CAR T-Cell Indications and Post-Treatment Care

West Virginia Oncology Society

Salahuddin Safi, MD, MS
Assistant Professor of Medicine
Section of Hematology and Oncology
West Virginia University Cancer Institute

WVUMedicine

Disclosures

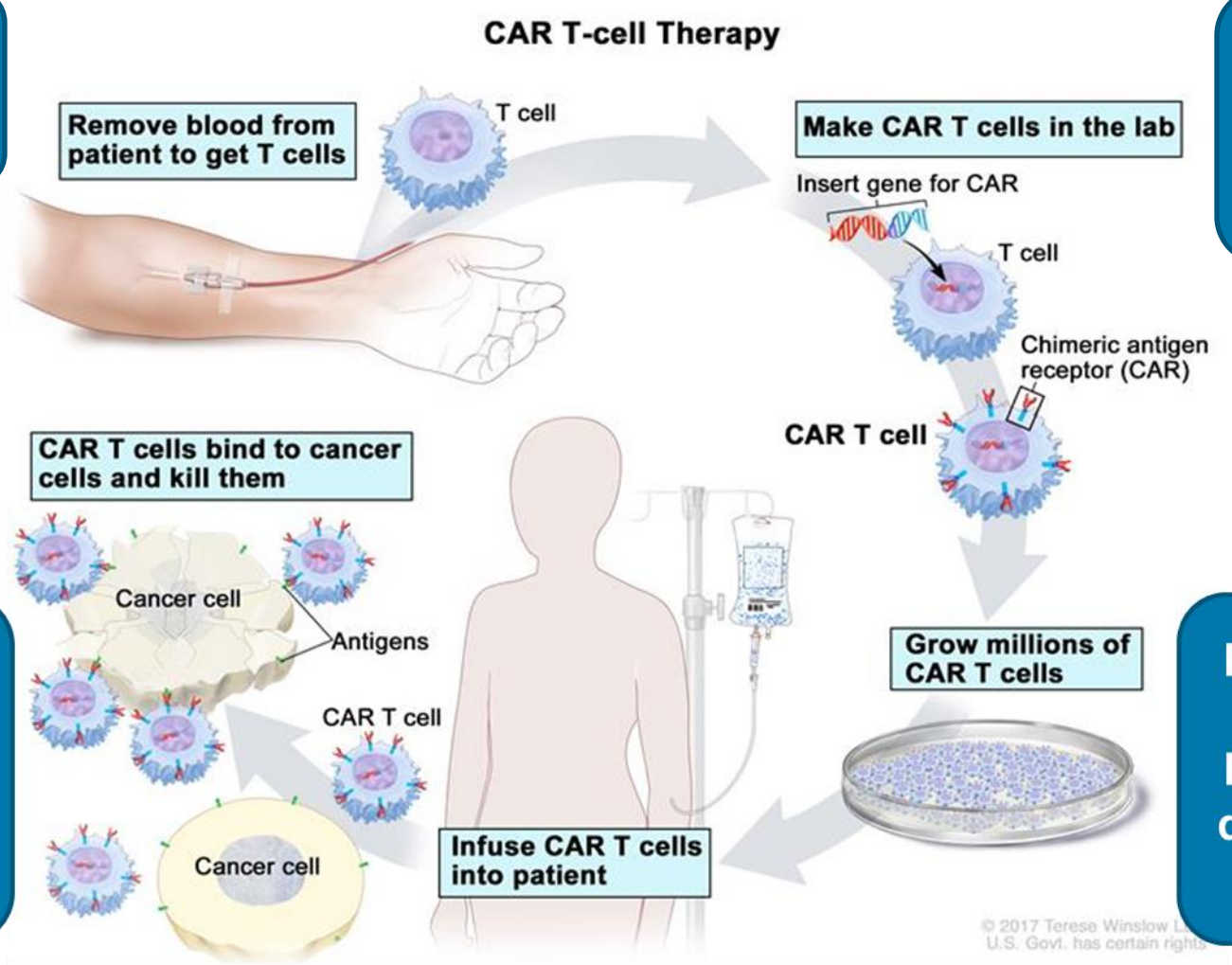
- None

Objectives

- Familiarize yourself with the basics of administering CAR T-cell therapy as well as general principles of CAR T-cell related supportive care
- Identify currently available CAR T-cell products and their respective indications
- Identify Key aspects of Post-Treatment Care

Workup for CAR T-cell Eligibility

- Adequate renal, hepatic, cardiac, and pulmonary function
- No active infection
- No uncontrolled endocrine comorbidities
- Adequate performance status
- Insurance approval



Estimated 3-6 weeks manufacturing time (variable)

Bridging chemotherapy as clinically indicated

Patient required to stay within 2 hours of treatment center for 28 days per all current REMS programs

Institutional monitoring: 3x daily outpatient appointments x 14 days, then daily until Day 30 post-infusion

Day 0 to Day 28: Post-infusion monitoring

Day -6 to Day -1: Lympho-depleting chemo

Variable per product, commonly ~3 days of fludarabine + cyclophosphamide and ~ 2 days of rest prior to cell infusion

