

Study Agent	ZUMA1[a] Axicabtagene Ciloleucel	JULIET[b] Tisagenlecleucel	TRANSCEND[c] JCAR017
CAR T design	CD19/CD3z/CD28	CD19/CD3z/4-1BB	CD19/CD3z/4-1BB
Sample size	101	51	54
ORR, %	82	59	76
CR, %	54	43	52
CRS grade ≥ 3, %	13	26	2
Neurotoxicity grade ≥ 3	28	13	16

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND and U Penn criteria on JULIET
- 3 deaths on ZUMA1 due to AEs -- 2 CRS and 1 pulmonary embolism

a. Neelapu SS, et al. ICML 2017. Abstract 8; b. Schuster SJ, et al. ICML 2017. Abstract 7; c. Abramson J, et al. ICML 2017. Abstract 128.

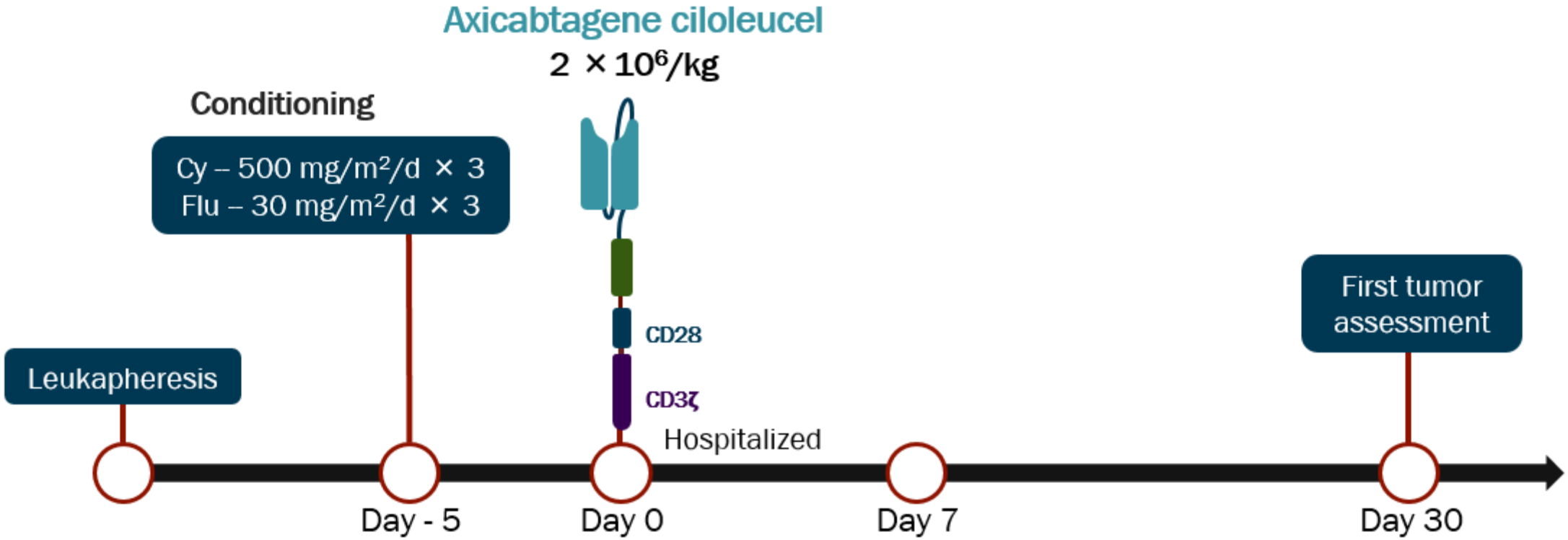
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL



Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

Slide credit: clinicaloptions.com

ZUMA1: First Multicenter Trial of CD19 CAR T-Cell: Therapy in Refractory Aggressive B-Cell NHL



Eligibility

- DLBCL (cohort 1), PMBCL, or TFL (cohort 2)
- Chemorefractory disease: PD or SD as best response to most recent chemotherapy or relapse ≤ 12 months of ASCT

Phase 2 Endpoints

- Primary: ORR
- Secondary: DOR, PFS, OS, safety, CAR levels, biomarkers

Locke FL, et al. *Lancet Oncol*. 2019;20(1):31-42.

ZUMA1: Efficacy

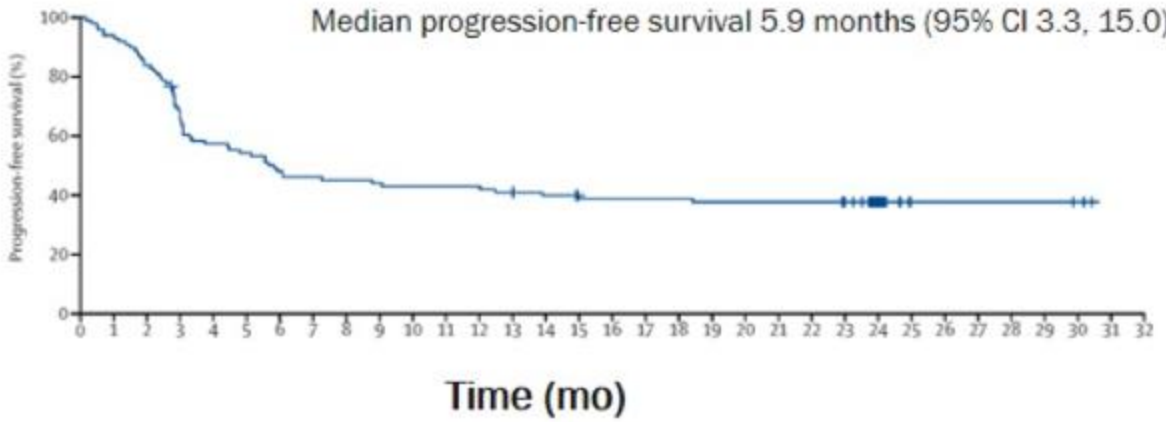
	Investigator-Assessed, n (%) n = 101	IRC-Assessed, n (%) n = 101
Objective response	84 (83)	75 (74)
Complete response	59 (58)	55 (54)
Partial response	25 (25)	20 (20)
Ongoing response	39 (39)	36 (36)
Complete response	37 (37)	35 (35)
Partial response	2 (2)	1 (1)

- Median DOR was 11.1 months (investigator assessed) and not reached (IRC assessed)

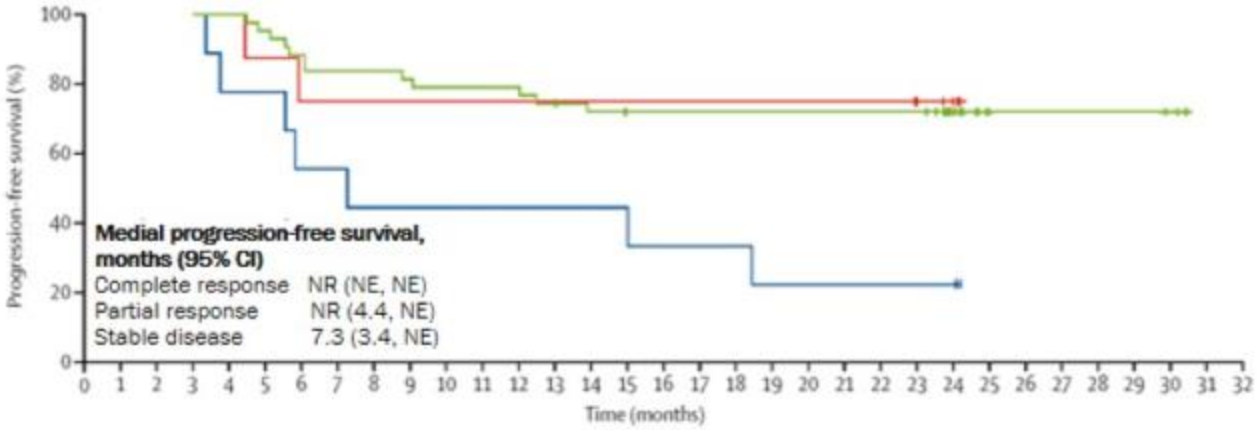
Locke FL, et al. *Lancet Oncol.* 2019;20(1):31-42.

ZUMA1: Progression-Free Survival

Progression-Free Survival

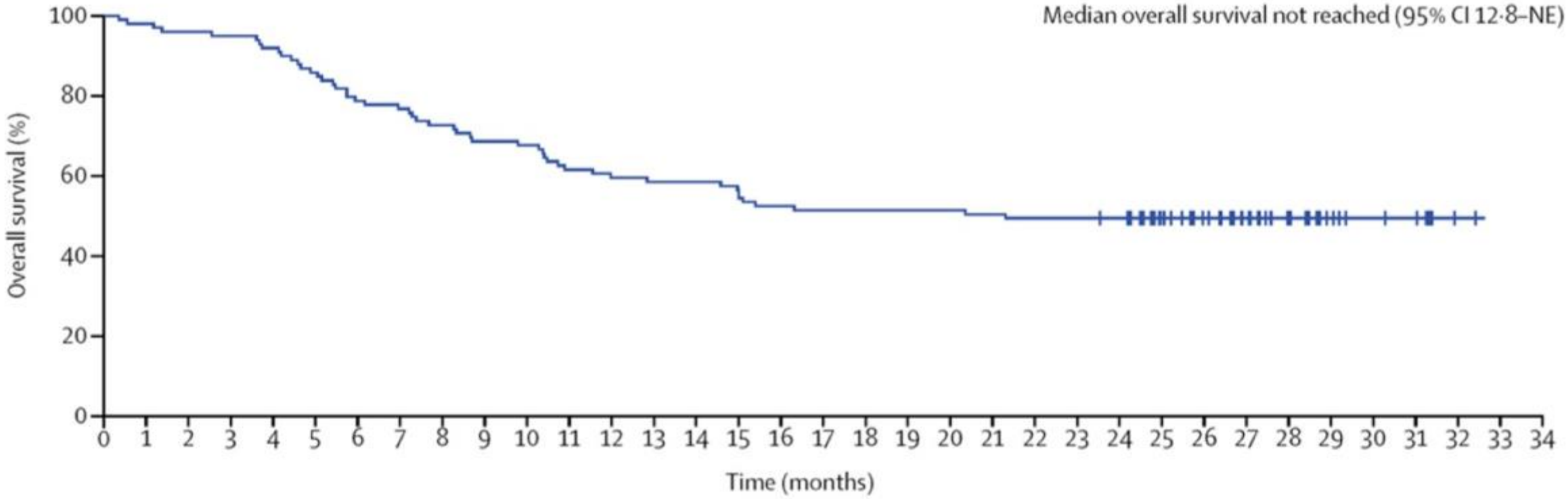


Progression-Free Survival by Response Status



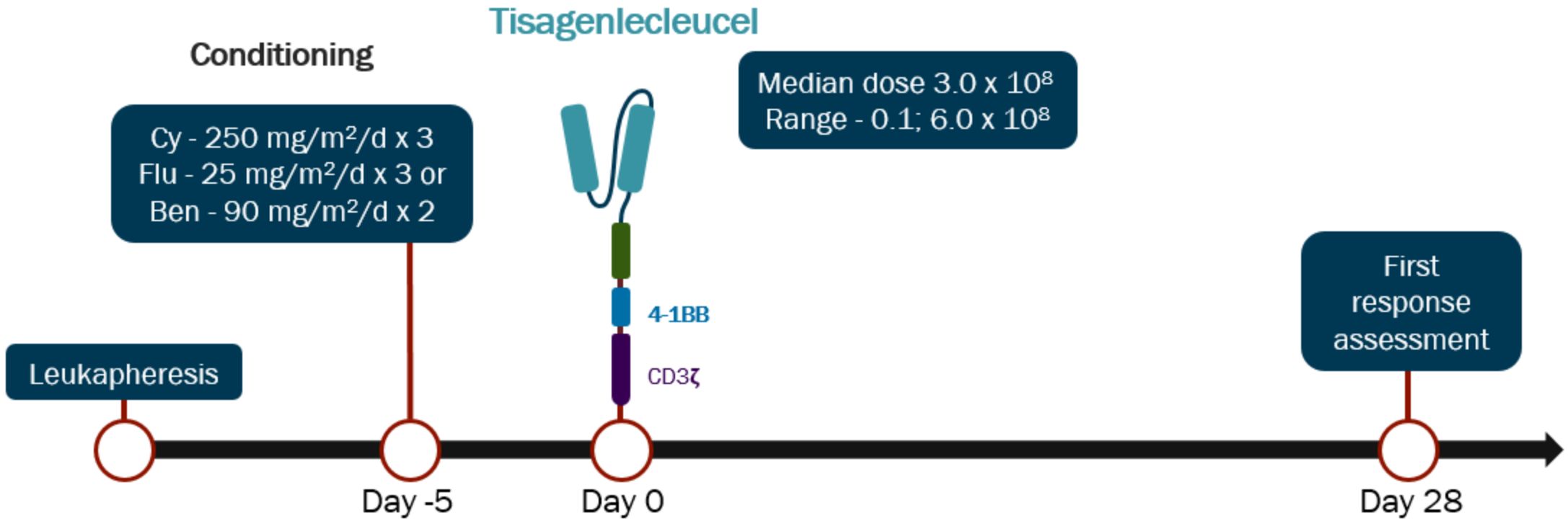
Reprinted from Lancet Oncol.,20, Locke FL, et al., Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial, 31-42, 2019, with permission from Elsevier.

ZUMA1: Overall Survival



Reprinted from Lancet Oncol.,20, Locke FL, et al., Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial, 31-42, 2019, with permission from Elsevier.

JULIET Phase 2 Trial of Tisagenlecleucel in R/R Diffuse Large B-Cell Lymphoma



Eligibility

- R/R DLBCL
- ≥ 2 prior lines of therapy, including rituximab and anthracycline

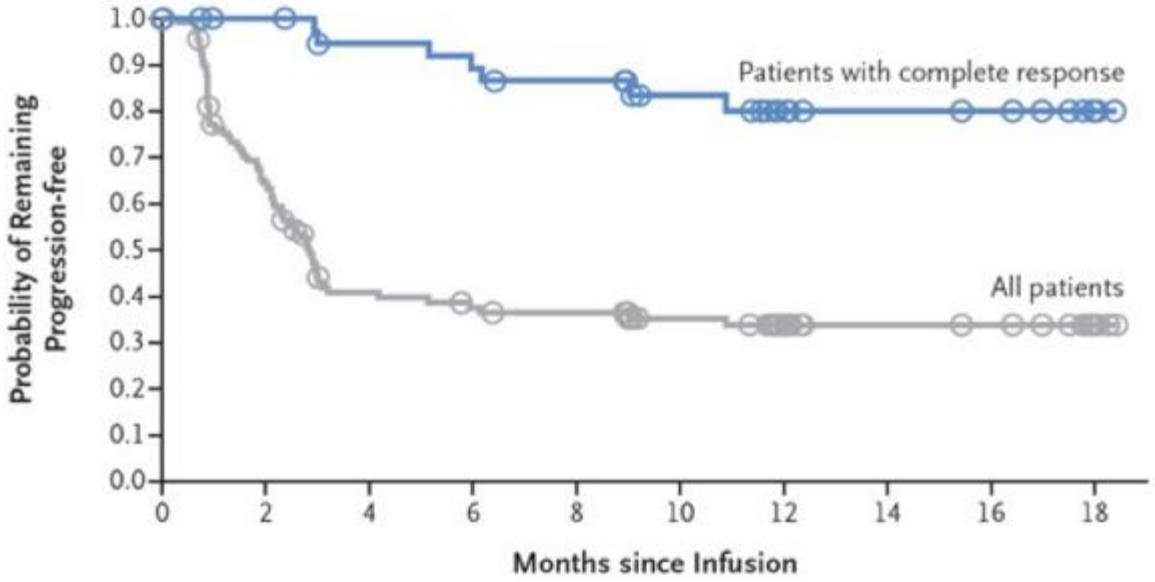
Endpoints

- Primary: Best ORR
- Secondary: DOR, OS, safety, cellular kinetics

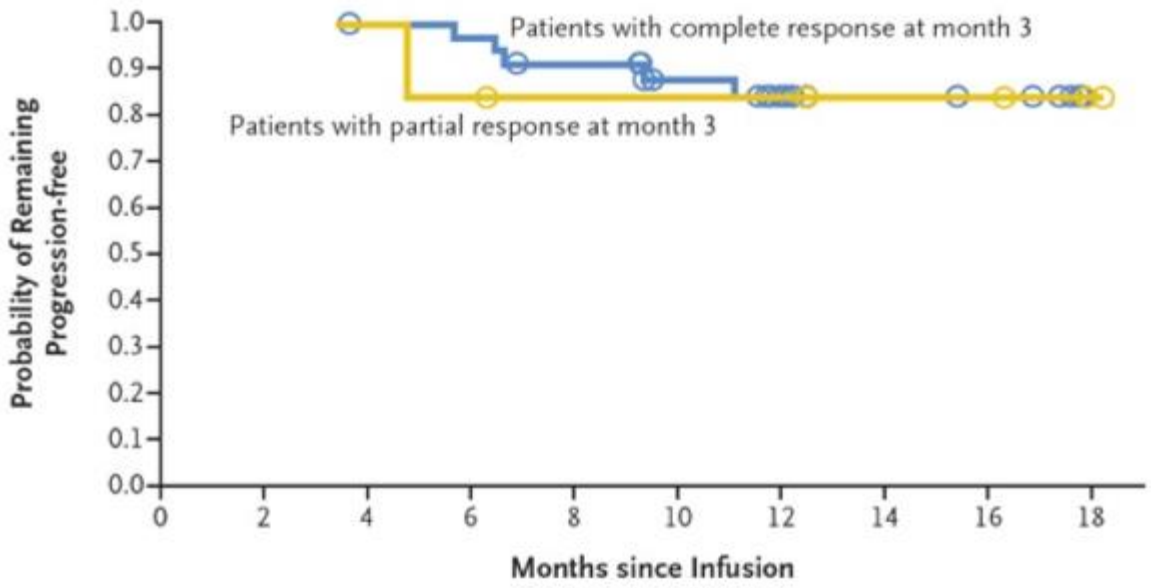
Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56.

