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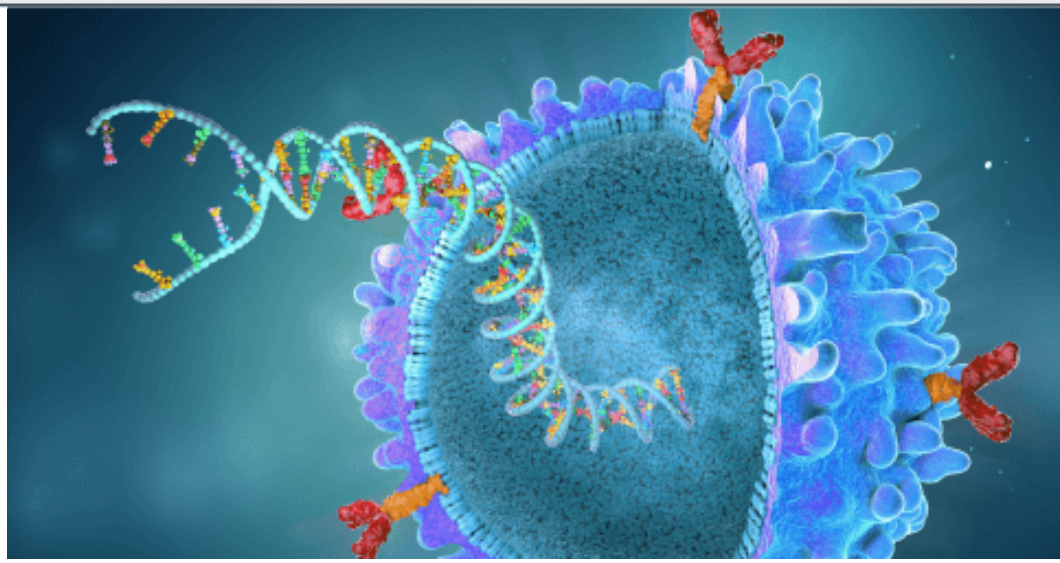
Caring for Patients Receiving CAR T-Cell Therapy: Expert Guidance for Community Practice

Saturday, September 10, 2022 | 1:00 PM PT
GLAONS 6th Annual Oncology Care Summit
Los Angeles, CA



Supported by educational grants from Bristol-Myers Squibb;
Kite, a Gilead Company; and Novartis Pharmaceuticals Corporation.

Faculty

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Joshua Sasine, MD, PhD: no relevant financial relationships to disclose.

First, a Few Quick Polling Questions

Poll 1: If you are a practicing healthcare professional, how many patients with hematologic malignancies do you provide care for in a typical month?

1. 1-4
2. 5-10
3. 11-15
4. 16-20
5. >20

Poll 2: Which clinical setting best describes your practice?

1. Academic
2. Hospital or health system owned
3. Physician owned
4. Federal government owned (eg, Veterans Affairs hospitals)
5. Research

Poll 3: Have you been part of a care team for a patient who has undergone CAR T-cell therapy?

1. Yes
2. No

Presurvey 1: In your current practice, which of the following most accurately describes your confidence level in referring appropriate patients for CAR T-cell therapy?

Please rate your confidence from 1-7 on the scale below

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

Presurvey 2: Each of the following patients with large B-cell lymphoma would be an appropriate candidate to receive an approved CAR T-cell therapy EXCEPT which one?

1. A newly diagnosed high-risk patient with bulky lymphadenopathy
2. A patient who relapsed 6 mo after initial chemoimmunotherapy with R-CHOP
3. A patient who relapsed following initial chemoimmunotherapy and an autologous stem cell transplant
4. A patient who has relapsed after 3 prior lines of chemoimmunotherapy and an autologous stem cell transplant
5. Uncertain

Presurvey 2: Each of the following patients with large B-cell lymphoma would be an appropriate candidate to receive an approved CAR T-cell therapy EXCEPT which one?

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4. A patient who has relapsed after 3 prior lines of chemoimmunotherapy and an autologous stem cell transplant
5. Uncertain

Presurvey 3: On Day 5 following an infusion of CAR T-cells, a patient becomes confused and increasingly disoriented and drowsy; the patient is assessed as having grade 2 immune effector cell–associated neurotoxicity syndrome. Which of the following treatment options would you recommend to manage this adverse event?

1. Anakinra
2. Cyclophosphamide
3. Steroids
4. Siltuximab
5. Tocilizumab
6. Uncertain

Presurvey 3: On Day 5 following an infusion of CAR T-cells, a patient becomes confused and increasingly disoriented and drowsy; the patient is assessed as having grade 2 immune effector cell–associated neurotoxicity syndrome. Which of the following treatment options would you recommend to manage this adverse event?

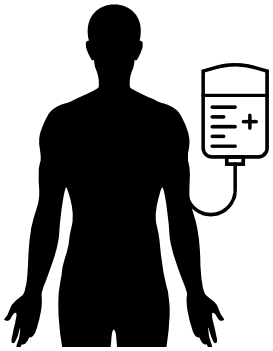
1. Anakinra
2. Cyclophosphamide
3. Steroids
4. Siltuximab
5. Tocilizumab
6. Uncertain

Overview of CAR T-Cell Therapy

Autologous CAR T-Cell Therapy: Underlying Principles

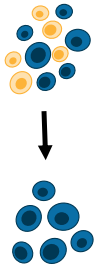
Leukapheresis

Collect patient's white blood cells

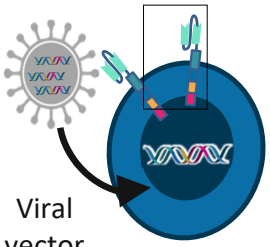


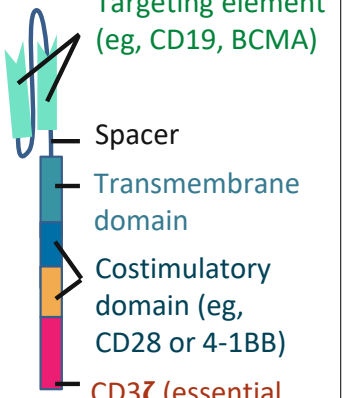
Manufacturing

Isolate and activate T-cells

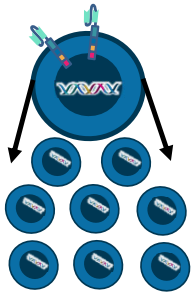


Engineer T-cells with CAR gene





Expand CAR T-cells

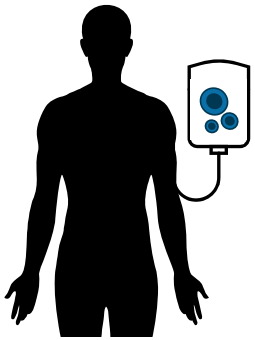


Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

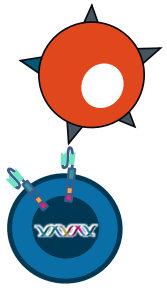
Infusion

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.

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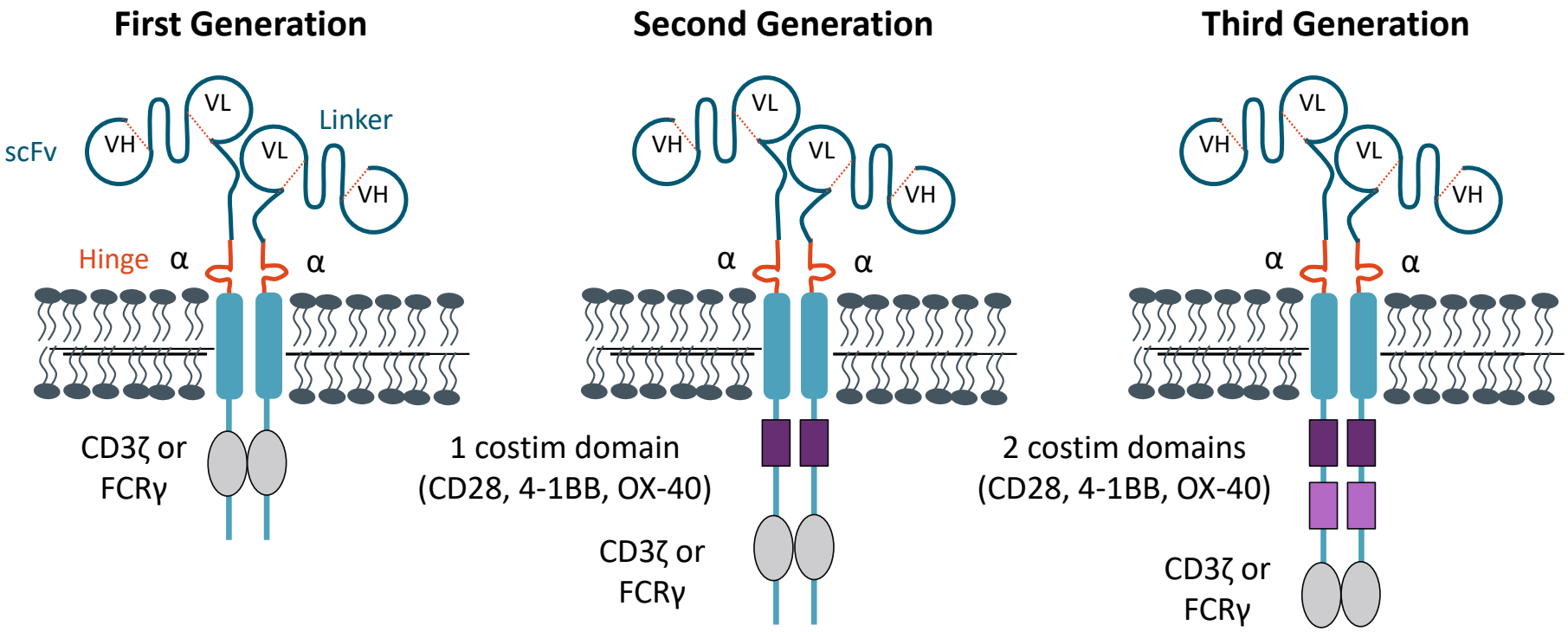
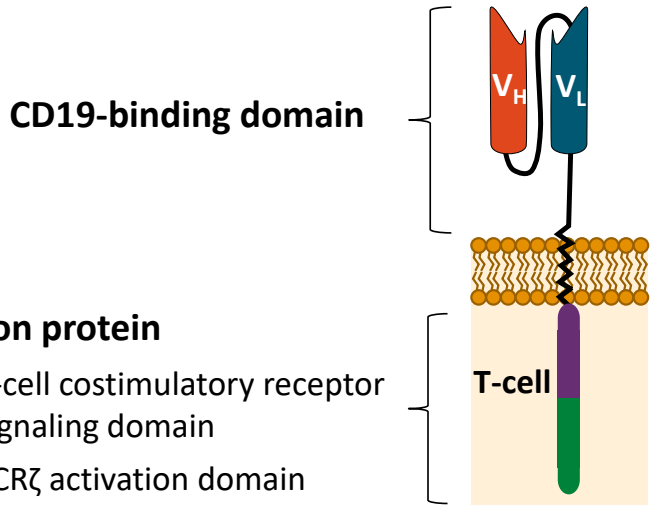
Multiple Generations of CAR T-Cell Technology



Park. JCO. 2015;33:651. van der Stegen. Nat Rev Drug Discov. 2015;14:499.

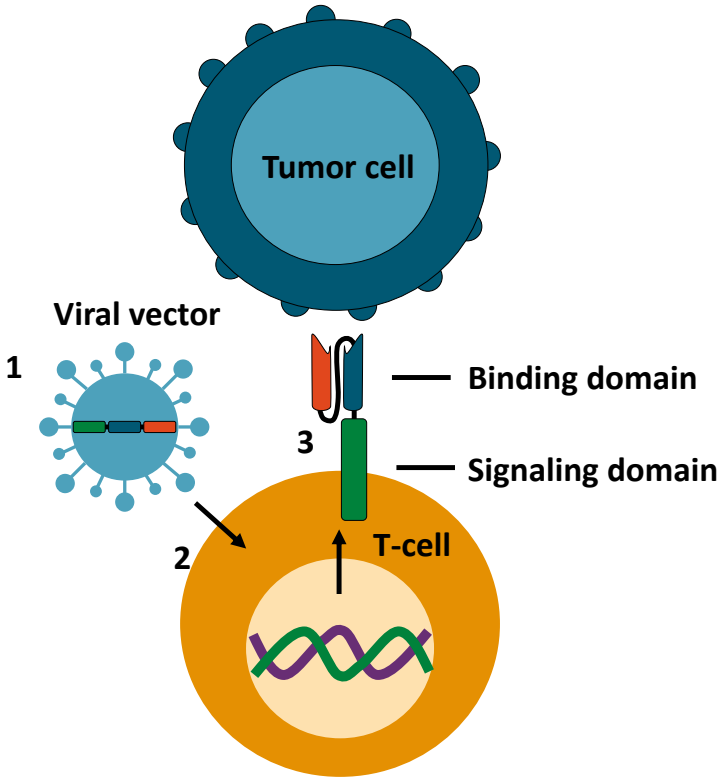
Slide credit: clinicaloptions.com

CD19-Directed CAR T-Cell: An Example



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

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

Slide credit: clinicaloptions.com

What Makes a Patient a Candidate for CAR T-Cell Therapy?

