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CCO LIVE

Optimizing the Clinical Application of CAR T-Cell Therapy: Best Practices for the Community Setting

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Greater Los Angeles ONS Chapter

Day of Education 2019

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Joshua P. Sasine, MD, PhD, has no relevant conflicts of interest to report.

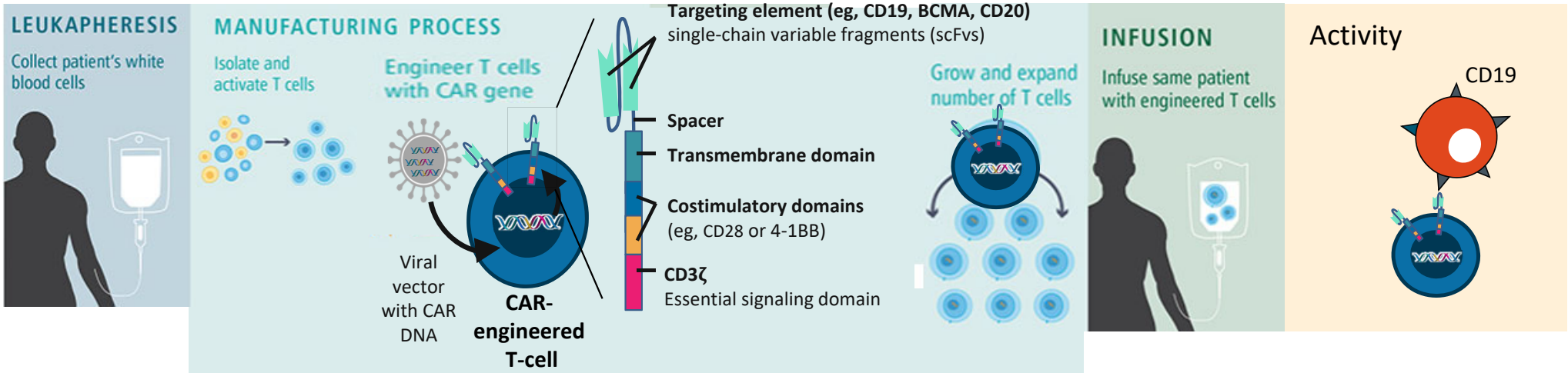
Outcomes Analysis: What Did You Learn?

- Some questions in this activity will be presented twice:
  once before the content, and then again later in the activity

- Discussion of the correct answers and a summary of your responses will appear only after the posteducation questions
- All responses will only be measured in aggregate (ie, your individual responses will not be identified)
- Thank you for helping us assess the impact of this educational activity

Overview of CAR T-Cell Therapy

CAR T-Cell Therapy: Underlying Principles



- Median manufacturing time: 17-28 days
- Patients undergo lymphodepleting (and possibly salvage/bridging) therapy during this time

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

Slide credit: clinicaloptions.com

Discussion: Principles of CAR T-Cell Therapy

- What are best practices in explaining the process and underlying mechanisms of CAR T-cell therapy to patients?

Indications and Clinical Data

Case: Patient With Stage III DLBCL

- 64-yr-old male was diagnosed with stage IIIB DLBCL after presenting with increasing bilateral axillary adenopathy and an IPI score of 2/5
  - PET/CT was FDG avid in cervical, axillary, and retroperitoneal lymph nodes; bone marrow was negative for involvement; LDH elevated at 324 U/L
  - Cells expressed CD19, CD20, MUM-1, CD10, and BCL-2; negative for c-myc; Ki-67 was 30% to 40%
- He was treated with R-CHOP x 6 cycles and achieved a PET-negative CR
- 10 mos later, the patient relapsed with a biopsy-proven recurrence in a right cervical lymph node
  - Cells now expressed c-myc; Ki-67 was 30% to 40%; patient reports fatigue but organ function and PS good

Slide credit: clinicaloptions.com

Case Continued: Patient With Stage III DLBCL

- The patient was treated with salvage R-ICE x 2 cycles
  - Assessment of disease status by PET/CT following cycle 2 of R-ICE demonstrated a 40% reduction in prior adenopathy and a new FDG-avid lesion in the liver
- The patient's organ functions and PS remain stable
- HLA typing of a sibling reveals no matches, but several well-matched volunteer donors are identified by a preliminary search

SCHOLAR-1: Outcomes With Non–CAR T-Cell Therapy for Refractory DLBCL

- Pooled retrospective analysis of 3 phase III trials and 2 observational cohorts in which patients received treatment (non–CAR T-cell) for refractory disease after first-/second-line therapy or relapsed disease after ASCT (N = 636)

	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled* (N = 636)
Patients evaluated for response, n†	165	82	106	170	523
Response rate, % (95% CI)	20	26	26	31	26 (21-31)
CR rate	7	7	2	15	7 (3-15)
PR rate	13	18	25	16	18 (13-23)
Response rate by refractory category, % (95% CI)					
Primary refractory	—	25	27	10	20 (11-34)
Refractory to second-line or later-line therapy	20	21	20	40	26 (17-39)
Relapse ≤12 mo post-ASCT	19	35	—	39	34 (24-45)
Median, mo (95% CI)	6.6	5.0	6.6	6.5	6.3 (5.9-7.0

OS

Crump. Blood. 2017;130:1800.

Slide credit: clinicaloptions.com

FDA-Approved CAR T-Cell Therapies

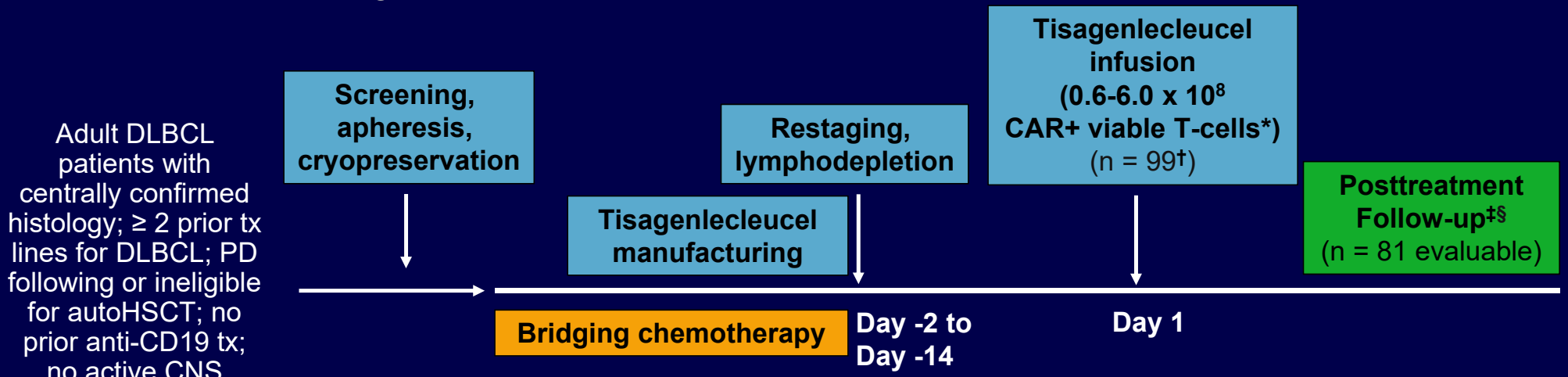
Therapy	Target	Indications
Tisagenlecleucel	CD19	▪ Patients aged up to 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse ▪ Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including: • DLBCL NOS • DLBCL arising from follicular lymphoma • High-grade B-cell lymphoma
Axicabtagene ciloleucel	CD19	▪ 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

Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

JULIET: Tisagenlecleucel in Adults With R/R Large B-Cell Lymphoma

- International, single-arm, open-label phase II trial



*Inpatient or outpatient, with 26% receiving outpatient infusion. †D/c before preinfusion: n = 43 (inability to manufacture, n = 9; related to pt status, n = 34). ‡§Imaging every 3 mos.

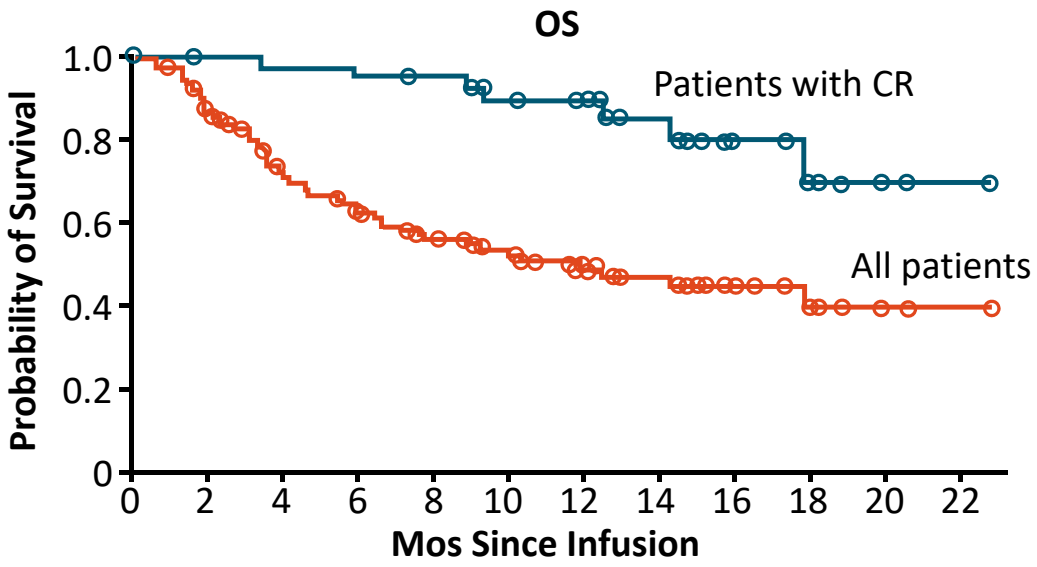
- Primary endpoint: ORR; secondary endpoints: DoR, OS, safety
- Baseline (%): prior lines of therapy (2/3/4-6), 44/31/19; refractory/relapsed to last therapy, 52/48; prior auto-HSCT, 47%

Schuster. NEJM. 2019;380:45.