JULIET: Progression-Free Survival

B Progression-free Survival

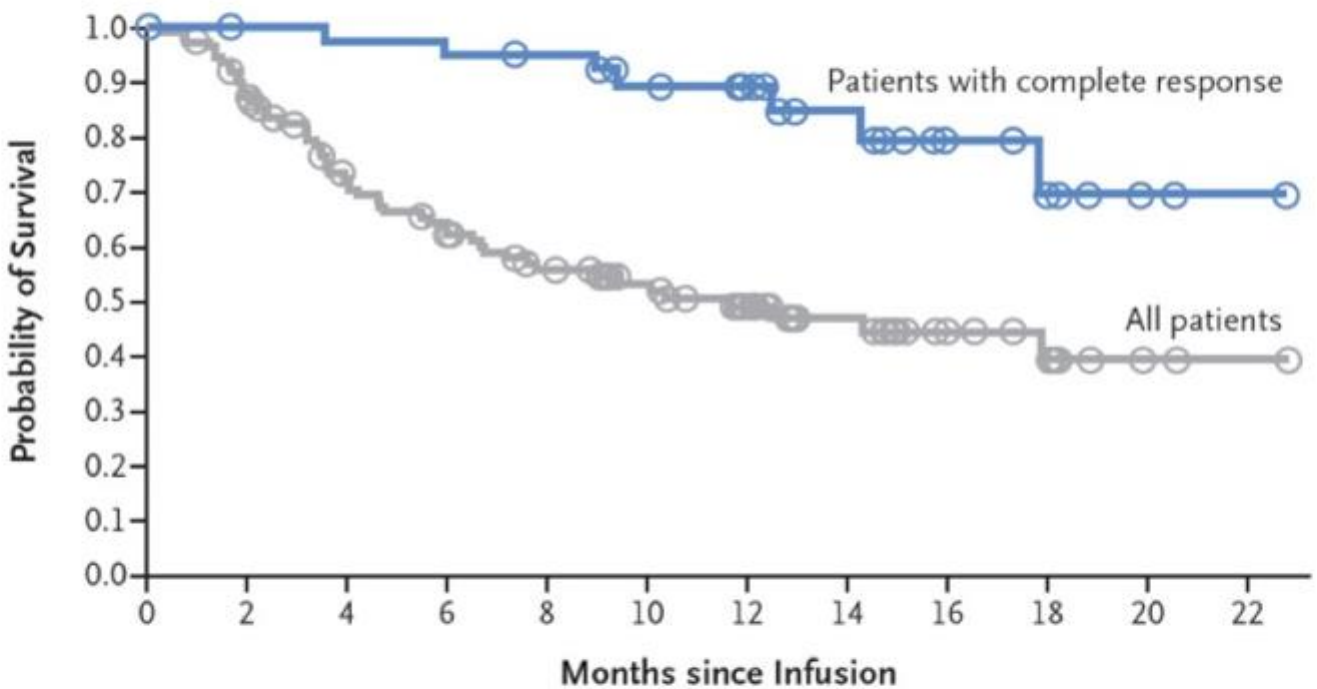


C Progression-free Survival among Patients with a Response



Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56.

JULIET: Overall Survival



Schuster SJ, et al. *N Engl J Med*. 2019;380(1):45-56.

JULIET vs Real-World Tisa-cel Experience

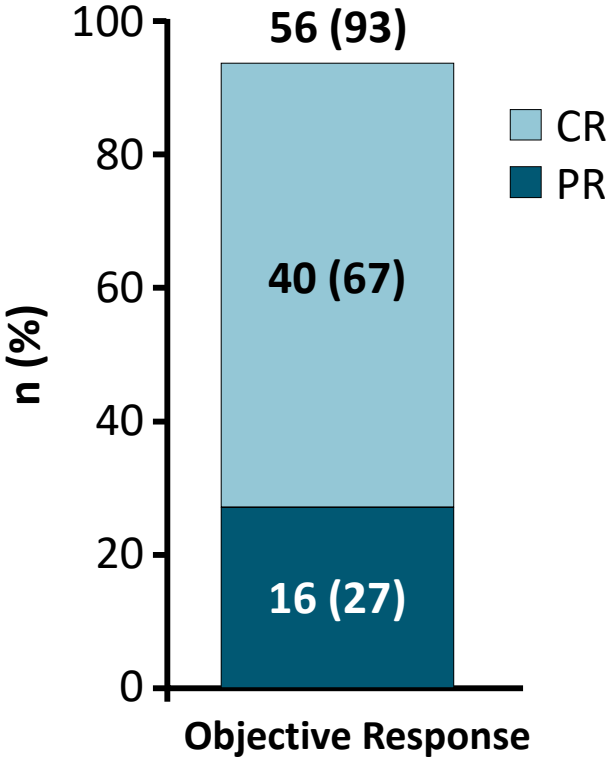
Parameter	JULIET	Real-World Tisa-cel (CIBMTR Data)
Patients infused, n	111	70
Median age, yr (range)	56 (22-76)	65.1 (18.5-88.9)
ECOG PS 0/1, %	100	81
ORR, %	52	60
CR, %	40	38
Grade ≥3 CRS, %	22	4.3
Grade ≥3 neurotoxicity, %	12	4.4
Tocilizumab, %	14	41
Steroids, %	10	9
CRS grading scale	PENN	ASTCT

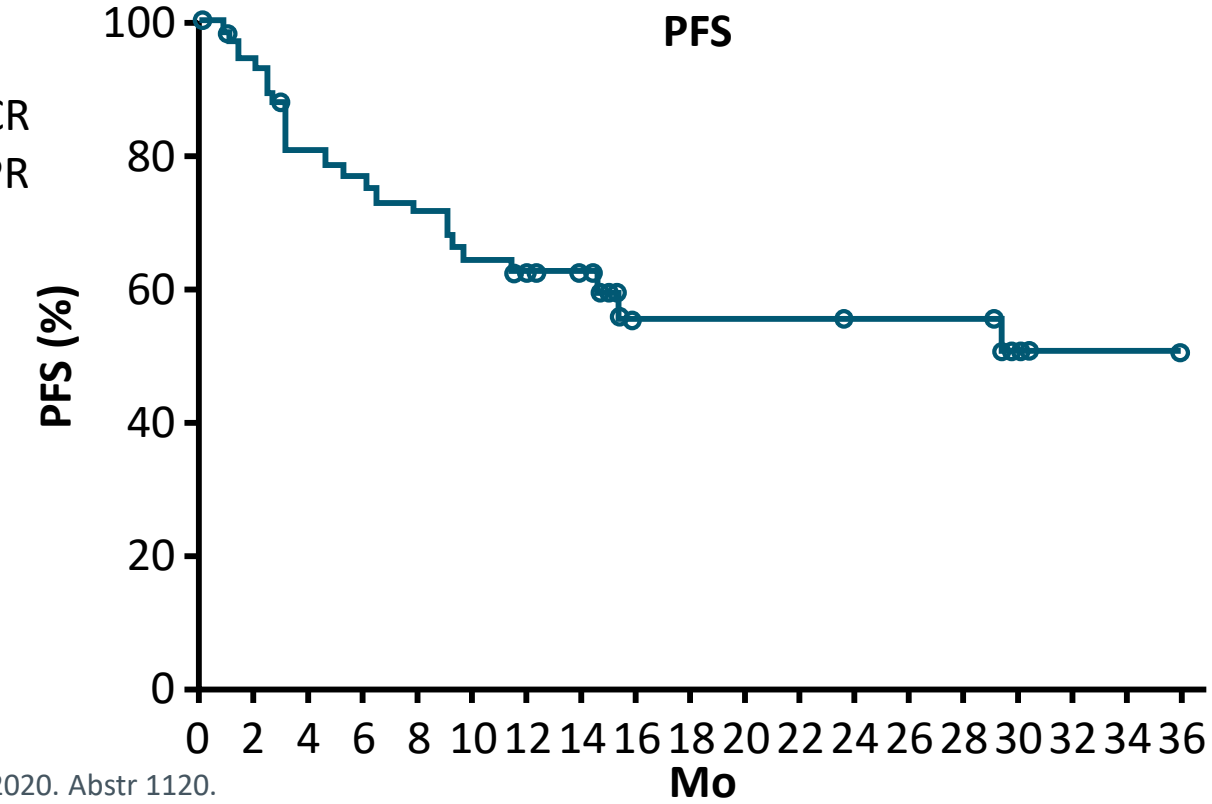
Schuster. NEJM. 2019;380:45. Jaglowski. ASH 2019. Abstr 766.

Slide credit: clinicaloptions.com

ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Relapsed/Refractory MCL

- Multicenter, single-arm, open-label phase II trial of brexucabtagene autoleucel for adults with relapsed/refractory mantle cell lymphoma (N = 68 received agent)
  - After failure of BTKi and up to 5 prior therapies; bridging steroid ± BTKi permitted (37%)



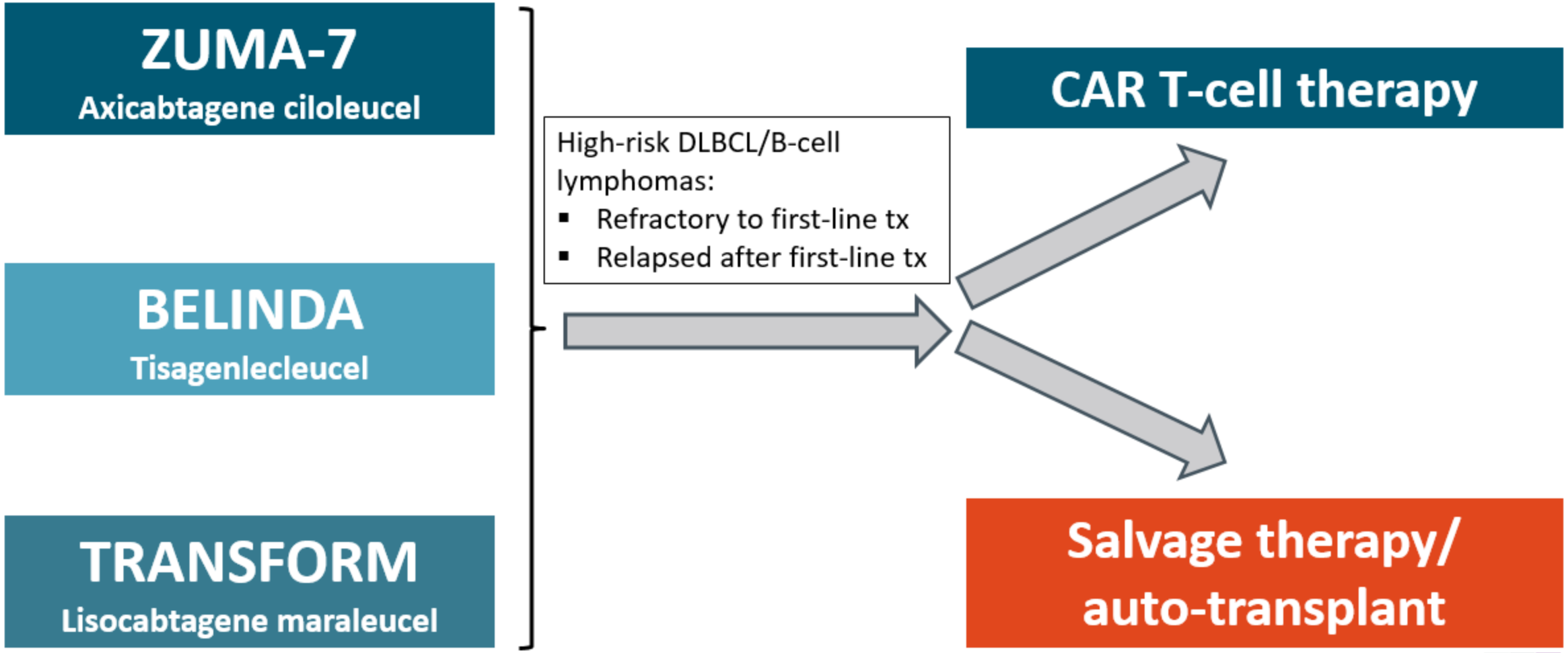


- CRS grade >3: 15%
- Neurotoxicity grade >3: 31%
- Tocilizumab: 59%

Wang. NEJM. 2020;382:1331. Wang. ASH 2020. Abstr 1120.

Slide credit: clinicaloptions.com

Ongoing Clinical Trials in B-Cell Lymphomas: Will CD19 CAR T-cell Therapy Replace Auto-transplant?



NCT03391466. NCT03570892. NCT03575351.

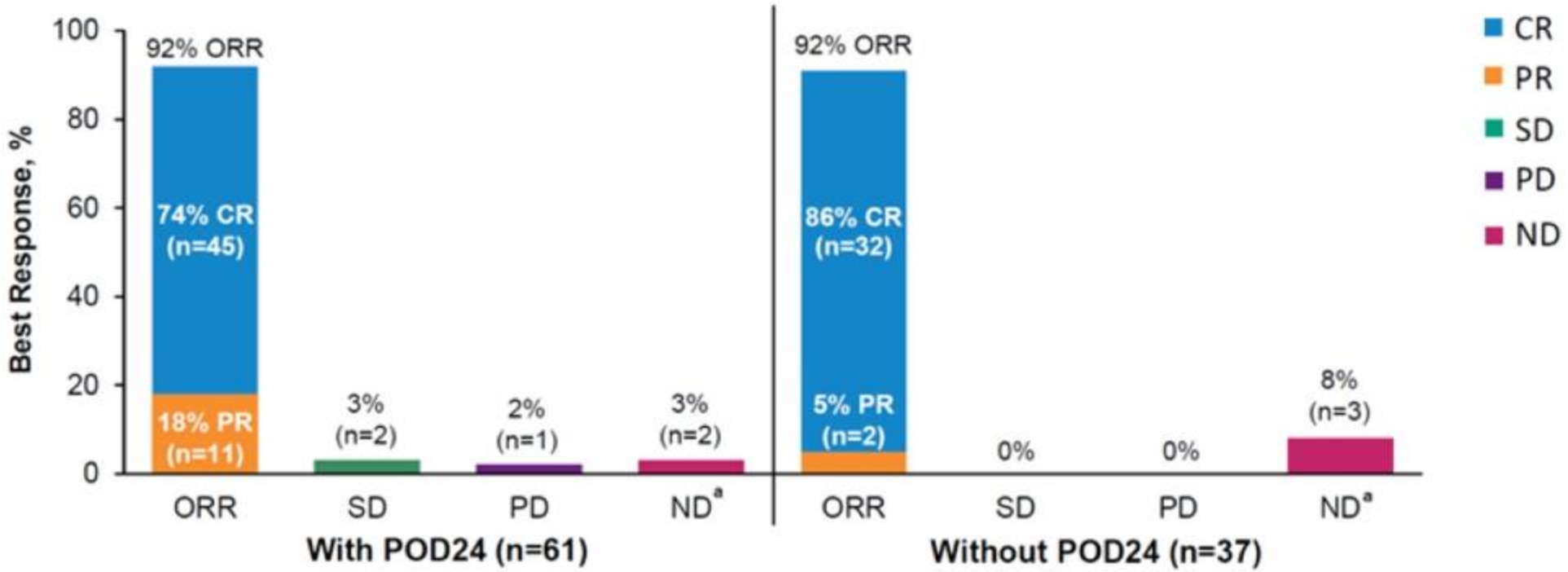
Slide credit: clinicaloptions.com

ZUMA-5 Trial: Axicabtagene Ciloleucel Therapy
ORR by IRC

ORR by IRC assessment in patients with iNHL by POD24 status

Trial features:

