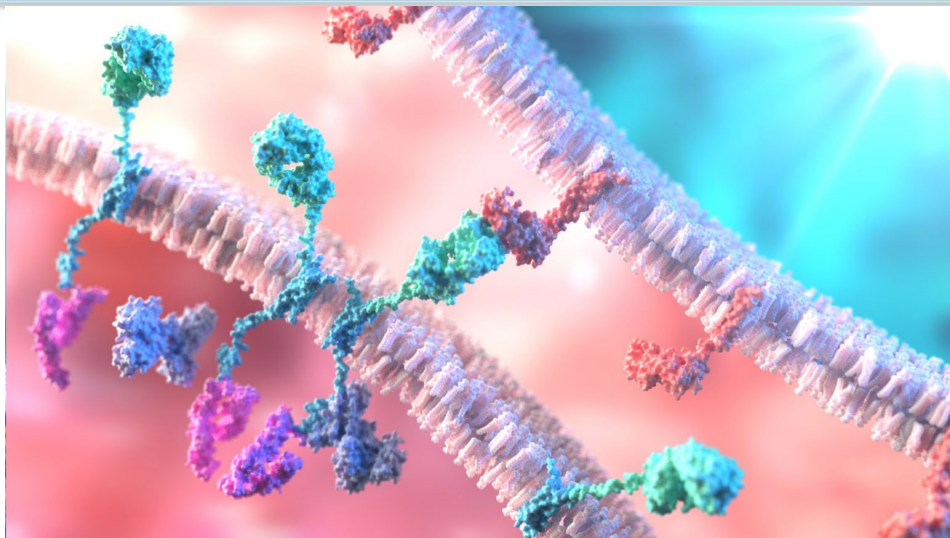
PleXus Communications

CAR T-Cell Therapies for B-Cell Lymphoma in the Community Setting: Empowering Peer-to-Peer Education

Reference Aid



Four Major Anti-CD19 CAR T-Cell Products for B-Cell NHL

	Axicabtagene ciloleucel[1]	Brexucabtagene autoleucel[2]	Tisagenlecleucel[3]	Lisocabtagene maraleucel[4]
Construct	antiCD19-**CD28**-CD28TM-CD3z	antiCD19-**CD28**-CD28TM-CD3z	antiCD19-**4-1BB**-CD8αTM-CD3z	antiCD19-**4-1BB**-CD28TM-CD3z
Vector	Retrovirus	Retrovirus	Lentivirus	Lentivirus
T-cell manufacturing	Bulk	Bulk	Bulk	Defined doses CD4, CD8
Dose	2 × 10^6/kg (max 2 x 10^8)	r/r MCL: 2 × 10^6/kg (max 2 x 10^8) r/r B-ALL: 1 × 10^6/kg (max 1 x 10^8)	Pedi B-ALL: <50 kg, 0.2 to 5.0 x 10^6/kg >50 kg, 0.1 to 2.5 x 10^8 r/r DLBCL, r/r FL: 0.6 to 6.0 x 10^8	90 to 110 x 10^6 (2^{nd}+ line) 50 to 110 x 10^6 (3^{rd}+ line)
Lymphodepletion	Flu/Cy 30/500 x 3d	r/r MCL: Flu/Cy 30/500 x 3d r/r B-ALL: Flu 25 x 3d, Cy 900 x 1d	Pedi B-ALL: Flu 30 x 4d, Cy 500 x 2d r/r DLBCL, r/r FL: Flu/Cy 25/250 x 3d, or Benda 90 x 2d	Flu/Cy 30/300 x 3d
Clinical role	2^{nd}+ line if r/r within 12 m; 3^{rd}+ line DLBCL, PMBCL, high grade BCL, transformed FL; 3^{rd}+ line FL	r/r MCL and r/r B-ALL	3^{rd}+ line DLBCL, high grade BCL, transformed FL; 3^{rd}+ line FL; pedi B-ALL	3^{rd}+ line DLBCL, high grade BCL, PMBCL, grade 3B FL; 2^{nd}+ line if primary r/r within 12 m or if HSCT ineligible; 3^{rd}+ line CLL/SLL after prior BTKi & BCL2i

NHL, non-Hodgkin lymphoma; B-ALL, B-cell acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplantation; PMBCL, primary mediastinal large B-cell lymphoma; r/r, relapsed/refractory

1. YESCARTA® (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma, Inc.;2023. 2. TECARTUS® (brexucabtagene autoleucel) [package insert]. Santa Monica, CA: Kite Pharma, Inc.;2023. 3. KYMRIAH® (tisangenlecleucel) [package insert]. Morris Plains, NJ: Novartis Pharmaceuticals Corp.; 2022. 4. BREYANZI® (lisocabtagene maraleucel) [package insert]. Bothel, WA: Juno Therapeutics Inc.; 2024.

CD19 CAR T Cells for DLBCL

Pivotal Trial Results After 2 or More Lines of Systemic Therapy

	ZUMA-1[1,2]	JULIET[3,4]	TRANSCEND[5,6]
Product	**Axi-cel***	**Tisa-cel****	**Liso-cel*****
Costimulatory domain	CD28	4-1BB	4-1BB
# pheresed	111	167	344
# treated	101	115	270
ORR, %	83	53	73
CR, %	58	39	53
mPFS, months	5.9	2.9	6.8
mOS, months	25.8	11.1	27.3

Cross-trial comparisons are for discussion purposes only

*Median follow-up of 63.1 months. **Median follow-up of 40.3 months. ***Median follow-up of 19.9 months.

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Neelapu SS, et al. *Blood*. 2023;141(19):2307-2315. 3. Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56. 4. Schuster SJ, et al. *Lancet Oncol.* 2021;22(10)1403-1415. 5. Abramson JS, et al. *Lancet*. 2020;396:839-852. 6. Abramson JS, et al. *Blood*. 2024;143(5):404-416.

ZUMA-7, TRANSFORM, BELINDA Results: Second-Line Treatment

	ZUMA-7[1,2]	TRANSFORM[3,4]	BELINDA[5*]
Product	**Axi-cel vs SoC**	**Liso-cel vs SoC**	**Tisa-cel vs SoC**
Costimulatory domain[6]	CD28	4-1BB	4-1BB
ORR (%)	83% vs 50%	87% vs 49%	46% vs 43%
CR (%)	65% vs 32%	74% vs 43%	28% vs 28%
mEFS (months)	10.8 vs 2.3	NR vs 2.4	3.0 vs 3.0
EFS rate (%)	4-year: 39% vs 17%	18-month: 53% vs 21%	---
mPFS (months)	14.7 vs 3.7	NR vs 6.2	---
PFS rate (%)	4-year: 42% vs 24%	18-month: 58% vs 29%	---
mOS (months)	NR vs 31.1	NR vs 29	---
OS rate (%)	4-year: 55% vs 46%	18-month: 73% vs 61%	---

Cross-trial comparisons are for discussion purposes only

*Not an FDA approved indication for relapsed disease or primary refractory disease within 12 months of first-line therapy.

1. Locke et al. *N Engl J Med*. 2022;386(7):640-654. 2. Westin J, et al. *N Engl J Med*. 2023;389:148-157. 3. Kamdar M, et al. *Lancet*. 2022;399(10343):2294-2308. 4. Abramson J, et al. *Blood*. 2023;141(14):1675-1684. 5. Bishop et al. *N Engl J Med*. 2022;386(7):629-639. 6. Meng J, et al. *Front Oncol*. 2021;11:698607.