Case 1: Patient With DLBCL

- A 68-yr-old woman presented with fatigue, night sweats, and abdominal pain
- CT scans showed a 6-cm retroperitoneal nodal mass; labs showed elevated LDH
- Biopsy showed a non-GCB DLBCL; staging PET showed FDG-avid lymph nodes above and below the diaphragm
- She received R-CHOP x 6 cycles and had residual, biopsy-proven FDG-avid disease in the RP nodal mass; she received R-ICE x 2 cycles, and repeat PET showed no improvement in this RP nodal mass

Poll 4: Would you consider this patient a potential candidate for CAR T-cell therapy?

1. Yes
2. No
3. Uncertain

- A 68-yr-old woman presented with 6-cm retroperitoneal nodal mass; biopsy showed a non-GCB DLBCL
- Received R-CHOP x 6 cycles; residual FDG-avid disease in the nodal mass; received R-ICE x 2 cycles with no improvement in nodal mass

FDA-Approved CAR T-Cell Therapies

Therapy	Indications
CD19-Targeting Therapies	
Axicabtagene ciloleucel	▪ **Adults with large B-cell lymphoma refractory to or relapsed within 12 mo of first-line chemoimmunotherapy** ▪ **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**
Brexucabtagene autoleucel	▪ **Adults with R/R MCL** ▪ **Adults with R/R B-cell ALL**

Lisocabtagene maraleucel	▪ **Adults with large B-cell lymphoma** (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) that is:
	  ▪ **Refractory to or relapsed within 12 mo of first-line chemoimmunotherapy**
	  ▪ **R/R after first-line chemoimmunotherapy and not eligible for HSCT due to comorbidities or age**
	  ▪ **R/R after ≥2 lines of systemic therapy**

Tisagenlecleucel	▪ **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 ▪ **Adults with R/R follicular lymphoma after ≥2 lines of systemic therapy** ▪ **Patients aged up to 25 yr with B-cell precursor ALL that is refractory or in second/later relapse**
BCMA-Targeted Therapies	
Idecabtagene vicleucel Ciltacabtagene autoleucel	▪ **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

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

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CAR T-Cell Therapy: Lymphomas

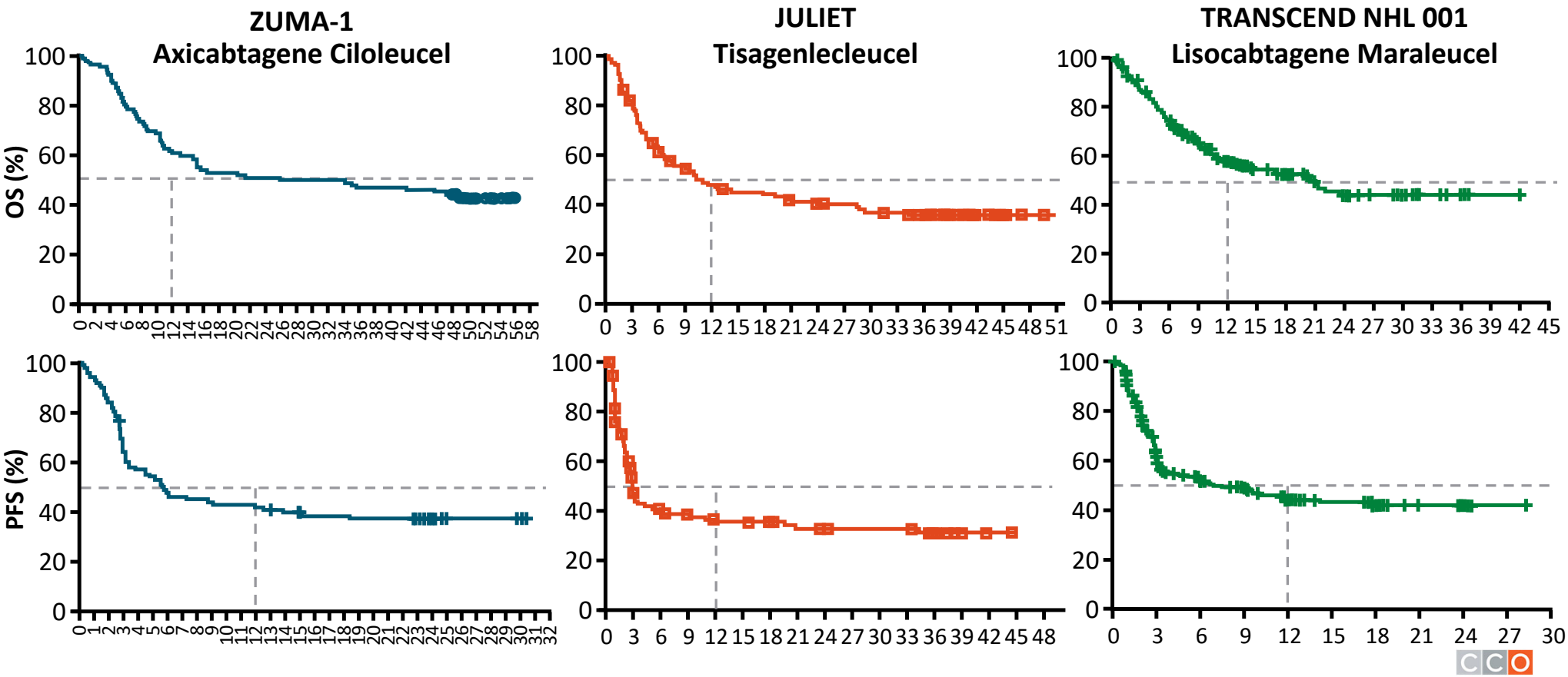
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL

	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.

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

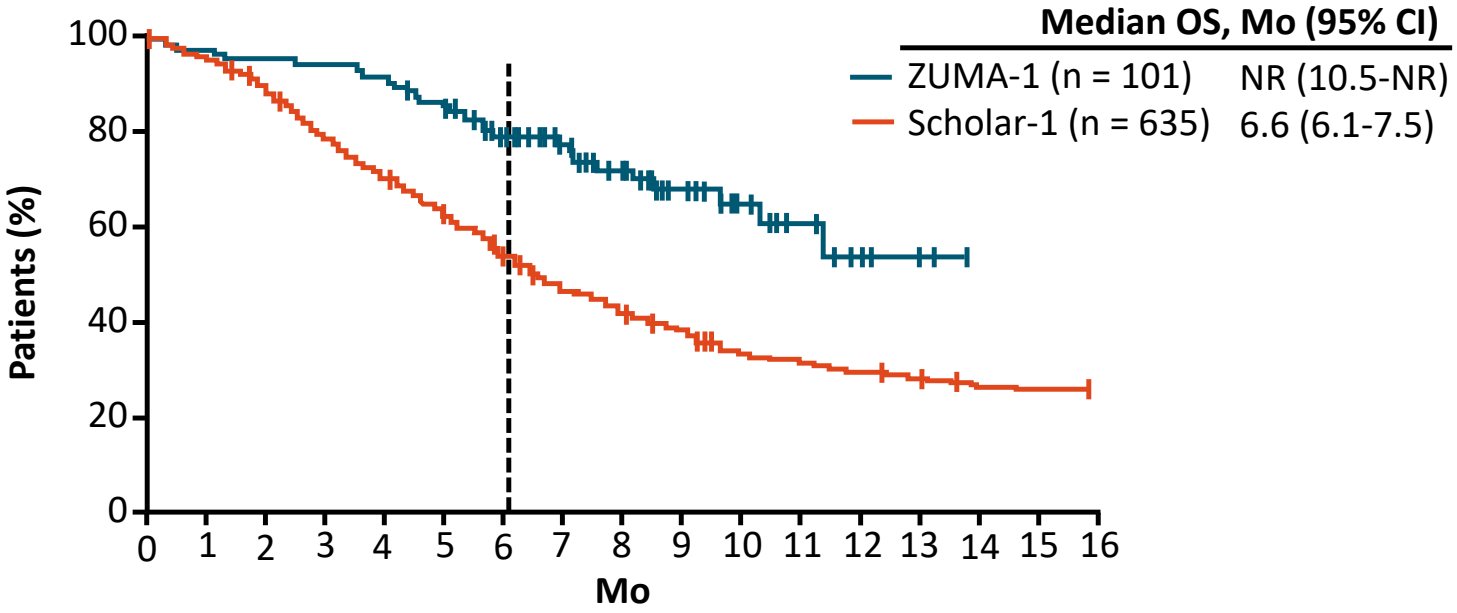


Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

Slide credit: clinicaloptions.com

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 2 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.

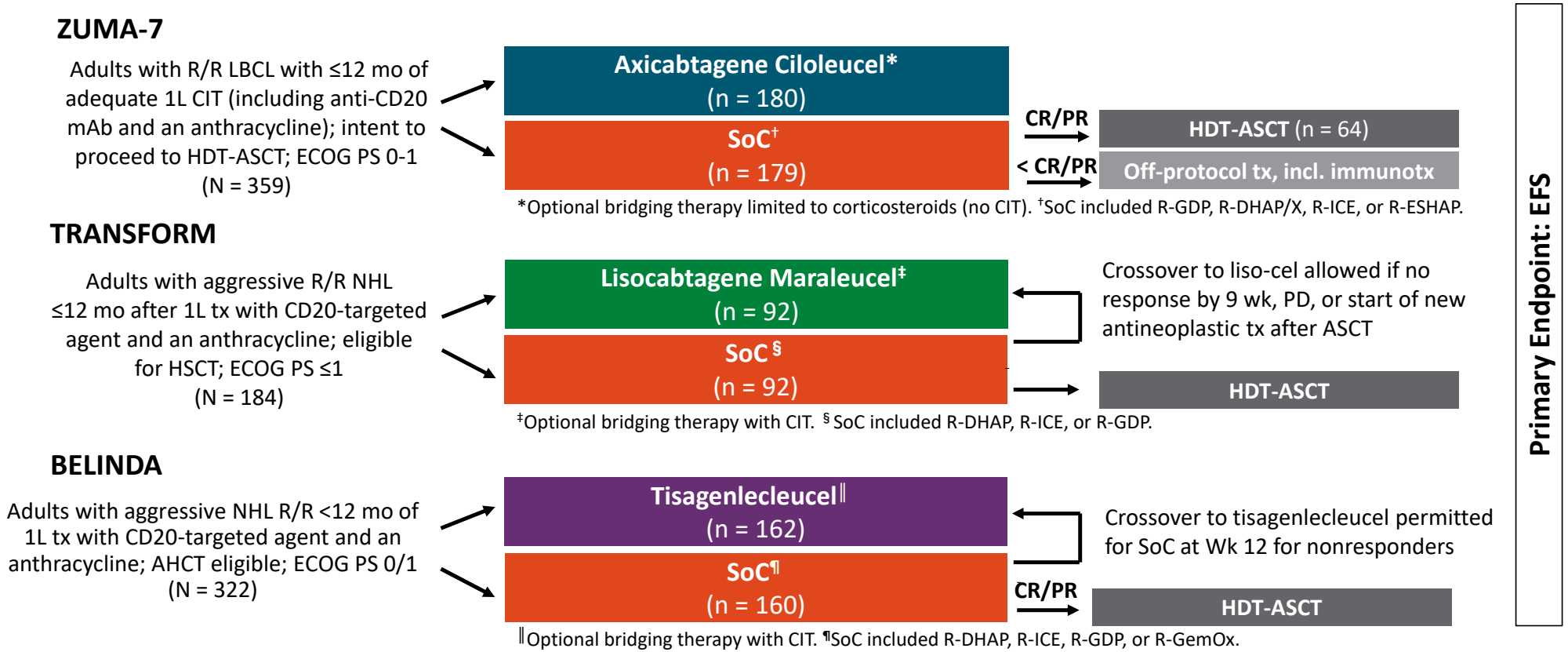
Slide credit: clinicaloptions.com

Real-world Experiences With CD19 CAR T-Cells for LBCL

	Jacobson 2020[1] (US)	Nastoupil 2020[2] (US)	Pasquini 2019[3] (US)	Pasquini 2020[4] (NA)	Riedell 2020[5] (US)		Kuhnl 2019[6] (UK Fit)		Kuhnl 2021[7] (UK Unfit)	
Product	Axi-cel	Axi-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel
Treated, n	122	275	533	155	158	86	62	29	25	28
ORR/CR, %	70/50	82/64	74	62/40	75/53	59/42	37/21	29/17	47/45	
6-mo ORR, %	41	NR	NR	NR	~51	~35-40	~35-40		41	
CRS, %	93	91	81	45	85	41	NR		85	
Gr ≥3 CRS, %	16	7	9	5	8	1	11		2	
NT, %	70	69	58	18	53	14	NR		40	
Gr ≥3 NT, %	35	31	20	5	33	0	13		11	

1. Jacobson. JCO. 2020;38:3095. 2. Nastoupil. JCO. 2020;38:3119. 3. Pasquini. ASH 2019. Abstr 764.
4. Pasquini. Blood Adv. 2020;4:5414. 5. Riedell. TCT 2020. Abstr 52. 6. Kuhnl. ASH 2019. Abstr 767. 7. Kuhnl. EHA 2021. Abstr EP498.

