# New horizons in R/R follicular lymphoma: Focus on risk stratification and managing the practicalities of CAR T-cell therapy

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# Utilizing prognostic factors in FL to identify high-risk patients and guide treatment decisions

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# Challenges for clinical decision making in FL

## Key clinical considerations for patients with FL

- Timing of treatment initiation
- Optimal treatment choice: first/later lines

- Potential for histological transformation
- Presence of POD24

- Meaningful remission
- Palliation of symptoms
- Prolongation of life

- Cumulative toxicities and impact on patient mortality/morbidity

Given the variable clinical behaviour of FL, the decision of **when** to treat is as important as **how** to treat. There are several prognostic indices, but none dictate the timing or type of treatment at the level of an individual patient

FL, follicular lymphoma; POD24, progression of disease within 24 months.

Cahill KE, Smith SM. *Oncology (Williston Park)*. 2022;36:97–106.

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# Models used to predict survival in patients with FL[1]

## Risk factors

**Pre-treatment**

1. >60 years
2. Ann Arbor stage: III–IV
3. Affected nodal regions: >4
4. Hb: <12 g/dL
5. Serum LDH: >ULN
6. Largest node: >6 cm
7. Bone marrow involvement
8. β2-microglobulin levels*
9. Mutational profile†
10. ECOG PS >1

**Post-treatment**

POD24

PET scan (positive)‡

## Pre-treatment prognostic models

| Model | Risk factors | Risk stratification | Prognosis |
|---|---|---|---|
| **FLIPI-1** | 1–5 | Low vs int vs high | **5-yr OS:** 91 vs 78 vs 53%[2] |
| **FLIPI-2** | 1, 4, 6–8 | Low vs int vs high | **3-yr OS:** 99 vs 96 vs 84% |
| **PRIMA-PI** | 7, 8 | Low vs int vs high | **5-yr PFS:** 69 vs 55 vs 37% |
| **m7-FLIPI** | FLIPI-H, 9, 10 | Low vs high | **5-yr FFS:** 77 vs 38% |

## Post-treatment prognostic model

| | | |
|---|---|---|
| **POD24** | <24 vs >24 months | **5-yr OS:** 50 vs 90% |

*FLIPI-2, >ULN; PRIMA-PI, >3 g/L. †Mutations in *EP300*, *CREBBP*, *CARD11*, *MEF2B*, *EZH2*, *ARID1A* and *FOX01*.
‡A positive PET scan at the end of treatment is indicative of a poor prognosis.
ECOG PS, Eastern Cooperative Oncology Group performance status; FFS, failure-free survival; FL, follicular lymphoma;
FLIPI, Follicular Lymphoma International Prognostic Index; H, high risk; Hb, haemoglobin; int, intermediate; LDH, lactate dehydrogenase;
m7, including the mutation status of seven genes; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival;
POD24, progression of disease within 24 months; PRIMA-PI, Primary Rituximab and Maintenance Study Prognostic Index; ULN, upper limit of normal; yr, year.

1. Gupta G, et al. *Am J Blood Res*. 2022;12:105–24; 2. Solal-Celigny P, et al. *Blood*. 2004;104:1258–65.

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# Latest evidence for CAR T-cell therapies in R/R FL, their place in the treatment sequence and considerations for patient selection

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# NCCN 2023 guidelines for treating R/R FL

## Preferred regimens for sufficiently fit patients

**2L***

- Bendamustine + obinutuzumab or rituximab†
- CHOP + obinutuzumab or rituximab
- CVP + obinutuzumab or rituximab
- Lenalidomide + rituximab

**3L‡**

### Small molecule inhibitors

**PI3K inhibitor**

- Copanlisib

***EZH2* inhibitor**

- Tazemetostat *(irrespective of EZH2 mutation status)*

### T-cell–mediated therapy

**Anti-CD19 CAR T-cell therapy§**

- Axicabtagene ciloleucel
- Tisagenlecleucel

**Bispecific antibody therapy**

- Mosunetuzumab

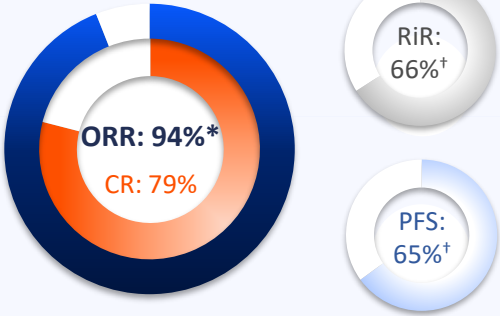
*The same regimens are used in the first line; generally, a first-line therapy is not repeated. †Not recommended if treated with prior bendamustine.
‡Third-line and subsequent systemic therapy includes second-line therapies that have not been used previously. §In alphabetical order.
CAR, chimeric antigen receptor; CD, cluster of differentiation; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; CVP, cyclophosphamide + vincristine + prednisone; EZH2, enhancer of zeste homolog 2; L, line; NCCN, National Comprehensive Cancer Network; PI3K, phosphoinositide 3 kinase; R/R FL, relapsed or refractory follicular lymphoma.