How to Sequence Newer 2nd- and 3rd-Line Therapies For LBCL

HYPOTHETICAL CONCERN:

Targeting CD19 ahead of CD19 CAR T cells, so best to avoid if CD19 CAR T cells are planned

- Tafasitamab: receptor occupancy issue, wash-out of at least 6-12 wks is ideal
- Loncastuximab: less of a concern but still best to reserve for CD19+ relapses AFTER CAR or for CAR ineligible
  - Loncastuximab after CAR has been shown to be safe and effective

HYPOTHETICAL CONCERN:

T cell exhaustion due to bispecific antibody engagement if bispecifics used prior to CAR T cells

- Try to avoid bispecifics ahead of CAR T cells until proven effective (early studies suggest they are)
- CAR T cells before bispecific known to be safe and effective from trials
- If cannot avoid, try to have a 12+ wk wash out

VALID CONCERN:

T-cell toxic therapies ahead of leukapheresis and/or lymphodepletion

- Bendamustine within 6-12 m of leukapheresis
- High doses of corticosteroids within 7 d of leukapheresis and 5 d of CAR T-cell infusion
- Other immunosuppressants within 5 half-lives of leukapheresis and/or CAR T-cell infusion

Expert opinion; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

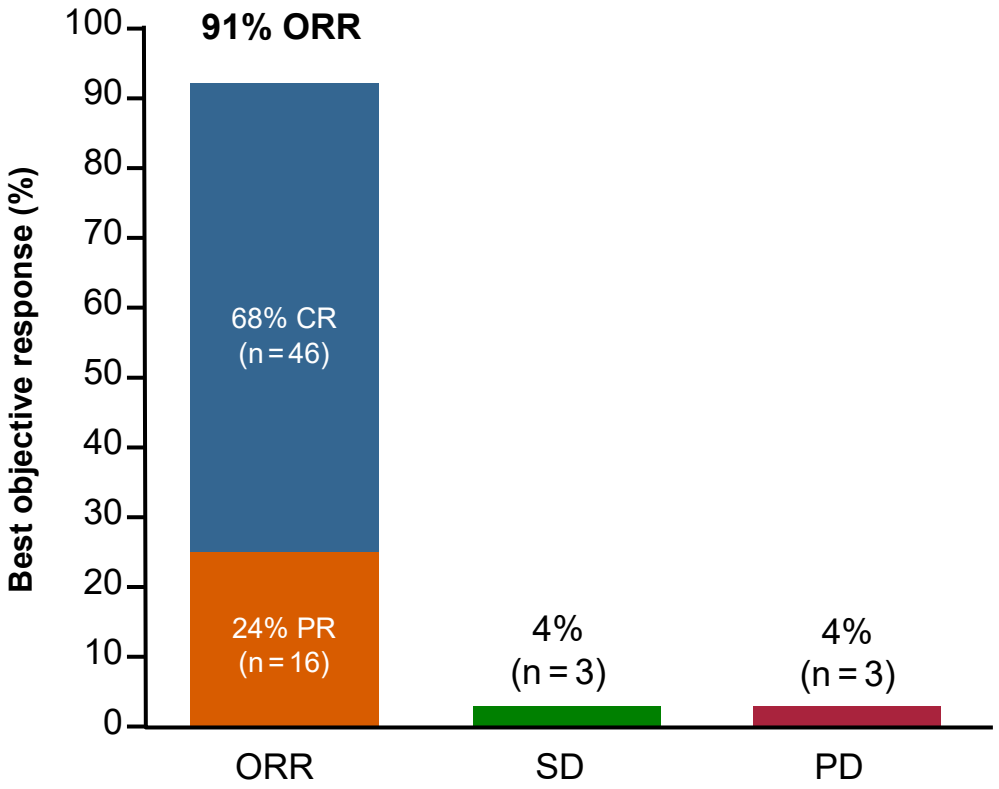
CD19 CAR T Cells for LBCL: Product Choice

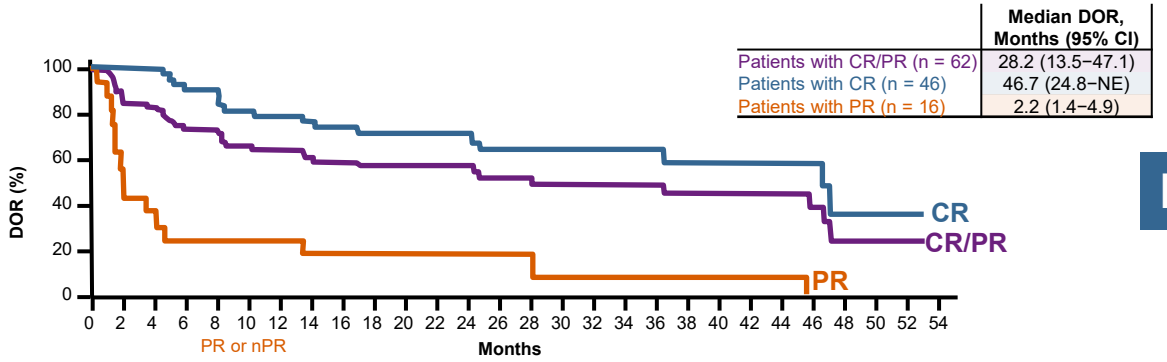
GENERAL CONSIDERATIONS[1,2]

- Comparing across trials and series is impossible and should be avoided (except for the purposes of this slide!)
- First and foremost: Balance of safety and efficacy
  - Axi-cel: Great efficacy, acceptable but greater toxicity
  - Tisa-cel: Slightly lower efficacy, better toxicity profile
  - Liso-cel: Great efficacy and better toxicity profile; reduced risk of in-patient procedures in the 30 days after infusion and critical care admission compared with axi-cel[3]
- However, balance of safety and efficacy become moot if the product comes back too late (or not at all) for the patient
  - Axi-cel: Fastest and highly reliable turnaround
  - Tisa-cel: Initial manufacturing kinks but MUCH improved now; still takes almost a week longer than axi-cel
  - Liso-cel: Has the longest estimated turnaround time
- Product choice becomes skewed for different types of patients, making cross-series comparisons even more dangerous
  - Axi-cel: Patients with the fastest growing and highest burden of disease lymphoma
  - Tisa-cel and Liso-cel: patients with “better” lymphomas but perhaps older and with comorbidities

1. Expert opinion. 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. 3. Tiwana SK. Tandem, 2024; Abstract 485.

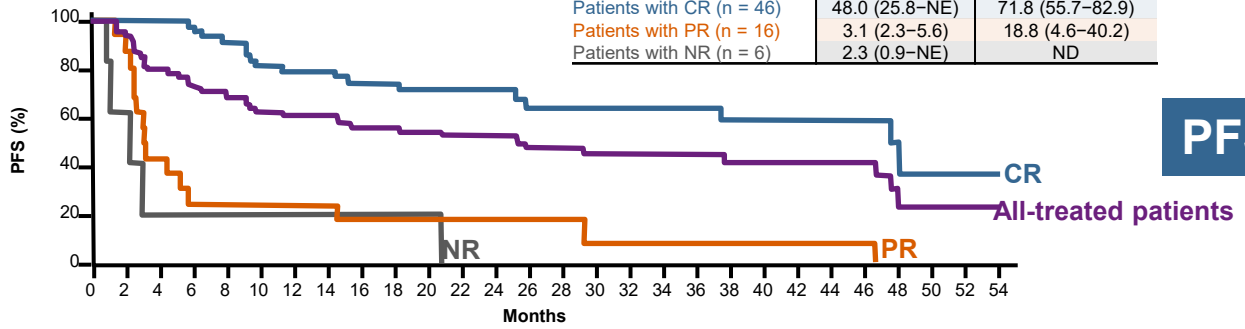
ZUMA-2: Brexucabtagene autoleucel in MCL