- **Single-arm trial of axi-cel**
- **Population: FL, MCL**



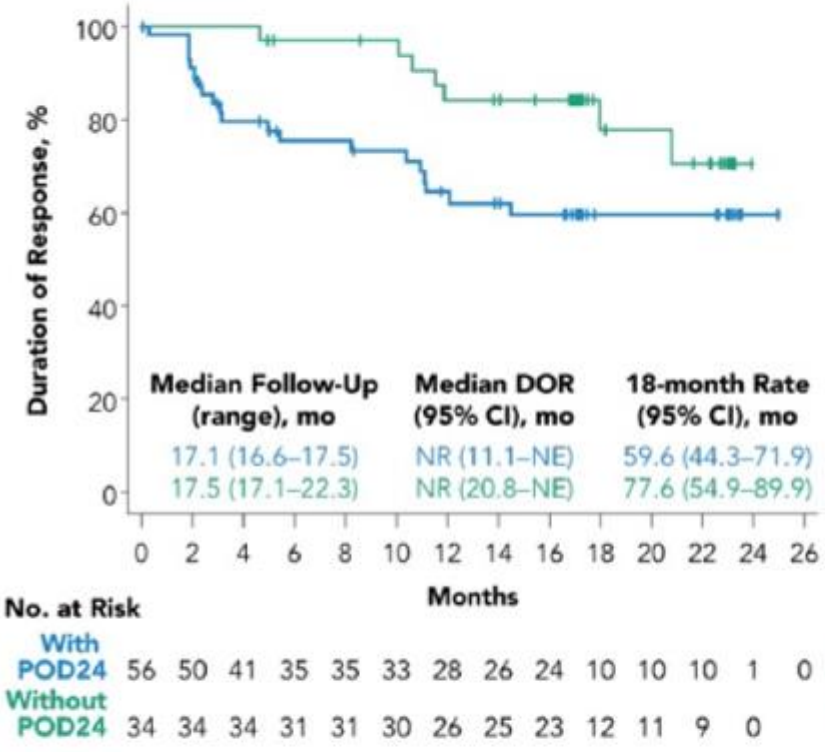
ORR was similar among efficacy-evaluable patients with and without POD24 status

IRC, independent review committee; ND, newly diagnosed; POD24, progression of disease within 2 years.

Jacobson CA, et al. Presented at: EHA 2021 Virtual; June 9-17, 2021. Abstract S213.

ZUMA-5 Trial: Axicabtagene Ciloleucel Therapy
Efficacy and Safety

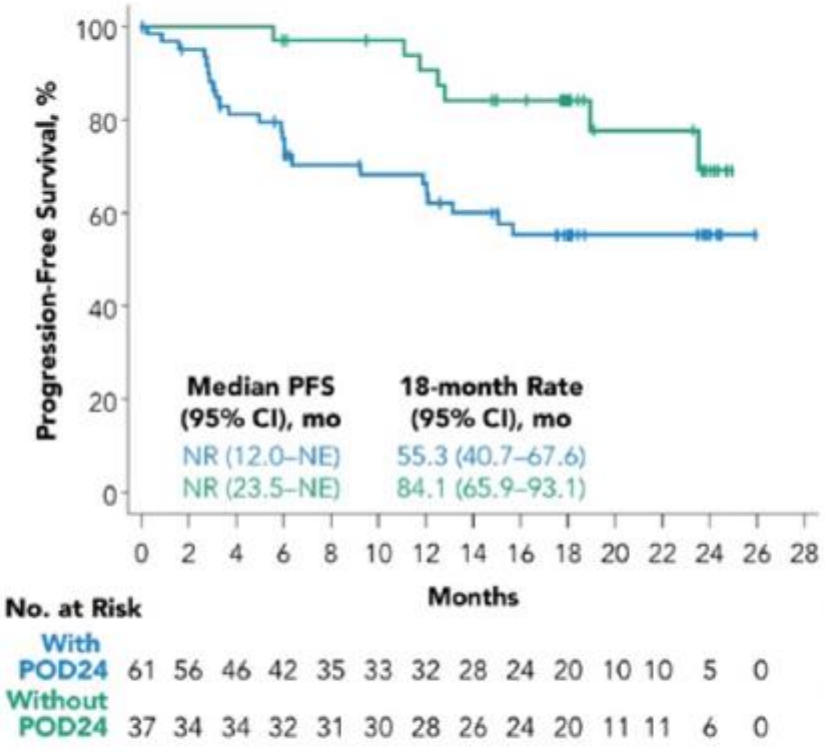
Duration of Response



No. at Risk

With POD24	56	50	41	35	35	33	28	26	24	10	10	10	1	0
Without POD24	34	34	34	31	31	30	26	25	23	12	11	9	0	

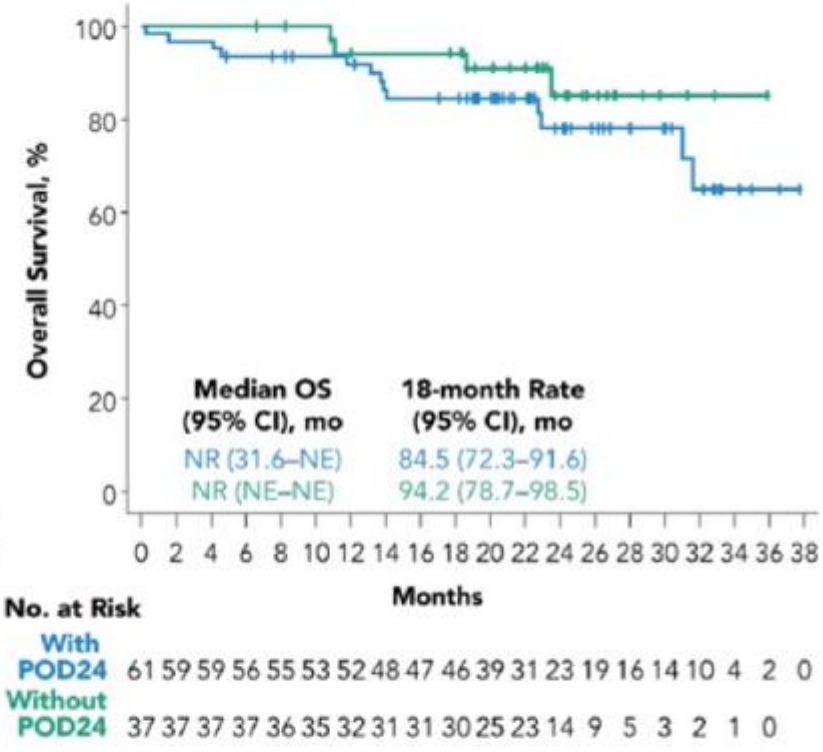
Progression-Free Survival



No. at Risk

With POD24	61	56	46	42	35	33	32	28	24	20	10	10	5	0
Without POD24	37	34	34	32	31	30	28	26	24	20	11	11	6	0

Overall Survival



No. at Risk

With POD24	61	59	59	56	55	53	52	48	47	46	39	31	23	19	16	14	10	4	2	0											
Without POD24	37	37	37	37	36	35	32	31	31	30	25	23	14	9	5	3	2	1	0												

With median follow-up of 17.1 mo and 17.5 mo at data cut-off, responses were ongoing in 52% of efficacy-evaluable patients with POD24 and 70% of those without POD24, respectively

CRS, n (%)	66 (81)	42 (88)
Grade ≥3	7 (9)	1 (2)
Median time to onset, days	4	4
Median duration, days	7	5

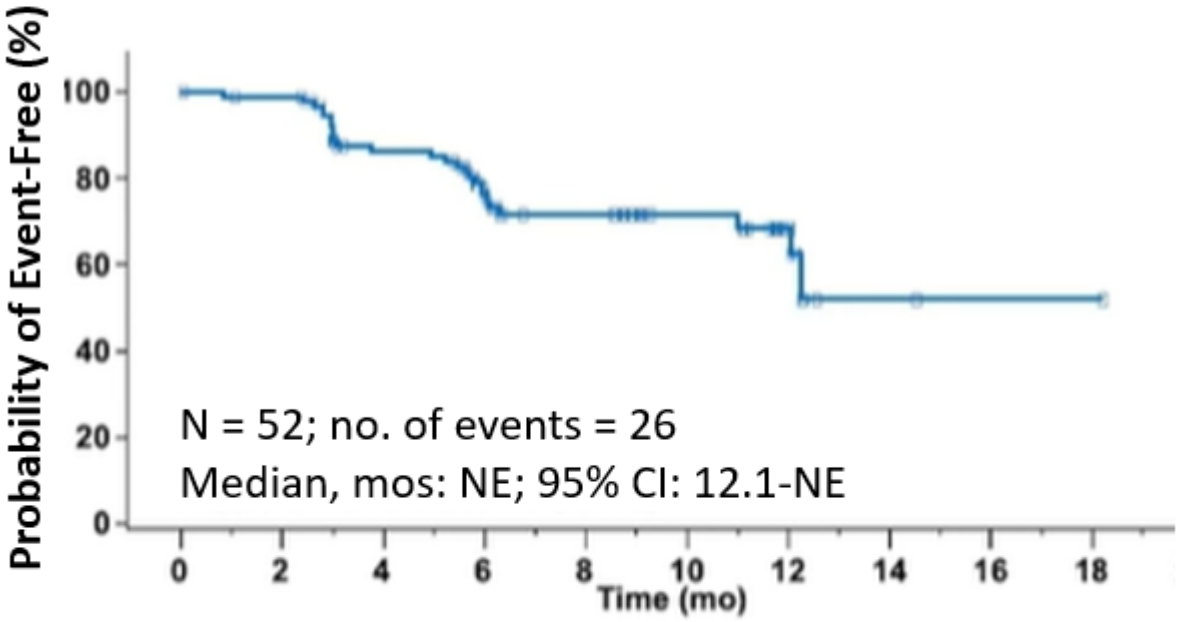
Any neurologic event, n (%)	46 (57)	31 (65)
Grade ≥3	14 (17)	8 (17)
Median time to onset, days	8	7
Median duration, days	11	13

mo, months; NE, not estimable; Jacobson CA, et al. Presented at: EHA 2021 Virtual; June 9-17, 2021. Abstract S213.

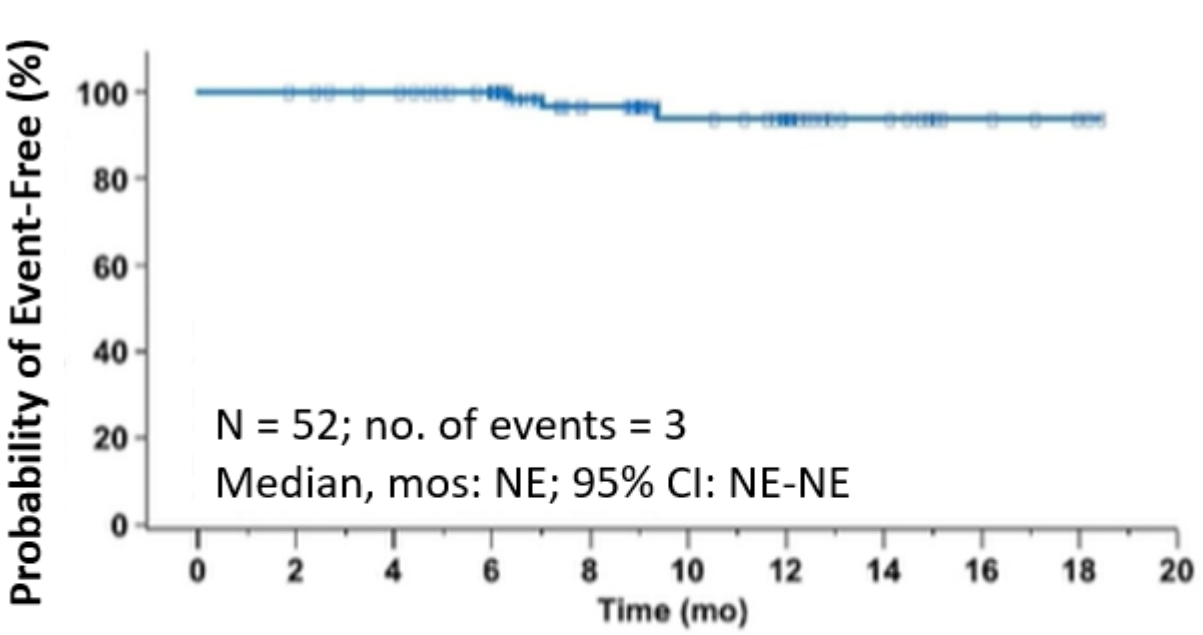
ELARA: Tisagenlecleucel for Patients With Relapsed/Refractory FL

- Single-arm phase II study of tisagenlecleucel for patients with R/R FL (N = 97 at interim analysis)

PFS



OS



- ORR (IRC): 86.2%; CR rate: 66.0%

Schuster. ASCO 2021. Abstr 7508.

Slide credit: clinicaloptions.com

ELARA Trial: Tisagenlecleucel in R/R FL
Special AEs of Interest

- ELARA is a single-arm, international trial of tisagenlecleucel in adults with R/R FL
- Primary endpoint (CR rate): was not met at the interim analysis

	Treated Patients N=97	
AESI (within 8 weeks of infusion)	**All grades, %**	**Grade ≥3, %**
Cytokine release syndrome[a,1]	48.5	**0**
Neurological adverse reactions	9.3	**1.0**
Infections	18.6	5.2
Tumor lysis syndrome	1.0	1.0
Prolonged depletion of B cells and/or agammaglobulinemia[b]	10.3	0
Hematologic disorders including cytopenias		
Neutropenia[c,d]	30.9	15.5
Anemia[c]	24.7	0
Thrombocytopenia[c]	16.5	3.1

- Median onset of neurological events was 8.5d
  - Median time to resolution was 2d
- CRS median onset was 4.0d and all cases were low grade
- 74.5% of the CRS events and 100% of the ICANS occurred in patients with bulky disease
- All neurological and CRS events resolved with appropriate management

AESI, adverse event of special interest.

Schuster SJ, et al. Presented at: EHA 2021 Virtual; June 9-17, 2021. Abstract S210.