NCCN. B-cell lymphomas. V6.2023. Available at: www.nccn.org (accessed 8 November 2023).

# CAR T-cell therapy to treat R/R FL: Efficacy

## Axi-cel
**Approved 2021; ≥3L**

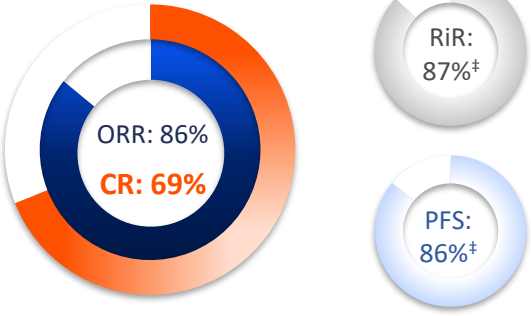
**ZUMA-5**[1] (n=124; mFU: 17.5 mo)
**FLIPI-H:** 44%; **POD24:** 55%;
**high tumour bulk (GELF):** 52%




**3-year follow-up**[2] (mFU: 41.7 mo)
mDoR: 38.6 mo; OS: 75%

## Tisa-cel
**Approved 2022; ≥3L**

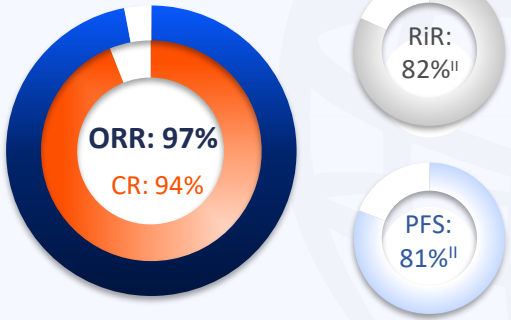
**ELARA**[3] (N=97; mFU: 16.6 mo)
**FLIPI-H:** 60%; **POD24:** 63%;
**high tumour bulk (GELF):** N/R




**2-year follow-up**[4] (mFU: 28.9 mo)
RiR: 65%; PFS: 57%; OS: 88%

## Liso-cel
**Investigational**

**TRANSCEND FL**[5] (n=101;§ mFU: 18.9 mo)
**FLIPI-H:** 57%; **POD24:** 43%;
**high tumour bulk (GELF):** 53%




**Direct comparisons between trials should not be made due to differences in trial design.**
*Eligible for activity analysis, n=86. †At 18 months. ‡RiR: at 9 months; PFS: at 12 months. §≥3 prior lines of treatment. ‖Median not reached; mFU (RiR): 16.6 months; mFU (PFS): 17.5 months. Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DoR, duration of response; FLIPI-H, Follicular Lymphoma International Prognostic Index – high risk; FU, follow-up; GELF, Groupe d'Étude des Lymphomes Folliculaires; L, lines of prior therapy; Liso-cel, lisocabtagene maraleucel; m, median; mo, months; N/R, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 24 months; RiR, remaining in response; R/R FL, relapsed or refractory follicular lymphoma; Tisa-cel, tisagenlecleucel.

1. Jacobson CA, et al. *Lancet Oncol*. 2022;23:91–103; 2. Neelapu SS. et al. *Blood.* 2022;140(Suppl. 1):10380–3; 3. Fowler NH, et al. *Nat Med.* 2022;28:325–32; 4. Dreyling M, et al. *Blood*. 2022;140(Suppl. 1):1459–63; 5. Morschhauser F, et al. *Hematol Oncol.* 2023;41(Suppl. 2):877–80.

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# Managing the practicalities of CAR T-cell therapies in the clinic: Focus on safety and the multidisciplinary team approach

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# CAR T-cell therapy to treat R/R FL: Safety

## Axi-cel

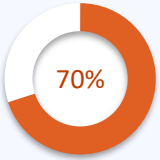
**ZUMA-5** (n=124)[1]

**Immunologic**

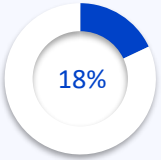

gr <3
gr ≥3

**Neurologic**


**Haematologic (gr ≥3)***




**Infections (gr ≥3)***




- One TEAE death*,†

## Tisa-cel

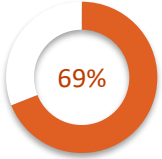
**ELARA** (N=97)[2]

**Immunologic**

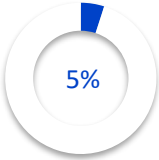

gr <3
gr ≥3

**Neurologic**


**Haematologic (gr ≥3)**




**Infections (gr ≥3)**




- No TEAE deaths

## Liso-cel

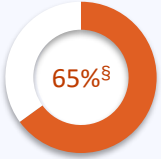
**TRANSCEND FL** (N=130‡)[3]