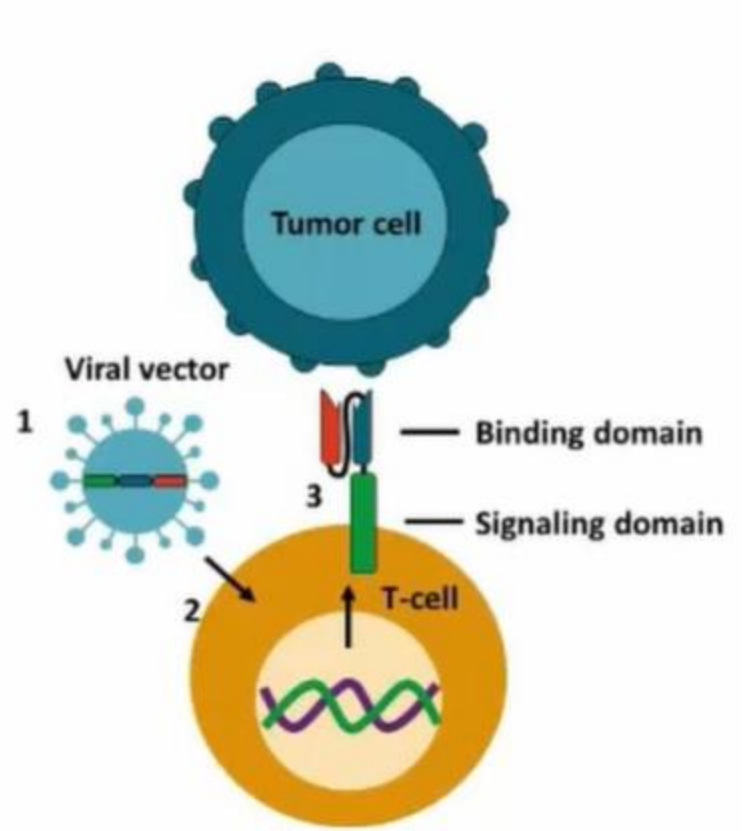
Day 0

Must have 2 patient-specific doses of tocilizumab on hand & give patient wallet card prior to infusion

NCI Dictionary of Cancer Terms. *NIH.* Accessed 5/2018.

Genetic Modification of T-cells

- Chimeric antigen receptor (CAR) = engineered synthetic receptor that redirects lymphocytes
- CAR genes are transfected into T-cells using an inactivated virus
- Allows for T-cells to be encoded to recognize, target, and eliminate cells expressing a specific antigen



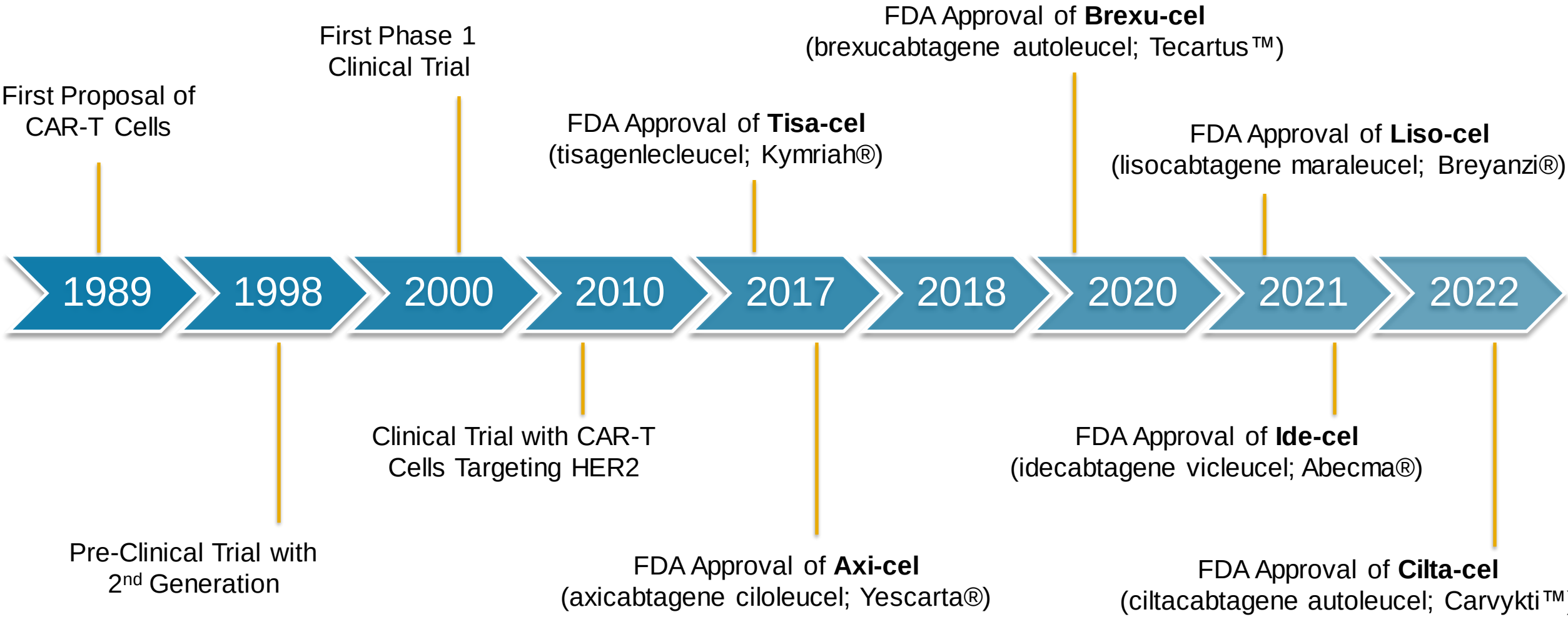
Cytotherapy. 2020; 22:57-69.
Blood Cancer Journal. 2021; 11:69.
https://www.clinicaloptions.com/oncology/programs/car-t-advances-2020