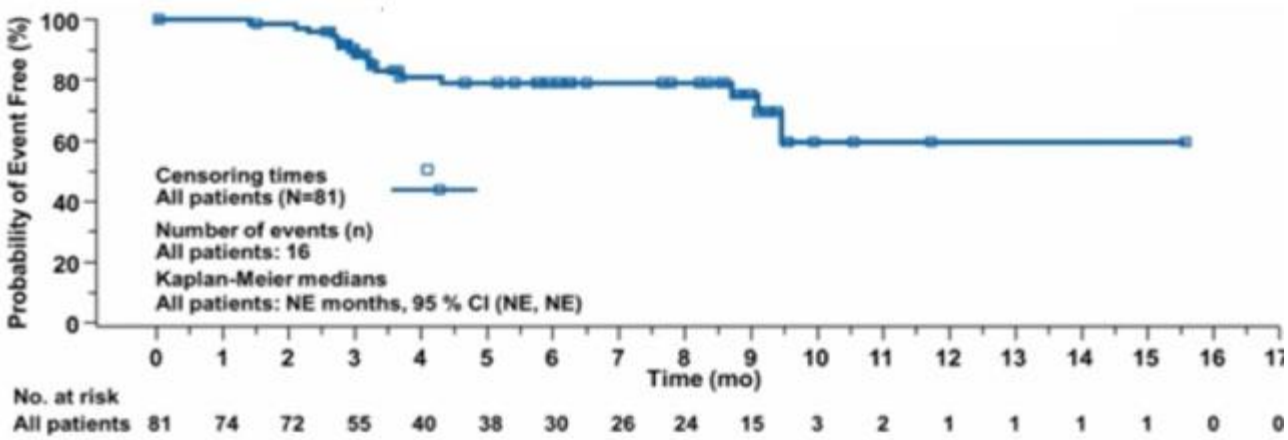
ELARA Trial: Tisagenlecleucel in R/R FL
Key Efficacy Data: Complete Response Rate by IRC

Response Rate

Response Rate, %	Patients Evaluable for Efficacy[b] (n=94)
CR	66.0[b]
PR	20.2
ORR (CR+PR)	86.2

- Investigator-assessed CRR was 69.1% (ORR: 90.4%)
- CRRS/ORRs were comparable about high-risk groups

Kaplan-Meier Plot of DOR by IRC

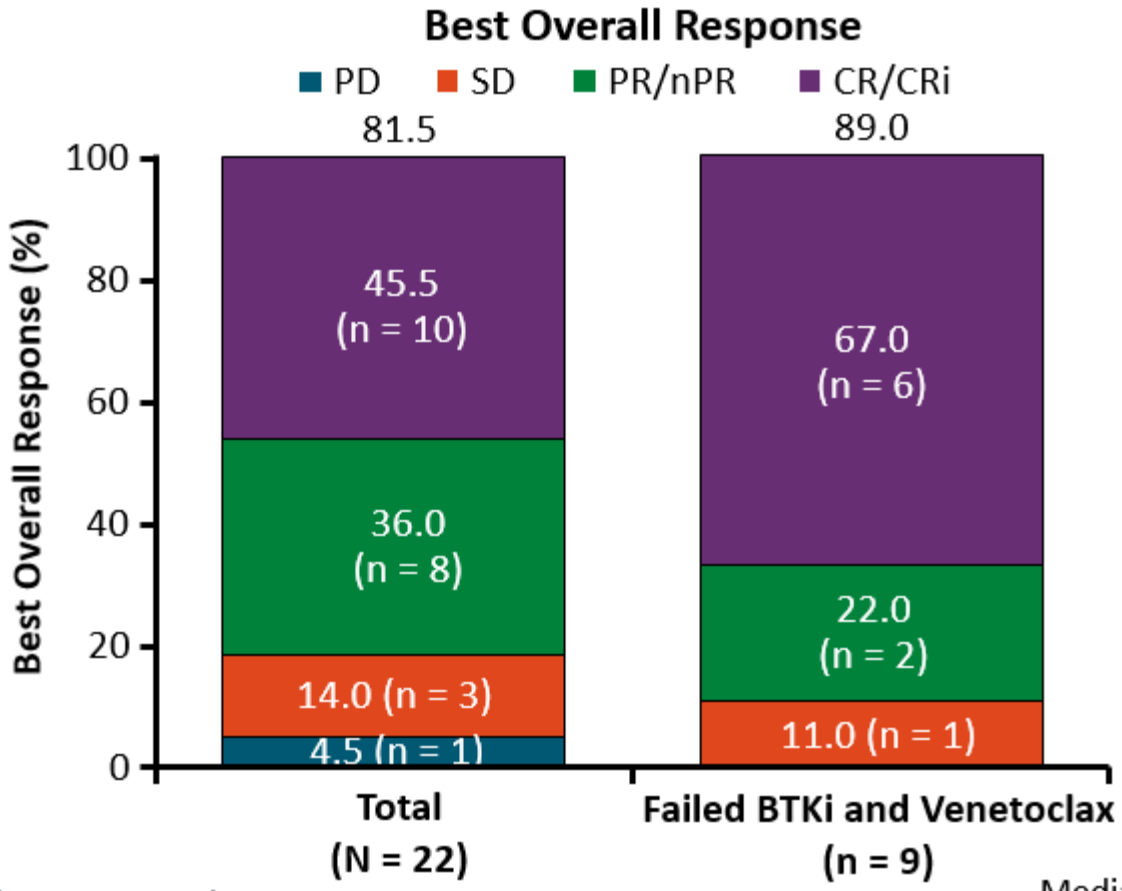


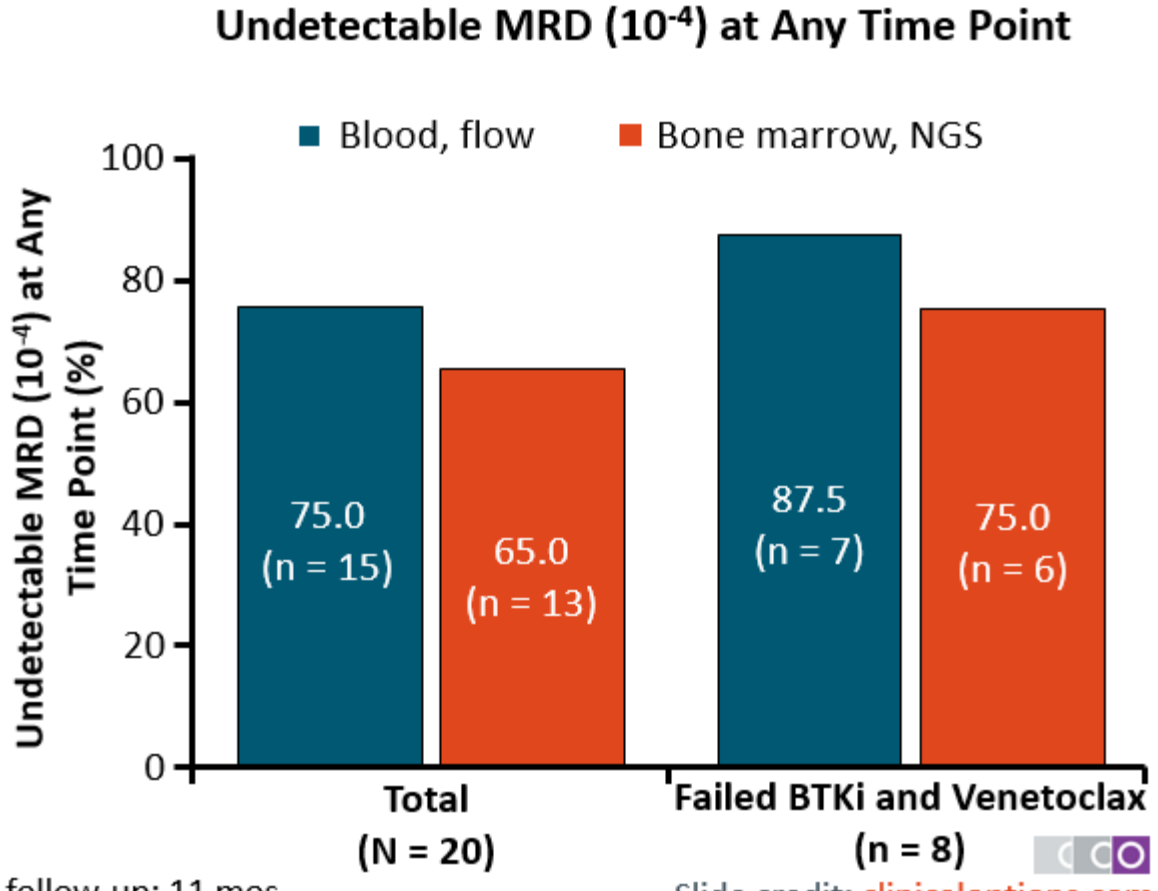
- Median follow-up for efficacy (n = 94): 11 (4.3 to 19.7) mo
- Probability for a responding patient to remain in response ≥ 6 mo was 79% (95% CI, 66, 87)
- 12 of 18 PRs (66.6%) converted to CRs
- Median time to next anti-lymphoma treatment was not reached

Schuster SJ, et al. Presented at: EHA 2021 Virtual; June 9-17, 2021. Abstract S210.

TRANSCEND CLL 004: Lisocabtagene Maraleucel in Patients With Relapsed/Refractory CLL or SLL

- Open-label phase I/II study of **lisocabtagene maraleucel** for patients with R/R CLL or SLL who had failed/were ineligible for BTK inhibitors (N = 23)





Siddiqi. ASH 2019. Abstr 503.

Median follow-up: 11 mos

Slide credit: clinicaloptions.com

CAR T-cell Therapy: Future Directions

- Safer CARs?
  - CARs that increase signaling complexity at immunologic synapse and/or utilize more physiologic (ie, TCR) T-cell signaling (Boolean [logic] gated CARs, TAC T-cells, precisely integrated CARs)
- Overcoming mechanisms of resistance
  - T-cell exhaustion: combination therapy with checkpoint and other immunomodulatory agents, gene editing out immunomodulatory genes (ie, PD-1); alternative conditioning regimens
  - Antigen loss: dual antigen targeting CARs (CD19/CD20; CD19/CD22, CD19/CD79b)
- Composition of the T-cell product (shift towards an early memory differentiation phenotype)
  - Pre-leukapheresis and/or conditioning regimens (BTK inhibitors, PI3K inhibitors); postleukaphersis T-cell/product manipulation (PI3K inhibitors)
- Increasing accessibility (cost and manufacturing time being rate limiting factors)
  - Allogeneic CAR T-cells, NK CARs

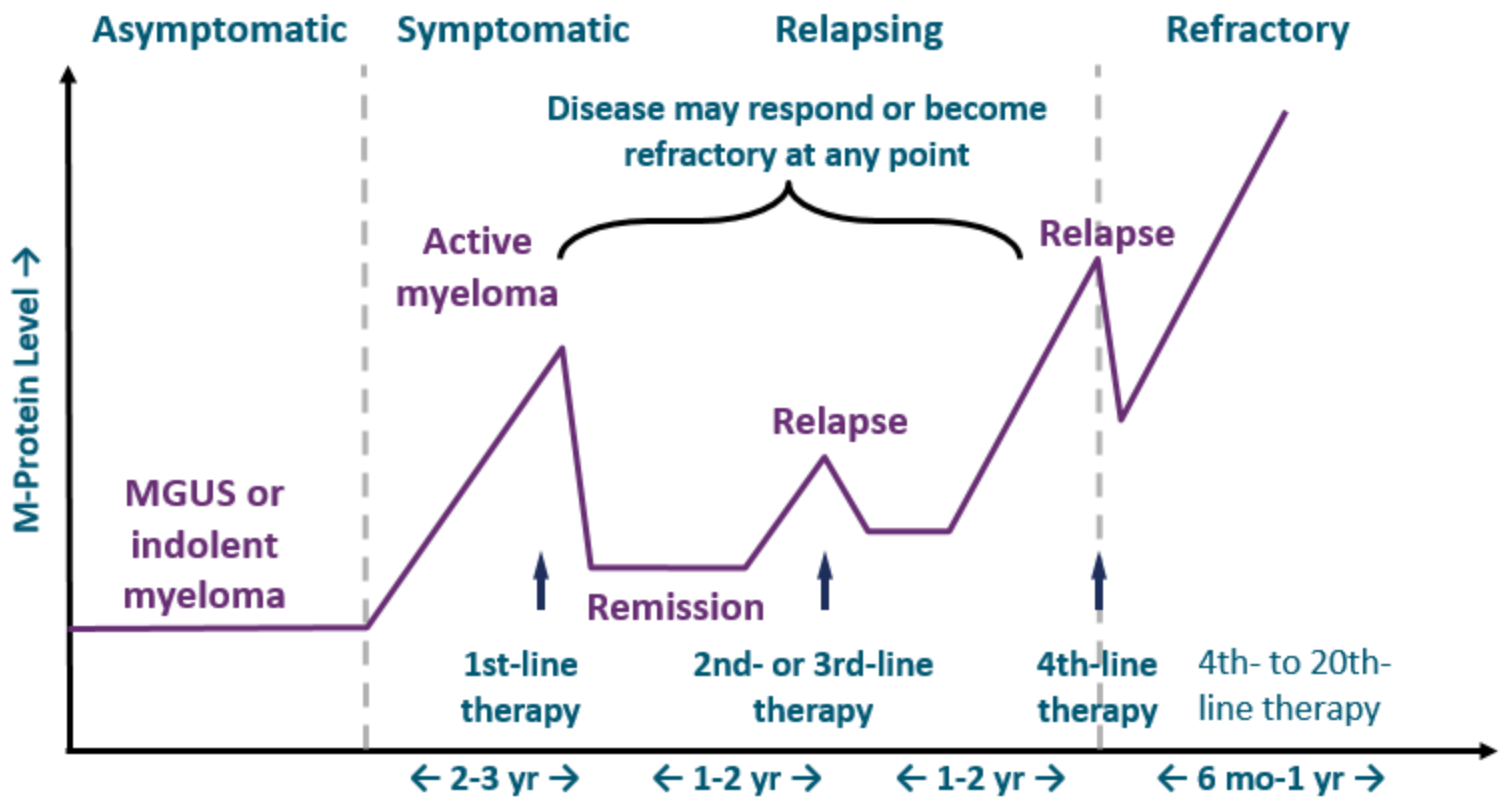
Slide credit: clinicaloptions.com

CLINICAL CARE OPTIONS®
ONCOLOGY

CAR T-Cell Therapies for Myeloma

Supported by an educational grant from Bristol-Myers Squibb.

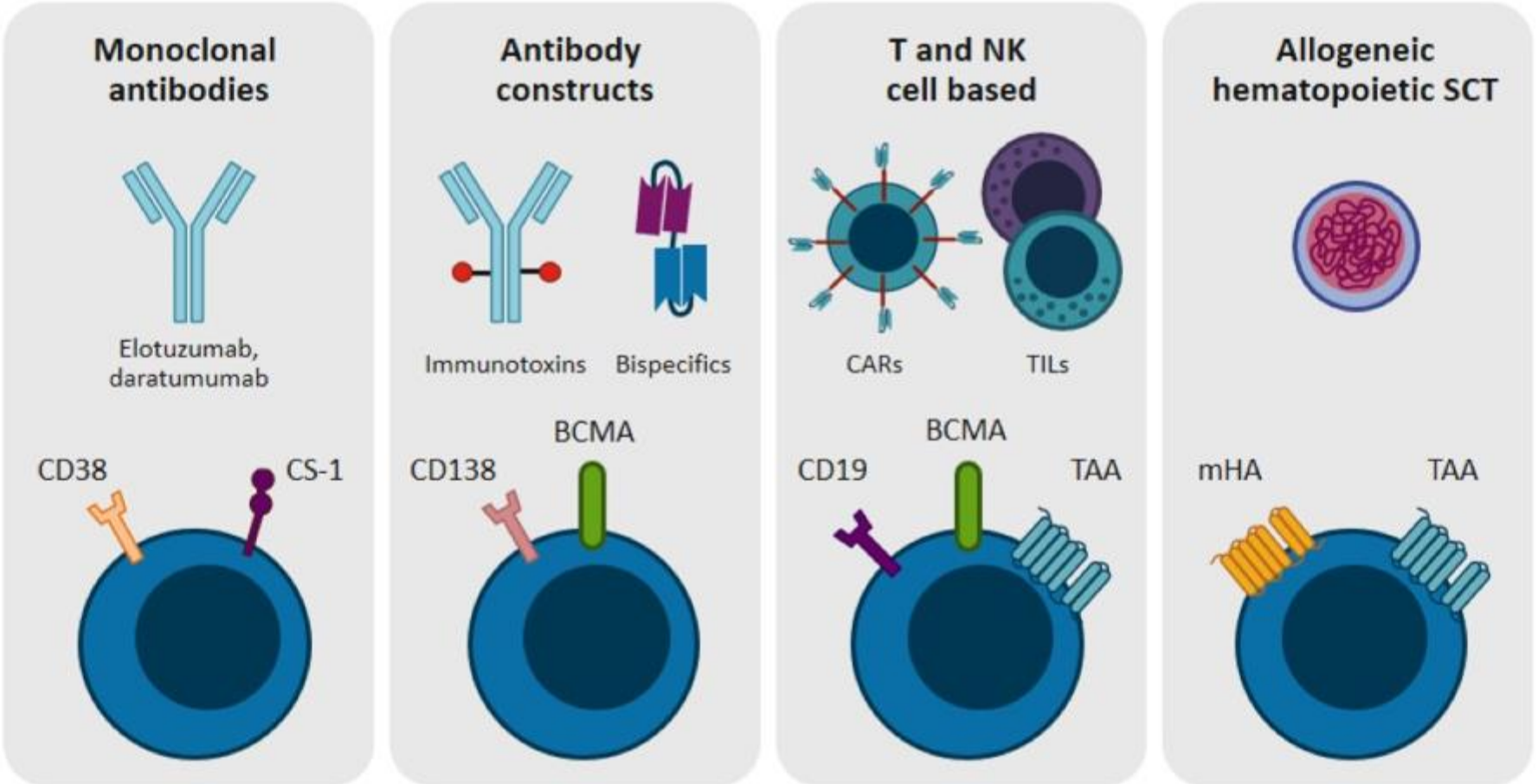
Natural History of Multiple Myeloma



Durie. IMF Concise Review. 2018.