CD19 CAR T-Cell Therapy in Second-line LBCL: Randomized Phase III Trials



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.

ZUMA-7, TRANSFORM, BELINDA: Outcomes

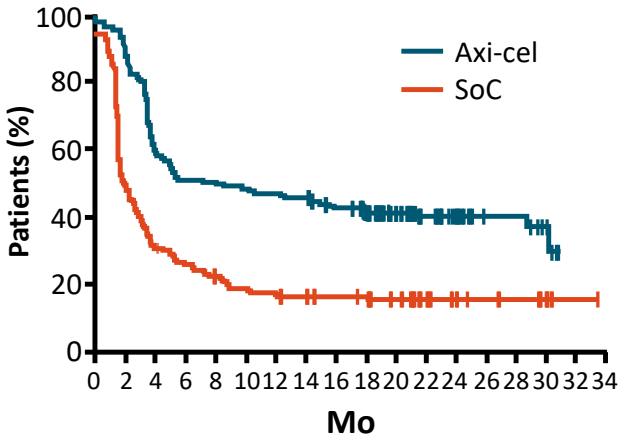
	ZUMA-7[1]	TRANSFORM[2]	BELINDA[3]
Product	Axi-cel vs SoC	Liso-cel vs SoC	Tisa-cel vs SoC
ORR, %	83 vs 50	86 vs 48	46 vs 43
CR, %	65 vs 32	66 vs 39	28 vs 28
Median EFS, mo	8.3 vs 2.0	10.1 vs 2.3	3.0 vs 3.0
EFS, %	2-yr: 41 vs 16	1-yr: 44.5 vs 23.7	--
Median PFS, mo	14.7 vs 3.7	14.8 vs 5.7	--
PFS, %	2-yr: 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.

ZUMA-7, TRANSFORM, BELINDA: EFS

ZUMA-7

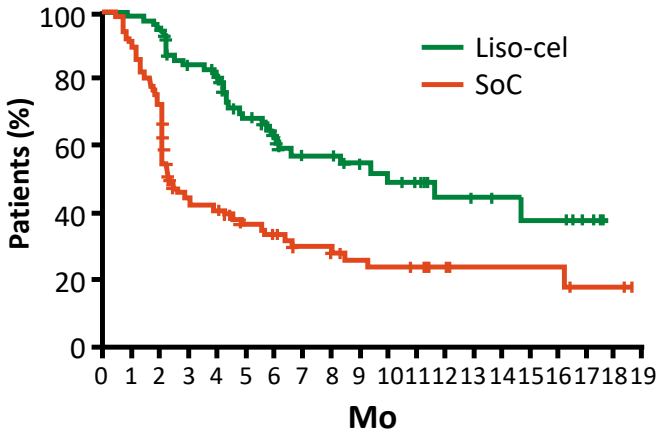
	Axi-Cel (n = 180)	SoC (n = 179)
Median, mo (95% CI)	8.3 (4.5-15.8)	2.0 (1.6-2.8)
HR (95% CI)	0.40 (0.310.51)	
P value	<.0001	



Median follow-up: 24.9 mo

TRANSFORM

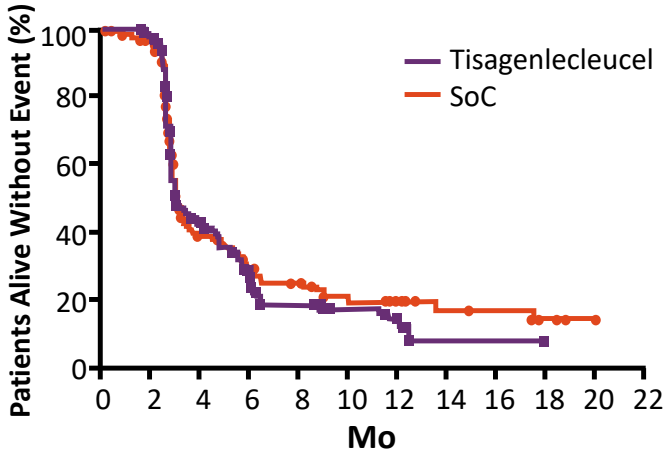
	Liso-Cel (n = 92)	SoC (n = 92)
Median, mo (95% CI)	10.1 (6.1-NE)	2.3 (2.2-4.3)
HR (95% CI):	0.349 (0.229-0.530)	
P value	<.0001	



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	

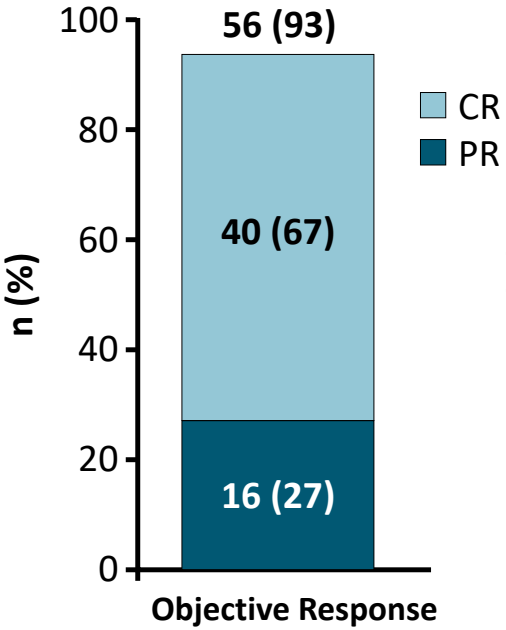


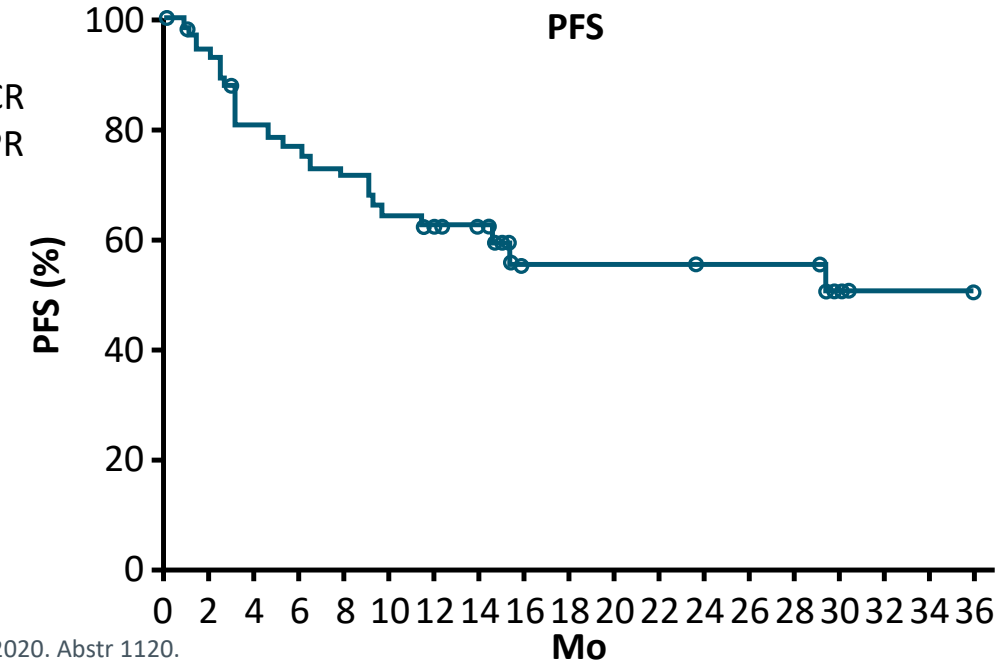
Median follow-up: 10 mo

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.

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.

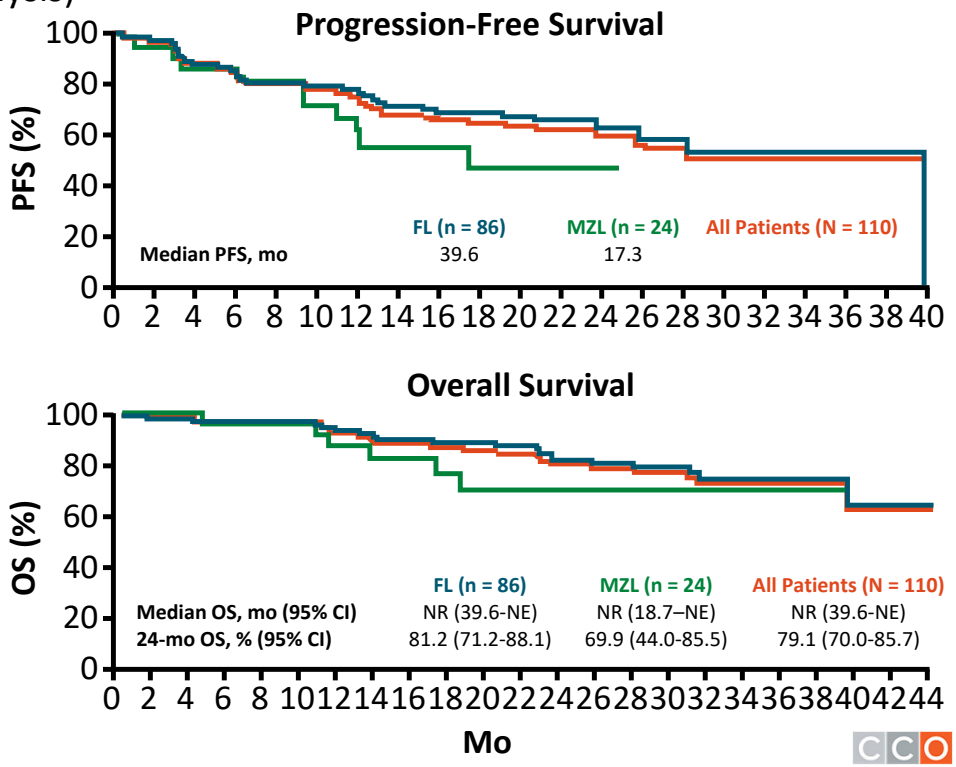
Slide credit: clinicaloptions.com

ZUMA-5: Axicabtagene Ciloleucel for Relapsed/Refractory Indolent NHL (FL or MZL)

- Single-arm phase II study of axicabtagene ciloleucel for patients with R/R indolent B-cell NHL (FL or MZL) **with ≥2 prior therapies** (N = 110 eligible for efficacy analysis)

Outcome	FL (n = 86)	MZL (n = 24)	All (N = 110)
ORR, n (%)	81 (94)	20 (83)	--
▪ CR	68 (79)	15 (63)	--
▪ PR	13 (15)	5 (21)	--
▪ SD	3 (3)	0	--
▪ PD	0	1 (4)	--
▪ ND	2 (2)	3 (13)	
Median DoR, mo (95% CI)	38.6 (24.7-NE)	NR (8.2-NE)	38.6 (24.7-NE)
24-mo DoR, % (95% CI)	66.1 (53.9-75.8)	NR (NE-NE)	63.5 (52.4-72.7)

- CRS grade ≥3, 7% (6% FL); neurotoxicity grade ≥3, 19% (15% FL); tocilizumab, 49%; corticosteroids, 36%



Neelapu. ASH 2021. Abstr 93.