Unique Features of CAR T-cell Therapy

- HLA-independent antigen recognition, therefore universal application
- Active in both CD4+ and CD8+ T-cells
- Target antigens can be anything
- Rapid generation of tumor specific T-cells
- Minimal risk of autoimmunity or graft-versus-host disease
- A living drug, and needs only single infusion

Batlevi CL et al. Nat Rev Clin Oncol. 2016;13(1):25-40.
Porter DL et al. J Cancer. 2011;2(1):331-332.

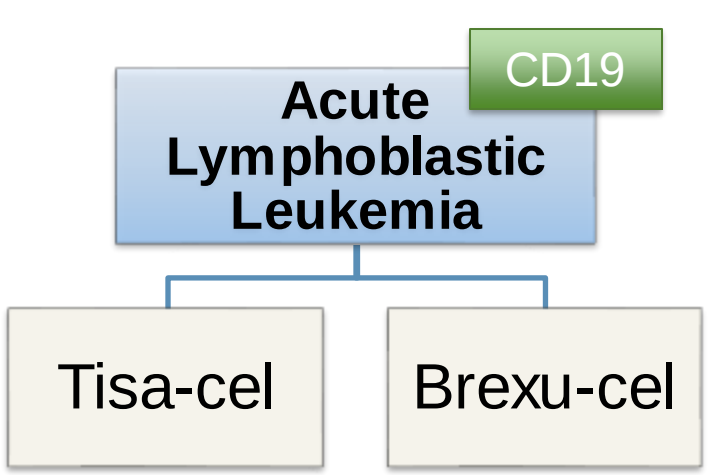
Timeline of CAR T-Cell Therapies

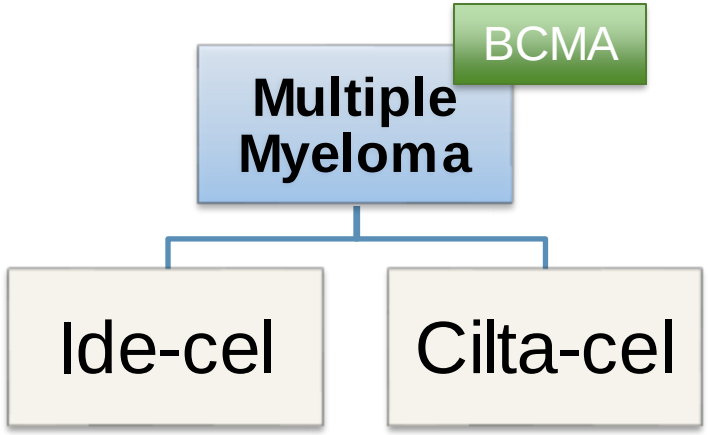


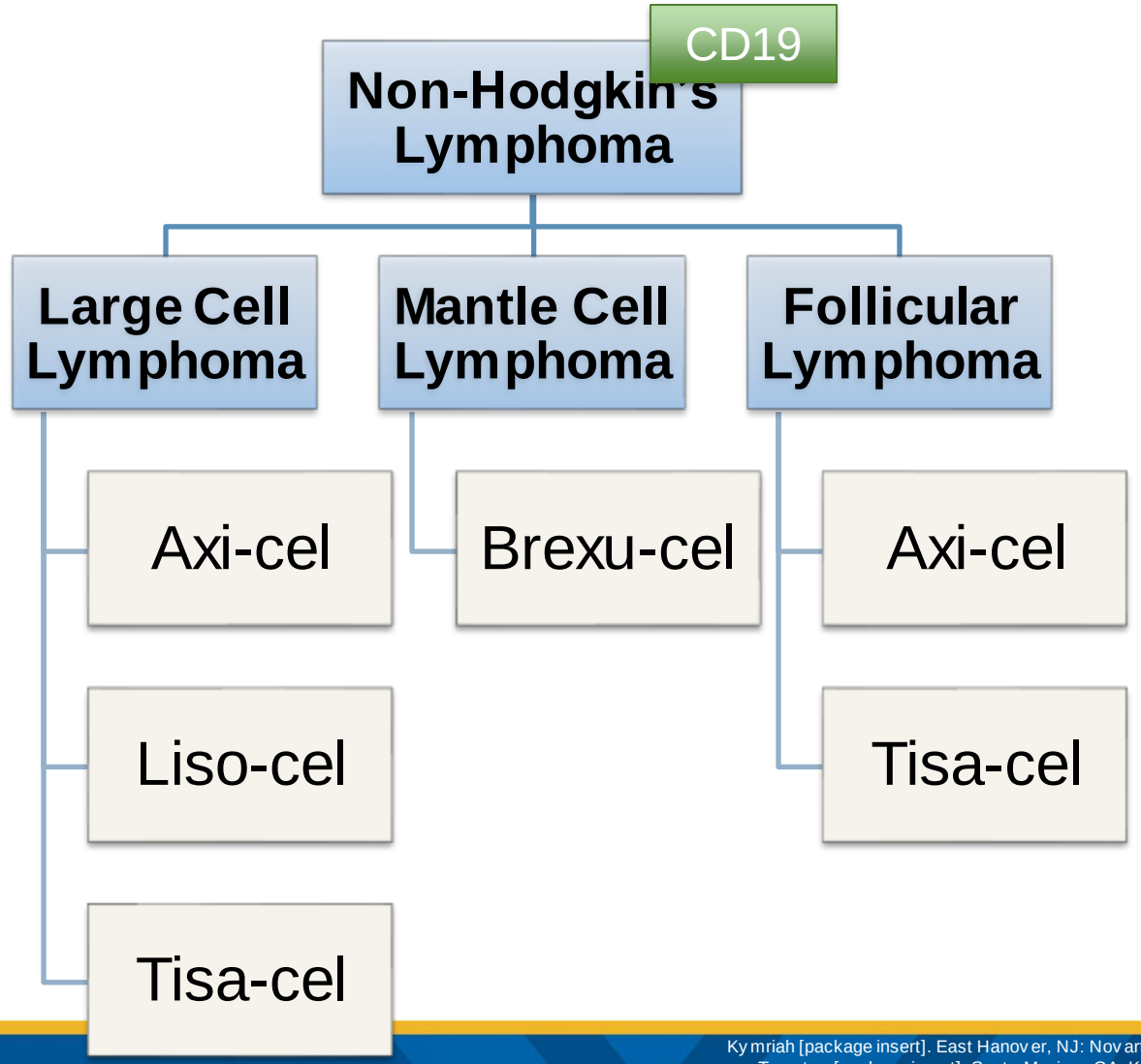
Cancer Sci. 2017; 6 (108): 1109-1118.

Kymriah [package insert]. East Hanover, NJ: Novartis; 2022.
Tecartus [package insert]. Santa Monica, CA: Kite; 2021.
Yescarta [package insert]. Santa Monica, CA: Kite; 2022.
Abecma [package insert]. Summit, NJ: BMS; 2021.
Carvykti [package insert]. Somerset, NJ: Janssen Biotech; 2022.
Breyanzi [package insert]. Bothell, WA: BMS; 2022.

Indications for Available CAR T-cell Agents







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Carvykti [package insert]. Somerset, NJ: Janssen Biotech; 2022.
Breyanzi [package insert]. Bothell, WA: BMS; 2022.

Large B-cell Lymphoma Approvals Decoded

Product	1st line	2nd line		3rd line +
		Primary refractory / Relapse ≤ 12 months	*Transplant ineligible regardless of timing*	
Axi-cel	▭	☺ ZUMA-7	▭	☺ ZUMA-1
Liso-cel	▭	☺ TRANSFORM	☺ PILOT	☺ TRANSCEND
Tisa-cel	▭	⊘ BELINDA	▭	☺ JULIET

Kymriah [package insert]. East Hanover, NJ: Novartis; 2022.
Yescarta [package insert]. Santa Monica, CA: Kite; 2022.
Breyanzi [package insert]. Bothell, WA: BMS; 2022.