Slide credit: clinicaloptions.com

Immunotherapy Approaches for MM

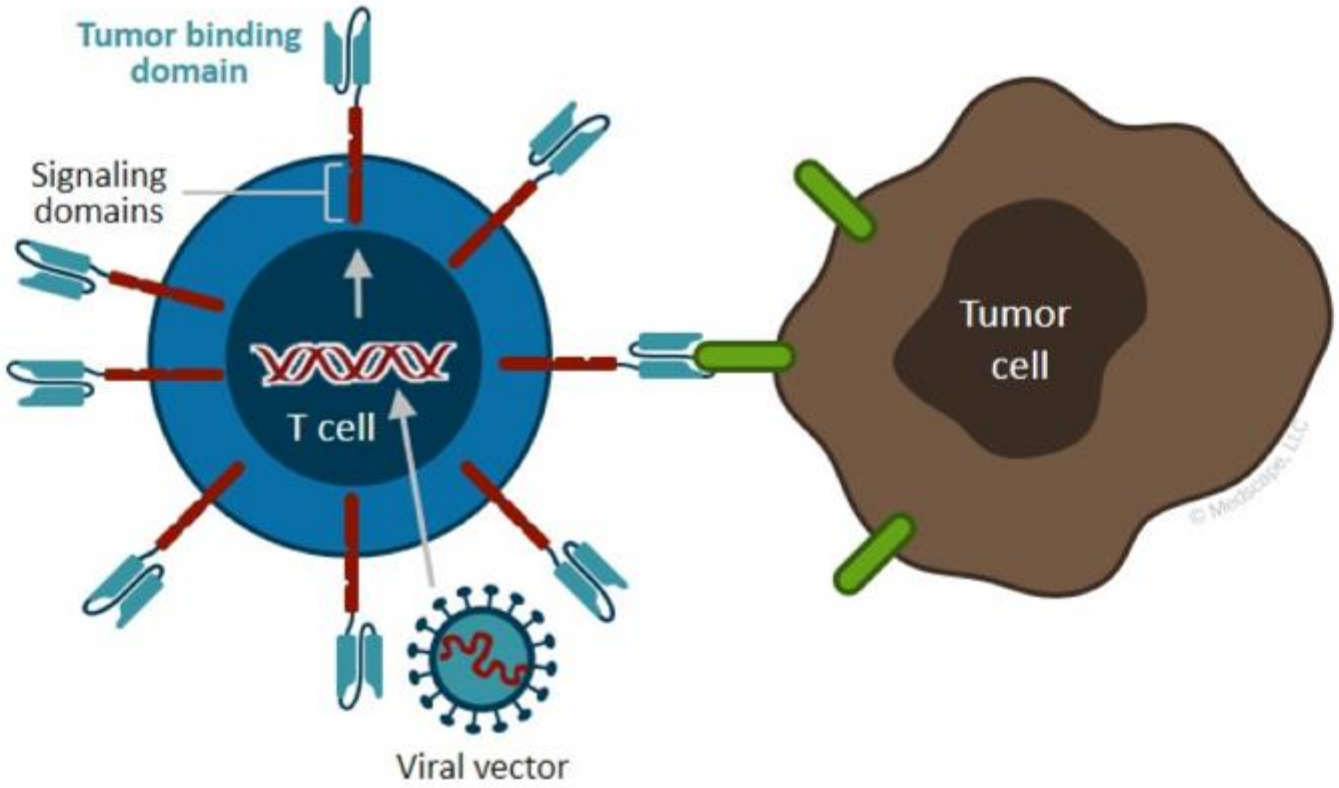


Rasche L, et al. *Cancer Treat Rev*. 2017;55:190-199.

CAR T-Cell Therapy[a,b]

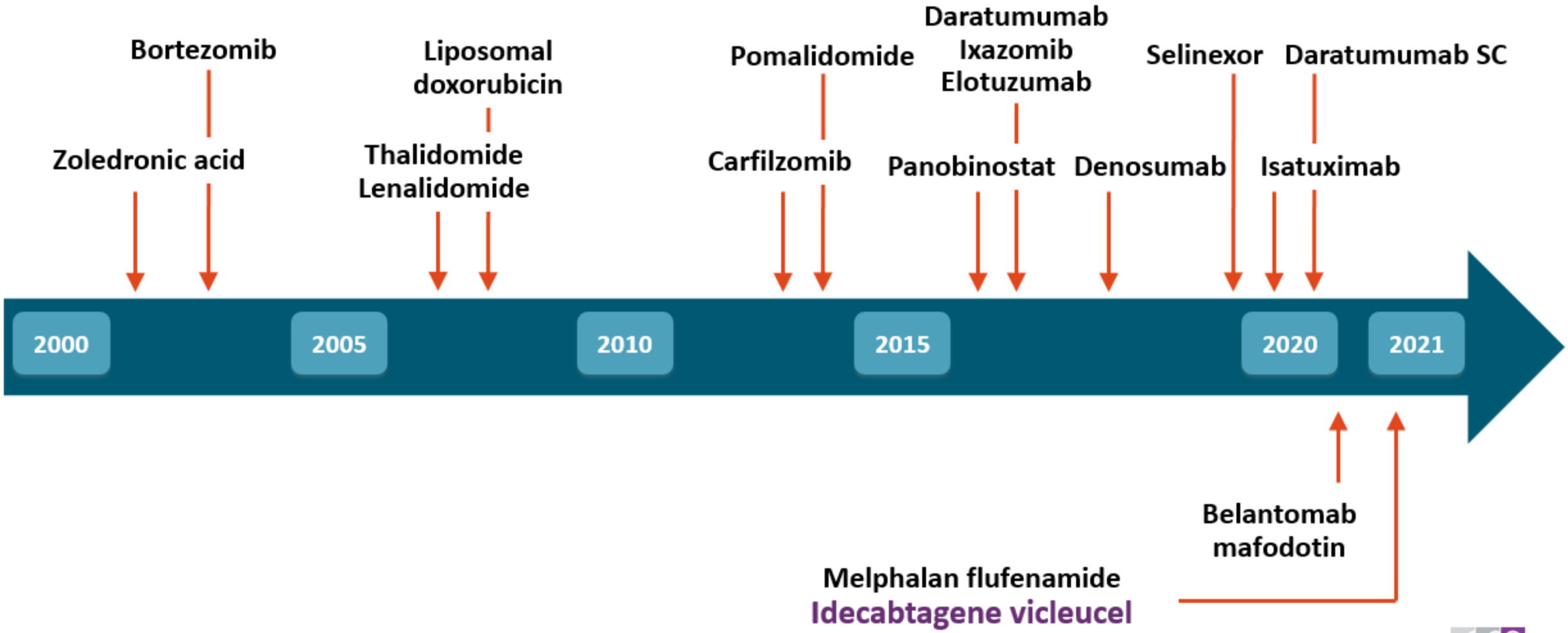
Targets in MM

- CD19
- BCMA
- SLAMF7



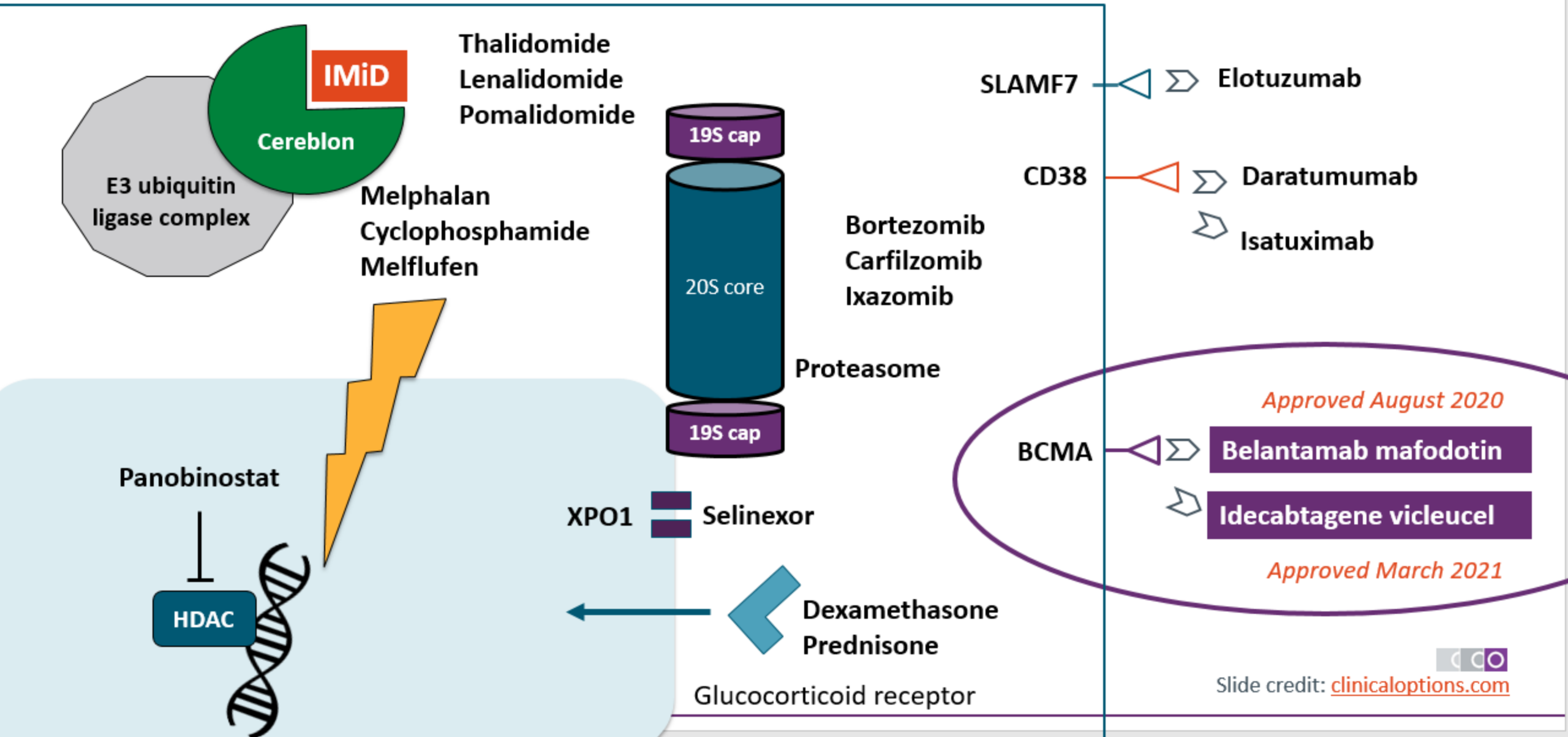
a. Raje NS, et al. ASCO® 2018. Abstract 8007; b. Rasche L, et al. *Cancer Treat Rev*. 2017;55:190-199.

Myeloma Drugs Approved Since 2000



Slide credit: clinicaloptions.com

Treatment Options for Multiple Myeloma

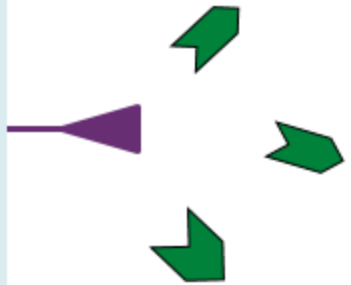


Slide credit: clinicaloptions.com

BCMA-Targeted Therapies

Myeloma cell

BCMA



Antibody–Drug Conjugates

Belantamab mafodotin
MEDI2228
CC-99712

Bispecific T-Cell Engagers

AMG 420
AMG 701
CC-93269
REGN5458
JNJ-64007957
PF-06863135

CAR T-Cell Therapies

Idecabtagene vicleucel
Ciltacabtagene autoleucel
Orvacabtagene autoleucel
P-BCMA-101
bb21217
ALLO-715

Slide credit: clinicaloptions.com

Targeting BCMA ~~May Be~~ Is a New Standard

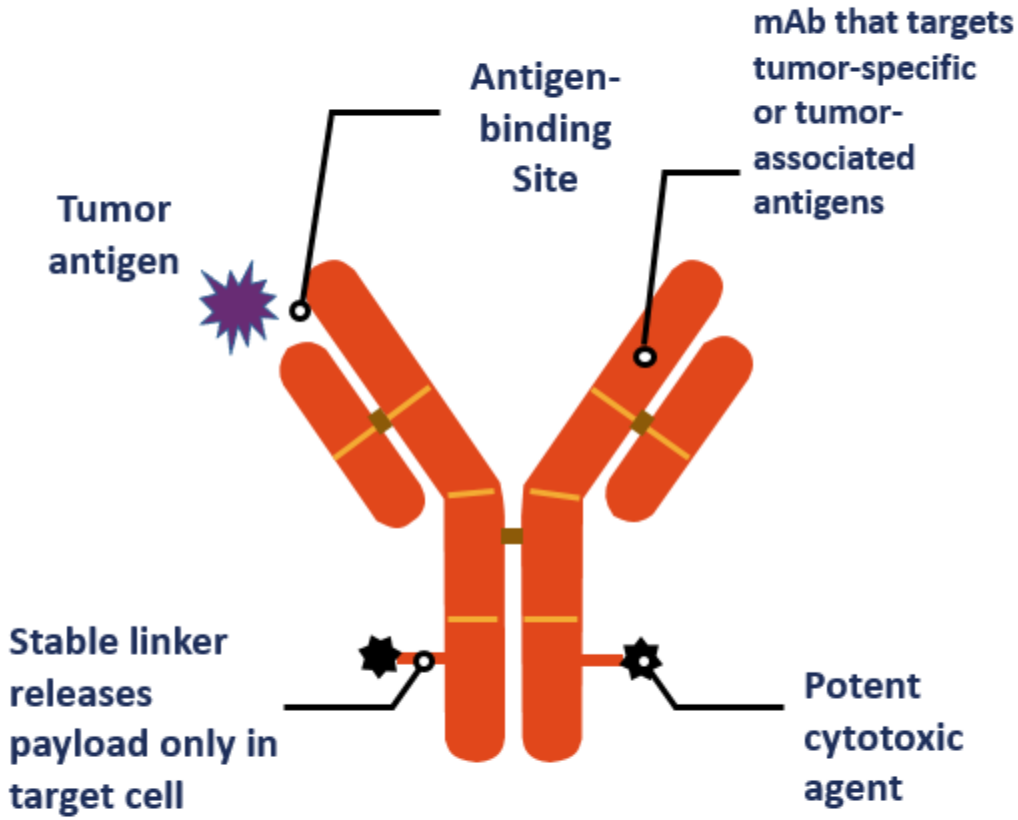
	Antibody–Drug Conjugate	Bispecific Antibodies	CAR T-Cell Therapy
Approved product	Belantamab mafodotin (August 2020)	Several in development	Idecabtagene vicleucel (March 2021)
Efficacy	++ (as single agent; higher in combinations)	+++	++++
How given	IV, Q3W until progression	IV or SC, QW or Q2W until progression	IV one-and-done
Where given	Community	Academic medical centers	Academic medical centers
Notable adverse events	Ocular (corneal)	CRS and neurotoxicity	CRS and neurotoxicity
CRS	Not seen	++	+++
Neurotoxicity	Not seen	+	++
Availability	Off the shelf after ophthalmology evaluation	Off the shelf	Wait time for manufacturing

Slide credit: clinicaloptions.com

Belantamab Mafodotin: BCMA-Targeted ADC

- **Belantamab mafodotin (GSK2857916)**: humanized, afucosylated, IgG1 **BCMA-targeted ADC** that neutralizes soluble BCMA

Cytotoxic agent	–MMAF (non–cell-permeable, highly potent auristatin)
Afucosylation	–Enhanced ADCC
Linker	–Stable in circulation



Tai. Blood. 2014;123:3128. Trudel. Lancet Oncol. 2018;19:1641. Trudel. Blood Cancer J. 2019;9:37. Belantamab mafodotin PI.

Slide credit: clinicaloptions.com

Select Ongoing Studies of BCMA-Targeted CAR T-Cell Therapies for R/R Multiple Myeloma

Study	CAR T-Cell Therapy	Phase	Key Findings
KarMMa-3 (NCT03651128)	Idecabtagene vicleucel	III	▪ Ongoing; **RCT vs standard triplet therapy**
KarMMa-2 (NCT03601078)	Idecabtagene vicleucel	II	▪ Ongoing
CARTITUDE-4 (NCT04181827)	Ciltacabtagene autoleucel	III	▪ Ongoing; **RCT vs standard triplet therapy**
CARTITUDE-2 (NCT04133636)	Ciltacabtagene autoleucel	II	▪ Ongoing; ORR 95% (N = 20)[1]
CARTIFAN-1 (NCT03758417)	Ciltacabtagene autoleucel	I/II	▪ Ongoing
NCT03288493	P-BCMA-101	I/II	▪ Ongoing
CRB-402 (NCT03274219)	bb21217	I	▪ Ongoing; ORR 83% (n = 18)[2]

- **bb21217**: same CAR construct as idecabtagene vicleucel (bb2121); cultured with PI3K inhibitor bb007 to enrich for T-cells displaying a memory-like phenotype, potentially improving duration of persistence and function[3,4]
- **P-BCMA-101**: targets BCMA via Centyrin scaffold molecules fused to a CD3ζ/4-1BB signaling domain (different from scFv); unique platform based on nonviral gene transduction of autologous T-cells; "safety switch"[5]
- Additional targets in MM: CD44v6, CD70, CD56, CD38, CD138, CD19, SLAMF7[6]

1. Agha. ASCO 2021. Abstr 8013. 2. Berdeja. ASH 2019. Abstr 927. 3. Friedman. Hum Gen Ther. 2018;29:585.
4. Fraietta. Nat Med. 2018;24:563. 5. Gregory. ASH 2018. Abstr 1012. 6. Mikkilineni. Blood. 2017;130:2594.