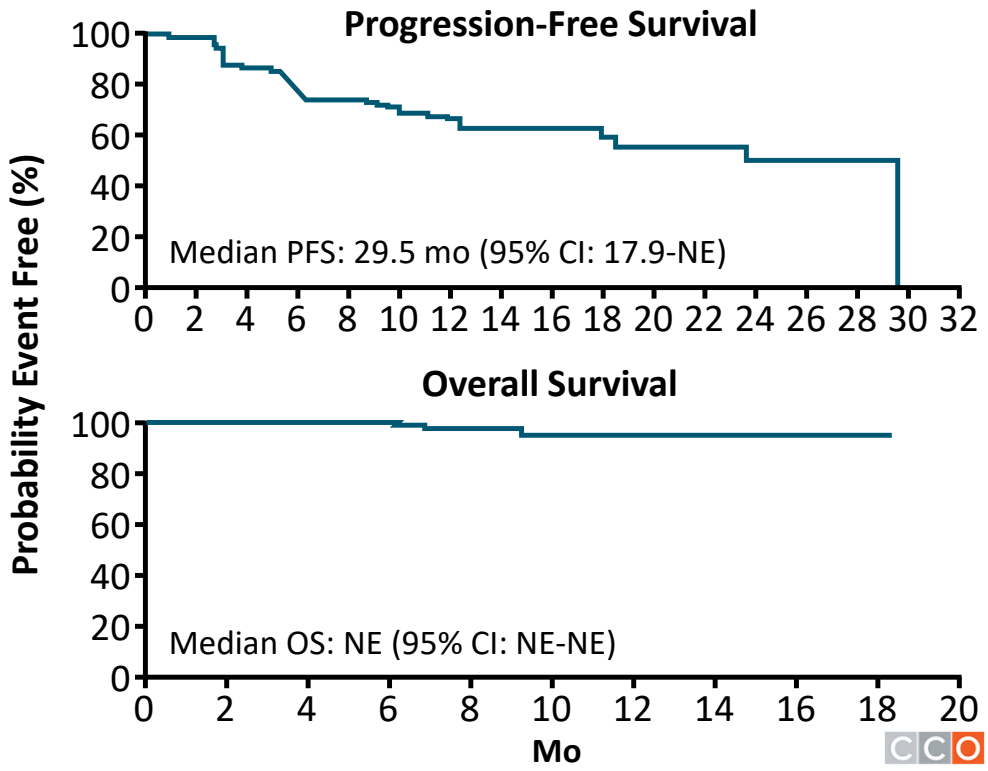
Slide credit: clinicaloptions.com

ELARA: Tisagenlecleucel for Patients With Relapsed/Refractory FL

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

Outcome	Evaluable Patients (n = 94)
ORR (IRC), n (%)	81 (86.2)
▪ CR	65 (69.1)
▪ PR	16 (17.0)
▪ SD	3 (3.2)
▪ PD	9 (9.6)
▪ ND	1 (1.1)
Median DoR, mo (95% CI)	NE (15.6-NE)
9-mo DoR, % (95% CI)	76.0 (64.6-84.2)

- CRS, 49% (grade ≥3, 0%); neurotoxicity, 10% (grade ≥3, 1%)



Thieblemont. ASH 2021. Abstr 131. Fowler. Nat Med. 2022;28:325.

Slide credit: clinicaloptions.com

FDA-Approved CAR T-Cell Therapies: Lymphomas

Therapy	Indications
CD19-Targeting Therapies	
Axicabtagene ciloleucel	▪ **Adults with large B-cell lymphoma refractory to or relapsed within 12 mo of first-line chemoimmunotherapy** ▪ **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**
Brexucabtagene autoleucel	▪ **Adults with R/R MCL**

Lisocabtagene maraleucel	▪ **Adults with large B-cell lymphoma** (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) that is:
	  ▪ **Refractory to or relapsed within 12 mo of first-line chemoimmunotherapy**
	  ▪ **R/R after first-line chemoimmunotherapy and not eligible for HSCT due to comorbidities or age**
	  ▪ **R/R after ≥2 lines of systemic therapy**

Tisagenlecleucel	▪ **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 ▪ **Adults with R/R follicular lymphoma after ≥2 lines of systemic therapy**

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

CCO

Slide credit: clinicaloptions.com

Ongoing/Recent Clinical Trials in Lymphoma

Trial	Design	Key Findings
ALPHA	ALLO-501 (anti-CD19 CAR T) with ALLO-647 (anti-CD52 mAb) for R/R LBCL or FL (N = 41)	▪ ORR 75%, CR 47%; no GVHD, CRS 27% (no grade ≥3), ICANS 2%
ALPHA2	ALLO-501 (anti-CD19 CAR T) with ALLO-647 (anti-CD52 mAb) for R/R LBCL (N = 13)	▪ ORR 56%, CR 44%; no ICANS or GVHD, CRS 18%
ZUMA-12	Axicabtagene ciloleucel in high-risk frontline LBCL	▪ ORR 85%, CR 74%
NCT03960840	YTB323 in R/R DLBCL	▪ ORR/CR up to 75%
TRANSCEND CLL 004	Lisocabtagene maraleucel in R/R CLL	▪ ORR 82%, CR/CRi 45%
TRANSCEND NHL 001	Lisocabtagene maraleucel in R/R MCL	▪ ORR 84%, CR 66%

Depil. Nat Rev Drug Discov. 2020;19:185. Locke. ASCO 2021. Abstr 2529. Neelapu. ASH 2020. Abstr 405. Flinn. ASH 2021. Abstr 740. Siddiqi. Blood. 2022;139:1794. Palomba. ASH 2020. Abstr 118.

Assessment 2: Each of the following patients with large B-cell lymphoma would be an appropriate candidate to receive an approved CAR T-cell therapy EXCEPT which one?

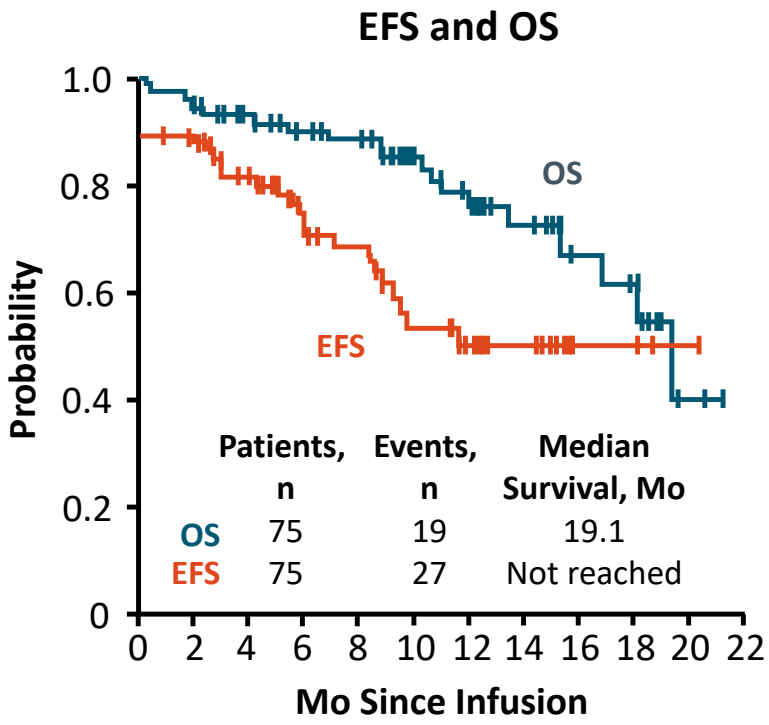
1. A newly diagnosed high-risk patient with bulky lymphadenopathy
2. A patient who relapsed 6 mo after initial chemoimmunotherapy with R-CHOP
3. A patient who relapsed following initial chemoimmunotherapy and an autologous stem cell transplant
4. A patient who has relapsed after 3 prior lines of chemoimmunotherapy and an autologous stem cell transplant
5. Uncertain

CAR T-Cell Therapy:
ALL

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 yr 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 mo: 81%

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

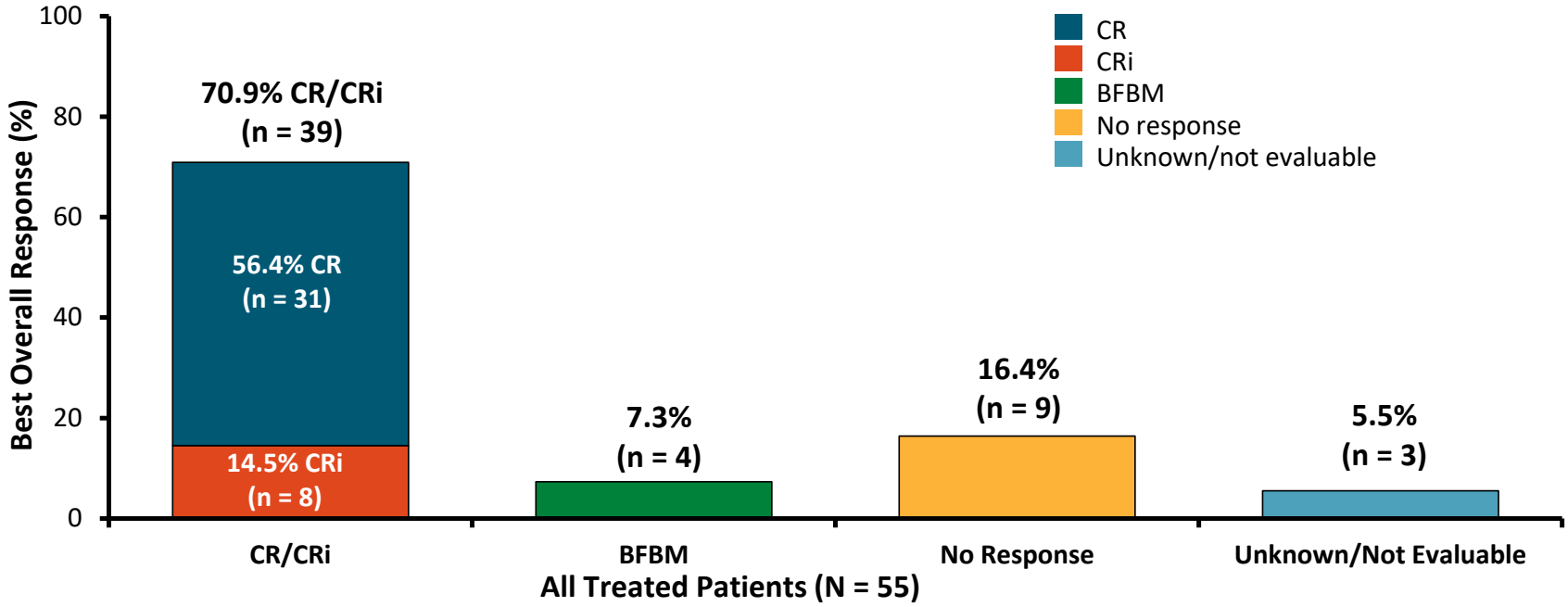


Maude. NEJM. 2018;378:439.

Slide credit: clinicaloptions.com

ZUMA-3 (Phase II): Brexucabtagene Autoleucel for Adults With Relapsed/Refractory ALL

- Multicenter, open-label phase I/II trial of brexucabtagene autoleucel for adults with R/R B-cell ALL and BM blasts >5% (N = 71)



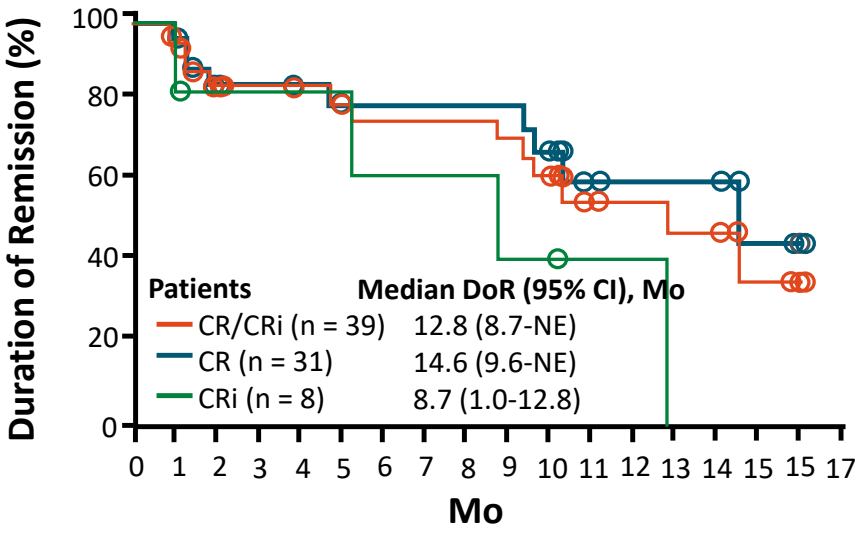
- CRS: all grades, 89%; grade ≥3, 24%; ICANS: all grades, 60%; grade ≥3, 25%

Shah. Lancet. 2021;398:491.