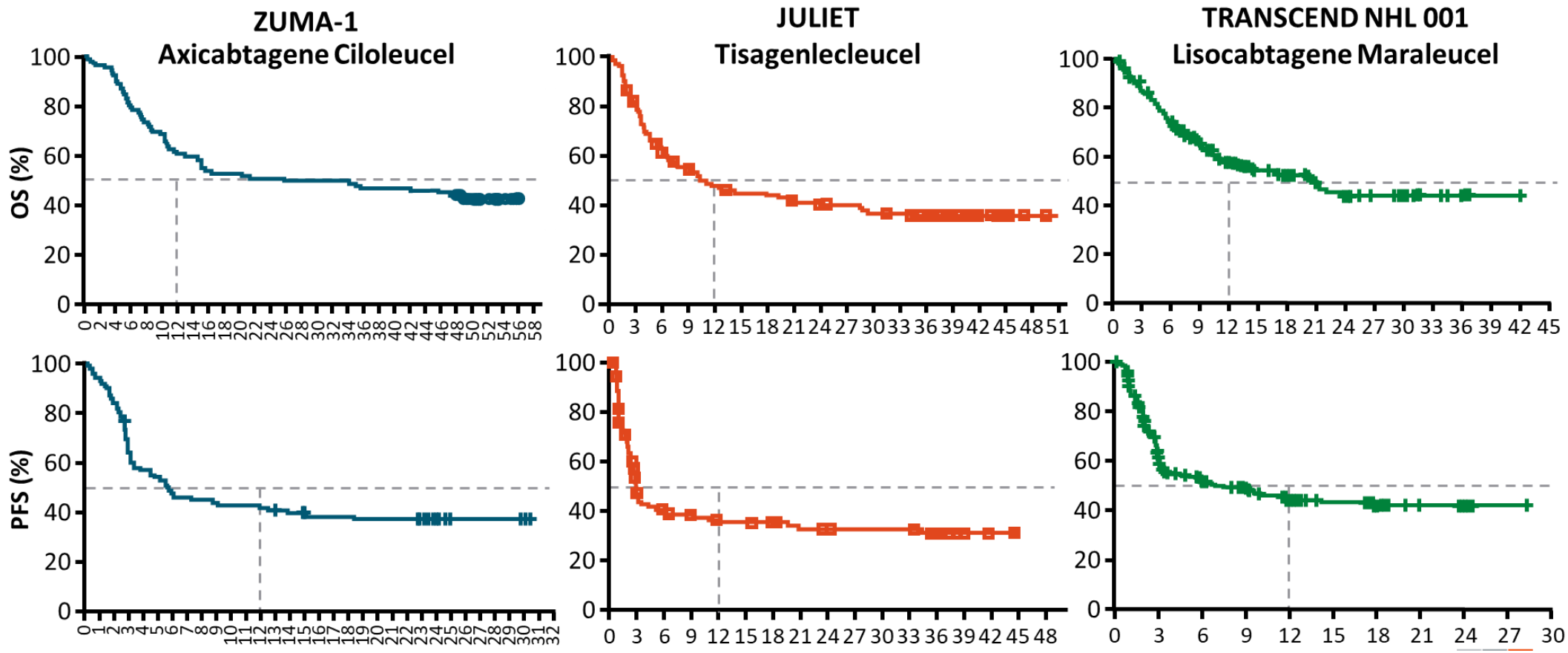
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL 3rd Line

	ZUMA-1[1,2]	JULIET[3]	TRANSCEND NHL 001[4]
CAR T-cell agent	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Study phase	II	II	I
Patient population	Adults with refractory DLBCL	Adults with R/R DLBCL	Adults with R/R DLBCL
Patients pheresed/ treated, n	111/101	165/111	344/269*
Bridging therapy, %	None allowed in pivotal trial, often used in standard practice	92	59
ORR, %	82	52	73
CR, %	54	40	53

*256 included in the efficacy-evaluable set.

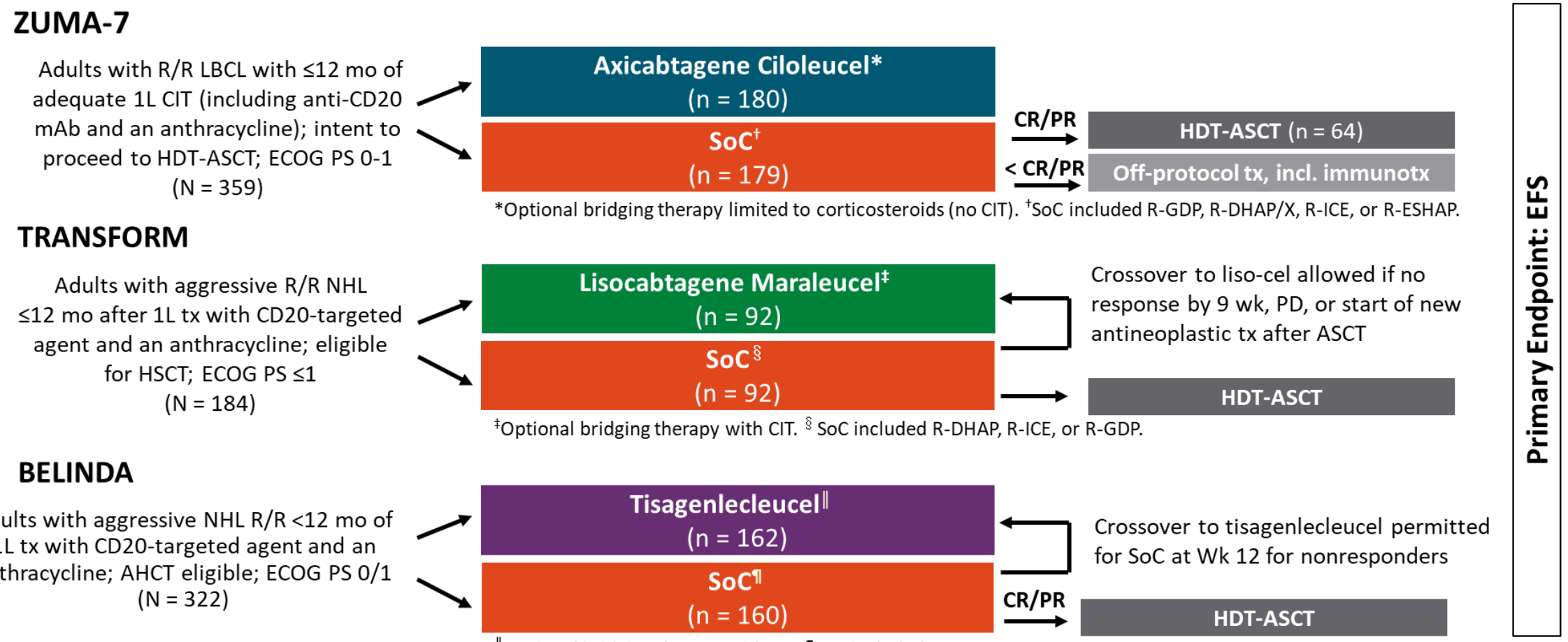
1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31.
3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.
Slide credit: clinicaloptions.com

Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL 3rd Line



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

CD19 CAR T-Cell Therapy in 2nd line DLBCL: Randomized Phase III Trials



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Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2. Kamdar. Lancet. 2022;399:2294. Kamdar. ASH 2021. Abstr 91. Bishop. NEJM. 2022. 386:629. Bishop. ASH 2021. Abstr LBA-6.
Slide credit: clinicaloptions.com

2nd line DLBCL Outcomes

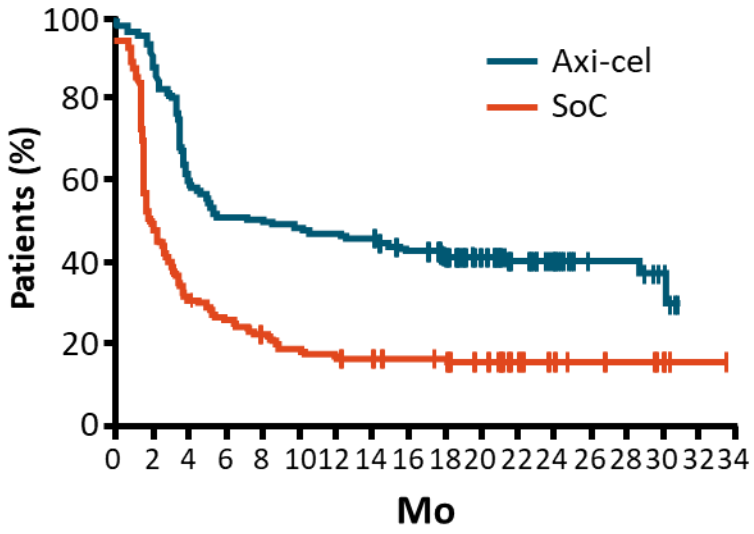
	ZUMA-7[1]	TRANSFORM[2]	BELINDA[3]
Product	Axi-cel vs SoC	Liso-cel vs SoC	Tisa-cel vs SoC
ORR, %	83 vs 50	86 vs 48	46 vs 43
CR, %	65 vs 32	66 vs 39	28 vs 28
Median EFS, mo	8.3 vs 2.0	10.1 vs 2.3	3.0 vs 3.0
EFS, %	2-yr: 41 vs 16	1-yr: 44.5 vs 23.7	--
Median PFS, mo	14.7 vs 3.7	14.8 vs 5.7	--
PFS, %	2-yr: 46 vs 27	1-yr: 52.3 vs 33.9	--
Median OS, mo	NR vs 35.1	NR vs 16.4	16.9 vs 15.3
OS, %	2-yr: 61 vs 51	1-yr: 79.1 vs 64.2	--

1. Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2. 2. Kamdar. Lancet. 2022;399:2294. Kamdar. ASH 2021. Abstr 91. 3. Bishop. NEJM. 2022. 386:629. Bishop. ASH 2021. Abstr LBA-6.