Efficacy and Safety Across BCMA CAR T Trials in R/R MM

Parameter	Cilta-cel[1,2] (n = 97)	Ide-cel[3,4] (n = 54)	Ide-cel[3,4] (n = 128)
Dose	0.75 x 10^6 cells/kg	450 x 10^6 cells	150-450 x 10^6 cells
Median prior lines of tx, n (range)	6 (3-18)	6 (3-16)	6 (3-16)
Triple-class refractory, %	88	81	84
ORR, %	97.9	81	73
MRD−, %	57.7	48	26
≥CR, %	43	39	33
PFS	66% at 18 mo	Median: 12.1 mo	Median: 8.8 mo

Parameter, %	Cilta-cel[1,2] (n = 97)	Ide-cel[3,4] (n = 54)
CRS	94.8	96
▪ Grade ≥3	5.2	6
Tocilizumab	69.1	67
Corticosteroids	21.6	22
Anakinra	18.6	0
Neurotoxicity	20.6	20
▪ Grade ≥3	10.3	6
▪ Other (not ICANS)	12.4	Not reported
▪ Other grade ≥3	9.3	Not reported

1. Madduri. ASH 2020. Abstr 177. 2. Usmani. ASCO 2021. Abstr 8005. 3. Anderson. ASCO 2021. Abstr 8016.
4. Munshi. NEJM. 2021;384:705.

bb2121 Phase 1 Trial
Study Design

Phase 1, open-label, multicenter trial: CD3/41BB (bb2121)

Study populations (N = 33)

- Patients with RRMM received 50×10^6 up to 800×10^6 CAR+ T cells/kg (dose-escalation phase) and 150×10^6 or 450×10^6 total CAR+ T cells/kg (expansion phase)
- Conditioning chemotherapy of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2

Primary endpoint

- Safety

Raje N, et al. *N Engl J Med*. 2019;380:1726-1737.

bb2121 Phase 1 Trial

Study Results: Efficacy and Safety

Efficacy

- ORR: 85%
- CR: 45%
- Median PFS: 11.8 mo

Safety

AEs (grade 3 or higher)

- Neutropenia: 85%
- Leukopenia: 58%
- Anemia: 45%
- Thrombocytopenia: 45%
- 17 patient deaths*

CRS: 76%

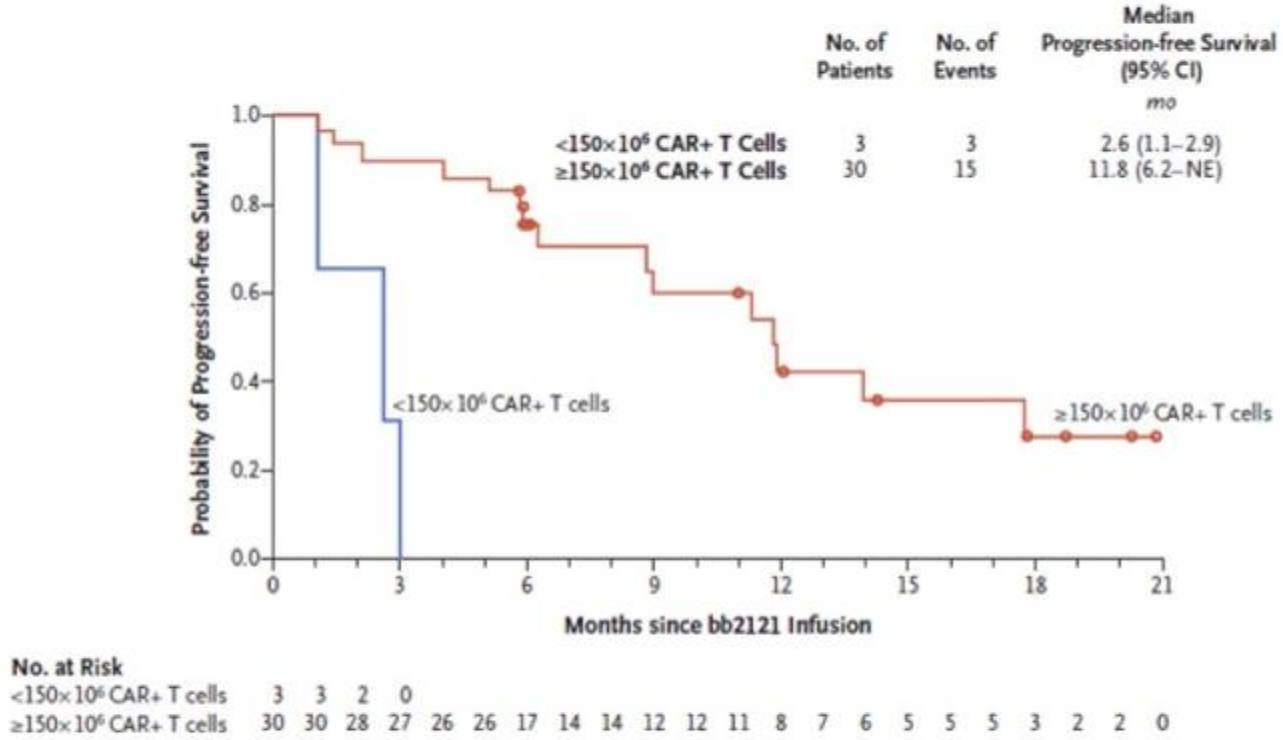
- Grades 1-2: 70%
- Grade 3: 6 %

CRS occurred early in treatment, with a median time to onset of 2 d and median duration of 5 d

*PD (n = 11); progressive disease, PD + lung infection, suicide after PD, esophageal carcinoma, infection, and pulmonary embolism and acute coronary syndrome (n = 1 each).

Raje N, et al. *N Engl J Med*. 2019;380:1726-1737.

bb2121 Phase 1 Trial
Study Results: mPFS Rates

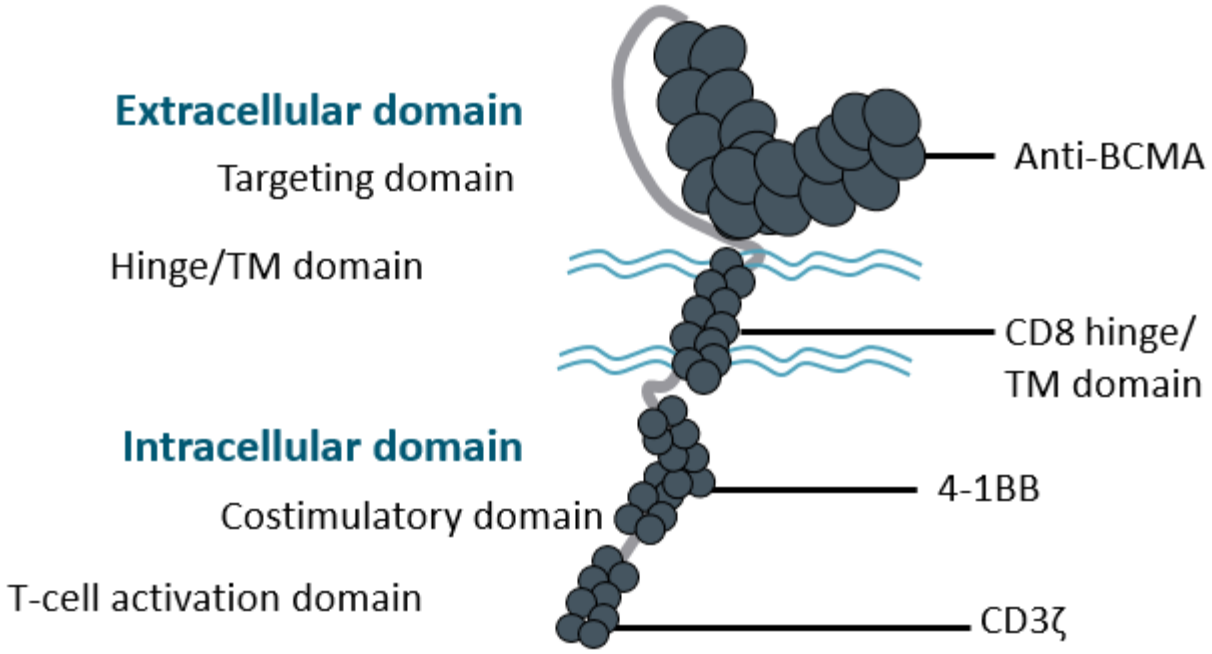


- mPFS at active doses* in dose escalation phase: 11.8 mo
- mPFS in MRD-negative patients: 17.7 mo

*≥ 150 × 10^6 CAR+ T cells.

Raje N, et al. *N Engl J Med.* 2019;380:1726-1737.

Idecabtagene Vicleucel for R/R MM



- Now approved for adults with R/R multiple myeloma **after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab** (March 2021)
- FDA approved dose: 300-460 x 10^6 cells

Idecabtagene vicleucel PI. Raje. ASCO 2018. Abstr 8007.

Slide credit: clinicaloptions.com

KarMMa: Idecabtagene Vicleucel for R/R MM

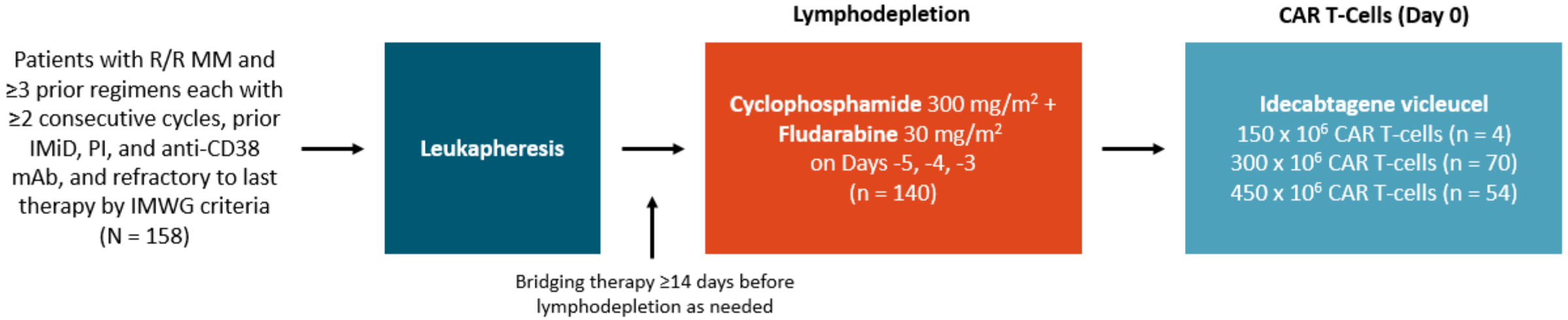
- Multicenter, single-arm phase II trial (N = 128)
- Patient population:
  - R/R MM, ≥3 prior regimens each with ≥2 consecutive cycles, prior IMiD, PI, and anti-CD38 mAb, refractory to last therapy by IMWG criteria
- Flu/Cy lymphodepletion + single infusion ide-cel (150, 300, or 450 x 10^6/kg)
- Bridging therapy permitted

Munshi. NEJM. 2021;384:705.

Slide credit: clinicaloptions.com

KarMMa: Idecabtagene Vicleucel for R/R MM

- Multicenter, single-arm phase II trial

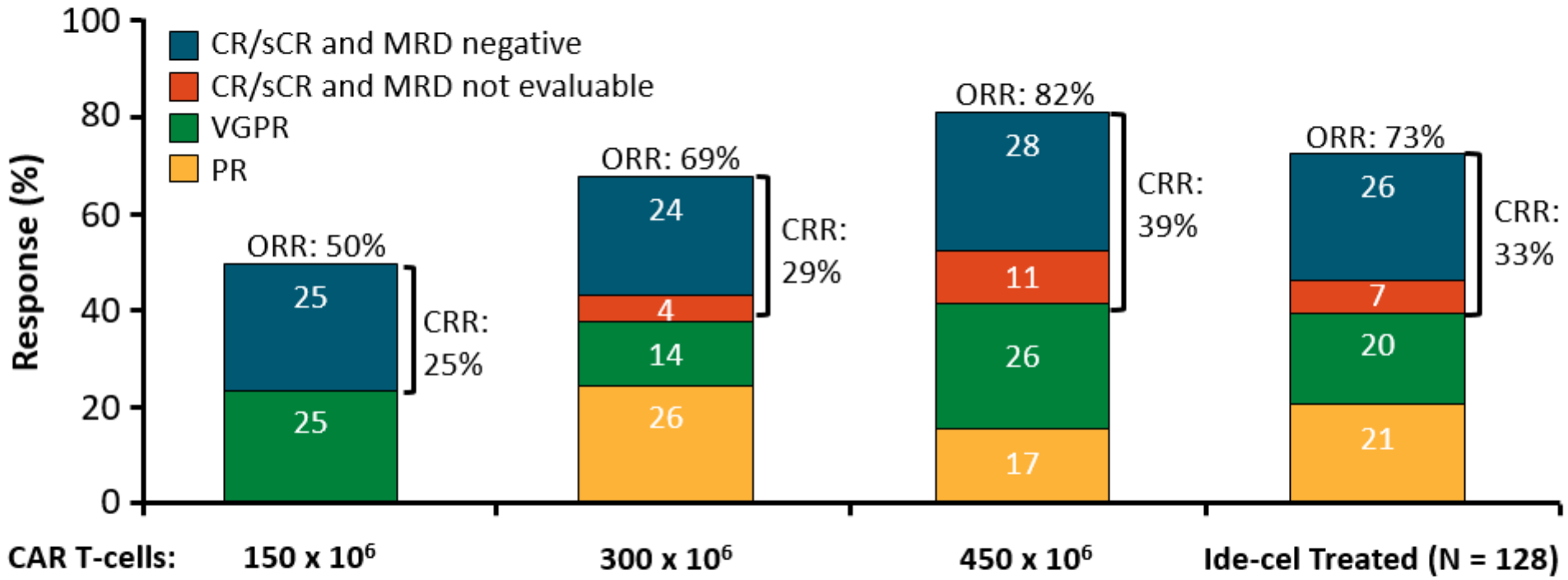


- One treatment followed by observation: "one and done"
- Primary endpoint: ORR; secondary endpoints: CR (key), safety, DoR, PFS, OS, PK, MRD, QoL, HEOR
- FDA approved dose: 300-460 x 10^6 cells; **now approved for adults with R/R multiple myeloma after ≥ 4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab;**

Munshi. NEJM. 2021;384:705.

Slide credit: clinicaloptions.com

KarMMa: Response



- Primary endpoint (ORR >50%) and secondary response endpoint (CRR >10%) met
- Median f/u: 13.3 mo; median TTFR: 1.0 mo (range 0.5-8.8); median time to CR: 2.8 mo (range: 1.0-11.8)

Munshi. NEJM. 2021;384:705.

Slide credit: clinicaloptions.com

KarMMa: Updated Response

- Median follow-up: 24.8 mo (range: 1.7-33.6)

Outcome, n (%)	Ide-cel 150 x 10^6 (n = 4)	Ide-cel 300 x 10^6 (n = 70)	Ide-cel 450 x 10^6 (n = 54)	All Ide-cel Patients (n = 128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	42 (33)

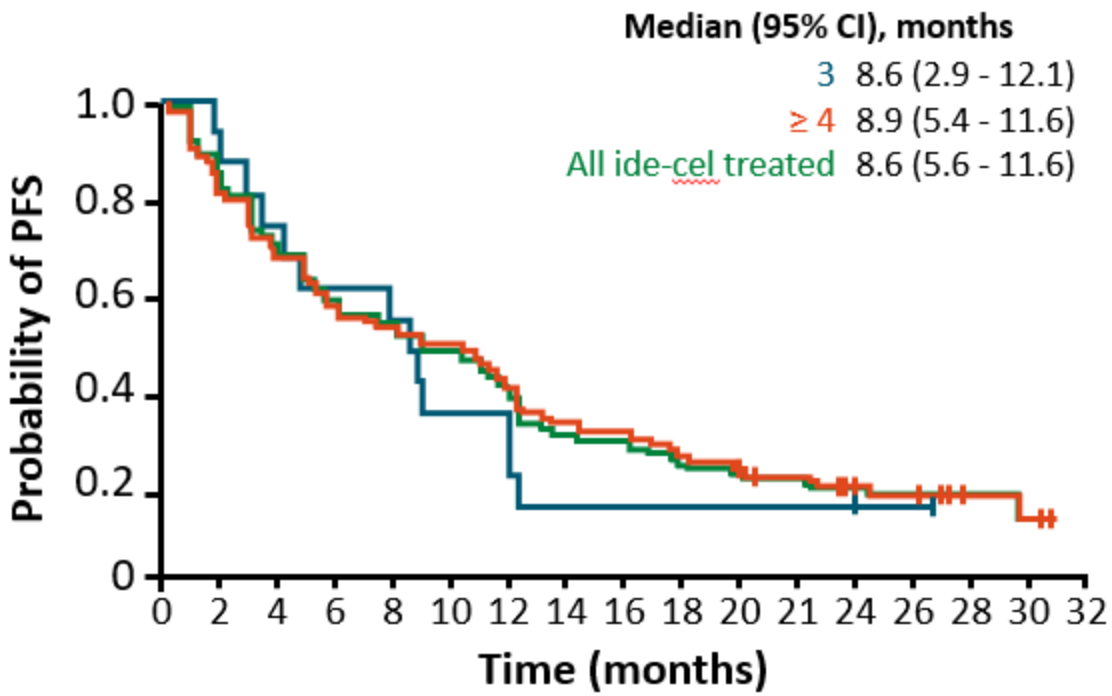
Outcome by Prior Lines of Tx, %	3 Lines (n = 15)	≥4 Lines (n = 113)	All Ide-cel Patients (n = 128)
ORR	73	73	73
CR/sCR	53	30	33
VGPR	0	23	20
PR	20	20	20

Anderson. ASCO 2021. Abstr 8016.