Slide credit: clinicaloptions.com

JULIET: Efficacy

- ORR: 52%; CR rate: 40%
- Estimated 12-mo rate of relapse-free survival: 65% (among patients with CR: 79%)



Schuster. NEJM. 2019;380:45.

Slide credit: clinicaloptions.com

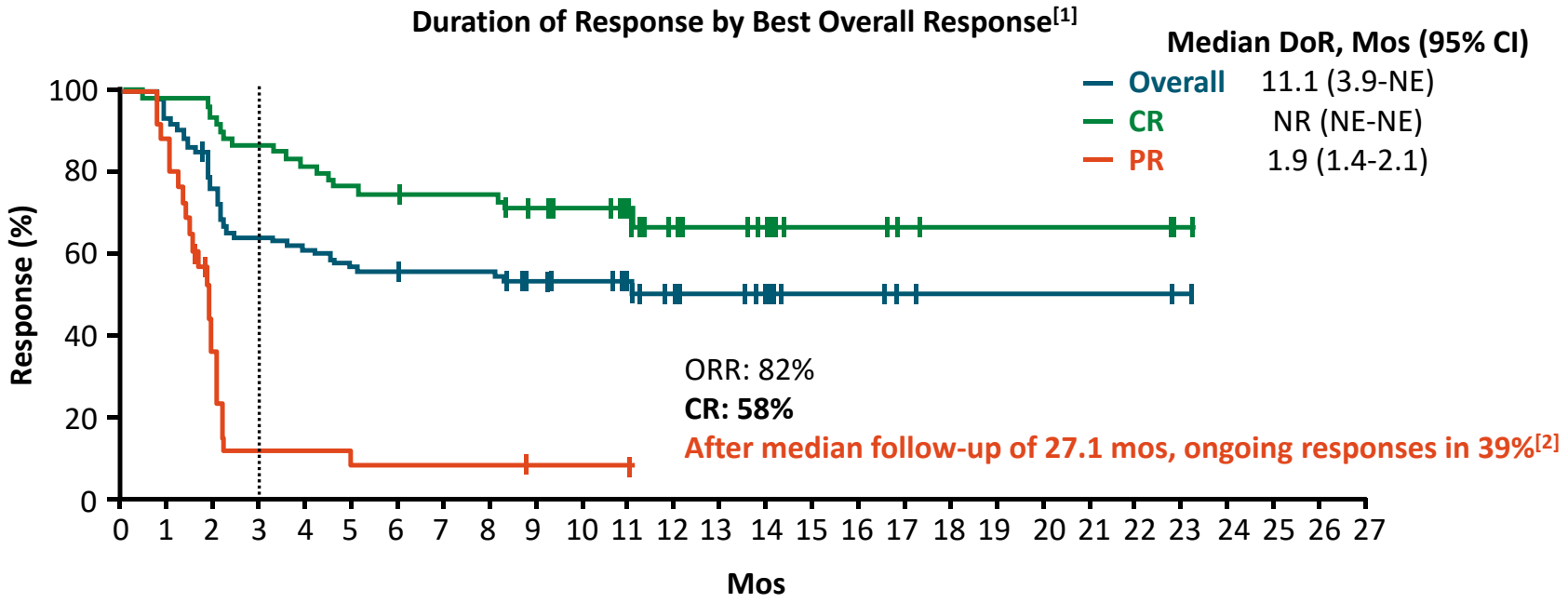
ZUMA-1: Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma

- Multicenter phase II trial in 2 cohorts defined by tumor type
  - Cohort 1: refractory DLBCL (n = 73)
  - Cohort 2: PMBCL/transformed follicular lymphoma (TFL; n = 20)
- Key inclusion criteria
  - Aggressive NHL (DLBCL, PMBCL, or TFL)
  - ECOG PS ≤ 1
  - No response to previous chemotherapy or relapsed within 12 mos of ASCT
  - Prior tx: anthracycline and anti-CD20 mAb
- Treatment
  - Leukapheresis (no bridging therapy)
  - Conditioning: cyclophosphamide 500 mg/m^2 + fludarabine 30 mg/m^2 x 3 days
  - Axicabtagene ciloleucel 2 x 10^6/kg
- Primary endpoint: ORR
- Secondary endpoints: DoR, OS, safety, CAR T-cell levels, cytokine levels
- Baseline: median prior therapies, 3; primary refractory, 26%; relapsed after autologous SCT, 21%

Neelapu. NEJM. 2017;377:2531.

Slide credit: clinicaloptions.com

ZUMA-1: Efficacy



- At median follow-up of 27.1 mos, median OS: not reached (12.8 mos to NE); median PFS: 5.9 mos

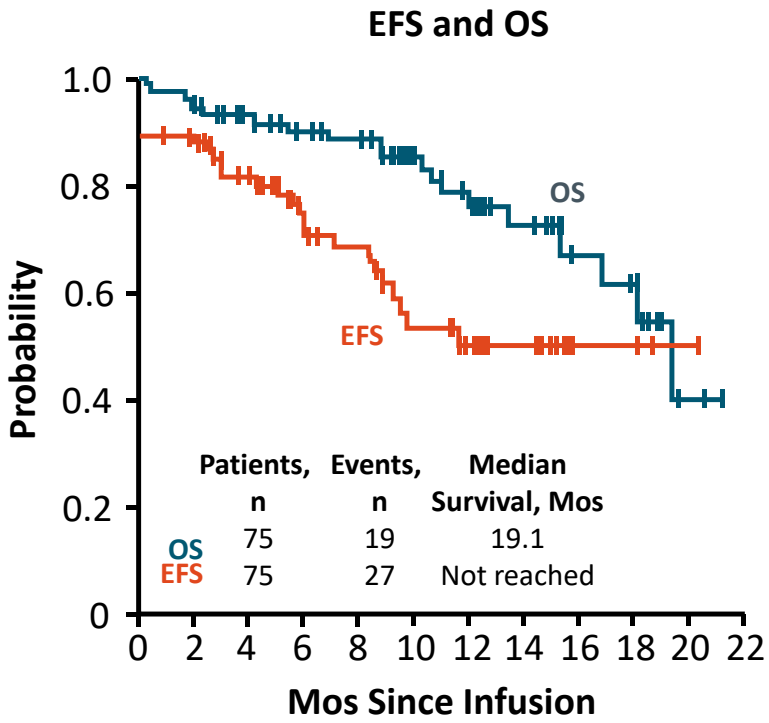
1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31.

Slide credit: clinicaloptions.com

ELIANA: Tisagenlecleucel in Children and Young Adults With R/R B-ALL

- International, open-label, single-arm phase II study (N = 92)
  - Patients aged 3-21 yrs with relapsed or refractory B-cell ALL
  - Patients underwent lymphodepletion with fludarabine + cyclophosphamide followed by single-dose tisagenlecleucel
  - At baseline: median number of prior therapies, 3; prior allogeneic SCT, 46%; median BM blast count at time of treatment, 74%
- ORR at 3 mos: 81%

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

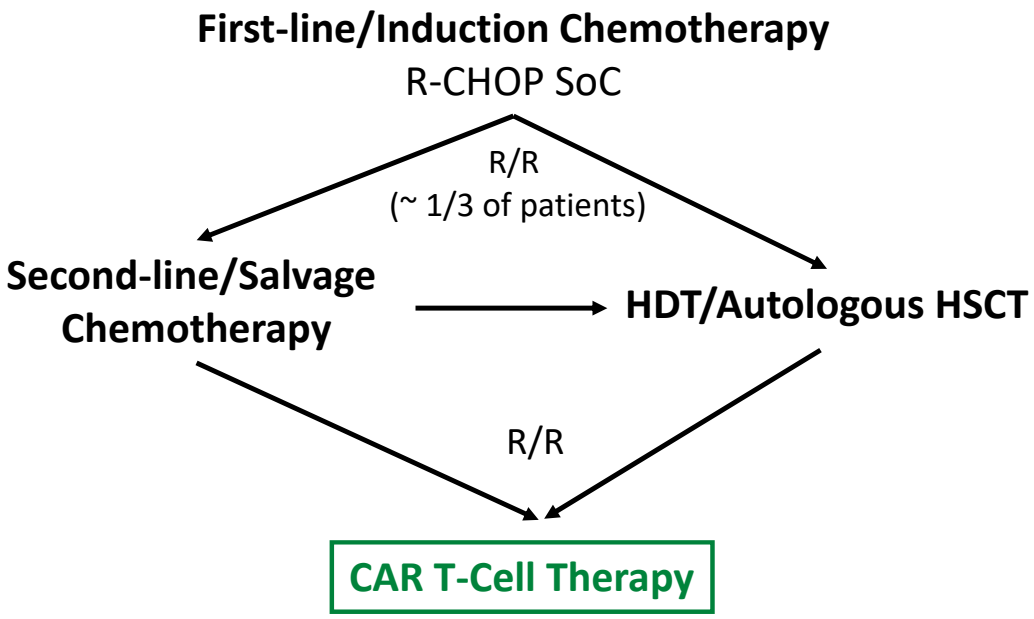


Maude. NEJM. 2018;378:439.