**Immunologic**

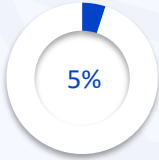

gr <3
gr ≥3

**Neurologic**


**Haematologic (gr ≥3)**




**Infections (gr ≥3)**




- One TEAE death‖

**Direct comparisons between trials should not be made due to differences in trial design.**

*Safety set, N=148. †Multisystem organ failure. ‡Safety set ≥2 prior lines of treatment. §Neutropenia, most common haematologic adverse event.
‖Grade 5 macrophage activation syndrome.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; gr, grade; Liso-cel, lisocabtagene maraleucel; NE, neurological events; R/R FL, relapsed or refractory follicular lymphoma; TEAE, treatment-emergent adverse event; Tisa-cel, tisagenlecleucel.

1. Jacobson CA, et al. *Lancet Oncol*. 2022;23:91–103; 2. Fowler NH, et al. *Nat Med*. 2022;28:325–32; 3. Morschhauser F, et al. *Hematol Oncol*. 2023;41(Suppl. 2):877–80.

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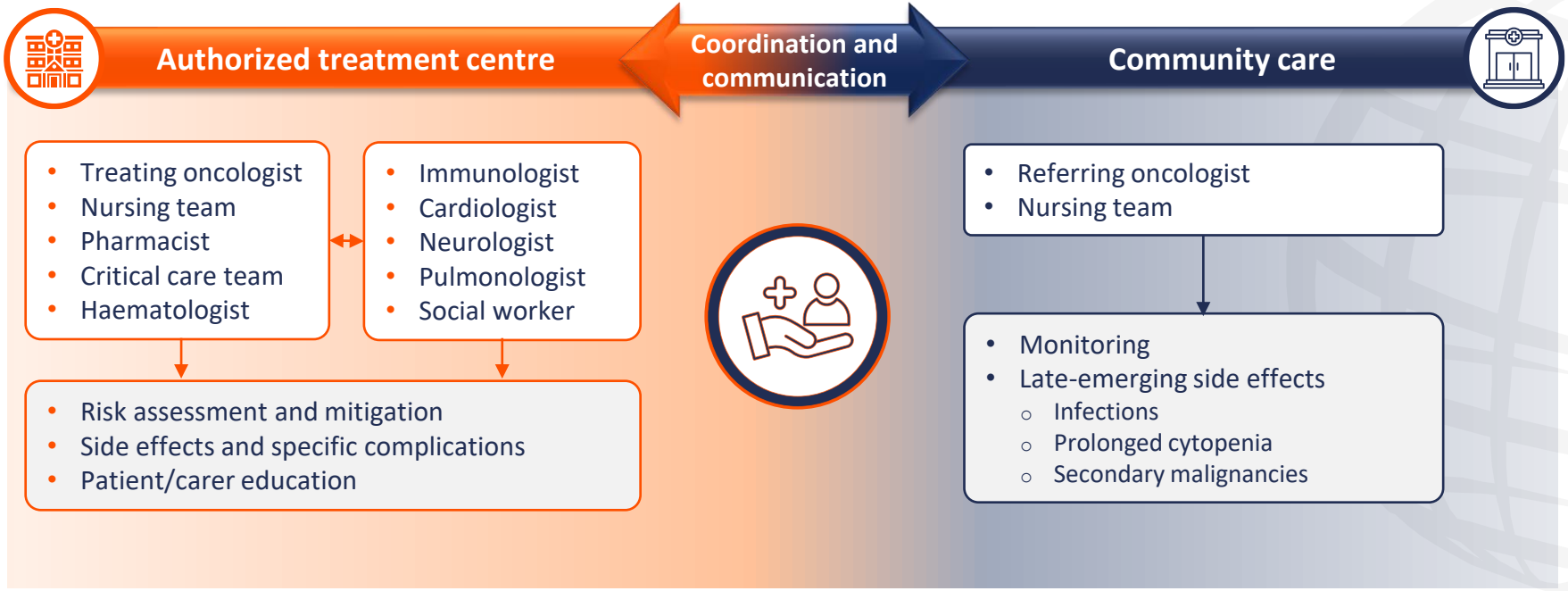
# Multidisciplinary management of side effects associated with CAR T-cell therapies[1–5]




CAR, chimeric antigen receptor.

1. Thompson JA, et al. *J Natl Compr Canc Netw*. 2022;20:387–405; 2. Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(Suppl. 3):29–40;
3. Gutierrez C, et al. *Blood*. 2023;141:2452–9; 4. Jain T, et al. *Biol Blood Marrow Transplant*. 2019;25:2305–21; 5. Marzal-Alfaro MB, et al. *Front Oncol*. 2021;11:636068.

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