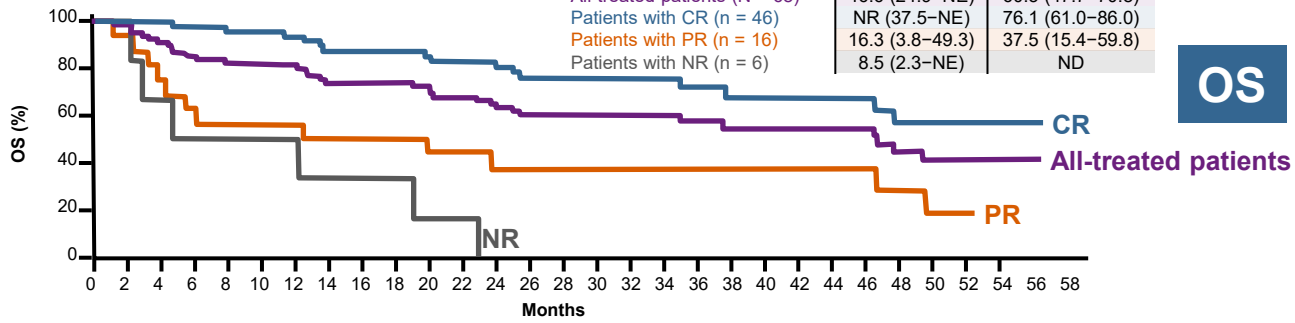
	Median DOR, Months (95% CI)
Patients with CR/PR (n = 62)	28.2 (13.5–47.1)
Patients with CR (n = 46)	46.7 (24.8–NE)
Patients with PR (n = 16)	2.2 (1.4–4.9)

DOR



	Median PFS, Months (95% CI)	24-Months PFS rate % (95% CI)
All-treated patients (N = 68)	25.8 (9.6–47.6)	52.9 (39.9–64.3)
Patients with CR (n = 46)	48.0 (25.8–NE)	71.8 (55.7–82.9)
Patients with PR (n = 16)	3.1 (2.3–5.6)	18.8 (4.6–40.2)
Patients with NR (n = 6)	2.3 (0.9–NE)	ND

PFS



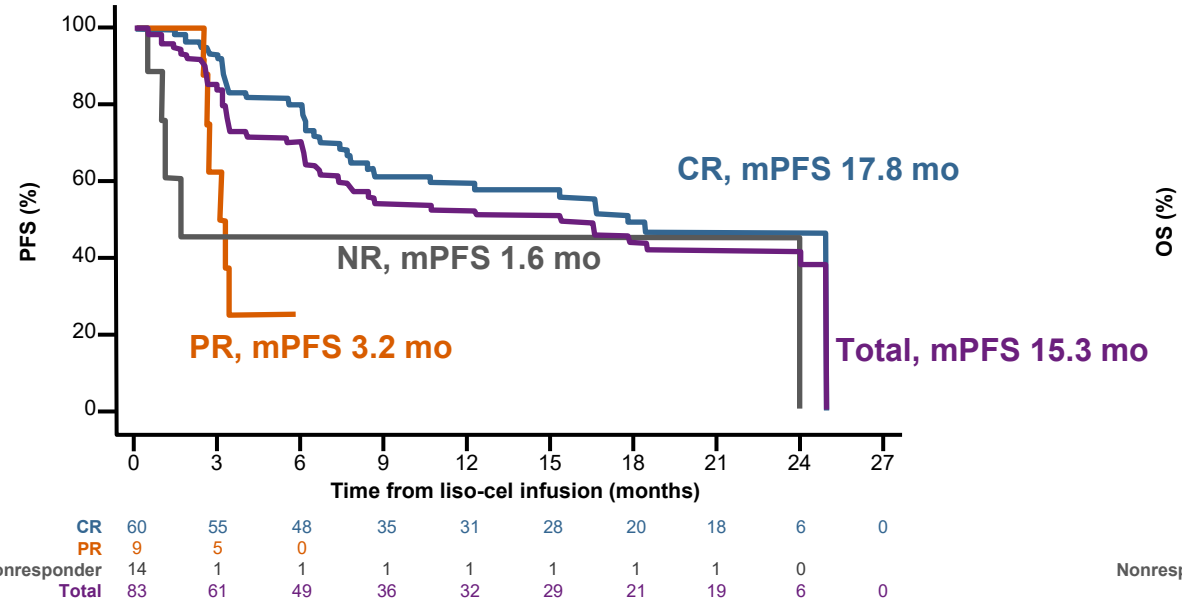
	Median OS, Months (95% CI)	30-Months OS rate % (95% CI)
All-treated patients (N = 68)	46.6 (24.9–NE)	60.3 (47.7–70.8)
Patients with CR (n = 46)	NR (37.5–NE)	76.1 (61.0–86.0)
Patients with PR (n = 16)	16.3 (3.8–49.3)	37.5 (15.4–59.8)
Patients with NR (n = 6)	8.5 (2.3–NE)	ND

OS

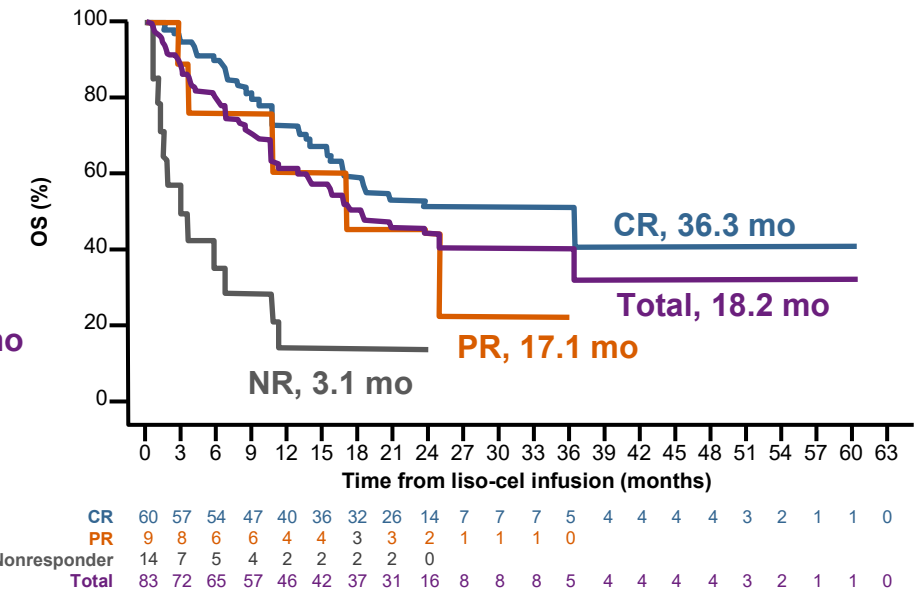
Wang M, et al. *J Clin Oncol.* 2023;41(3):555-567.