2nd line DLBCL Outcomes: EFS

ZUMA-7

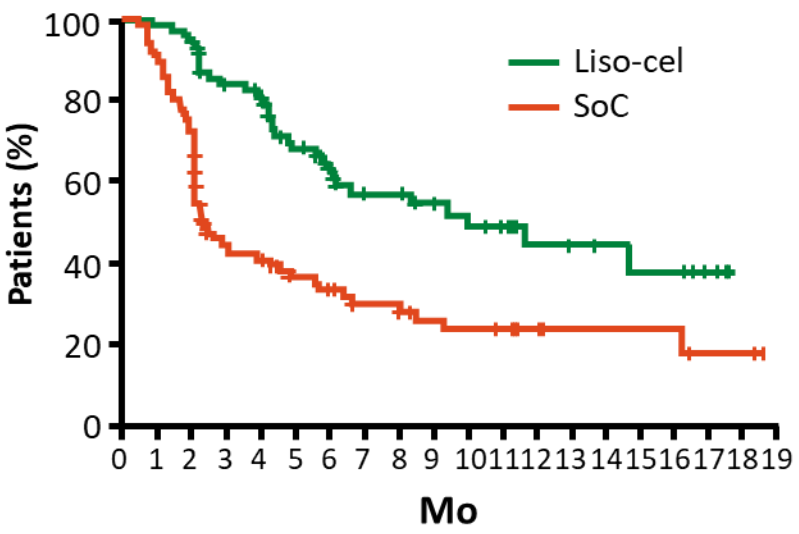
	Axi-Cel (n = 180)	SoC (n = 179)
Median, mo (95% CI)	8.3 (4.5-15.8)	2.0 (1.6-2.8)
HR (95% CI)	0.40 (0.310.51)	
P value	<.0001	



Median follow-up: 24.9 mo

TRANSFORM

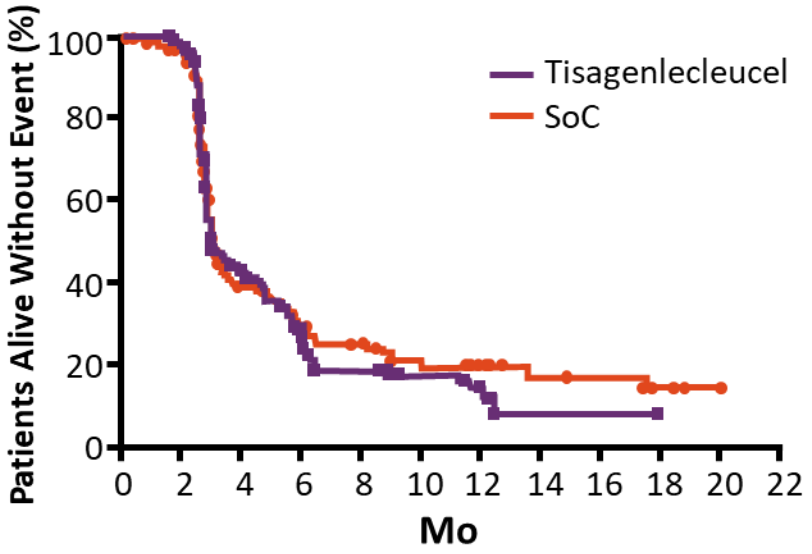
	Liso-Cel (n = 92)	SoC (n = 92)
Median, mo (95% CI)	10.1 (6.1-NE)	2.3 (2.2-4.3)
HR (95% CI):	0.349 (0.229-0.530)	
P value	<.0001	



Median follow-up: 6.2 mo

BELINDA

	Tisa-Cel (n = 162)	SoC (n = 160)
Median, mo (95% CI)	3.0 (2.9-4.2)	3.0 (3.0-3.5)
HR (95% CI)	1.07 (0.82-1.40)	
P value	.61	



Median follow-up: 10 mo

Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2. Kamdar. Lancet. 2022;399:2294. Kamdar. ASH 2021. Abstr 91. Bishop. NEJM. 2022. 386:629. Bishop. ASH 2021. Abstr LBA-6.