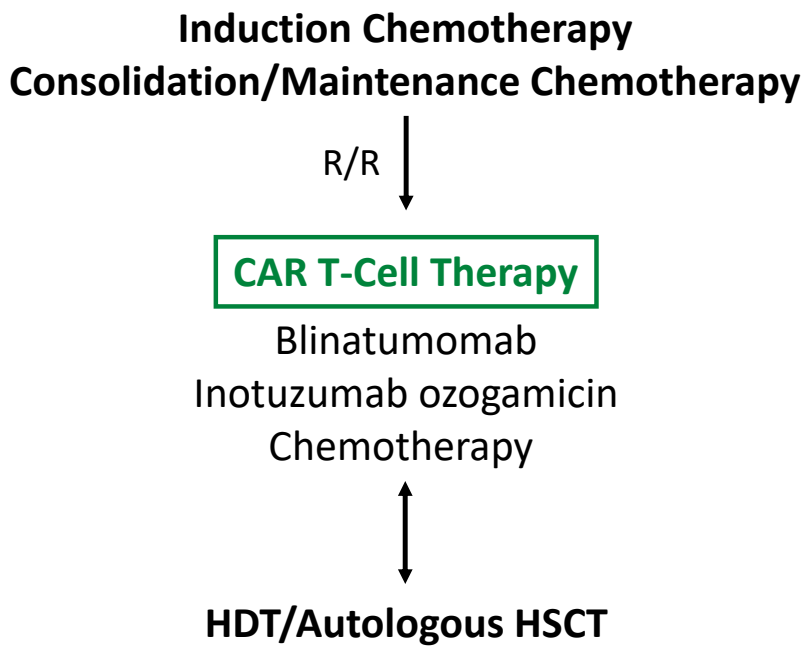
Slide credit: clinicaloptions.com

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

DLBCL



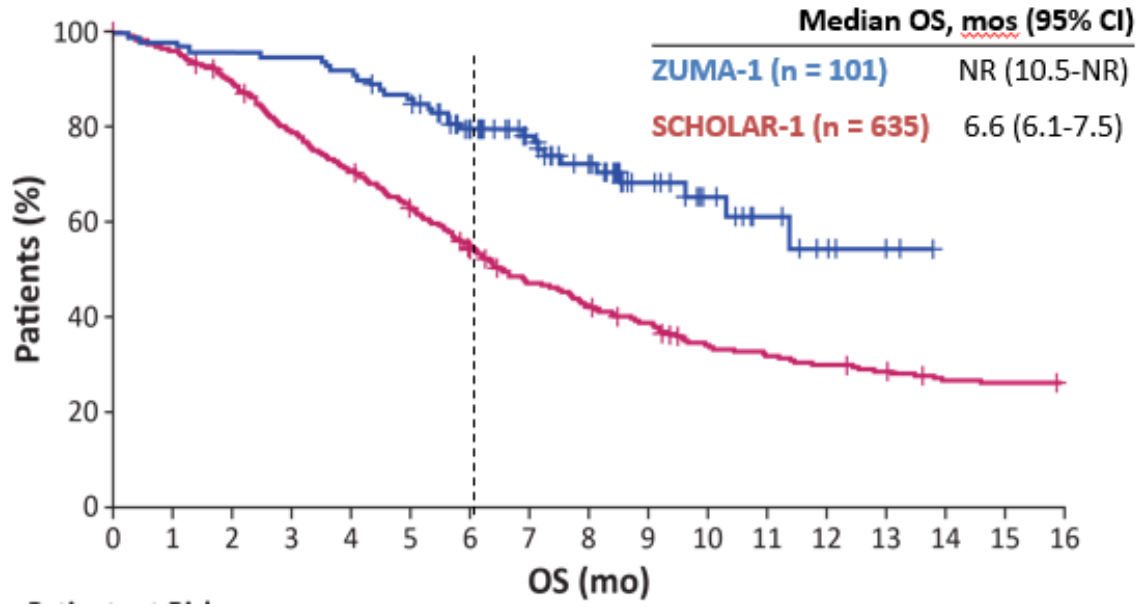
ALL (Younger Patients)



Slide credit: clinicaloptions.com

ZUMA-1 vs SCHOLAR-1: Outcomes With Axicabtagene Ciloleucel vs SoC for Refractory DLBCL

- Retrospective analysis comparing outcomes with axicabtagene ciloleucel (in ZUMA-1) vs SoC (in SCHOLAR-1*)[1]



*Retrospective analysis of 3 phase III trials and 2 observational cohorts in which patients received treatment for refractory disease after first/second-line therapy or relapsed disease after ASCT.[2]

1. Neelapu. SOHO 2017. Abstr NHL-023. 2. Crump. Blood. 2017;130:1800.

Slide credit: clinicaloptions.com

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

- **Indications**
  - Does the patient have relapsed/refractory B-cell lymphoma after ≥ 2 lines of systemic therapy *or* B-cell precursor ALL that is refractory or in second or later relapse (younger patients)?
  - 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 or chemotherapy) and remain stable until the T-cell infusion (2-3 wks)?
  - 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 medical comorbidities**: eg, severe cardiac dysfunction, active symptomatic neurologic symptoms (difficult to accurately assess neurotoxicity)

Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Faculty communication.

Slide credit: clinicaloptions.com

Bridging Therapy in B-Cell Lymphoma

- **Indications**
  - Rapidly growing lymphoma
  - Bulky disease
  - Symptomatic patient (pain)
  - Major organ involvement or obstruction
  - Expected delay in CAR T-cell production
- **Regimens**
  - Steroids (eg, dexamethasone)
  - Rituximab ± gemcitabine, etoposide, carboplatin/cisplatin, cytarabine, or lenalidomide
  - Ibrutinib
  - Radiation
- **Regimen selection** depends on prior therapies, regimen-related toxicities, site(s) of disease, comorbidities, blood counts, simplicity of administration

Slide credit: clinicaloptions.com

Case Revisited: Patient With Stage III DLBCL

- It was recommended that the patient receive CAR T-cell therapy
  - Patient provided informed consent; insurance approval provided within 10 days of submission
  - Patient had adequate peripheral venous access with ALC = 0.7; he underwent successful collection of lymphocytes without complication
- Patient was relatively asymptomatic but had palpable adenopathy and his LDH doubled in the wk after collection of lymphocytes; the patient remained stable while providing weekly labs
- CAR T-cells were successfully produced and shipped back to the treating center
- Patient underwent pretreatment evaluation and was found to have bulky retroperitoneal adenopathy and new liver lesions
- He received allopurinol and aggressive hydration for TLS prophylaxis and began lymphodepleting chemotherapy with fludarabine and cyclophosphamide (completed without complication)
- CAR T-cells were successfully infused without complication

Slide credit: clinicaloptions.com

Discussion: Patient Case

- What were the keys in determining the case patient's eligibility for CAR T-cell therapy? Would you have any concerns recommending the patient for CAR T-cell therapy?
  - For this type of patient, what are other alternatives?
- Could this patient have been referred for CAR T-cell therapy earlier in his treatment course?
- Would you have recommended bridging therapy while the patient waited for CAR T-cell infusion?