Slide credit: clinicaloptions.com

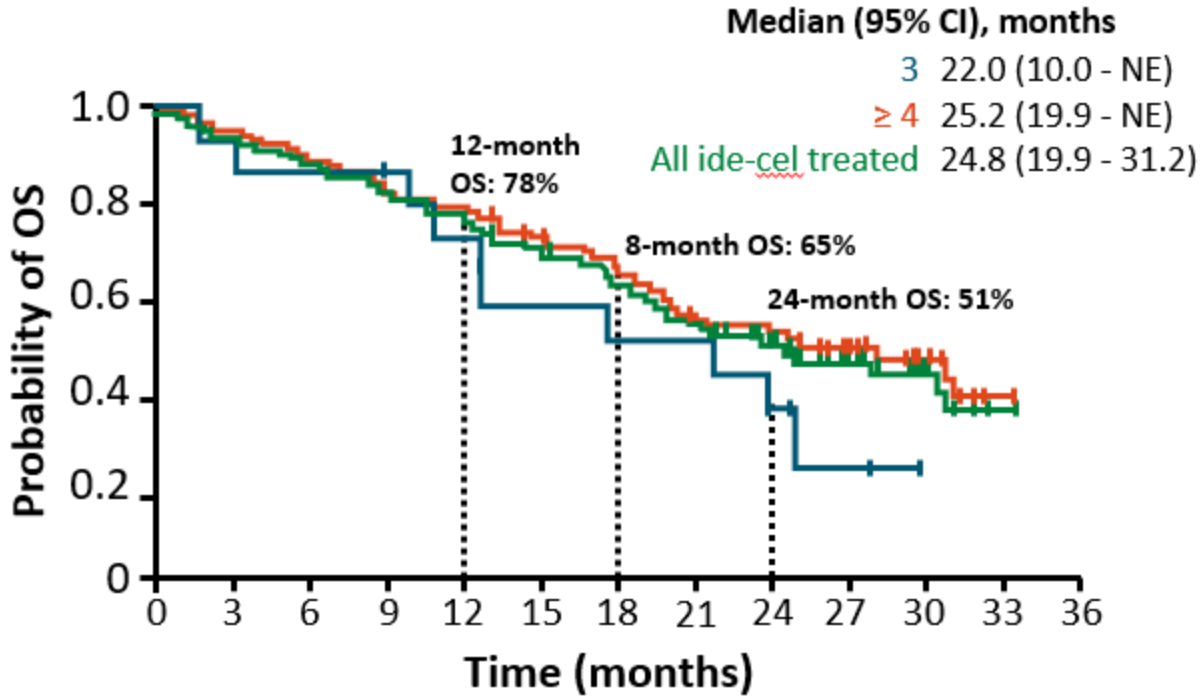
KarMMa: Updated PFS and OS

PFS by Number of Prior Lines of Therapy



At risk																	
3	15	13	11	9	8	5	5	2	2	2	2	2	2	1	0	0	
≥ 4	113	89	73	62	56	51	41	33	31	25	22	19	10	9	3	2	0
All ide-cel treated	128	102	84	71	64	56	46	35	33	27	24	21	12	10	3	2	0

OS by Number of Prior Lines of Therapy



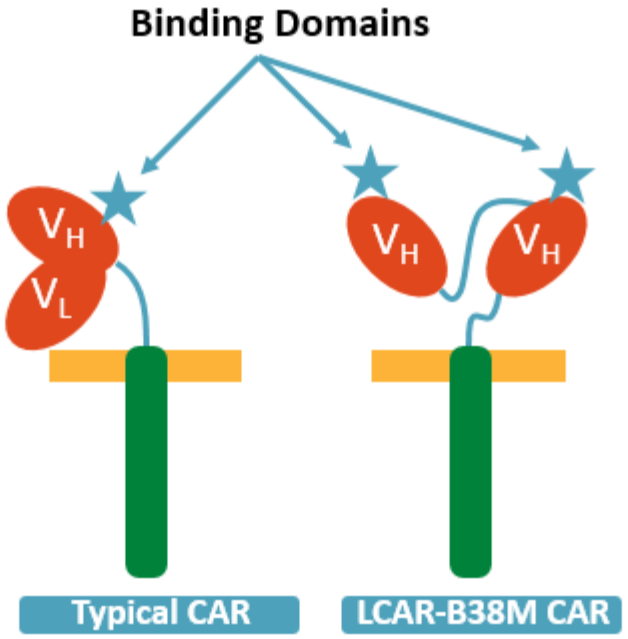
15	14	13	13	10	8	7	7	5	2	0	0		
113	106	94	87	80	71	65	52	43	24	14	1	0	
128	120	107	100	90	79	72	59	48	26	14	1	0	

Anderson. ASCO 2021. Abstr 8016.

Slide credit: clinicaloptions.com

Ciltacabtagene Autoleucel (LCAR-B38M/JNJ-4528): BCMA-Targeted CAR T-Cell Therapy

- Lentiviral vector-based + 4-1BB costimulatory domain; BCMA-catching domain **targets 2 different epitopes** simultaneously

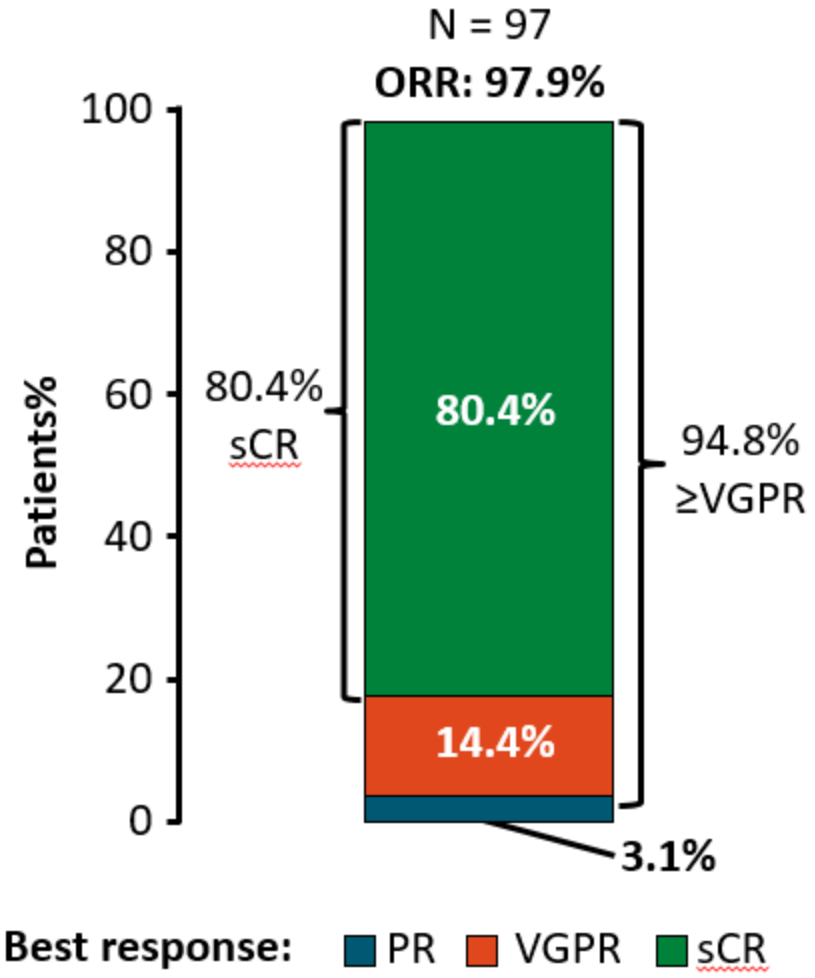


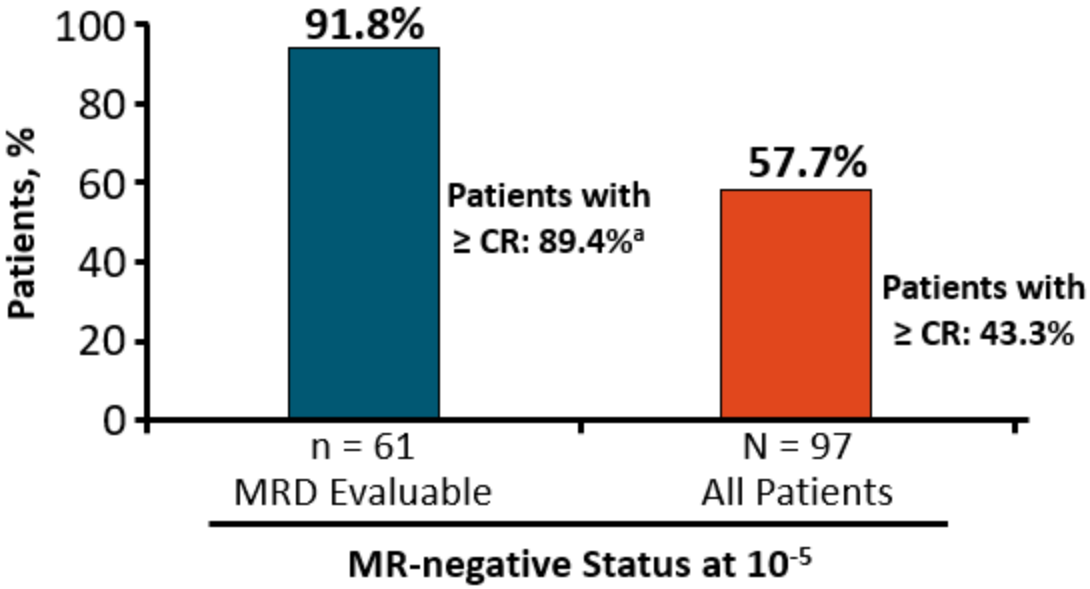
- **LEGEND-2:** single-arm, open-label phase I trial in which patients with R/R MM (resistant to ≥3 prior tx lines) treated with increasing doses of LCAR-B38M (N = 57)[1,2]
- **CARTITUDE-1:** single-arm, open-label phase Ib/II trial in which patients with R/R MM (resistant to ≥3 prior tx lines) treated with increasing doses of JNJ-4528 (N = 29)[3]

1. Zhao. ASH 2018. Abstr 955. 2. Wang. ASH 2019. Abstr 579. 3. Berdeja. ASCO 2020. Abstr 8505.

Slide credit: clinicaloptions.com

CARTITUDE-1: Response



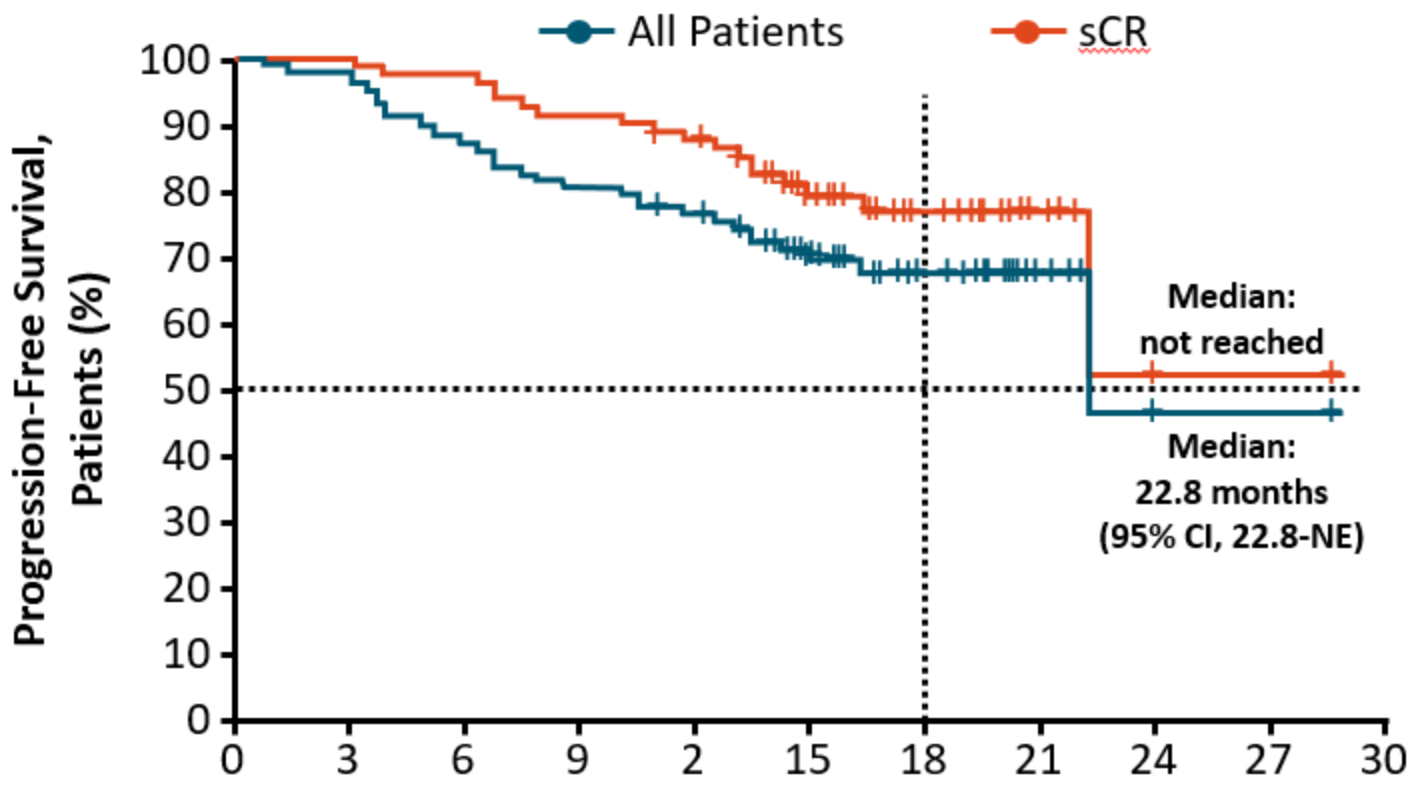


- Median time to first response: 1 month (range, 0.9-10.7)
- Median time to best response: 2.6 months (range, 0.9-15.2)
- Median time to ≥CR: 2.6 months (range, 0.9-15.2)
- Median duration of response: 21.8 months (95% CI, 21.8-NE)
  - Estimated 73% of responders have not progress or died at 12 months
  - Median duration of response not reached in patients with sCR

Usmani. ASCO 2021. Abstr 8005.

Slide credit: clinicaloptions.com

CARTITUDE-1: PFS



Number at risk

All patients	97	95	85	77	73	55	26	9	1	1	0
Responders with sCR	78	78	76	71	71	51	26	9	1	1	0

Median duration of follow-up: 18 months (range, 1.5-30.5)

18-month PFS
All patients: 66.0% (95% CI, 54.9-75.0)
sCR: 75.9% (95% CI, 63.6-84.5)

18-month OS
All patients: 80.9% (95% CI, 71.4-87.6)

Usmani. ASCO 2021. Abstr 8005.