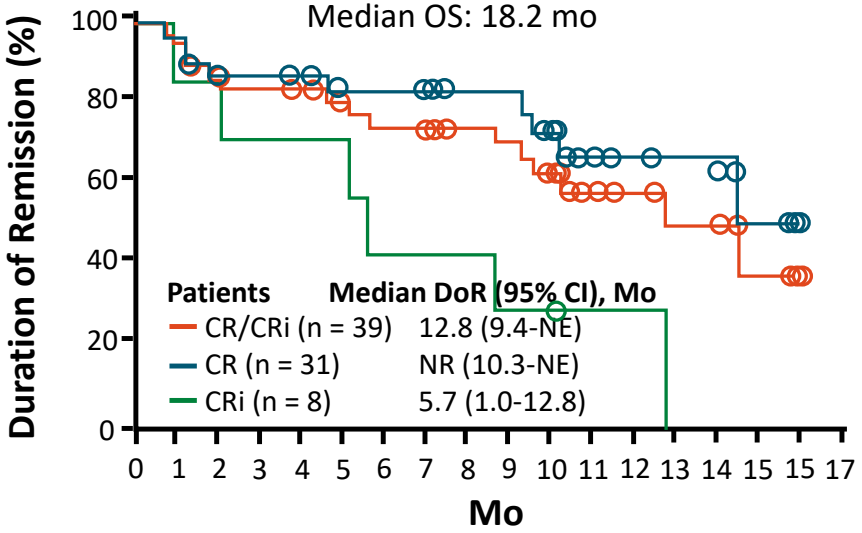
Slide credit: clinicaloptions.com

ZUMA-3 (Phase II): Duration of Remission

DoR With Censoring at Subsequent AlloSCT



DoR Without Censoring at Subsequent AlloSCT



- 10 patients (18%), including 9 with CR/CRi and 1 with BFBM, received alloSCT at a median of 98 days (range: 60-207) post infusion
- As of the data cutoff, 12 of 39 patients who achieved CR/CRi (31%) were in ongoing remission without alloSCT

Shah. Lancet. 2021;398:491. Shah. EHA 2021. Abstr S117.

Slide credit: clinicaloptions.com

FDA-Approved CAR T-Cell Therapies: ALL

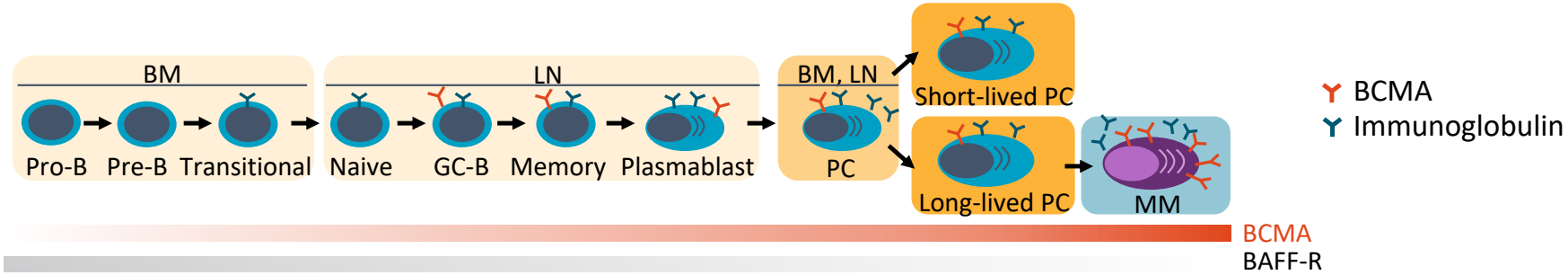
Therapy	Indications
CD19-Targeting Therapies	
Brexucabtagene autoleucel	▪ **Adults with relapsed or refractory B-cell ALL**
Tisagenlecleucel	▪ **Patients aged up to 25 yr with B-cell precursor ALL that is refractory or in second/later relapse**

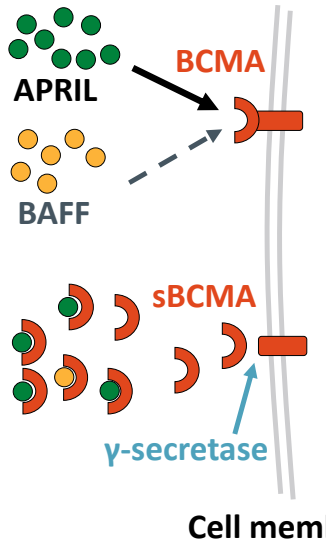
Brexucabtagene autoleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

CAR T-Cell Therapy: Myeloma

BCMA as a Target in Myeloma Treatment





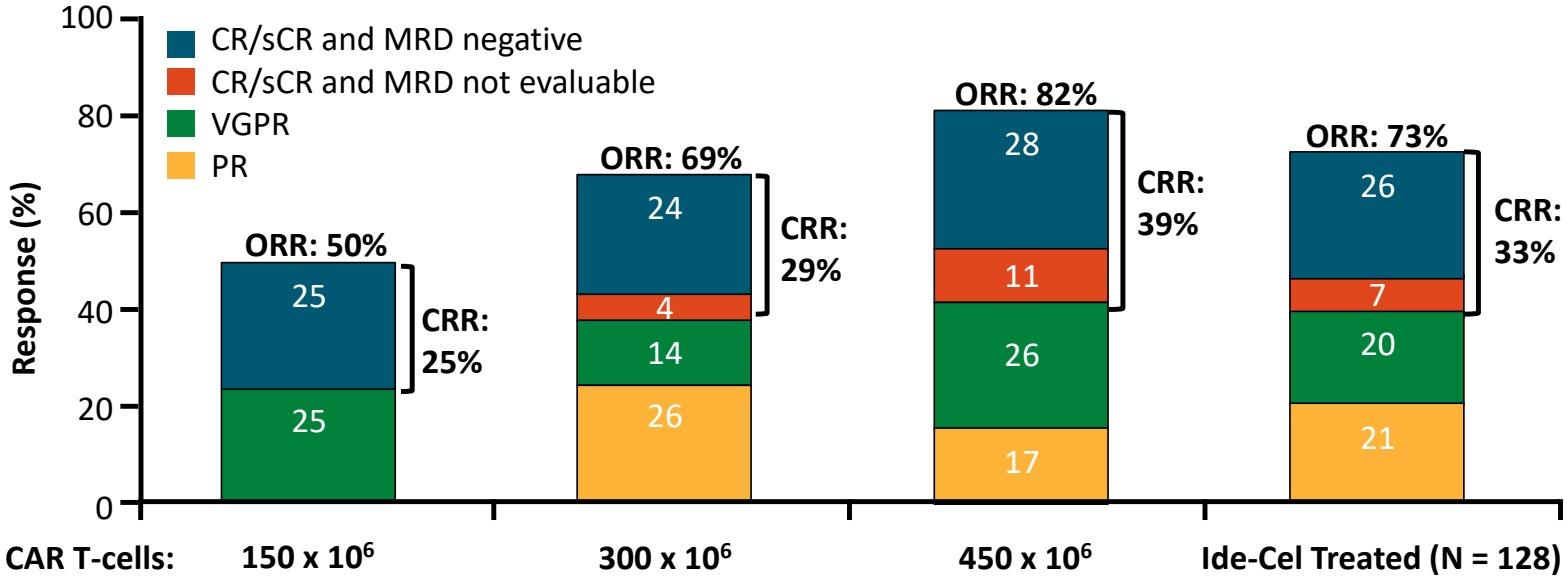
- BCMA: antigen expressed specifically on PCs and myeloma cells
- Cell-surface receptor in TNF superfamily
- Higher expression on myeloma cells than normal PCs
- Not expressed in other tissues
- Key role in B-cell maturation and differentiation
- Promotes myeloma cell growth, chemotherapy resistance, immunosuppression in bone marrow microenvironment
- Expression of BCMA increases with progression from MGUS to advanced myeloma
- Additional ligands for BMCA include APRIL and BAFF

Cho. Front Immunol. 2018;9:1821. Moreaux. Blood. 2004;103:3148. Sanchez. Br J Haematol. 2012;158:727.

Slide credit: clinicaloptions.com

KarMMa: Idecabtagene Vicleucel for R/R MM

- Single-arm phase II trial of 3 doses of idecabtagene vicleucel for patients with R/R MM and ≥3 prior regimens each with ≥2 consecutive cycles, prior IMiD, PI, and anti-CD38 mAb and refractory to last therapy (N = 158)

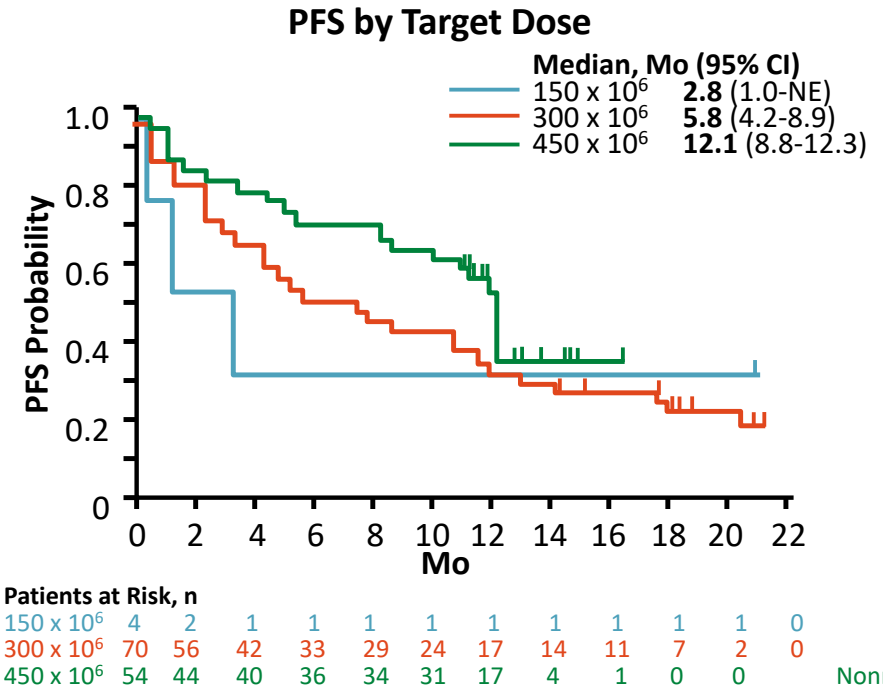


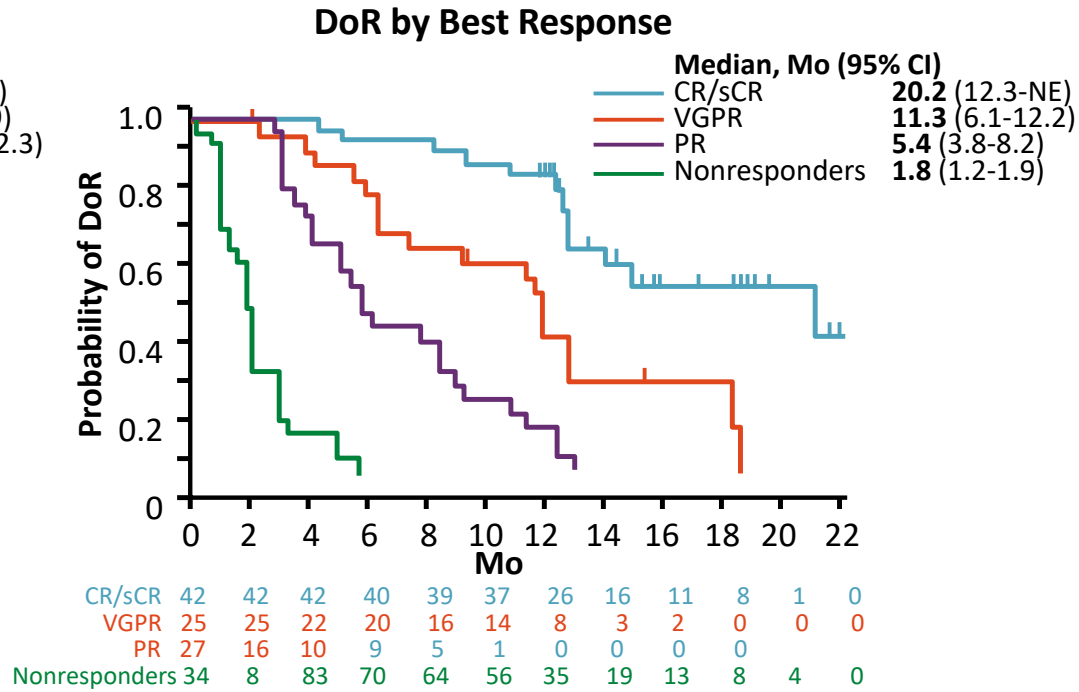
- Median f/u: 13.3 mo; median TTFR: 1.0 mo (range: 0.5-8.8); median time to CR: 2.8 mo (range: 1.0-11.8)
- MRD-negative in all patients in ≥CR was 26% (79% in evaluable patients for MRD and in ≥ CR)

Munshi. NEJM. 2021;384:705.

