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

touch
HAEMATOLOGY

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*

- *The presenting faculty have been advised by USF Health and touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*

- *No endorsement by USF Health and touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in USF Health and touchIME activities*

- *USF Health and touchIME accept no responsibility for errors or omissions*

touch
HAEMATOLOGY

A conversation between:

Dr Peter Riedell
UChicago Medicine
Chicago, IL, USA

Dr Nilanjan Ghosh
Atrium Health Levine Cancer Institute
Charlotte, NC, USA

touch
HAEMATOLOGY

Agenda

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

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

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

CAR, chimeric antigen receptor; FL, follicular lymphoma; R/R, relapsed or refractory.

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

touch
HAEMATOLOGY

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.

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

Small molecule inhibitors

T-cell–mediated therapy

3L[‡]

PI3K inhibitor
- Copanlisib

***EZH2* inhibitor**
- Tazemetostat
(irrespective of EZH2 mutation status)

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;
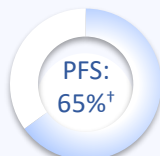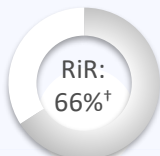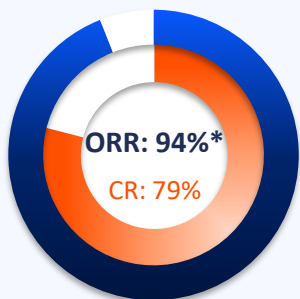R/R FL, relapsed or refractory follicular lymphoma.
NCCN. B-cell lymphomas. V6.2023. Available at: www.nccn.org (accessed 8 November 2023).

touch HAEMATOLOGY

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%

ORR: 94%*
CR: 79%

RiR: 66%[†]

PFS: 65%[†]

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

ORR: 86%
CR: 69%

RiR: 87%[‡]

PFS: 86%[‡]
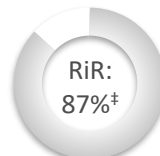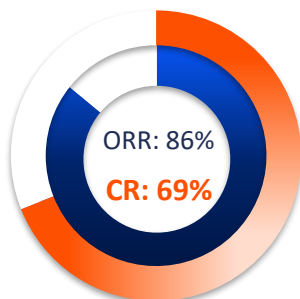
2-year follow-up[4] (mFU: 28.9 mo)
RiR: 65%; PFS: 57%; OS: 88%

Liso-cel
Investigational

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

ORR: 97%
CR: 94%

RiR: 82%[∥]

PFS: 81%[∥]
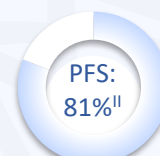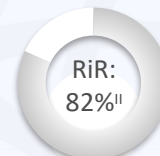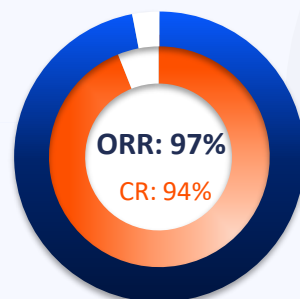
Direct comparisons between trials should not be made due to differences in trial design.
*Eligible for activity analysis, n=86. [†]At 18 months. [‡]RiR: at 9 months; PFS: at 12 months. [§]≥3 prior lines of treatment. [∥]Median not reached; mFU (RiR): 16.6 months; mFU (PFS): 17.5 months. Axi-cel, axicabtagene 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.
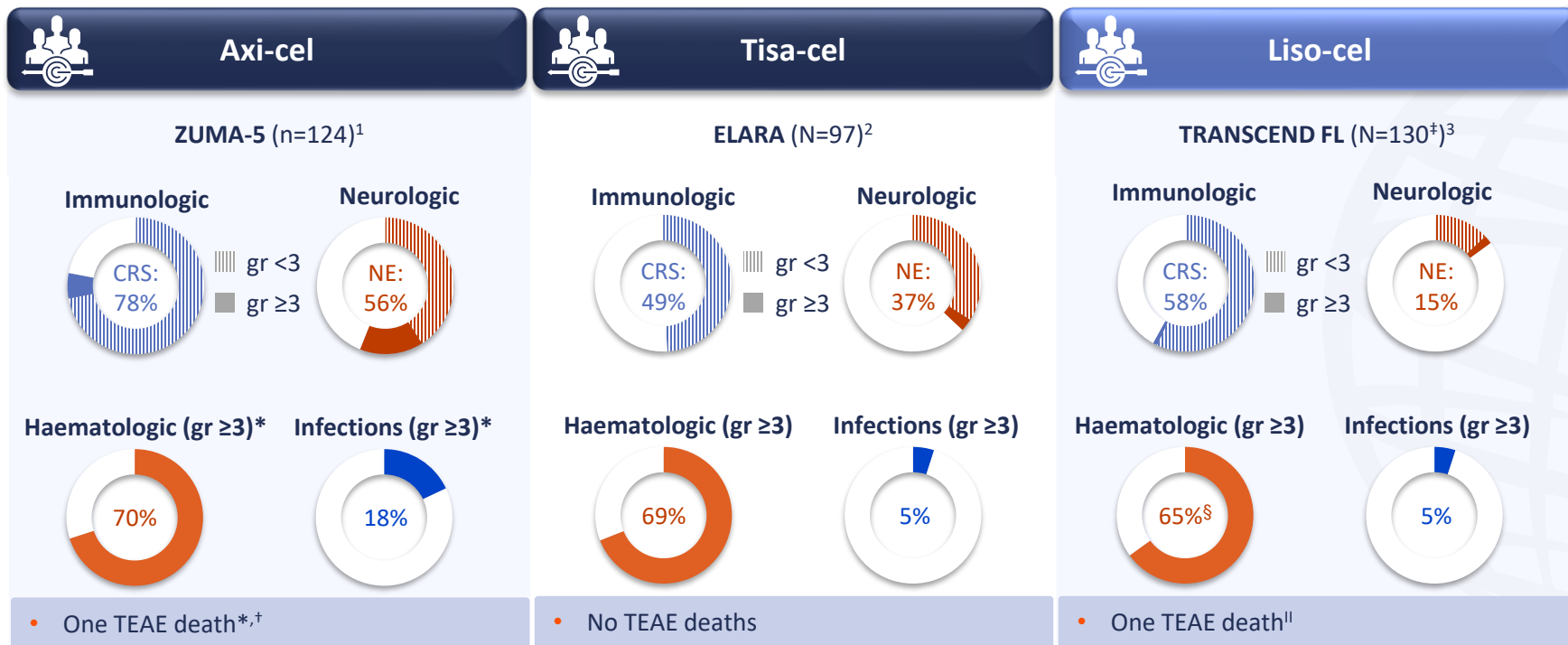
CAR T-cell therapy to treat R/R FL: Safety