TRANSCEND NHL-001: Liso-cel in MCL

PFS per IRC (Efficacy Analysis Set, n = 83)



OS per IRC (Efficacy Analysis Set, n = 83)



CRS and NEs (Liso-cel-treated set, n = 88)		CRS	NEs
Any grade, n (%)		54 (61)	27 (31)
Grade 1/2		53 (60)	19 (22)
Grade 3		0	7 (8)
Grade 4		1 (1)	1 (1)
Grade 5		0	0
Median time to: (range), days	Onset	4.0 (1-10)	8.0 (1-25)
	Resolution	4.0 (1-14)	5.0 (1-45)

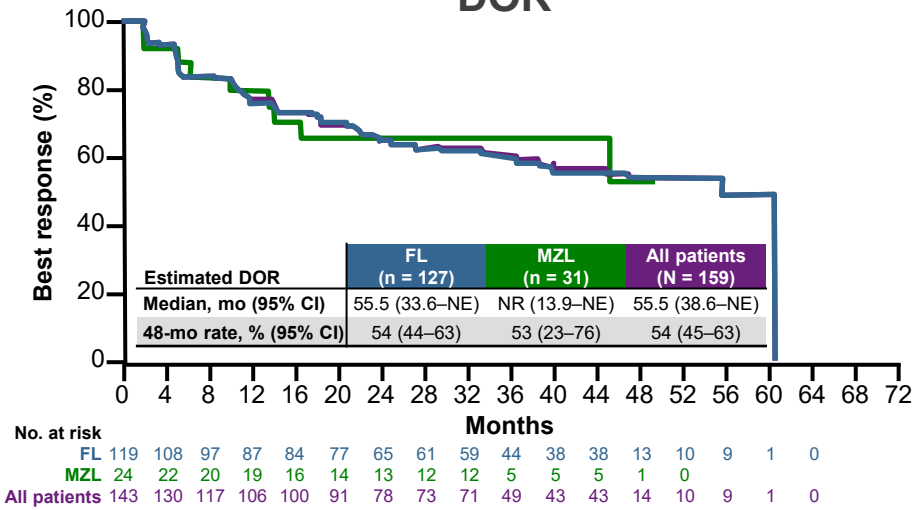
Other AEs of special interest, n (%)	Liso-cel-treated set (n = 88)
Prolonged cytopenias	35 (40)
Grade ≥ 3 infections	13 (15)
Hypogammaglobulinemia	6 (7)

Not an FDA-approved indication.

Wang M, et al. *J Clin Oncol*. 2023:JCO2302214.

ZUMA-5: Axi-Cel in iNHL

DOR

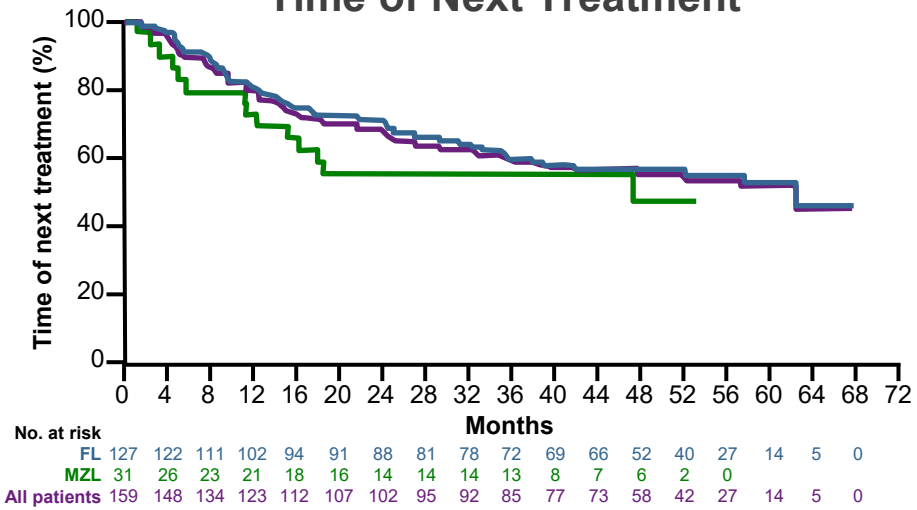


Estimated DOR	FL (n = 127)	MZL (n = 31)	All patients (N = 159)
Median, mo (95% CI)	55.5 (33.6–NE)	NR (13.9–NE)	55.5 (38.6–NE)
48-mo rate, % (95% CI)	54 (44–63)	53 (23–76)	54 (45–63)

No. at risk

FL	119	108	97	87	84	77	65	61	59	44	38	38	13	10	9	1	0
MZL	24	22	20	19	16	14	13	12	12	5	5	5	1	0			
All patients	143	130	117	106	100	91	78	73	71	49	43	43	14	10	9	1	0

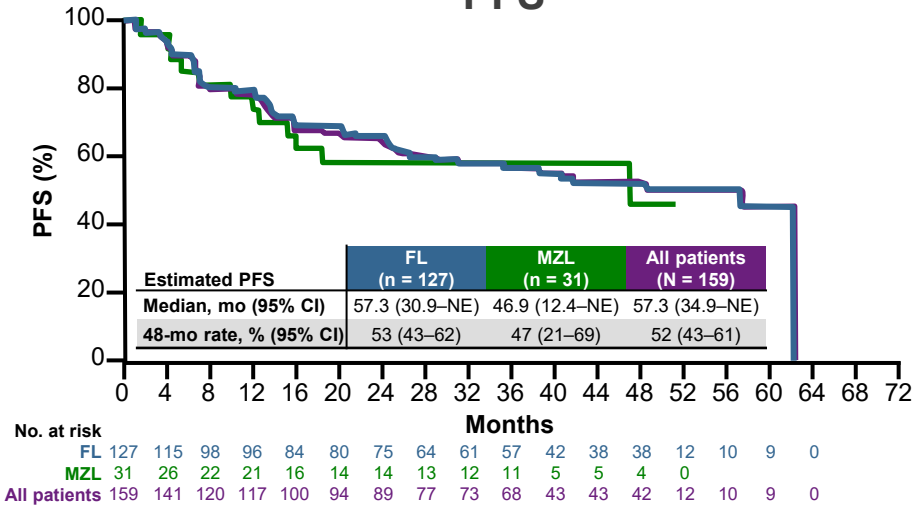
Time of Next Treatment



No. at risk

FL	127	122	111	102	94	91	88	81	78	72	69	66	52	40	27	14	5	0
MZL	31	26	23	21	18	16	14	14	14	13	8	7	6	2	0			
All patients	159	148	134	123	112	107	102	95	92	85	77	73	58	42	27	14	5	0

PFS

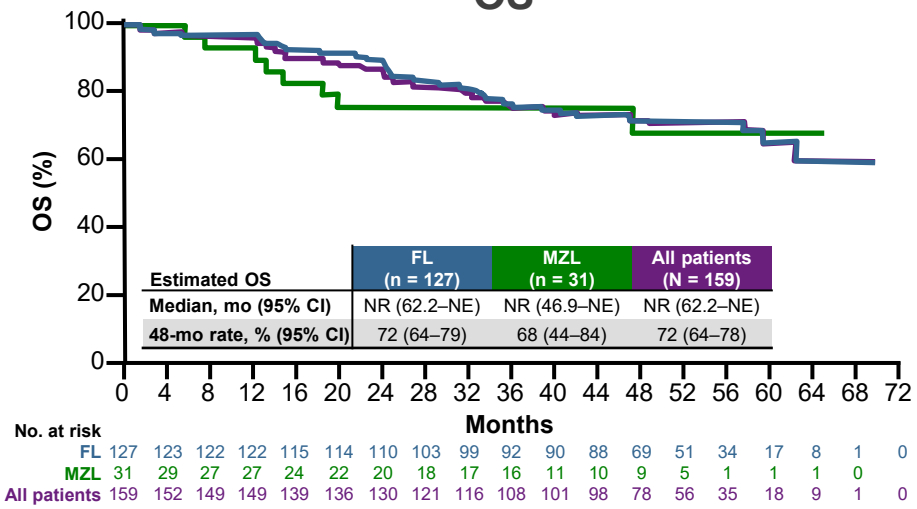


Estimated PFS	FL (n = 127)	MZL (n = 31)	All patients (N = 159)
Median, mo (95% CI)	57.3 (30.9–NE)	46.9 (12.4–NE)	57.3 (34.9–NE)
48-mo rate, % (95% CI)	53 (43–62)	47 (21–69)	52 (43–61)