Slide credit: clinicaloptions.com

Select Ongoing Studies of BCMA-Targeted CAR T-Cell Therapies for R/R Multiple Myeloma

Study	CAR T-Cell Therapy	Phase	Key Findings
KarMMa-3 (NCT03651128)	Idecabtagene vicleucel	III	▪ Ongoing; **RCT vs standard triplet therapy**
KarMMa-2 (NCT03601078)	Idecabtagene vicleucel	II	▪ Ongoing
CARTITUDE-4 (NCT04181827)	Ciltacabtagene autoleucel	III	▪ Ongoing; **RCT vs standard triplet therapy**
CARTITUDE-2 (NCT04133636)	Ciltacabtagene autoleucel	II	▪ Ongoing
CARTIFAN-1 (NCT03758417)	Ciltacabtagene autoleucel	I/II	▪ Ongoing
PRIME (NCT03288493)	P-BCMA-101	I/II	▪ Ongoing; ORR 44%-75% by dose (n = 30)[1]
CRB-402 (NCT03274219)	bb21217	I	▪ Ongoing; ORR 43%-83% by dose (n = 69)[2]

1. Costello. ASH 2020. Abstr 134. 2. Alsina. ASH 2020. Abstr 130.

Identifying and Managing CAR T-Cell–Mediated Toxicities

CAR T-Cell Toxicities: Acute

Cytokine-Release Syndrome (CRS)

- Onset typically 2-3 days, duration 7-8 days
- Symptoms: fever, hypotension, tachycardia, hypoxia, chills
- Can range in severity from low-grade to high-grade symptoms with life-threatening multiorgan system failure

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Onset typically 4-10 days, duration 14-17 days
- Toxic encephalopathy with symptoms of headaches, confusion, and delirium; expressive aphasia; occasional seizures; and rarely, cerebral edema
- Can occur in the presence or absence of systemic CRS
- Severe neurotoxicity associated with endothelial activation (eg, disseminated intravascular coagulation, capillary leak, increased blood–brain barrier permeability)

Jacobson. Oncologist. 2020;25:e138. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v3.2021. Gust. Cancer Discov. 2017;7:1404.

Class Effects of the Cell-Mediated Immune Response: CRS and Neurotoxicity

	B-ALL		DLBCL			MCL	MM
	ELIANA[1]	ZUMA-3[2]	JULIET[3]	ZUMA-1[4]	TRANSCEND[5]	ZUMA-2[6]	KarMMa[7]
CAR T-cell agent	Tisagenlecleucel	Brex. autoleucel	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel	Brex. autoleucel	Idecabtagene Vicleucel
Construct	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z	Anti-BCMA
N treated	75	55	111	101	269	68	128
CRS, %	77*	89†	58*	93†	42†	91†	84†
Grade ≥3 CRS, %	46*	24†	22*	13†	2†	15†	5†
NT, %	40	60	21	64	30	63	18
Grade ≥3 NT, %	13	25	12	28	10	31	3

*Per Penn scale. †Per Lee Scale.

1. Maude. NEJM. 2018;378:439. 2. Shah. Lancet. 2021;[Epub]. 3. Schuster. NEJM. 2019;380:45. 4. Neelapu. NEJM. 2017;377:2531.
5. Abramson. Lancet. 2020;396:839. 6. Wang. NEJM. 2020;382:1331. 7. Munshi. NEJM. 2021;384:705.

Slide credit: clinicaloptions.com

Time Course of Toxicities Associated With FDA-Approved CAR T-Cell Therapies

Number of Days (Range)	CRS		Neurologic AEs	
	Median Time to Onset	Median Duration	Median Time to Onset	Median Duration
Axicabtagene ciloleucel[1]	LBCL: 2 (1-12) iNHL: 4 (1-20)	LBCL: 7 (2-58) iNHL: 6 (1-27)	LBCL: 4 (1-43) iNHL: 6 (1-79)	LBCL: 17 iNHL: 16
Brexucabtagene autoleucel[2]	3 (1-13)	10 (1-50)	6 (1-32)	2 (2-454)
Idecabtagene vicleucel[5]	1 (1-23)	7 (1-63)	2 (1-42)	6 (1-578)
Lisocabtagene maraleucel[3]	5 (1-15)	5 (1-17)	8 (1-46)	12 (1-87)
Tisagenlecleucel[4]	ALL: 3 (1-22) DLBCL: 3 (1-51)	ALL: 8 (1-36) DLBCL: 7 (2-30)	ALL: 6 (1-301) DLBCL: 5 (1-368)	ALL: 7 DLBCL: 17

Axicabtagene ciloleucel PI. Brexucabtagene autoleucel PI. Idecabtagene vicleucel PI. Lisocabtagene maraleucel PI. Tisagenlecleucel PI.

ASTCT Guidelines for Grading of CRS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Slide credit: clinicaloptions.com

ASTCT Guidelines for Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

*See next slide; an ICE score of 0 may be classified as grade 3 ICANS if patient is awake with global aphasia; otherwise classified as grade 4 ICANS if unarousable.

Lee. Biol Blood Marrow Transplant. 2019;25:625.

ASTCT Guidelines for Grading of ICANS: ICE Score

Parameter	Score (Points)
Orientation: yr, month, city, hospital	4
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3
Following commands: ability to follow simple commands (eg, “show me 2 fingers” or “close your eyes and stick out your tongue”)	1
Writing: ability to write a standard sentence (eg, “our national bird is the bald eagle”)	1
Attention: ability to count backwards from 100 by 10	1

Scoring:
10, no impairment
7-9, grade 1 ICANS
3-6, grade 2 ICANS
0-2, grade 3 ICANS
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Slide credit: clinicaloptions.com

Acute CAR T-Cell Toxicities: Management

Cytokine-Release Syndrome (CRS)

- Supportive care (antipyretics, hydration)
- Tocilizumab (IL-6)
  - Must have 2 doses readily available to administer due to REMS requirements
- Corticosteroids
- Secondary agents: anakinra (IL-1), siltuximab (IL-6)
- Vasopressors

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Supportive care
- Corticosteroids
- Seizure prophylaxis

No universal guideline for toxicity management; protocols vary by institution

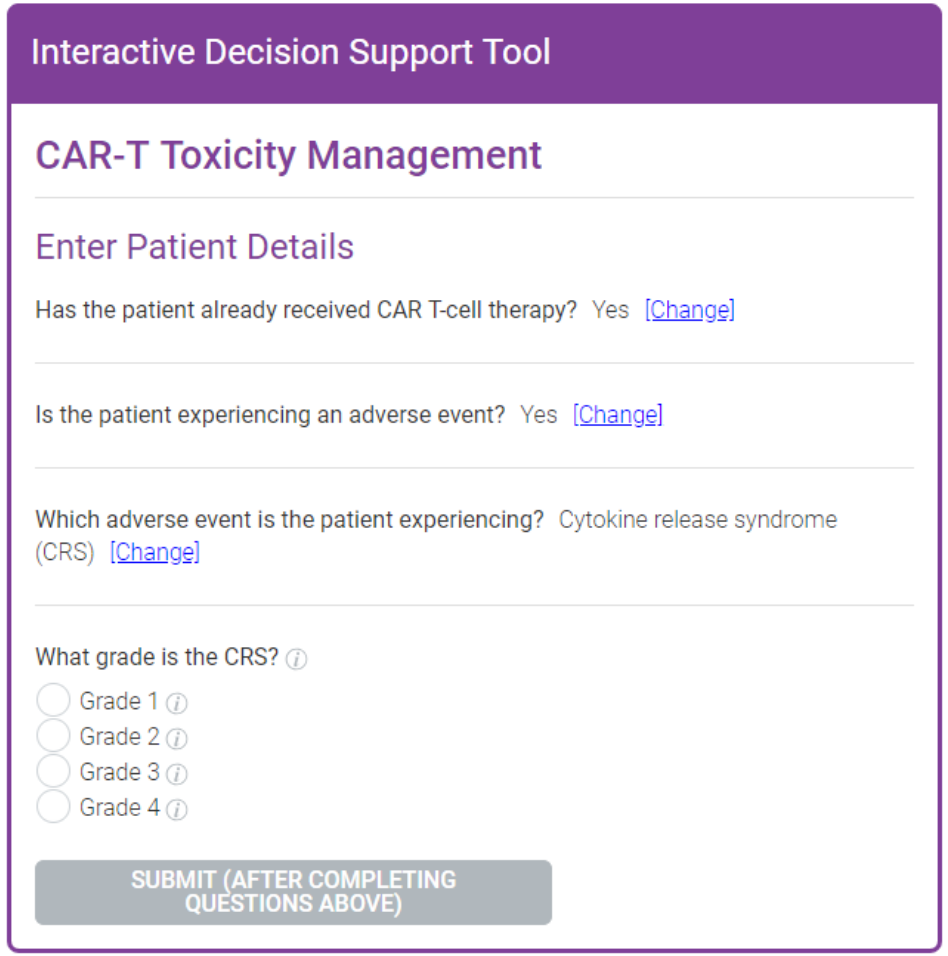
Rates of CRS and neurotoxicity vary among products, disease states, and patient characteristics

National Comprehensive Cancer Network. Clinical practice guidelines in oncology: management of immunotherapy-related toxicities. v.3.2021. nccn.org. Accessed July 26, 2021.

Slide credit: clinicaloptions.com

CCO Online Interactive Treatment Decision Support Tool for CAR T-Cell Therapy–Associated AE Management

- Enter CAR T-cell therapy history and AE characteristics by answering a series of multiple choice questions and get consensus recommendations for your specific patient case from 5 multidisciplinary experts
  - *Matthew J. Frigault, MD; Daniel J. DeAngelo, MD, PhD; Ilene A. Galinsky, NP; Jae H. Park, MD; and Shilpa Paul, PharmD, BCOP*
  - *Released July 9, 2021*



Available at: clinicaloptions.com/CARTtool

or as an app in your app store

Slide credit: clinicaloptions.com

Predictors of Response and Toxicity

	Predictors of Improved Response
Patient	▪ Low tumor burden, LDH, pretreatment inflammatory markers ▪ Absence of medical comorbidities ▪ Lack of need for bridging therapy
T-cells	▪ Proportion of CCR7+ and other early memory T-cells in the CAR product ▪ Faster doubling time in vitro ▪ Higher CAR T-cell peak to tumor burden ratio
Tumor	▪ Absence of CD58 mutations, MYC overexpression ▪ Low tumor MDSCs ▪ High TILs

	Predictors of Increased Toxicity
Pretreatment	▪ High tumor burden, pretreatment LDH, pretreatment inflammatory markers ▪ ? High pretreatment monocyte levels
Post-treatment	▪ High peak CAR T-cell, cytokine levels ▪ Markers of DIC (including fibrinogen levels) ▪ Early CRS

Nastoupil. JCO. 2020;38:3119. Locke. Blood Adv. 2020;4:4898. Du. Biomark Res. 2020;8:13. Jaeger. ASH 2020. Abstr 1194. Majzner. ASH 2020. Abstr 556.

Ongoing Strategies to Manage Acute Toxicities

- Risk-adapted tocilizumab[1]
- Earlier use of corticosteroids[2]
- Fractionating CAR-T doses[3]
- Anakinra[4]
- Ruxolitinib[5]
- Dasatinib[6]
- Lenzilumab[7]

1. Kadauke. JCO. 2021;39:920. 2. Topp. ASH 2019. Abstr 243. 3. Frey. JCO. 2020;38:415. 4. Strati. Blood Adv. 2020;4:3123.
5. Wei. Immunotherapy. 2020;12:1049. 6. Mestermann. Sci Transl Med. 2019;11:eaau5907. 7. Sterner. Blood. 2019;133:697.

Delayed CAR T-Cell Toxicities: Management

Prolonged Cytopenias

- May last for weeks to months post CAR T-cell infusion
- Increased risk of infection and other complications
- Management: primarily supportive care, G-CSF

B-Cell Aplasia and Hypogammaglobulinemia

- Increased risk of infection
- Antimicrobial prophylaxis is needed
- Frequent use of intravenous immune globulin (IVIG)

National Comprehensive Cancer Network. Clinical practice guidelines in oncology: management of immunotherapy-related toxicities. v.3.2021. nccn.org. Accessed July 26, 2021. MDACC. IEC therapy toxicity assessment and management. Approved September 15, 2021. Maus. J Immunother Cancer. 2020;8:e001511.

CAR T-Cell Therapy: Cost-effectiveness

Cost-effectiveness of Axi-cel and Tisa-cel in Adult R/R NHL

Axi-cel

5-Yr PFS Rate, %	QALY	ICER, $/QALY
40	5.50	129,000
30	4.74	159,000
20	4.28	194,000

Tisa-cel

5-Yr PFS Rate, %	QALY	ICER, $/QALY
35	3.92	168,000
25	3.36	223,000
15	2.82	337,000

- Wholesale acquisition cost: $373,000
- Administration to all indicated patients may increase US health care costs by $10 billion/5 yr
- Price to cost <$150,000/QALY with 5-yr PFS rate of 25%:
  - Axi-cel: $250,000
  - Tisa-cel: $200,000

Lin. JCO. 2019;37:2105.

Slide credit: clinicaloptions.com

Cost-effectiveness of Tisa-cel in Pediatric R/R ALL

Scenario	QALY	ICER ($/QALY)
40% 5-yr RFS	8.74	61,000
20% 5-yr RFS	5.50	151,000
Bridge to HSCT	5.92	184,000

- Wholesale acquisition cost: $475,000
- Only charged if response
- Willingness to pay = $150,000/yr
- Price to cost <$150,000/QALY in all scenarios: $350,000

Scenario	Cost ($)	QALY	ICER ($/QALY)
Tisa-cel	968,800	16.76	
SoC CT	440,600	8.58	
Difference	528,200	8.18	64,600

- SoC: clofarabine/etoposide/Cy chemotherapy
- Willingness to pay = $100,000/yr
- Assumed 81% CR and 1-yr OS rate of 76.0% with tisa-cel; if CR <56.2% or <57.8%, not cost effective
- Assumed IVIG necessary for 18 mo in responders; if IVIG needed >15 yr, not cost effective
- ICER $75,600 if charged regardless of response

Lin. JCO. 2018;36:3192. Sarkar. J Natl Cancer Inst. 2019;111:719.

Slide credit: clinicaloptions.com

Cost-Effectiveness of BCMA CAR-T in R/R MM

Cost by Treatment, $	WAC per Unit	Cost per QALY Gained	Cost per Life Year Gained	Cost per Additional PFS Month Gained
Ide-cel	419,500	319,000	250,000	35,000
Cilta-cel (preliminary)	N/A	253,000	207,000	17,000
Belantamab	8,277	98,000	70,000	18,000

- ICER estimates the health benefit price benchmark to be:
  - Ide-cel: $192,000-265,000
  - Cilta-cel: $230,000-312,000
  - Belantamab: $8300-9500
- ~43% (ide-cel) and 50% (cilta-cel) of eligible triple-/quad-refractory MM could be treated within 5 yr before crossing ICER budget impact threshold of $819 million/yr → ICER issued access and affordability alert for ide-cel and cilta-cel

ICER. Anti B-cell maturation antigen CAR T-cell and antibody drug conjugate therapy for heavily pre-treated relapsed and refractory multiple myeloma; final evidence report. Updated July 9, 2021.

Slide credit: clinicaloptions.com

Cost of Adverse Event Management Following CAR-T

- Cost comparison of real-world evidence studies with tisa-cel and axi-cel across 4 studies

Parameter	Axi-cel	Tisa-cel
Inpatient CAR-T infusion, %	92-100	36
Tocilizumab use, %	62-71	14-20
Median duration of hospitalization, days	15-16	2
ICU transfer, %	28-38	7
Total estimated cost for adverse event management ($/patient)	5979-10,878	843-1962
Total estimated healthcare resource utilization cost ($/patient)	32,394-33,166	3321

Yang. ASCO 2021. Abstr e19551.

Slide credit: clinicaloptions.com

The Cost of Care

- Direct costs
  - Direct drug costs: $373,000-475,000[1]
  - Cost of admission: ~$300,000-400,000
  - Costs related to bridging and lymphodepleting chemotherapy
  - Costs associated with toxicity management—acute and delayed
  - Nondrug costs: $30,000-56,000[1]
- Total cost of care
  - Estimated $450,000-480,000 or closer to $1-2 million

1. Hernandez. JAMA Oncol. 2018;4:994.

Slide credit: clinicaloptions.com

Remaining Challenges in CAR T-Cell Therapy

- Designing safer CARs and overcoming mechanisms of resistance
- Logistics of limiting lymphotoxic therapies to enable successful collection
- Bridging chemotherapy logistics
- Inpatient vs outpatient administration
- Out of specification CAR T-cell products
- Toxicity management
- Increasing accessibility
- Cost of care

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Conclusions

- Cellular therapeutics continue to expand across hematologic malignancies with impressive efficacy in the relapsed/refractory setting
- Research remains to ensure optimal toxicity management
- A multidisciplinary team is required to ensure optimal success of patient care
- Access to care remains a critical component of cellular therapies