- 64-yr-old male diagnosed with stage IIIB DLBCL; treated with R-CHOP x 6 cycles and achieved PET-negative CR
- Relapsed 10 mos later; treated with salvage R-ICE x 2 cycles; 40% reduction in adenopathy and new FDG-avid liver lesion
- HLA typing: no sibling match but several well-matched volunteer donors
- Started CAR T-cell therapy process; asymptomatic but palpable adenopathy; LDH doubled after collection of lymphocytes
- Received allopurinol/hydration for TLS prophylaxis and lymphodepleting chemotherapy with fludarabine/cyclophosphamide
- CAR T-cells successfully infused without complication

Best Practices in Referring Patients to CAR T-Cell Treatment Centers

- **Consider the therapy and refer early**: Plan patient's treatment course early; consider when more chemotherapy may be appropriate vs commercially approved CAR T-cell therapy or CAR T-cell therapy clinical trial
- No upper age limit, but special considerations may exist, so best to **consult early** to determine the best timing of potential CAR T-cell therapy referral
- **Maintain clear communication** prior to leukapheresis, during bridging chemotherapy, and prior to T-cell infusion to ensure successful collection and manufacturing of T-cells and safe administration

Slide credit: clinicaloptions.com

Select Ongoing US Studies of CAR T-Cell Therapies for ALL and Lymphoma

Study	CAR T-Cell Therapy	Setting	Phase
NCT03570892 (BELINDA)	Tisagenlecleucel (RCT vs autoHSCT)	▪ Adult aggressive B-cell **NHL**; R/R after first-line therapy	III
NCT03761056 (ZUMA-12)	Axicabtagene ciloleucel	▪ Adult large B-cell **lymphoma**; no prior treatment	II
NCT03105336 (ZUMA-5)	Axicabtagene ciloleucel	▪ Adult indolent B-cell **NHL**; R/R after 2 lines of therapy	II
NCT03483103 (TRANSCEND-PILOT)	Lisocabtagene maraleucel	▪ Adult aggressive B-cell **NHL**; R/R after first-line therapy	II
NCT03744676	Lisocabtagene maraleucel	▪ Adult aggressive B-cell **NHL**; R/R after 2 lines of therapy	II
NCT03876769 (CASSIOPEIA)	Tisagenlecleucel	▪ Pediatric/young adult B-cell **ALL**; MRD after first-line therapy	II
NCT03628053 (OBERON)			
NCT03289455 (AMELIA)			

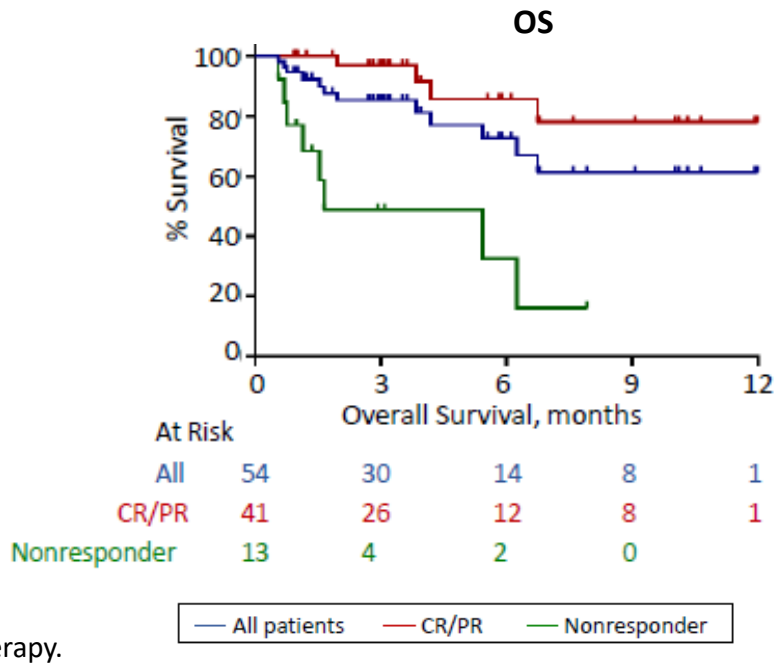
ClinicalTrials.gov.

Slide credit: clinicaloptions.com

TRANSCEND-NHL-001: Lisocabtagene Maraleucel for Patients With Relapsed/Refractory B-Cell NHL

- Multicenter, open-label phase I trial of lisocabtagene maraleucel for adult patients with R/R* aggressive B-cell NHL (including DLBCL, PMBCL, FL, and MCL) (N = 55)

	All Dose Levels	DL1S	DL2S	DL1D[a]
BOR, n[b]	54	30	18	6
ORR (95% CI), %	76 (62-87)	80 (61-92)	72 (47-90)	67 (23-96)
CR (95% CI), %	52 (38-66)	53 (34-72)	50 (26-74)	50 (12-88)
≥ 3-mo f/u, n[c]	41	24	11	6
3-mo ORR (95% CI), %	51 (35-67)	46 (26-67)	64 (31-89)	50 (12-88)
3-mo CR (95% CI), %	39 (24-56)	33 (16-55)	46 (17-77)	50 (12-88)



*For DLBCL cohort, after ≥ 2 lines of therapy; for MCL cohort, after ≥ 1 line of therapy.

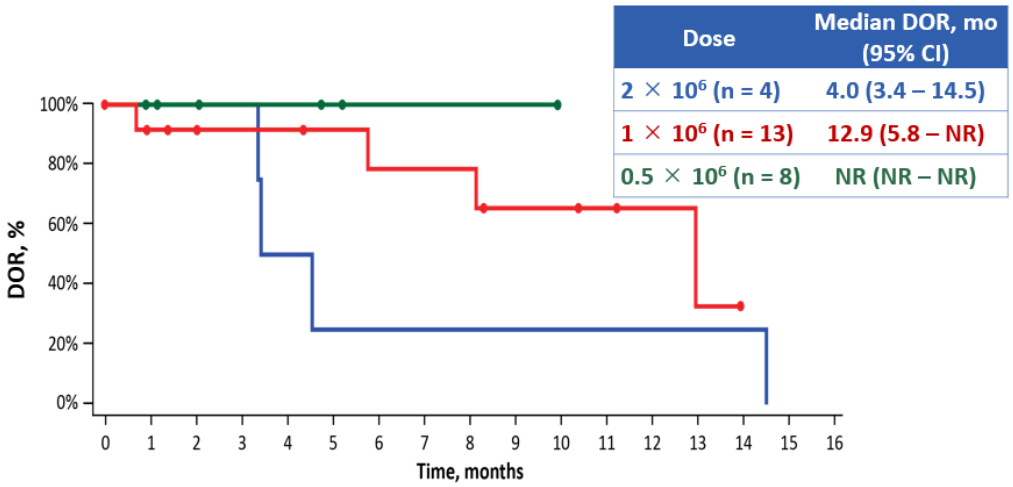
Abramson. ASCO 2017. Abstr 7513.

Slide credit: clinicaloptions.com

ZUMA-3: Axicabtagene Ciloleucel for Adult Patients With Relapsed/Refractory ALL

- Multicenter, open-label phase I/II trial of axicabtagene ciloleucel for adult patients with R/R* B-precursor ALL (planned N = 100)

	2×10^6 Dose (n = 6)	1×10^6 Dose (n = 14)	0.5×10^6 Dose (n = 16)	Overall (n = 36)
CR Rate (CR + CRi), n (%)	4 (67)	13 (93)	8 (50)	25 (69)
CR	3 (50)	10 (71)	6 (38)	19 (53)
CRi	1 (17)	3 (21)	2 (13)	6 (17)
PR, n (%)	0	1 (7)	0	1 (3)
BM U-MRD4, n (%)	4 (67)	14 (100)	9 (56)	27 (75)



- Phase II ongoing with 1×10^6 dose

Wierda. ASH 2018. Abstr 897. NCT02614066.

Slide credit: clinicaloptions.com

Select Ongoing US Studies of Investigational CAR T-Cell Therapies for Additional Conditions

Study	CAR T-Cell Therapy	Target	Setting	Phase
NCT03651128 (KarMMa-3)	Idecabtagene vicleucel*	BCMA	▪ Relapsed/refractory MM (vs standard triplet therapy)	III
NCT03601078 (KarMMa-2)	Idecabtagene vicleucel*	BCMA	▪ Relapsed/refractory MM	II
NCT03361748 (KarMMa)	Idecabtagene vicleucel*	BCMA	▪ Relapsed/refractory MM	I/II
NCT03548207 (CARTITUDE-1)	JNJ-68284528	BCMA	▪ Relapsed/refractory MM	I/II
NCT03430011 (EVOLVE)	JCARH125	BCMA	▪ Relapsed/refractory MM	I/II
NCT03331198	Lisocabtagene maraleucel	CD19	▪ Relapsed/refractory CLL/SLL	I/II
NCT03624036 (ZUMA-8)	Axicabtagene ciloleucel	CD19	▪ Relapsed/refractory CLL	I/II

*Formerly bb2121.

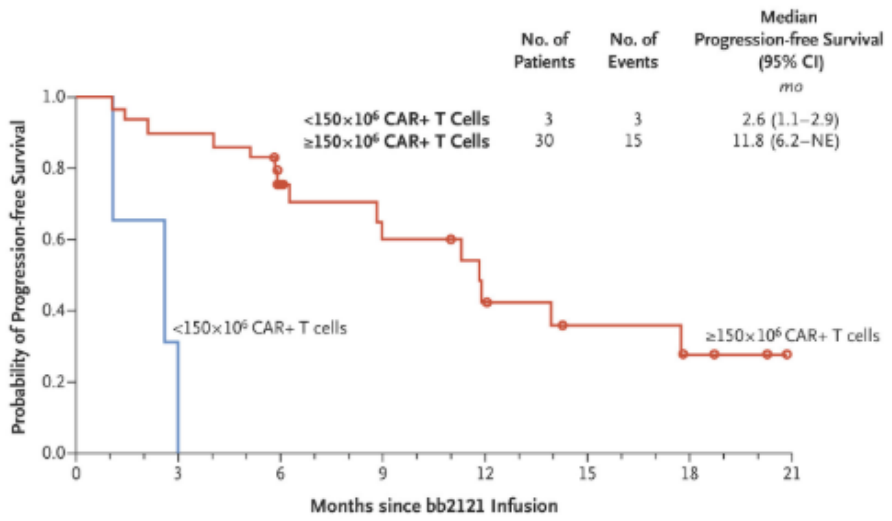
ClinicalTrials.gov.