No. at risk

FL	127	115	98	96	84	80	75	64	61	57	42	38	38	12	10	9	0
MZL	31	26	22	21	16	14	14	13	12	11	5	5	4	0			
All patients	159	141	120	117	100	94	89	77	73	68	43	43	42	12	10	9	0

OS



Estimated OS	FL (n = 127)	MZL (n = 31)	All patients (N = 159)
Median, mo (95% CI)	NR (62.2–NE)	NR (46.9–NE)	NR (62.2–NE)
48-mo rate, % (95% CI)	72 (64–79)	68 (44–84)	72 (64–78)

No. at risk

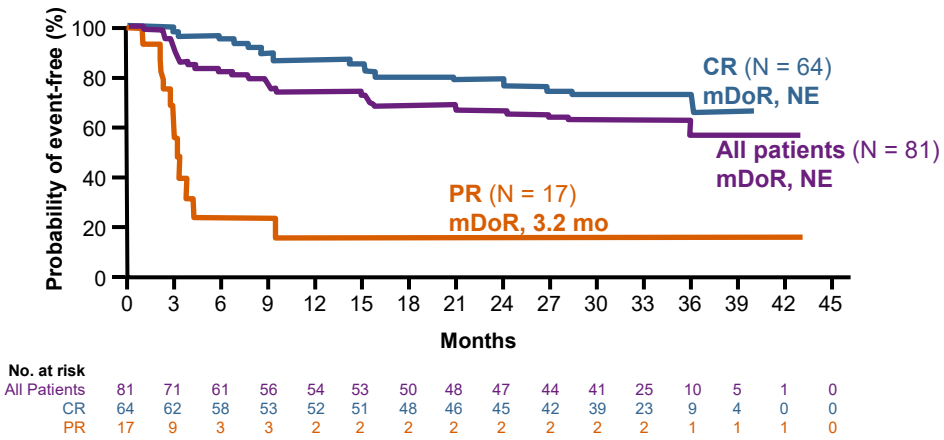
FL	127	123	122	122	115	114	110	103	99	92	90	88	69	51	34	17	8	1	0
MZL	31	29	27	27	24	22	20	18	17	16	11	10	9	5	1	1	1	0	
All patients	159	152	149	149	139	136	130	121	116	108	101	98	78	56	35	18	9	1	0

Neelapu S, et al. *Blood*. 2023;142 (suppl 1):4868

ELARA: Tisa-Cel in FL

Endpoint in efficacy analysis set (IRC assessment)	% (95 % CI) N = 94
CRR	68 (58–77)
ORR	86 (78–92)

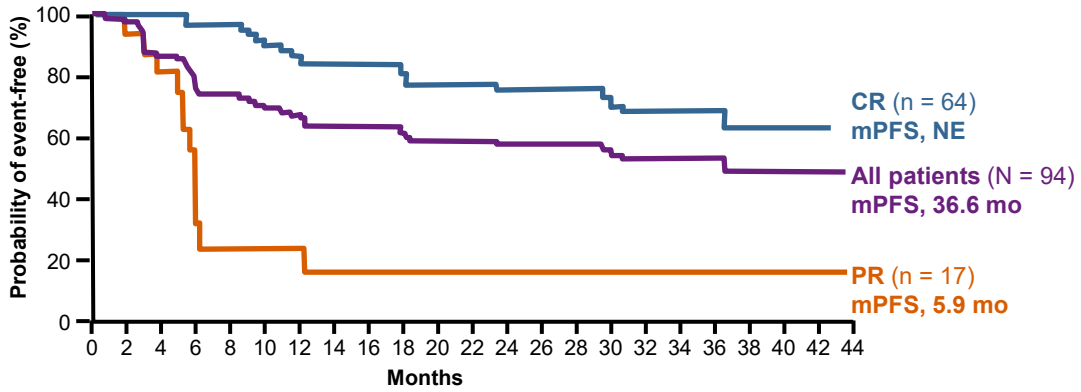
DOR



No. at risk

All Patients	81	71	61	56	54	53	50	48	47	44	41	25	10	5	1	0
CR	64	62	58	53	52	51	48	46	45	42	39	23	9	4	0	0
PR	17	9	3	3	2	2	2	2	2	2	2	2	1	1	1	0

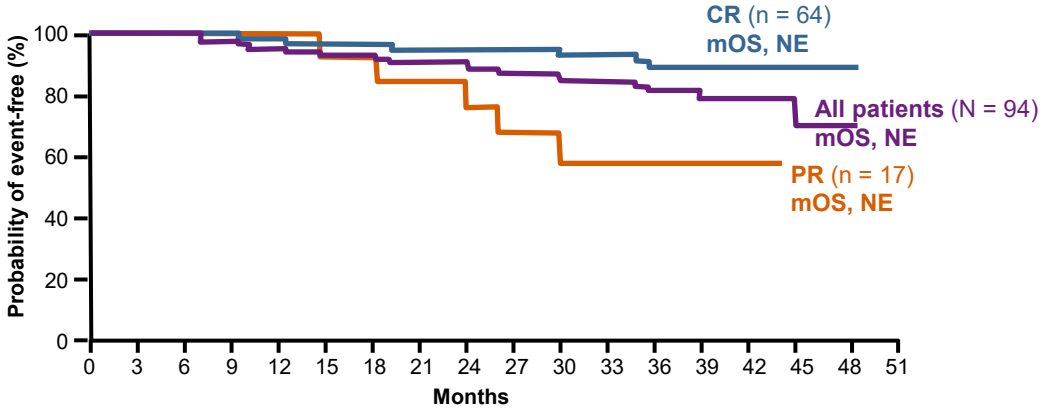
PFS



No. at risk

All Patients	94	91	78	67	63	59	57	54	54	52	50	50	48	48	48	45	42	40	22	10	9	4	0
CR	64	64	64	61	60	56	54	52	52	50	48	48	46	46	46	43	40	38	21	9	8	3	0
PR	17	16	13	5	3	3	3	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	0