Slide credit: clinicaloptions.com

KarMMa: PFS by Dose and Best Response





PFS may be dose dependent:
median PFS 12 mo at 450 x 10^6 CAR+ T-cells

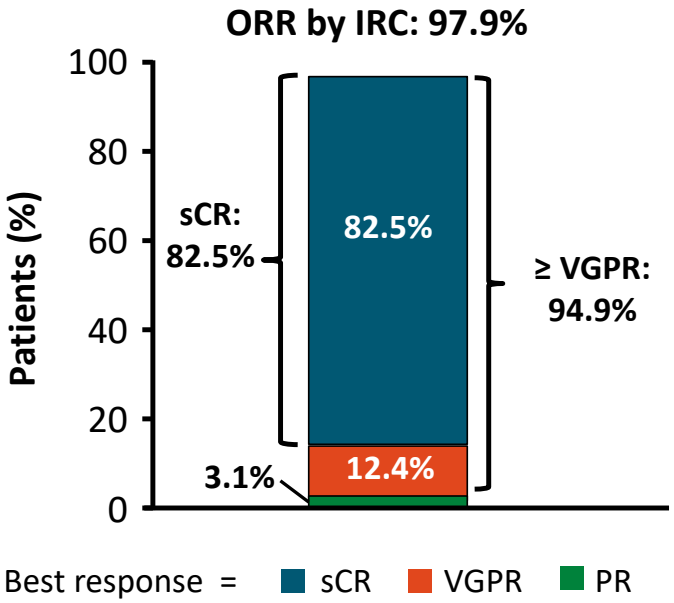
DoR improves with depth of response:
median DoR 20.2 mo in patients with CR/sCR

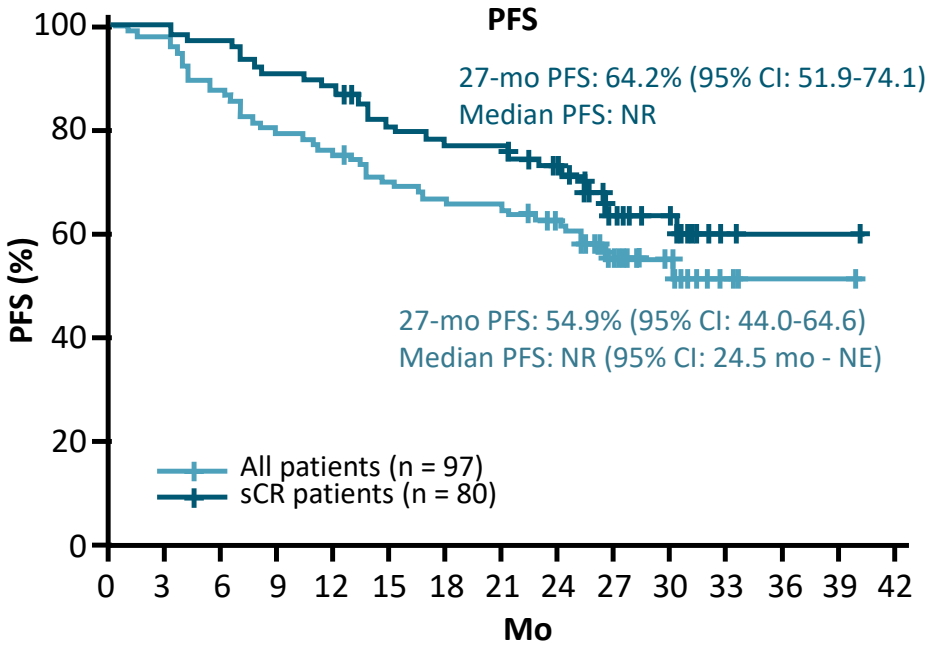
Munshi. ASCO 2020. Abstr 8503.

Slide credit: clinicaloptions.com

CARTITUDE-1: Ciltacabtagene Autoleucel for R/R MM

- Single-arm phase Ib/II trial of ciltacabtagene autoleucel for patients with R/R MM with measurable disease; ≥3 prior therapies including PI, IMiD, and anti-CD38 therapy; or double refractory to PI and IMiD (N = 113)





Martin. JCO. 2022;[Epub].

Slide credit: clinicaloptions.com

FDA-Approved CAR T-Cell Therapies: Myeloma

Therapy	Indications
BCMA-Targeted Therapies	
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
Ciltacabtagene autoleucel	

Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI.

Slide credit: clinicaloptions.com

Select Ongoing/Recent 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-6 (NCT05257083)	Ciltacabtagene autoleucel	III	▪ Ongoing
CARTITUDE-5 (NCT04923893)	Ciltacabtagene autoleucel	III	▪ Ongoing
CARTITUDE-4 (NCT04181827)	Ciltacabtagene autoleucel	III	▪ Ongoing; **RCT vs standard triplet therapy**
CARTITUDE-2 (NCT04133636)	Ciltacabtagene autoleucel	II	▪ Active
CARTIFAN-1 (NCT03758417)	Ciltacabtagene autoleucel	I/II	▪ Ongoing
LUMMICAR-2 (NCT03915184)	CT053 (Zevor-cel)	I/II	▪ Ongoing; ORR 100% (n = 10)[1]
NCT04155749	CART-ddBCMA	I	▪ Ongoing; ORR 100% (n = 16)[2]

- Additional products (trial): bb21217 (CRB-402), P-BCMA-101 (PRIME)

1. Kumar. ASH 2020. Abstr 28. 2. Frigault. ASCO 2022. Abstr 8003.

Slide credit: clinicaloptions.com

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

Factor	Comments
Indications	▪ Does the patient have a disease and therapy history that meets FDA label? ▪ 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	▪ Does the patient have organ function reserve to tolerate toxicities of CAR T-cell therapy, namely CRS and ICANS? Cardiac, pulmonary, renal, bone marrow, CNS

CCO

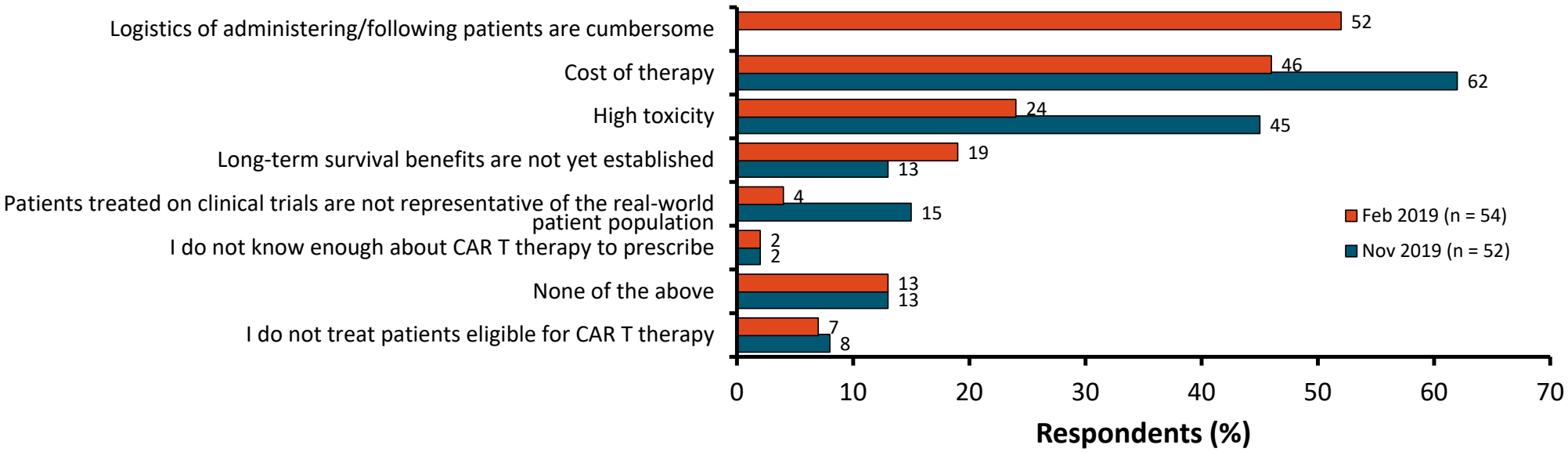
Slide credit: clinicaloptions.com

The Referring Oncologist Experience: Coordination of Care

Perceptions of Community Hematologists/Oncologists on Barriers to CAR T-Cell Therapy for DLBCL

- 2019 survey of US community hematologists and oncologists

In your opinion, which of the following are top barriers to prescribing/recommending CAR T-cell therapy?



Gajra. Immunotherapy. 2020;12:725.

Slide credit: clinicaloptions.com

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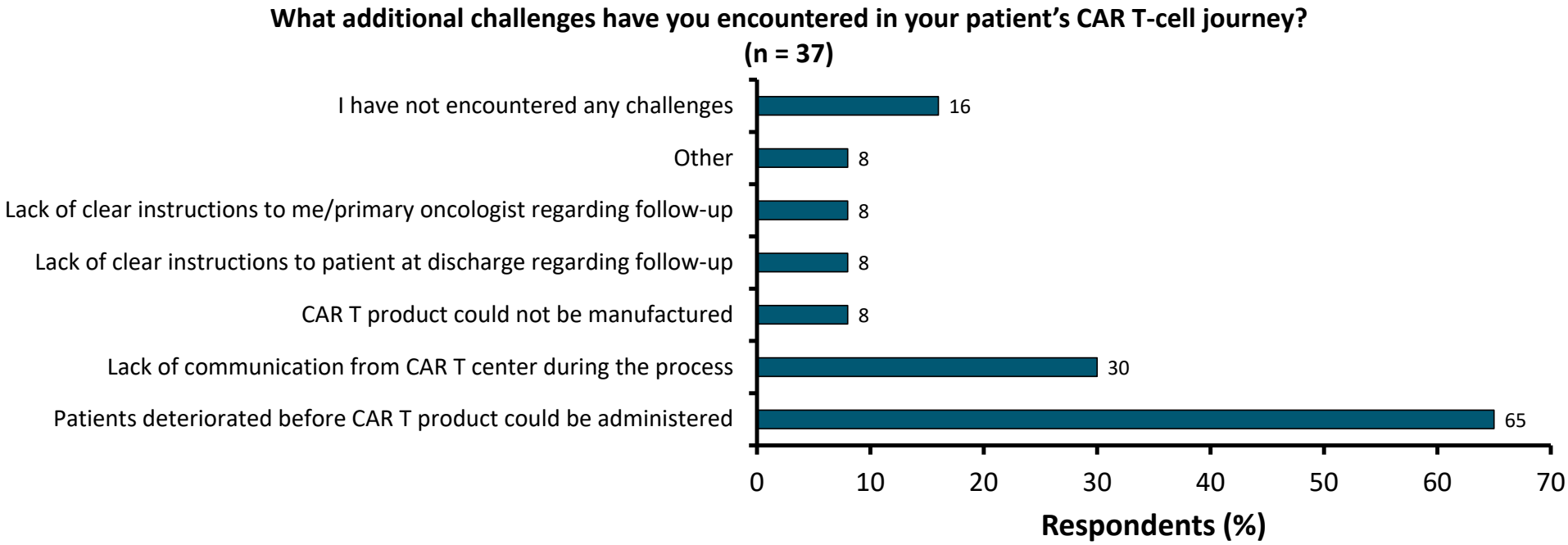

Gajra. Immunotherapy. 2020;12:725.

Slide credit: clinicaloptions.com

CAR T-Cell Therapy Patient Journey

Patient Identification (meets FDA label)

- No age cutoff
- No requirement for CD19+ or BCMA+
- CAR centers will have variable eligibility criteria, so best to refer and let them decide
- Patients can be CAR candidates who are not auto-transplant candidates
- The earlier the referral, the better!