Slide credit: clinicaloptions.com

Idecabtagene Vicleucel (bb2121) for Patients With Relapsed/Refractory Multiple Myeloma

- Multicenter, open-label phase I trial of idecabtagene vicleucel for patients with R/R multiple myeloma with ≥ 3 previous lines of therapy (incl. a proteasome inhibitor and immunomodulatory agent (N = 33)
  - Dose escalation phase (n = 21): ≥ 50% BCMA+; dose expansion phase (n = 12): prior daratumumab, refractory to last therapy, any BCMA expression

Variable	50×10^6 CAR+ T Cells (N=3)	150×10^6–800×10^6 CAR+ T Cells (N=30)	50×10^6–800×10^6 CAR+ T Cells (N=33)
Objective response‡			
No. of patients with a response	1	27	28
Rate — % (95% CI)	33 (1–91)	90 (74–98)	85 (68–95)
Best overall response — no. (%)			
Stringent complete response	0	12 (40)	12 (36)
Complete response	0	3 (10)	3 (9)
Very good partial response	0	9 (30)	9 (27)
Partial response	1 (33)	3 (10)	4 (12)
Stable disease	2 (67)	2 (7)	4 (12)
Progressive disease	0	1 (3)	1 (3)
Median duration of response (95% CI) — mo	1.9 (NE–NE)	10.9 (7.2–NE)	10.9 (7.2–NE)



Raje. NEJM. 2019;380:1726.

Slide credit: clinicaloptions.com

Managing Toxicities Associated With CAR T-Cell Therapy

Case: Patient With Relapsed/Refractory ALL Receiving CAR T-Cell Therapy

- A 39-yr-old man with Ph-negative B-cell ALL initially received pediatric chemotherapy regimen with asparaginase but experienced disease relapse within 1 yr of finishing maintenance therapy
  - Bone marrow biopsy: 76% lymphoblasts, CD19+, CD22+
- Patient received inotuzumab but had refractory disease (70% blasts, CD19+); remained otherwise well with good organ function
- The choice was made to enroll the patient on a CAR T-cell therapy clinical trial
  - Received bridging chemotherapy with liposomal vincristine + dexamethasone; posttherapy biopsy showed 45% blasts
  - Received conditioning chemotherapy with fludarabine + cyclophosphamide followed by CD19 CAR T-cells (Day 0)

Slide credit: clinicaloptions.com

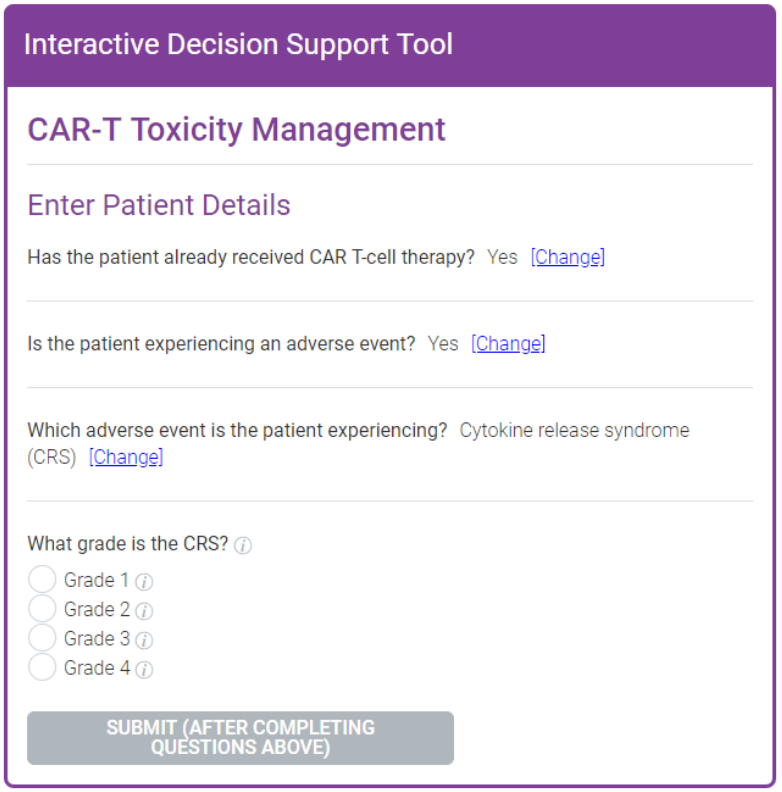
Case: Patient With Relapsed/Refractory ALL Receiving CAR T-Cell Therapy

- On Day 2, the patient developed a fever to 39.7°C that persisted despite acetaminophen; he experienced some fatigue but remained otherwise well
  - BP within normal range; CRP elevated at 12 mg/L
  - Supportive care is given
- On Day 3, fever persists, reaching 40°C; the patient is tachycardic
  - HR in 120s and SBP dropped to 90 mm Hg (his baseline SBP is 130 mm Hg); received 1L normal saline bolus with no increase in SBP
  - CRP is elevated at 23 mg/L; the patient's mentation is good but reports fatigue and mild shortness of breath with high fever; his oxygen saturation is 98%

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*



Available at: clinicaloptions.com/CARTtool

Slide credit: clinicaloptions.com

Case Patient: Expert Recommendations From CCO's Interactive Decision Support Tool

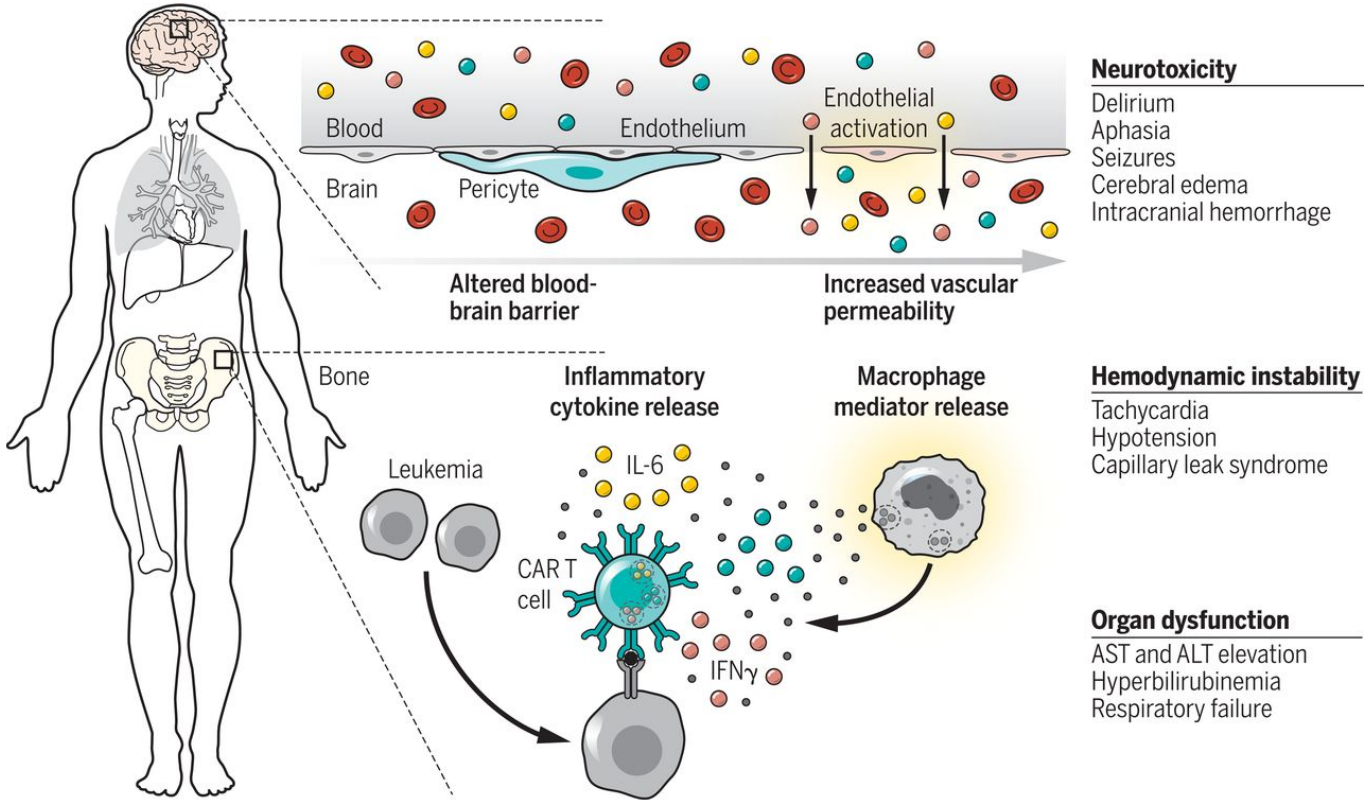
Recommendation Summary
Initiate tocilizumab for hypotension
Administer IV fluids as needed, including normal saline to maintain systolic blood pressure > 90 mmHg
Provide supportive care for fever and constitutional symptoms as needed