OS

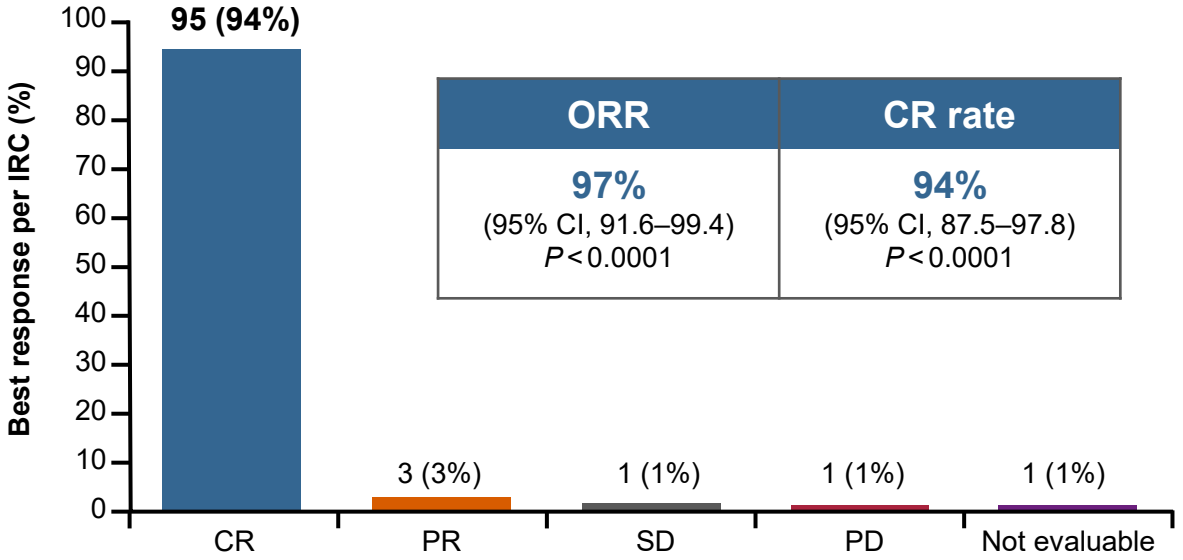


No. at risk

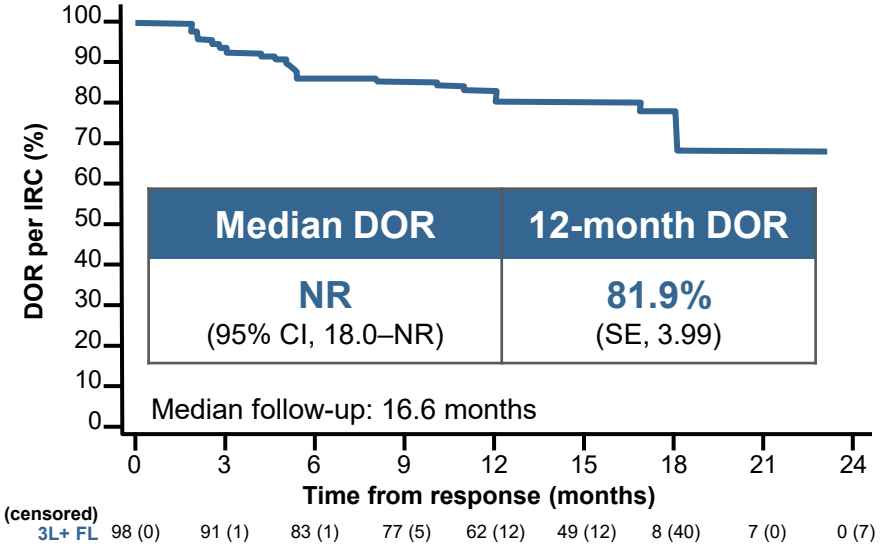
All Patients	94	92	91	84	81	78	78	74	72	71	67	66	47	28	20	5	2	0
CR	64	64	64	62	60	58	58	56	56	56	54	53	40	25	17	4	1	0
PR	17	16	16	13	13	12	12	10	9	8	6	6	3	1	1	0	0	0

Schuster S, et al. *Blood*. 2023;142 (suppl 1):601

TRANSCEND-FL: Liso-Cel Outcomes in 3L+ FL Efficacy Set (n = 101)



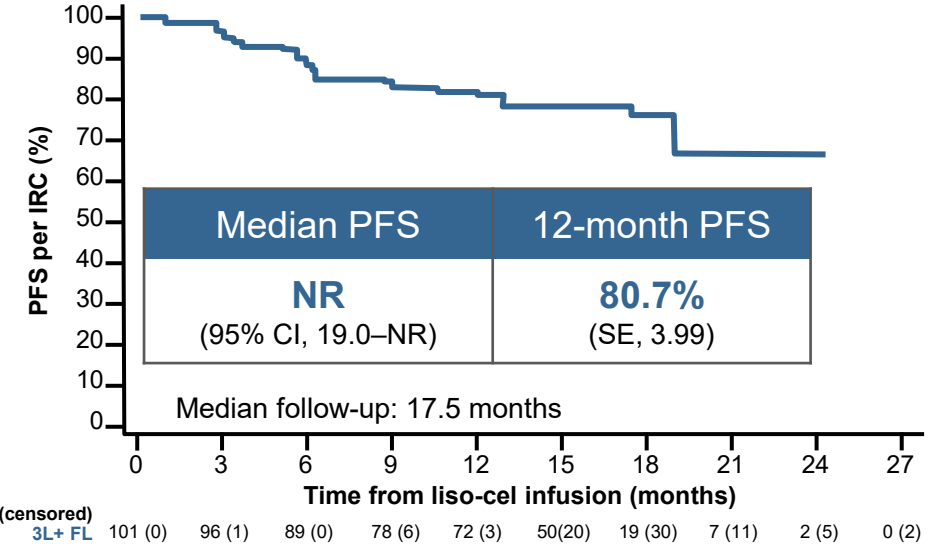
ORR	CR rate
97% (95% CI, 91.6–99.4) *P* < 0.0001	94% (95% CI, 87.5–97.8) *P* < 0.0001



Median DOR	12-month DOR
NR (95% CI, 18.0–NR)	81.9% (SE, 3.99)

No. at risk (censored)

3L+ FL	98 (0)	91 (1)	83 (1)	77 (5)	62 (12)	49 (12)	8 (40)	7 (0)	0 (7)



Median PFS	12-month PFS
NR (95% CI, 19.0–NR)	80.7% (SE, 3.99)

No. at risk (censored)

3L+ FL	101 (0)	96 (1)	89 (0)	78 (6)	72 (3)	50(20)	19 (30)	7 (11)	2 (5)	0 (2)

Morschhauser F, et al. *Hematol Oncol.* 2023;41(Suppl 2):877-880.

TRANSCEND CLL-004: Liso-cel Outcomes and New Approval in CLL

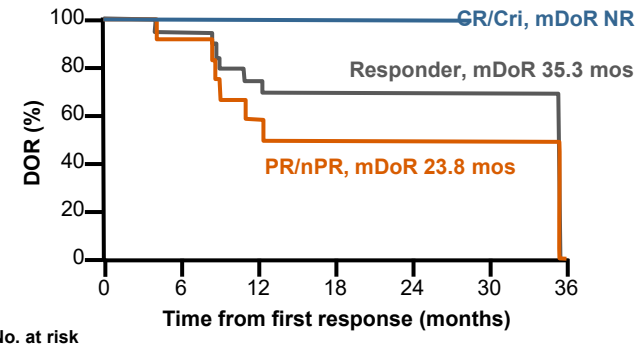
	Full population (N = 96)	BTKi/ venetoclax failure (n = 53)
ORR	48%	43%
CR/CRi	18%	19%
mDOR	35.25 m	35.25 m
mPFS	17.87 m	11.93 m
mOS	43.17 m	30.26 m
uMRD, blood	62%	33%
uMRD, marrow	57%	31%

Liso-cel is now **FDA approved** for treatment of adult patients with CLL/SLL after at least 2 prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor

Liso-cel is the first CAR T-cell therapy approved for CLL/SLL

DoR

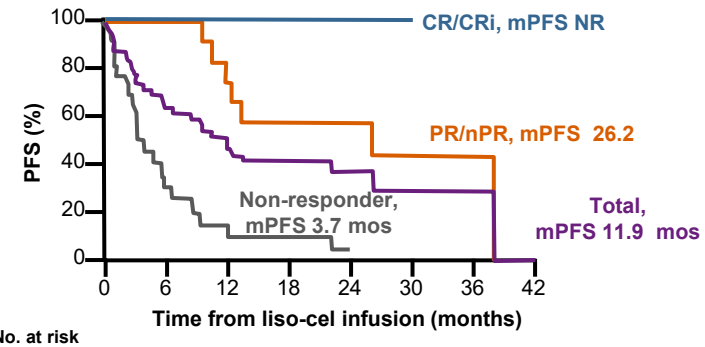
Median follow-up 19.7 months (95% CI 16.5–27.2)