Referral to CAR T Specialist

- Eligibility evaluation
- Insurance authorization
- Consent and education

T-Cell Collection

LD Chemotherapy and T-Cell Infusion

- LD chemo mostly outpatient (ie, Flu/Cy x 3 days)
- CAR T-cell infusion can be inpatient or outpatient
- Postinfusion monitoring involves daily labs, close vital sign monitoring, and exams for at least 7 days to assess for CRS/NT

Close Monitoring ± Bridging Therapy

- Is the patient experiencing significant symptoms or at risk for organ function impairment?
- Bridging could include steroids, palliative RT, chemotherapy, and/or newer targeted agents

Acute Post–CAR T Monitoring

- Patient remains within 2 hr of CAR center for 4 wk from infusion
- Monitor for late CRS/NT and/or ongoing cytopenias
- First response assessment often at 4-wk mark

Long-term Post–CAR T Monitoring

CCO

Slide credit: clinicaloptions.com

CAR T-Cell Therapy: Best Referral Practices

- **CAR T-cell therapy is incorporated into programs in different ways**
  - Transplant model: patients are referred to transplant/ cell therapists for consideration of therapy
  - Disease center model: patients are referred to the disease center physicians, who are also cell therapists, for consideration of therapy
- **Either way, refer early to optimize patient outcomes!**
  - Patients with lower volume disease and who are less heavily pretreated do better
- Treating center will evaluate patient for eligibility and coordinate insurance authorization, consent, screening (some of which can be done by the referring MD), and patient education (MD, RN, pharmacy) prior to scheduling leukapheresis
  - **Best to let the treating center decide on eligibility**; if patient meets FDA label, best to refer and let center make the call
- **Special considerations (center dependent and evolve with time):**
  - Can the patient wait? Tumor burden and/or potential for organ function compromise
  - Performance status; risk of bleeding; cardiac, renal, and/or pulmonary reserve; history of autoimmune disease or neurologic conditions
  - Prior history or current CNS involvement

CCO

Slide credit: clinicaloptions.com

Bridging Therapy for CAR T-Cell Therapy in Lymphoma: An Example

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)
- Polatuzumab ± rituximab
- Radiation therapy
- Rituximab ± chemotherapy
- Ibrutinib, lenalidomide, venetoclax

Regimen Selection

- Prior therapies
- Regimen-related toxicities
- Site(s) of disease
- Comorbidities
- Blood counts
- Simplicity of administration

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Slide credit: clinicaloptions.com

Short-term Monitoring: Days to Weeks From Infusion

- CAR T-cell infusion can be done inpatient or outpatient depending on patient, therapy, and disease being treated
- If outpatient, patients are:
  - Housed near the treating center for 4 wk
  - Educated on how to take vital signs and monitor for neurologic toxicity and given tools to do so and record data
  - Scheduled to return to the treating center daily for at least 7 days for labs and review of vital signs/labs
  - Admitted at the onset of fever and/or confusion through the resolution of CRS and/or NT
- If inpatient:
  - Patient is admitted for up to 7 days or until the resolution of CRS and/or NT
  - After discharge, patients remain within 2 hr of the treating center for up to 4 wk and abstain from driving for up to 8 wk following CAR T-cell infusion due to a low risk of recurrent CRS and/or NT
  - Patients are monitored for ongoing cytopenias, hydration status; first response assessment at 4 wk

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Slide credit: clinicaloptions.com

Outpatient CAR T-Cell Therapy

- Most outpatient experience thus far is using 4-1BB CAR T-cell therapies
- Patients without the bulky disease, organ dysfunction, progressive lymphoma symptoms may be considered for outpatient CAR T-cell administration
  - Older patients still eligible for outpatient infusion
- Patients generally need to stay within 1 hr driving distance AND have a 24-hr caregiver until Day 28
- Criteria for admission will be center dependent, but many admit for first fever
- Outpatient infusion is more cost favorable, associated with shorter hospitalization duration; no apparent clinical detriment has been identified
- Additional experience with CD28 CAR T-cell therapy needed

Nasta. ASH 2019. Abstr 3240. Abramson. Lancet. 2020;396:839. Bachier. ASCO 2020. Abstr 8037. Bansal. ASCO 2021. Abstr 7554.

Assessment 1: Now, which of the following most accurately describes your confidence level in referring appropriate patients for CAR T-cell therapy?

Please rate your confidence from 1-7 on the scale below

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

Effectively Identifying, Managing, and Referring Unique CAR T-Cell–Mediated Adverse Events

Case 1, Continued: Patient With DLBCL

- The 68-yr-old woman with refractory non-GCB DLBCL after R-CHOP and R-ICE received anti-CD19 CAR T-cells
- On Day 2 following her CAR T-cell infusion, she developed a fever up to 101°F with stable blood pressure and O_2 saturation
- The following day, she had persistent fever and developed hypotension with a BP of 84/54 that improved to 102/60 after 1L of normal saline
- CRP has risen from 12 mg/L to 36 mg/L, and ferritin has risen from 454 µg/L to 803 µg/L

Poll 5: In your current practice, which of the following would you consider the optimal therapy for this patient?

1. Supportive care and tocilizumab with or without a dose of dexamethasone
2. High-dose methylprednisolone (1 g IV daily x 3 days) followed by a taper
3. Dexamethasone 10 mg IV Q6H
4. Start IV vasopressors
5. Uncertain

- 68-yr-old woman with refractory non-GCB DLBCL after R-CHOP and R-ICE received anti-CD19 CAR T-cells
- Day 2: fever up to 101°F with stable blood pressure and O_2 saturation; Day 3: persistent fever and hypotension with a BP of 84/54 (improved to 102/60 after 1L of normal saline); CRP rise from 12 to 36 mg/L; ferritin rise from 454 to 803 µg/L

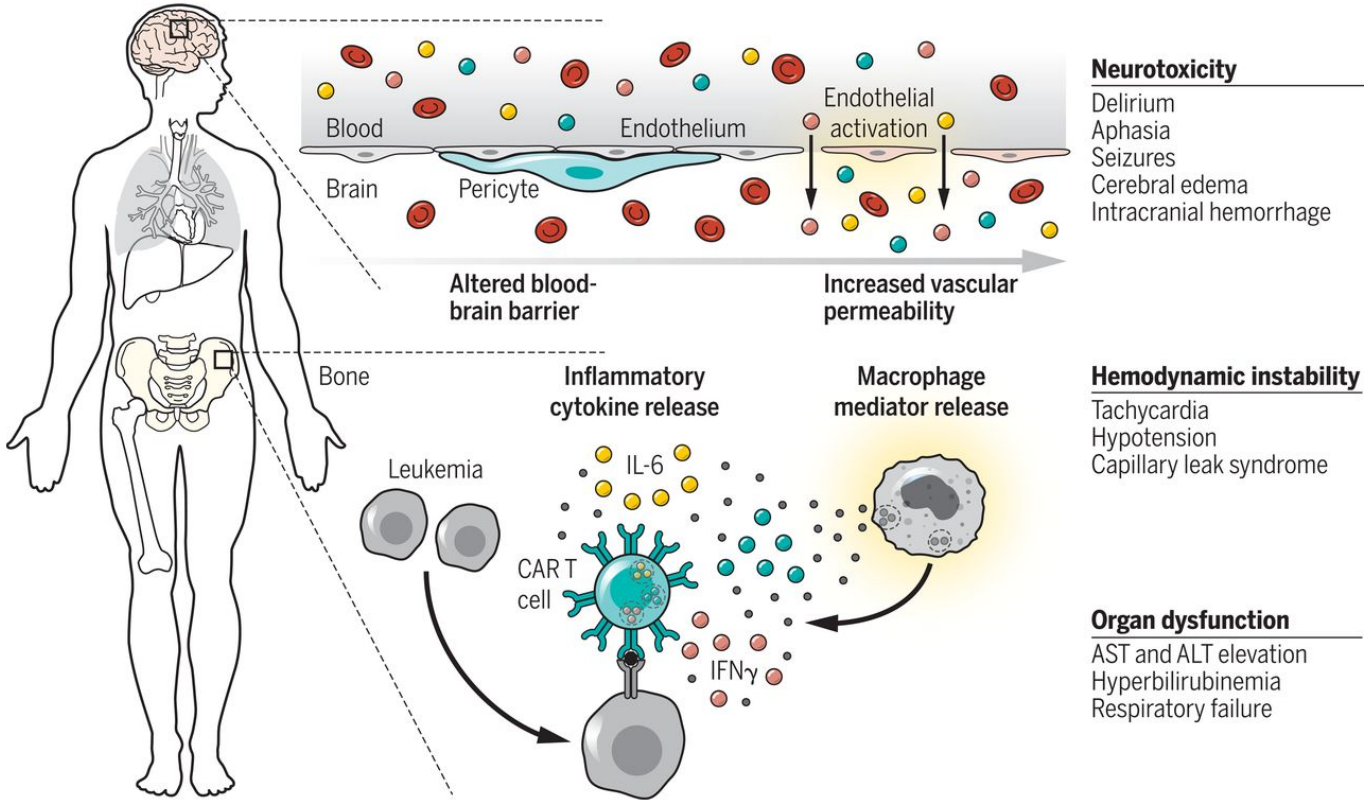
Poll 5: In your current practice, which of the following would you consider the optimal therapy for this patient?

1. Supportive care and tocilizumab with or without a dose of dexamethasone
2. High-dose methylprednisolone (1 g IV daily x 3 days) followed by a taper
3. Dexamethasone 10 mg IV Q6H
4. Start IV vasopressors
5. Uncertain

The patient is experiencing grade 2 CRS; tocilizumab ± dexamethasone is indicated

- 68-yr-old woman with refractory non-GCB DLBCL after R-CHOP and R-ICE received anti-CD19 CAR T-cells
- Day 2: fever up to 101°F with stable blood pressure and O_2 saturation; Day 3: persistent fever and hypotension with a BP of 84/54 (improved to 102/60 after 1L of normal saline); CRP rise from 12 to 36 mg/L; ferritin rise from 454 to 803 µg/L

Challenges of CAR T-Cell Therapy

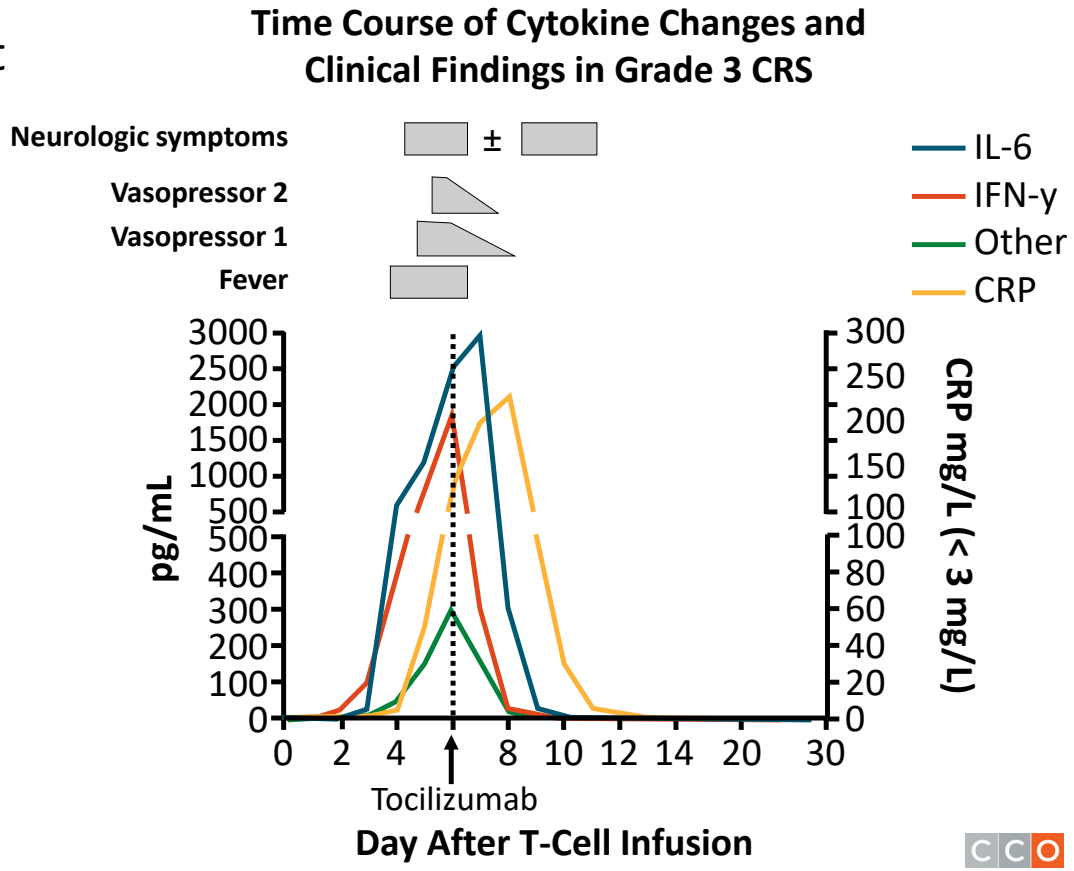


June. Science. 2018;359:1361.