Received CAR T-cell therapy? Yes	**Adverse event?** Cytokine-release syndrome (CRS)
Experiencing AE? Yes	**CRS grade?** Grade 2

Case: Patient With Relapsed/Refractory ALL Receiving CAR T-Cell Therapy

- The patient received tocilizumab and his fever resolved within a few hrs, with normalization of SBP and HR
- On Day 5, during morning rounds, he appears disoriented (cannot remember where he is), is not able to name objects, stutters to get words out, and falls asleep in middle of conversation
  - He has intermittent fever to 38.5-39.0°C, but other vitals remain within normal limits
  - CRP is slightly down to 18; CBC shows WBC 0.2 and PLT 30K

Challenges of CAR T-Cell Therapy



June. Science. 2018;359:1361.

Slide credit: clinicaloptions.com

Principles of Toxicity Management

- Appropriate screening per institutional standards
- Baseline labs
  - CRP, ferritin
  - CBC, CMP, coagulopathy
  - Tumor lysis syndrome labs
- Consider antiepileptic drugs
- Consider bacterial/fungal/viral prophylaxis per institutional standards
- Preinfusion/LD chemo
- Monitor baseline labs
- Daily assessments for 7-10 days
  - Fevers? Hypotension? Hypoxia?
  - Mental status
- Key acute toxicities: cytokine-release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS)

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

Frequency of CRS and Neurotoxicity With FDA-Approved CAR T-Cell Therapies

Parameter	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2,3]	
Setting	DLBCL	DLBCL	B-ALL
Trial	ZUMA-1	JULIET	ELIANA
Toxicity grading criteria	Lee 2014	Penn Grading Scale	Penn Grading Scale
Any-grade CRS, %	93	58	77
Grade ≥ 3 CRS, %	13	22	47
Any-grade neurotoxicity, %	64	21	40
Grade ≥ 3 neurotoxicity, %	28	12	13
Tocilizumab use, %	43	14	48

1. Neelapu. NEJM. 2017;377:2531. 2. Schuster. NEJM. 2019;380:45. 3. Maude. NEJM. 2018;378:439.

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]	2 (1-12)	7 (2-58)	4 (1-43)	17
Tisagenlecleucel[2]	3 (1-51)	8 (1-36)	6 (1-359)	ALL: 6 DLBCL: 14

*With tisagenlecleucel, encephalopathy has been observed to last up to 50 days.

- CRS: characterized by fever at the onset; symptoms can be progressive and, in addition to fever, may include capillary leak/hypoxia, end organ dysfunction, and hypotension
- ICANS: toxic encephalopathy with symptoms of mild headaches, confusion, and delirium; expressive aphasia; occasional seizures; and rarely, cerebral edema; can occur in the presence or absence of systemic CRS

1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. Lee. Blood. 2014;124:188.

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)

*Fever defined as temperature ≥ 38°C not attributable to other causes. In patients with CRS who receive antipyretics or anticytokine therapy (eg, tocilizumab, steroids), fever no longer required to grade subsequent CRS severity; CRS grading driven by hypotension and/or hypoxia. †CRS grade determined by more severe event: hypotension or hypoxia not attributable other causes; eg, temperature 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. ‡Low-flow nasal cannula defined as oxygen delivered at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula defined as oxygen delivered at > 6 L/min.

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

New 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 and unable to perform ICE)
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

*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. [†]Depressed level of consciousness not attributable to other cause. [‡]Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. [§]Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

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

New ASTCT Guidelines for Grading of ICANS: ICE Score

Parameter	Score (Points)
Orientation: year, 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

Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care	Supportive care	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

*Dexamethasone 10-20 mg IV either as a 1-time dose or Q6H. †Methylprednisolone 1 mg/kg IV Q12H. ‡High-dose methylprednisolone given at 500 mg IV Q12H for 3 days, then tapered over 2.5 wks.

- 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

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

Slide credit: clinicaloptions.com

Case Revisited: Patient With Relapsed/Refractory ALL Receiving CAR T-Cell Therapy

- 39-yr-old man with Ph-negative, relapsed/refractory, CD19+ B-cell ALL receives CAR T-cell therapy in trial
- On Day 2, the patient developed a fever to 39.7°C that persisted despite acetaminophen; he experienced some fatigue but remained otherwise well
  - BP within normal range; CRP elevated at 12 mg/L
  - Supportive care is given
- On day 3, fever persists, reaching 40°C; the patient is tachycardic
  - HR in 120s and SBP dropped to 90 mm Hg (his baseline SBP is 130 mm Hg); received 1L normal saline bolus with no increase in SBP
  - CRP is elevated at 23 mg/L; the patient's mentation is good but reports fatigue and mild shortness of breath with high fever; his oxygen saturation is 98%

Slide credit: clinicaloptions.com

Managing Long-term Toxicities

- Consult institutional guidelines for management of the following toxicities and contact CAR T-cell treatment center for special management questions
- B-cell aplasia/hypogammaglobulinemia
  - Occurred in ~ 15% of patients treated with axicabtagene ciloleucel or tisagenlecleucel in pivotal trials; immunoglobulin levels should be monitored following therapy
- Cytopenias
  - Grade 3 cytopenias unresolved by Day 30 post treatment occur in a significant proportion of patients; blood counts should be monitored following therapy
- Infections
  - Occurred in 38% to 55% of patients treated with axicabtagene ciloleucel or tisagenlecleucel in pivotal trials

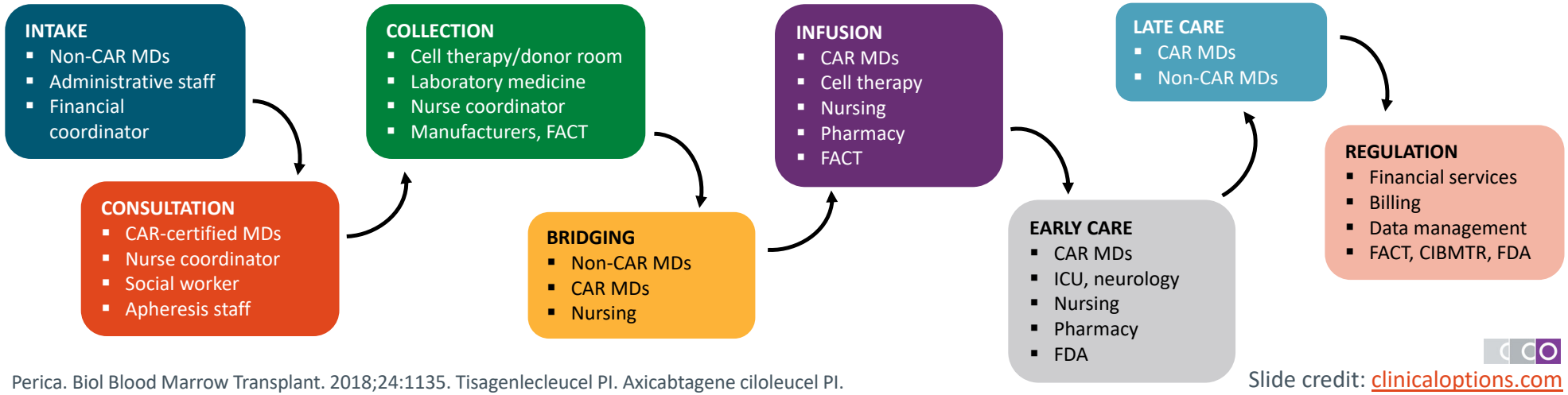
Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

Multidisciplinary Team Roles in Delivering CAR T-Cell Therapies

- All physicians, pharmacists, nurses, and other midlevel providers interacting with patients receiving CAR T-cell therapy must have FDA-mandated training in management of CRS 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 for the MSKCC CAR T-Cell Program



Perica. Biol Blood Marrow Transplant. 2018;24:1135. Tisagenlecleucel PI. Axicabtagene ciloleucel PI.

Slide credit: clinicaloptions.com

Pharmacist's Role in Toxicity Management

- Undergo FDA-mandated training under REMS program in management of CRS and neurologic toxicities associated with CAR T-cell therapies
- Ensure availability of tocilizumab
  - Must have on-site, immediate access
  - Must have minimum of 2 doses available for each patient per infusion within 2 hrs after infusion
- Develop ordering protocols and order sets to ensure timely administration of tocilizumab, corticosteroids, and supportive medications as needed for CAR T-cell–associated toxicities

Perica. Biol Blood Marrow Transplant. 2018;24:1135. Tisagenlecleucel PI. Axicabtagene ciloleucel PI.