No. at risk							
CR or CRi	9	8	7	3	1	0	0
PR or nPR	12	11	7	5	3	1	0
Responder	21	19	14	8	4	1	0

PFS by Response

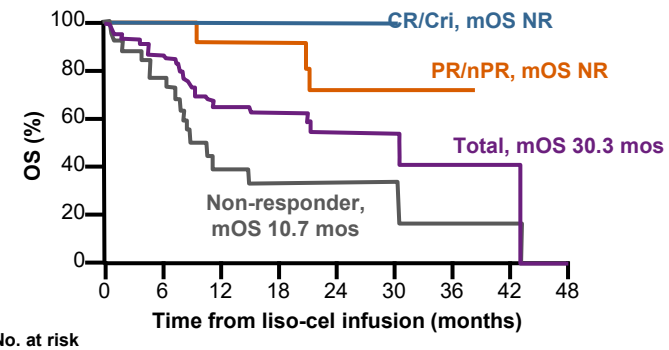
Median follow-up 20.8 months (95% CI 17.6–25.2)



No. at risk								
CR or CRi	9	8	8	5	2	1	0	0
PR or nPR	12	12	9	6	5	1	1	0
Non-responder	28	6	2	2	0	0	0	0
Total	49	26	19	13	7	2	1	0

OS by Response

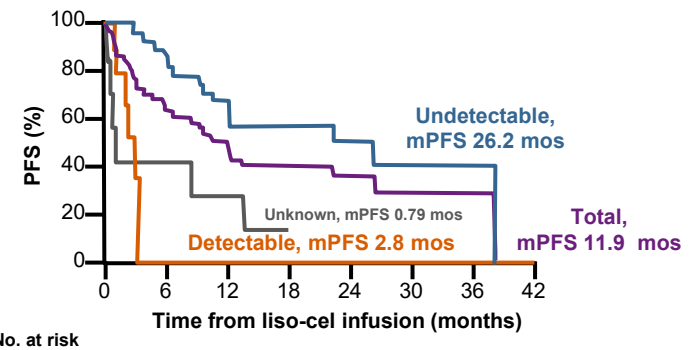
Median follow-up 20.8 months (95% CI 17.8–25.2)



No. at risk									
CR or CRi	9	8	8	6	2	1	0	0	0
PR or nPR	12	12	11	9	7	2	1	0	0
Non-responder	28	18	7	4	4	2	1	1	0
Total	49	38	26	19	13	5	2	1	0

PFS by MRD Status

Median follow-up 20.8 months (95% CI 17.6–25.2)



No. at risk								
Undetectable MRD	31	23	17	13	7	2	1	0
Detectable MRD	10	0	0	0	0	0	0	0
Unknown MRD status	8	3	2	0	0	0	0	0
Total	49	26	19	13	7	2	1	0

Siddiqi T, et al. *Lancet*. 2023;402:641-654.

Cytokine Release Syndrome (CRS)

Fever ≥38.5˚ C	Supportive Care Consider tocilizumab if >72h
Fever ≥38.5˚ C ***AND*** **Hypotension not requiring vasopressors** ***AND/OR*** **Hypoxia requiring low-flow O_2**	Tocilizumab Consider dexamethasone x1
Fever ≥38.5˚ C ***AND*** **Hypotension requiring a vasopressor** ***AND/OR*** **Hypoxia requiring high-flow NC, facemask, NRB**	Tocilizumab Dex 10mg q6h until ≤Gr2
Fever ≥38.5˚ C ***AND*** **Hypotension requiring multiple vasopressors** ***AND/OR*** **Hypoxia requiring positive pressure**	Tocilizumab Solumedrol 1g qd x3d, then taper

NC, nasal cannula; NRB, nonrebreather

Santomasso B, et al. *J Clin Oncol*. 2021;39(35):3978-3992. Neelapu et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62. Lee et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

CN VI, sixth cranial nerve

Santomasso B, et al. *J Clin Oncol*. 2021;39(35):3978-3992; Neelapu et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62; Lee et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Predictors of High-Grade CRS and ICANS

PRETREATMENT

- High tumor burden
- High pretreatment LDH
- High pretreatment inflammatory markers
- ? High pretreatment monocyte count

POSTTREATMENT

- High peak CAR T-Cell levels
- High peak cytokine levels
- Markers of DIC (including fibrinogen levels dropping)
- Early CRS

Rubin D, et al. *JAMA Neurol*. 2020;77(12):1536-1542.

Short-Term Monitoring: Days to Weeks From Infusion

OUTPATIENT

- Patient housed near treating center for **4 weeks**
  - **Abstain from driving for up to 8 weeks** following CAR T-cell infusion due to a low risk of recurrent CRS and/or NT
- Patient and caregiver instructed on how to take vital signs and monitor for neurologic toxicity and given tools (eg, thermometers) for assessing and recording these data
- Patient scheduled to return to the treating center daily for at least **7 days** for labs and review of vital signs/labs
- Patient admitted at the onset of fever and/or confusion until resolution of CRS and/or NT

INPATIENT

- Patient is admitted for up to **7 days** or until the resolution of CRS and/or NT
- After discharge, patients remain within 2 hours of the treating center for up to **4 weeks**
- **Abstain from driving for up to 8 weeks** 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 weeks**

Caregiver present 24h a day for whatever portion of the 4 weeks post-CAR-T is spent out of the hospital

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Management of Immunotherapy-Related Toxicities v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

CAR T-Cell Therapy and Long-Term Toxicities

B-CELL APLASIA/ HYPOGAMMAGLOBULINEMIA

- ~40-50% B-NHL pts s/p CD19 CARs will NOT have IgG recovery by 24 months
- Immunoglobulin levels should be monitored following therapy

CYTOPENIAS

- Grade ≥3 cytopenias unresolved by Day 30 posttreatment occur in 25-30% of patients
- Median time to recovery 6 m
- Blood counts should be monitored

INFECTIONS

- Occurred in 35-50% of patients treated with approved agents in pivotal trials
- Median time to infection is 1 m for bacterial infections, and 2-3 m for viral and fungal infections

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prevention and Treatment of Cancer-Related Infections v2.2023. https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf;
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Management of Immunotherapy-Related Toxicities v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Long-Term Monitoring: Weeks to Months From Infusion

ONGOING MONITORING

- Prolonged cytopenias – transfusions as indicated; G-CSF and TPO-mimetics as needed
- B-cell aplasia (IgG levels) – replete with IVIG for levels < 400
- Infection
- Relapse
- Secondary malignancies

PROPHYLAXIS

- Antibiotic (herpes and PJP) prophylaxis
  - Variable practices – we continue for at least 6 months at which time we measure the CD4 count and only discontinue when >200

VACCINATION

- Influenza – yearly
- Post-transplant vaccines – resume 12 months after CAR T-cell therapy?
- COVID vaccination – 3 months from CAR T-cell therapy (unknown)

Upon relapse patients should be biopsied whenever possible to help determine next treatment

G-CSF, granulocyte-colony stimulating factor; IVIG, intravenous immunoglobulin; PJP, *Pneumocystis jirovecii* pneumonia

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prevention and Treatment of Cancer-Related Infections v2.2023. https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf;
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Management of Immunotherapy-Related Toxicities v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Considerations for Community Oncologist: When to Ask for Help?