Slide credit: clinicaloptions.com

Cytokine-Release Syndrome

- Systemic inflammatory response that occurs as CAR T-cells activate and expand
- High levels of CRP, ferritin, IL-6, IL-10
- Flu-like symptoms with fever
- Can progress to life-threatening hypotension, hypoxia, and death
- High disease burden associated with more severe CRS



Lee. Blood. 2014;124:188.

Slide credit: clinicaloptions.com

Class Effects of Cell-Mediated Immune Response: CRS

Malig.	Product	Construct	CRS, %	Grade ≥3 CRS, %	Median Time to Onset, Days (Range)	Median Duration, Days (Range)
B-ALL	Brexu-cel	CD19-**CD28**	92	26*	5 (1-12)	8 (2-63)
	Tisa-cel	CD19-**41BB**	77	48[†]	3 (1-22)	8 (1-36)
LBCL	Axi-cel	CD19-**CD28**	93	9*	2 (1-12)[‡]; 3 (1-10)[§]	7 (2-58)[‡]; 7 (2-43)[§]
	Liso-cel	CD19-**41BB**	46[‖]; 45[¶]	4[‖]; 1[¶]*	5 (1-15)[‖]; 4 (1-63)[¶]	5 (1-17)[‖]; 4 (1-16)[¶]
	Tisa-cel	CD19-**41BB**	74	23[†]	3 (1-51)	7 (2-30)
FL	Axi-cel	CD19-**CD28**	84	8*	4 (1-20)	6 (1-27)
	Tisa-cel	CD19-**41BB**	53	0*	4 (1-14)	4 (1-13)
MCL	Brexu-cel	CD19-**CD28**	91	18*	3 (1-13)	10 (1-50)
MM	Cilta-cel	BCMA-**41BB**	95	5*	7 (1-12)	4 (1-40)
	Ide-cel	BCMA-**41BB**	85	9*	1 (1-23)	7 (1-63)

*Per Lee scale. [†]Per Penn scale. [‡]ZUMA-1. [§]ZUMA-7. [‖]≥2 previous lines of therapy. [¶]1 previous line of therapy.

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

Immune Effector Cell–Associated Neurotoxicity Syndrome

- Symptoms
  - Delirium
  - Encephalopathy
  - Aphasia
  - Lethargy
  - Difficulty concentrating
  - Agitation
  - Tremor
  - Seizures
  - Cerebral edema
  - (Headache)

"…an awake patient who is mute and does not respond verbally or physically to an examiner"

- Pathophysiology
  - Endothelial activation → blood–brain barrier disruption
  - Elevated levels of the excitatory NMDA receptor agonists?
  - Proinflammatory cytokines
  - Activated T-cells and myeloid cells

Gust. Cancer Discov. 2017;7:1404. Cancer Discov. 2018;8:4. Lee. Biol Blood Marrow Transplant. 2019;25:625.

Class Effects of Cell-Mediated Immune Response: Neurotoxicity

Malig.	Product	Construct	NT, %	Grade ≥3 NT, %	Median Time to Onset, Days (Range)	Median Duration, Days (Range)
B-ALL	Brexu-cel	CD19-**CD28**	87	35	7 (1-51)	15 (1-397)
	Tisa-cel	CD19-**41BB**	71	22	6 (1-301)	7
LBCL	Axi-cel	CD19-**CD28**	87*; 74†	31*; 25†	4 (1-43)*; 5 (1-133)†	17*; 15†
	Liso-cel	CD19-**41BB**	35‡; 27§	12‡; 7§	8 (1-46)‡; 8 (1-63)§	12 (1-87)‡; 6 (1-119)§
	Tisa-cel	CD19-**41BB**	60	19	5 (1-368)	17
FL	Axi-cel	CD19-**CD28**	77	21	6 (1-79)	16
	Tisa-cel	CD19-**41BB**	43	6	8 (1-345)	5
MCL	Brexu-cel	CD19-**CD28**	81	37	6 (1-32)	21 (2-454)
MM	Cilta-cel	BCMA-**41BB**	26	11	8 (1-28)‖	8 (2-927)‖
	Ide-cel	BCMA-**41BB**	23	4	2 (1-42)	6 (1-578)

*ZUMA-1. †ZUMA-7. ‡≥2 previous lines of therapy. §1 previous line of therapy. ‖Specifically for ICANS.

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

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 (CD19 products)

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.

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 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.

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.

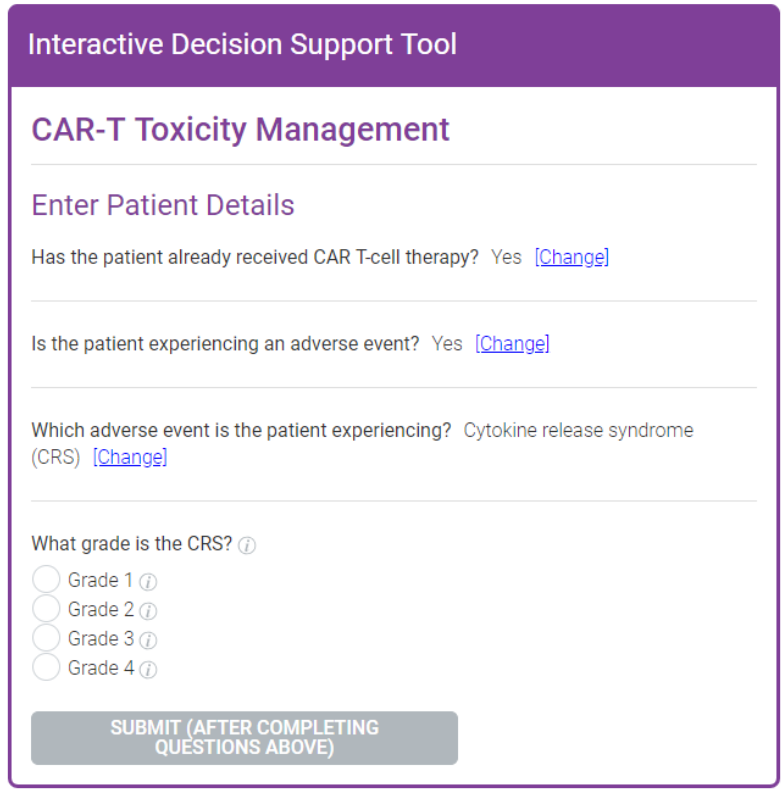
MD Anderson. CAR cell therapy toxicity assessment and management. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

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

Assessment 3: On Day 5 following an infusion of CAR T-cells, a patient becomes confused and increasingly disoriented and drowsy; the patient is assessed as having grade 2 immune effector cell–associated neurotoxicity syndrome. Which of the following treatment options would you recommend to manage this adverse event?

1. Anakinra
2. Cyclophosphamide
3. Steroids
4. Siltuximab
5. Tocilizumab
6. Uncertain

CAR T-Cell Therapy Patient Journey

Patient Identification (meets FDA label)

- No age cutoff
- No requirement for CD19+ or BCMA+
- CAR centers will have variable eligibility criteria, so best to refer and let them decide
- Patients can be CAR candidates who are not auto-transplant candidates
- The earlier the referral, the better!

Referral to CAR T Specialist

- Eligibility evaluation
- Insurance authorization
- Consent and education

T-Cell Collection

LD Chemotherapy and T-Cell Infusion

- LD chemo mostly outpatient (ie, Flu/Cy x 3 days)
- CAR T-cell infusion can be inpatient or outpatient
- Postinfusion monitoring involves daily labs, close vital sign monitoring, and exams for at least 7 days to assess for CRS/NT

Close Monitoring ± Bridging Therapy

- Is the patient experiencing significant symptoms or at risk for organ function impairment?
- Bridging could include steroids, palliative RT, chemotherapy, and/or newer targeted agents

Acute Post–CAR T Monitoring

- Patient remains within 2 hr of CAR center for 4 wk from infusion
- Monitor for late CRS/NT and/or ongoing cytopenias
- First response assessment often at 4-wk mark

Long-term Post–CAR T Monitoring

CCO

Slide credit: clinicaloptions.com

Poll 6: Which of the following AEs needs to specifically be monitored for in the longer term following CAR T-cell therapy?

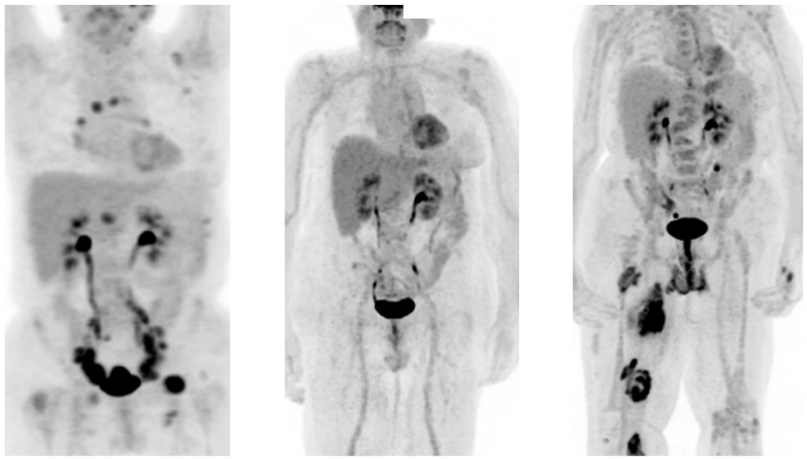
1. B-cell aplasia
2. Cytopenias
3. Infections
4. All of the above
5. Uncertain

Long-term Monitoring and Toxicities: Weeks to Months From Infusion

- Patients should be monitored for:
  - Prolonged cytopenias (transfusions as indicated, G-CSF as needed)
  - B-cell aplasia (IgG levels) (replete with IVIG for levels <400 µg/L)
  - Infection
  - Relapse
  - Secondary malignancies
- Antibiotic (herpes and PJP) prophylaxis
  - Variable practices; at core faculty's center, continue for at least 6 mo, at which time CD4 count is measured, with discontinuation only when >200
- Vaccination
  - Influenza (yearly)
  - Posttransplant vaccines (resume 12 mo after therapy)
  - COVID-19 vaccination (3 mo from CAR T-cell therapy [unknown])
- Late neurotoxicity

Case 2: Patient With Refractory FL

- 58-yr-old woman with refractory transformed follicular lymphoma received axi-cel
  - Experienced grade 1 CRS, no ICANS
  - PET: 1 mo, CR; 3 mo to 2.5 yr, continued CR
- 3-yr PET: several centrally necrotic, FDG-avid masses throughout the muscles of her LEs bilaterally, R > L, concerning for infection vs recurrent lymphoma; otherwise, no signs of recurrent lymphoma
  - Diagnostic evaluation revealed mycoplasma muscular infection in setting of chronic hypogammaglobulinemia



- Ongoing remission through 5 yr, with IVIG infusions every mo to prevent recurrent infection
- At Yr 5.5, after being vaccinated and boosted, developed severe COVID-19 infection; intubated in ICU for 30 days, eventually making a full recovery

Conclusions

- Anti-CD19 CAR T-cell therapy leads to high rates of durable remissions in patients with R/R aggressive B-cell lymphoma and B-ALL
- Anti-CD19 CAR T-cell therapy leads to high rates of complete/durable responses in R/R MCL and FL
  - Longer follow-up is needed to see if some of these patients are cured
- Anti-BCMA CAR T-cell therapy leads to high response rates in R/R MM, but durability of response remains a concern with currently FDA-approved therapies in the fifth-line setting and beyond
- Early referrals will ensure that both efficacy and safety are optimized, as outcomes are associated with patient fitness, T-cell fitness, and disease burden
- Earlier and more aggressive CRS and NT mitigation strategies have decreased high-grade toxicities, allowing for treatment of a broader patient population
- Relationships between referring and referral centers and oncologists in the short and long term are vital!

Questions?