Differences in 2nd line DLBCL positive trials

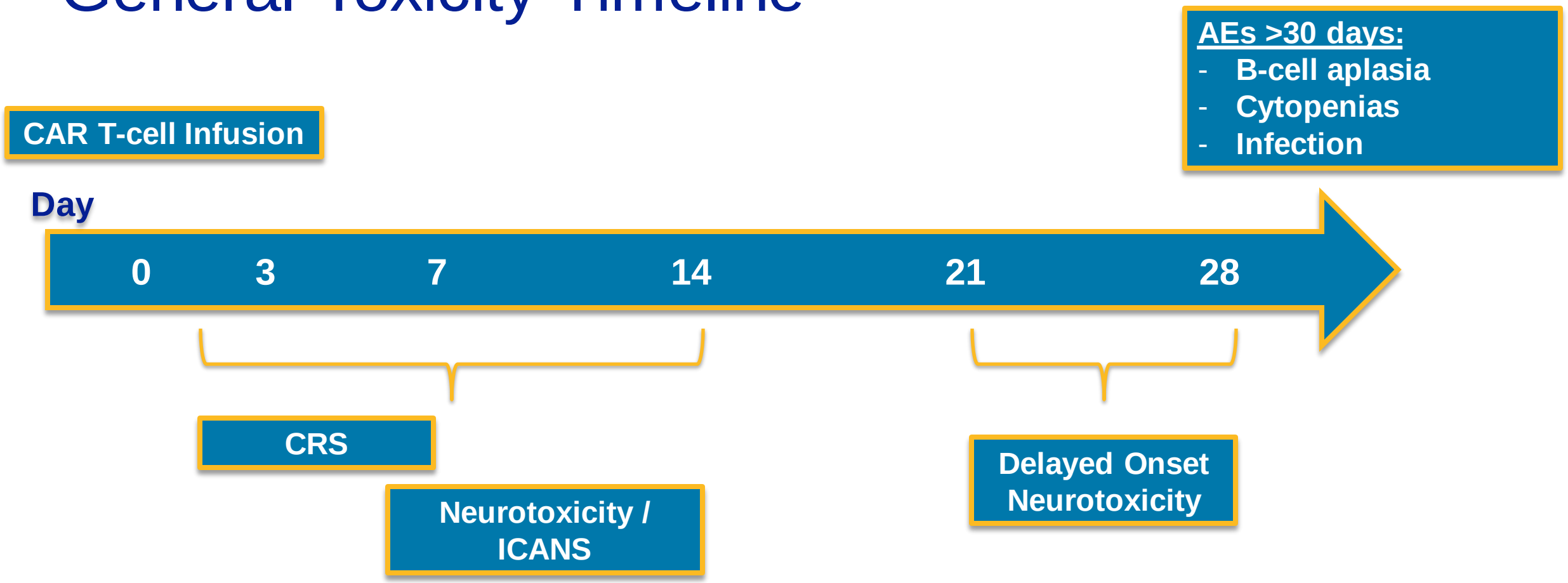
	Axi-cel vs SOC (ZUMA-7)	Liso-cel vs SOC (TRANSFORM)
CR rate	65% vs 32%	74% vs 43%
Number of Patients	359 ⬅	184
Bridging Therapies	Steroids only allowed (36%)	1 cycle of chemo allowed (63%)
Crossover	Not allowed	Allowed (67%)
Median follow up	25 months ⬅	17.5 months
Any grade CRS / Grade ≥3 CRS	92% / 6%	49% / 1% ⬅
Any grade NE / Grade ≥ 3 NE	60% / 21%	12% / 4% ⬅

N Engl J Med 2022; 386:640-654
Lancet 2022; 399:2294-304.
ASH Oral Abstract 655. 12.11.22

CAR T-cell Toxicities

- Cytokine release syndrome (CRS)
- Neurological events (NE) / Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Infection
- Tumor Lysis

General Toxicity Timeline



*Patients instructed to avoid driving or operating heavy machinery for 8 weeks after cell infusion per REMS requirements

Slide credit: Sarah Malcolm, PharmD
Clinical Care Options, LLC. Oncology. 2020.

ASTCT Toxicity Definitions

CRS

*"A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, **must include fever at the onset**, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."*

ICANS

"A disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema."

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

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	-	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			and/or	
Hypoxia	-	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 min) 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 triad

*ICE score measures degree of impairment using questions surrounding orientation, attention, writing, and ability to name objects and follow commands; 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.
Slide credit: clinicaloptions.com

General Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care (+/- toci)*	Supportive care (+/- steroid)*	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

*High-burden, high-risk products; older; comorbidities, etc.

MD Anderson. CAR cell therapy toxicity assessment and management. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

Slide credit: clinicaloptions.com

Post-Treatment Care

1. TLS Prevention

- Especially a concern if patients with high tumor burden get CAR T-cell therapy
- Often receive fluids with lymphodepleting chemotherapy
- Allopurinol throughout cell expansion

2. Infection Prevention

- Viral prophylaxis x 1 yr minimum; *PJP* prophylaxis x 6 mo minimum
- COVID-19 revaccination starting at D+100

G-CSF = granulocyte colony-stimulating factor

Annals of Oncology. 2021. 33(3);259-275.
Transplantation and Cellular Therapy. 2022. https://doi.org/10.1016/j.jtct.2022.10.010

Post-Treatment Care

3. Parkinson's disease:

- Relatively rare
- BCMA is expressed by both myeloma cells as well as by the basal ganglia
- Development of Parkinson's disease is unique to anti-BCMA CAR T-cell therapy (used in multiple myeloma)

4. B-cell aplasia and hypogammaglobinemia:

- "On target, off tumor" effect
- Monitoring Immunoglobulin levels periodically and use of IVIG as per institutional protocol (Typically used with IgG level <500)

Post-Treatment Care

5. Prolonged Cytopenias:

- Unclear etiology: Possibly related to
  a) Lymphodepleting chemotherapy
  b) “bridging” chemotherapy
  c) Disease status
  d) Direct effect of CAR-T cells on hematopoiesis

- Management is mostly supportive with growth factors. Can be difficult to manage.
- Bacterial + fungal prophylaxis
- G-CSF considered
- There is indication towards improved outcomes with persistent cytopenia

Summary

- CAR T-cell administration requires precise planning, timing, and combined effort from multiple healthcare disciplines
- Currently available CAR T-cell products target CD19 or BCMA and treat hematologic malignancies such as lymphoma (DLBCL, FL, MCL), ALL, and multiple myeloma
  - Indications continue to evolve rapidly
- Serious ADEs from CAR T-cell therapy include CRS and neurotoxicity, in addition to prolonged cytopenias, infection, etc
  - Continual efforts to minimize toxicity without sacrificing efficacy

Thank you