Cytopenias

- Neutropenia with ANC < 500: give G-CSF, consider IVIG
- Persistent, transfusion dependent thrombocytopenia: try TPO-mimetics
- Any cytopenias lasting more than 6 months: obtain bone marrow biopsy

Frequent or obscure infection

- Consider opportunistic infections like PJP, CMV, HHV6, and fungal infections
- Check IgG and replace if < 400 (q1-3 months)
- Continue trimethoprim / sulfamethoxazole and acyclovir through month 6 and only stop when CD4 count is > 200

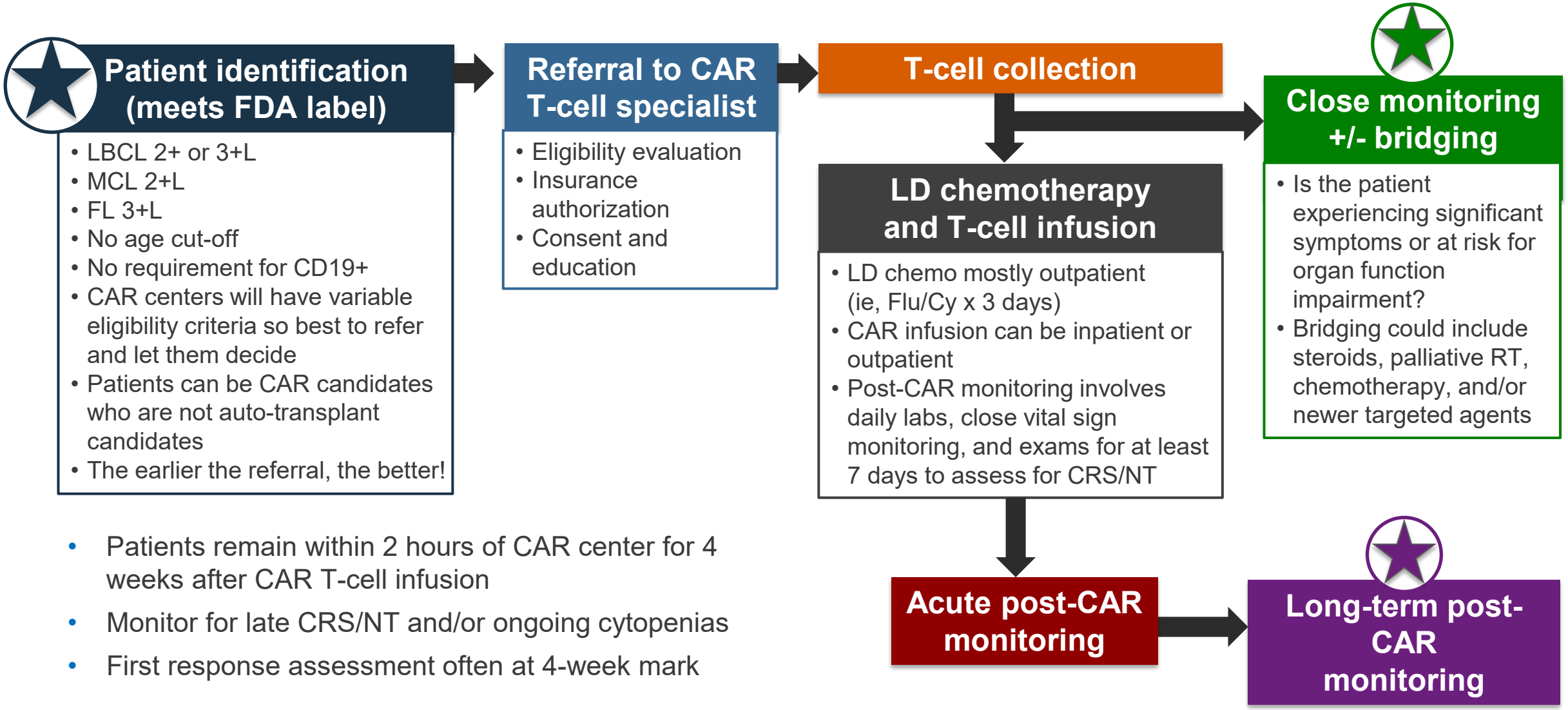
New neurologic signs or symptoms or syndromes

Relapsed disease

- Biopsy whenever possible to prove lymphoma and to understand available targets

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Management of Immunotherapy-Related Toxicities v1.2024 https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

A Patient's Journey With CAR T-Cell Therapy



- Patients remain within 2 hours of CAR center for 4 weeks after CAR T-cell infusion
- Monitor for late CRS/NT and/or ongoing cytopenias
- First response assessment often at 4-week mark

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

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

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

- Can the patient tolerate leukapheresis (without immediate use of steroids/chemotherapy) and remain stable until the T-cell infusion (3-4 weeks)?
- 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

Non–disease-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

Hayden P, et al. *Ann Oncol*. 2022;33(3):259-275. Amini L, et al. *Nat Rev Clin Oncol*. 2022;19(5):342-355.

CAR T-Cell Referral to and From the Community: Lessons Learned

REFERRALS

- Refer all eligible patients as early as possible – ideally 1 line of therapy BEFORE it is indicated
  - Regardless of age or comorbidities: let the treating center decide
  - Know your CAR T-cell MDs for easier and direct referral
  - Education, screening, and insurance authorization are all managed by the CAR T-cell treatment center

BRIDGING THERAPY

- Patient may require bridging and often prefer this to be done locally
  - Vital that the CAR T-cell center be forthcoming and specific with dates of collection and treatment for timing of bridging, recommendations for bridging, and monitoring for response and progression
  - Vital that the referring center communicate any new status changes with the patient with the CAR T-cell center in real-time

TIMING

- Patient will remain at CAR T-cell center for 4-5 wks from LD chemotherapy through 1 m following CAR T-cell infusion
  - This is when CRS and ICANS happen and are monitored and managed

ONGOING MANAGEMENT

- Upon referral back to community:
  - CAR T-cell center MUST update local practice about
    - CAR T-cell course and disease response assessment
    - Ongoing toxicities and how to monitor and manage them
    - Recommendations for long-term screening and surveillance
  - Community practices should update CAR T-cell center on persistence/resolution of ongoing toxicities, new toxicities, results of disease response surveillance assessments

Expert opinion; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

CAR T-Cell Updates in LBCL, MCL, and iNHL

CONCLUSIONS

- **Axi-cel, liso-cel, and tisa-cel** all induce durable responses in heavily pretreated **LBCLs** after **≥ 2 prior lines of therapy**. Axi-cel and Liso-cel may offer superior efficacy to tisa-cel.
- **Axi-cel and liso-cel** are superior to 2nd -line chemotherapy +/- ASCT in patients with **primary refractory or relapsed LBCL within 12 months of frontline therapy**. Liso-cel is also approved as 2nd-line therapy in transplant-ineligible patients regardless of initial remission duration.
- **Axi-cel** and **tisa-cel** are highly effective in **3rd-line or later follicular lymphoma**, for which they are FDA approved. **Liso-cel** is also highly effective and this data is being reviewed by the FDA.
- **Brexu-cel** is now a preferred treatment for **MCL** that is relapsed/refractory after chemoimmunotherapy and BTK inhibition. **Liso-cel** is also highly effective and this data is being reviewed by the FDA.
- **Liso-cel** demonstrates activity in BTK- and venetoclax-refractory CLL and is now approved for **SLL/CLL** after at least 2 prior lines of therapy, including a BTKi and a BCL-2i
- Toxicities are typically manageable and reversible but require trained centers
- Multiple strategies under investigation to enhance efficacy and reduce toxicity