Nursing Considerations: Before CAR T-Cell Infusion

- Undergo FDA-mandated training under REMS program in management of CRS and neurologic toxicities associated with CAR T-cell therapies
- Provide patient and caregiver education
  - Written, verbal education on CAR T-cell treatment and signs and symptoms of CRS, neurologic toxicities
- Ensure emergency equipment is available
  - Tocilizumab available, code cart on unit, hypersensitivity kit at bedside
- Initiate IV hydration
- Premedicate with oral acetaminophen and IV diphenhydramine ~ 30-60 mins before infusion

Halton. Clin J Oncol Nurs. 2017;21(2 suppl):35. Perica. Biol Blood Marrow Transplant. 2018;24:1135.
Tisagenlecleucel PI. Axicabtagene ciloleucel PI.

Nursing Considerations: After CAR T-Cell Infusion

- During first wk after infusion, monitor patients at certified healthcare facility for signs and symptoms of CRS, neurologic toxicities
  - Frequency: tisagenlecleucel, 2-3 x for first wk; axicabtagene ciloleucel, at least daily for first wk
- Tell patients to remain within proximity of certified healthcare facility for at least 4 wks after infusion

Nursing Standards of Care for Patients Experiencing CRS, Neurologic Toxicities

Event	Recommendation
CRS	▪ Educate patients, caregivers on signs and symptoms ▪ Take vital signs Q4H and as needed ▪ Weigh patient daily ▪ Record intake and output Q4H ▪ Implement interventions to manage rigors, fevers ▪ Monitor for signs of tumor lysis syndrome
Neurologic toxicities	▪ Maintain seizure precautions ▪ Assess neurologic status every shift and as needed ▪ Initiate neurologic checks as needed

Halton. Clin J Oncol Nurs. 2017;21(2 suppl):35. Tisagenlecleucel PI. Axicabtagene ciloleucel PI.

Concluding Remarks

Question and Answer Session

Go Online for More CCO Education on CAR T-Cell Therapy!

Downloadable slideset with all the key data from this presentation

Downloadable slidesets, text modules, and on-demand Webcasts covering key studies leveraging CAR T-cell therapies in ALL, DLBCL, and multiple myeloma

CAR-T Toxicity Management Interactive Decision Support Tool
Enter your own case scenarios to get the consensus recommendations from 5 multidisciplinary experts on how they would treat that patient!

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Proceeding With CAR T-Cell Therapy: Next Steps at Administering Center

- Obtain written, informed consent on the risks/benefits of CAR T-cell therapy
- Request insurance approval
- Discuss at cell therapy conference
- Coordinate and schedule lymphocyte apheresis
- Determine need for bridging therapy
- Discuss plan and coordinate with referring physician

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

- All CAR T-cell therapy candidates (after clinical evaluation) are presented and discussed at a weekly clinical care conference

- **Candidates: disease histology**
  - DLBCL, PMBCL, transformed FL (commercial product or clinical trial)
  - Other histologies considered for clinical trials
- **Candidates: disease characteristics**
  - Refractory disease (failure to achieve PR or CR) *or* disease progression after last regimen
  - Refractory to ≥ 2 lines of therapy
  - Ineligible for or relapsed after autologous HSCT

- **Candidates: clinical characteristics**
  - Medically compliant and free of an active substance abuse problem
  - Bilirubin < 3 mg/dL, INR < 1.6 (unless on oral anticoagulant), creatinine clearance > 60 mL/min, MUGA or ECHO with EF > 50%, SpO_2 > 91% on room air, ALC < 100/mm^3
  - Absence of fungal, bacterial, viral, or other infection that is uncontrolled or requires IV antimicrobials for management
  - Performance status (Karnofsky or Lansky) of > 70% (ECOG PS 0-2)

Faculty communication. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

In your current practice, how confident are you in identifying and managing toxicities associated with CAR T-cell therapy?

Please rate your confidence on a scale of 1 to 7, where 1 is not confident and 7 is very confident

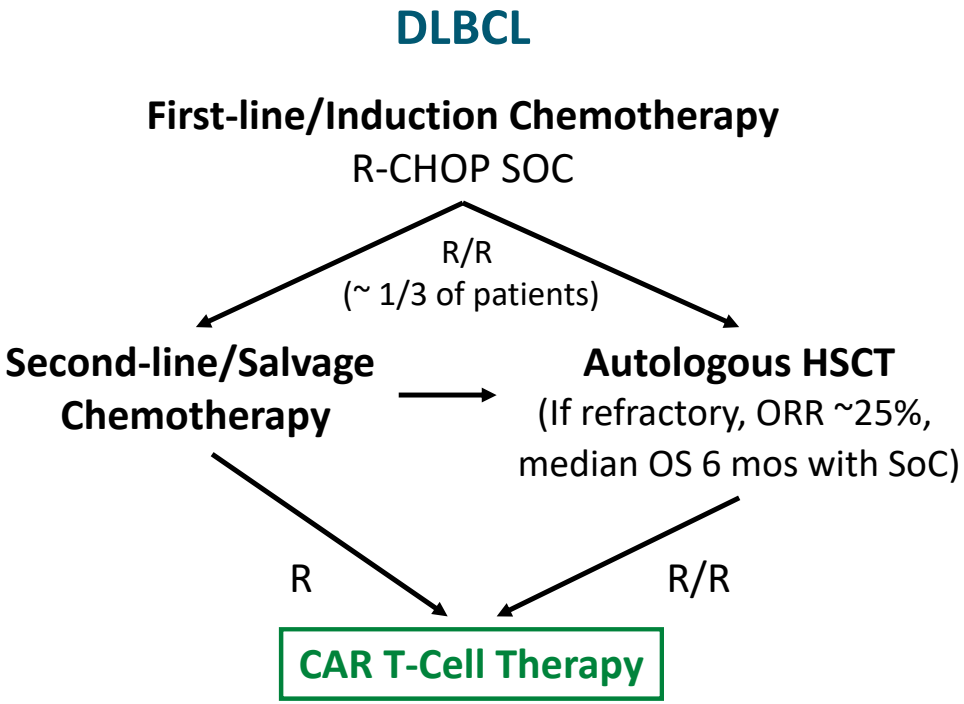
1. Not confident
2. --
3. --
4. --
5. --
6. --
7. Very confident

How confident are you now in identifying and managing toxicities associated with CAR T-cell therapy?

Please rate your confidence on a scale of 1 to 7, where 1 is not confident and 7 is very confident

1. Not confident
2. --
3. --
4. --
5. --
6. --
7. Very confident

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



Sehn. JCO. 2005;23:5027.

Slide credit: clinicaloptions.com

Case 2

56F has a relapsed Ph negative B-ALL after HyperCVAD chemotherapy. BMB revealed a hypercelluar marrow with 92% blasts, CD19+, CD22+. She received clofarabine-based regimen, and post-treatment BMB showed persistent disease with 40% blasts, CD19+. CBC shows WBC 0.1, Hgb 6 and PLT 8K. She suffered infectious complications during the chemo and is deconditioned. Her family is asking about CAR T therapy and would like to transfer her to the center that is conducting the clinical trial. Is she an appropriate candidate for CAR T?

- Yes, her disease still expresses CD19.
- Yes, her disease is stabilized with <50% blasts.
- No, her leukapheresis won't likely be successful due to recent clofarabine and her performance status is suboptimal.

Based on current approvals, for which of the following patients would you be most likely to recommend CAR T-cell therapy?