Axi-cel	Tisa-cel	Liso-cel

Axi-cel

ZUMA-5 (n=124)[1]

Immunologic

CRS: 78%

gr <3
gr ≥3

Neurologic

NE: 56%

Haematologic (gr ≥3)*

70%

Infections (gr ≥3)*

18%

- One TEAE death*,†

Tisa-cel

ELARA (N=97)[2]

Immunologic

CRS: 49%

gr <3
gr ≥3

Neurologic

NE: 37%

Haematologic (gr ≥3)

69%

Infections (gr ≥3)

5%

- No TEAE deaths

Liso-cel

TRANSCEND FL (N=130‡)[3]

Immunologic

CRS: 58%

gr <3
gr ≥3

Neurologic

NE: 15%

Haematologic (gr ≥3)

65%§

Infections (gr ≥3)

5%

- 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.
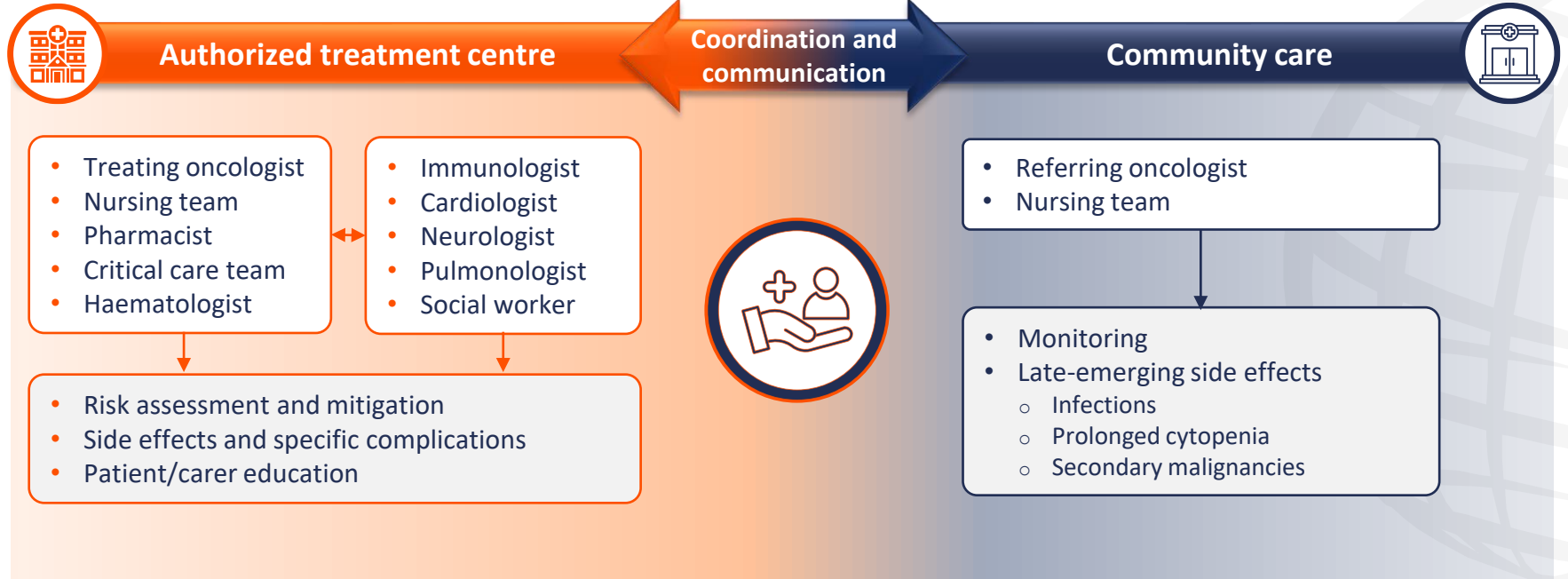‖Grade 5 macrophage activation syndrome.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; gr, grade; Liso-cel, lisocabtagene maraleucel; NE, neurological events; R/R FL, relapsed or refractory follicular lymphoma; TEAE, treatment-emergent adverse event; 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.

touch HAEMATOLOGY

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

Authorized treatment centre → **Coordination and communication** → **Community care**

Authorized treatment centre

- Treating oncologist
- Nursing team
- Pharmacist
- Critical care team
- Haematologist

- Immunologist
- Cardiologist
- Neurologist
- Pulmonologist
- Social worker

- Risk assessment and mitigation
- Side effects and specific complications
- Patient/carer education

Community care

- Referring oncologist
- Nursing team

- Monitoring
- Late-emerging side effects
  - Infections
  - Prolonged cytopenia
  - Secondary malignancies

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.