A. 57-yr-old man with diffuse large B-cell lymphoma with relapses after R-CHOP and ICE/ASCT

B. 42-yr-old woman newly diagnosed with follicular lymphoma

C. 49-yr-old man with multiple myeloma who relapsed after VRd and ASCT

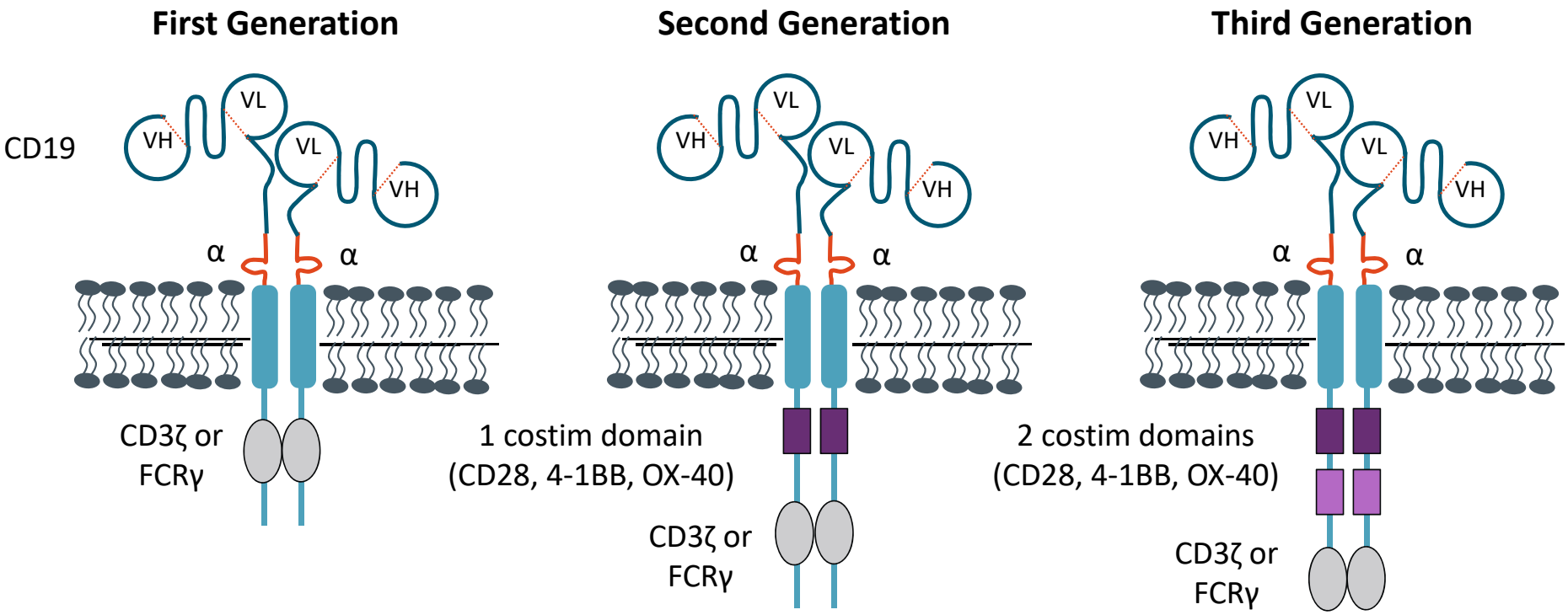
D. 38-yr-old woman with acute lymphocytic leukemia who relapsed after induction/consolidation chemotherapy

E. Uncertain

Current and Future Research Efforts in Cellular Therapy

- Bi-specific CAR T cells
- CAR NK Cells
- “Armored” CARs
- “On-Off switching”
- Allogeneic (“Universal”) CAR T cells
- CRSPR technology
- T-cell receptor (TCR) modified T and NK Cells

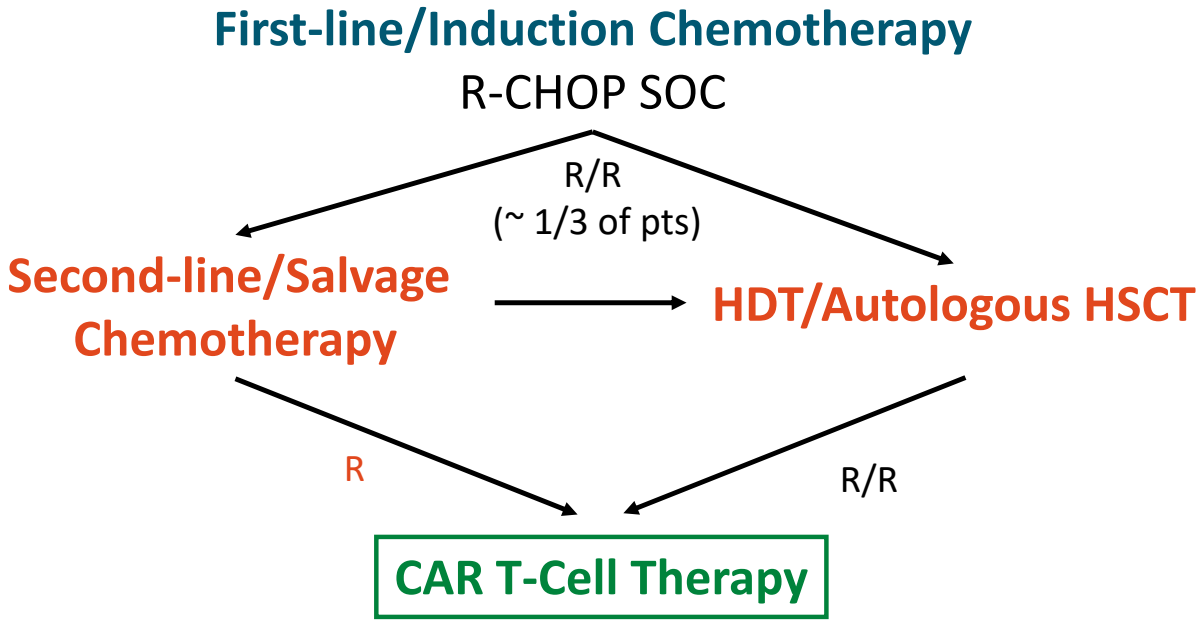
Anatomy of a CAR T-Cell



Park. JCO. 2015;33:651.

Slide credit: clinicaloptions.com

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

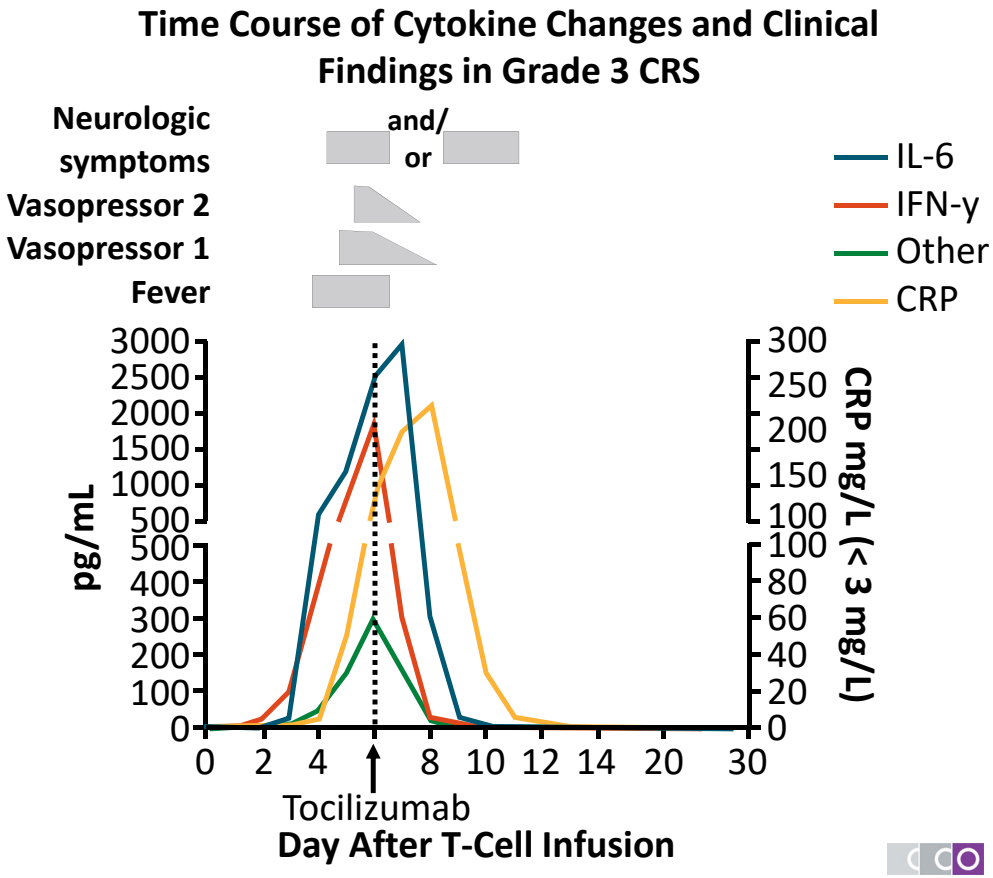


Sehn. JCO. 2005;23:5027.

Slide credit: clinicaloptions.com

Cytokine Release Syndrome (CRS)

- Typical onset 2-3 days, duration 7-8 days
- Characterized by ever at the onset of CRS; symptoms can be progressive and, in addition to fever, may include capillary leak/hypoxia, end organ dysfunction, and hypotension
  - Rarely, severe CRS can evolve into fulminant hemophagocytic lymphohistiocytosis
- Characterized by high levels of TNF-α, **IFN-γ**, IL-1β, IL-2, **IL-6**, IL-8, and IL-10
- Correlates with peak T-cell expansion



Lee. Blood. 2014;124:188.

Slide credit: clinicaloptions.com

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Typical onset 4-6 days, typical duration 14-17 days
- Toxic encephalopathy with symptoms of mild headaches, confusion, and delirium; expressive aphasia; occasional seizures; and rarely, cerebral edema
- Can occur in the presence or absence of systemic CRS
- Patients with severe neurotoxicity demonstrated evidence of endothelial activation, including disseminated intravascular coagulation, capillary leak, and increased blood–brain barrier permeability
- T-cells known to traffic into the CNS; however, no T-cells were found within the brain parenchyma of patients with ALL who died of severe CRS following infusion of JCAR015

Gust. Cancer Discov. 2017;7:1404. Cancer Discov. 2018;8:4.