Optimizing care with CAR T-cell therapy now and in the future for patients with B-cell malignancies

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What are the latest clinical trial and real-world data for CAR T-cell therapy?

Prof. Catherine Thieblemont

Head of the Department of Haemato-Oncology,
Hôpital Saint-Louis,
Paris, France

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What CAR T-cell therapies are currently available for B-cell malignancies?

Expanding options for CD19-targeting CAR T-cell therapies

Axicabtagene ciloleucel

Adult patients* with R/R:

- **DLBCL** and **PMBCL** after ≥2 lines of systemic therapy[1]
- **DLBCL, PMBCL, high-grade BCL, tFL** after ≥2 lines of systemic therapy[2]

Brexucabtagene autoleucel

- **Adult patients with R/R MCL**[3]
- Regulatory review for treatment of MCL in progress[4]

Tisagenlecleucel

Adult patients with R/R:

- **DLBCL** after ≥2 lines of systemic therapy[5]
- **DLBCL, PMBCL, high-grade BCL, tFL** after ≥2 lines of systemic therapy[6]
- **Paediatric and young adults aged ≤25 years with R/R B-cell ALL**[5,6]

Lisocabtagene maraleucel

- Investigational CAR T-cell therapy for adult patients with R/R LBCL
- Regulatory review in progress[7]

*Safety and efficacy in children and adults below 18 years of age have not yet been established.

ALL, acute lymphoblastic leukaemia; BCL, B-cell lymphoma; CAR, chimeric antigen receptor; CD, cluster of differentiation; DLBCL, diffuse LBCL; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; PMBCL, primary mediastinal LBCL; R/R, relapsed or refractory; tFL, transformed follicular lymphoma.

1. EMA SmPC: axicabtagene ciloleucel; 2. FDA PI: axicabtagene ciloleucel; 3. FDA PI: brexucabtagene autoleucel; 4. EMA Proceedings of CHMP Meeting 12–15 October 2020 available at: www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-12-15-october-2020 (accessed 13 January 2021); 5. EMA SmPC: tisagenlecleucel; 6. FDA PI: tisagenlecleucel; 7. Kersten MJ, et al. *Curr Opin Oncol.* 2020;32:408–17.
EMA SmPC and FDA PI available at: EMA www.ema.europa.eu/ and www.fda.gov/ (accessed 13 January 2021).

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What are the key clinical trial efficacy data for anti-CD19 CAR T-cell therapies in B-cell malignancies?

Anti-CD19 CAR T-cell therapies: Efficacy in B-cell malignancies

JULIET[1,2]
tisa-cel in adult R/R DLBCL

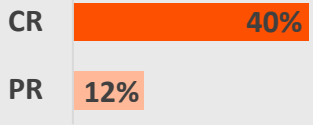
ZUMA-1[3]
axi-cel in adult R/R LBCL

TRANSCEND-001[4]
liso-cel in adult R/R LBCL

Objective response rate

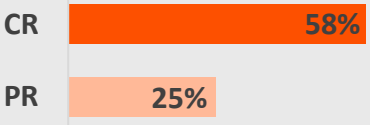
Median follow-up
14 months (range 0.1–26.0)

ORR 52%
95% CI 41–62%
n/N=48/93



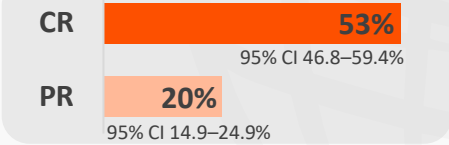
Median follow-up
27.1 months (IQR 25.7–28.8)

ORR 83%
n/N=84/101



Median follow-up
18.8 months (95% CI 15.0–19.3)

ORR 73%
95% CI 66.8–78.0%
n/N=186/256



Durability of response

24-month PFS **33%**
N=115

Ongoing response at 24 months **36%**
n/N=36/101

Estimated 24-month PFS **42%**

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CD, cluster of differentiation; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; ORR, objective response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed or refractory; tisa-cel, tisagenlecleucel.

1. Schuster SJ, et al. *N Engl J Med.* 2019;380:45–56; 2. Jaeger U, et al. *Blood.* 2020;136 (Suppl. 1):48–9; 3. Locke FL, et al. *Lancet Oncol.* 2019;20:31-42; 4. Abramson JS, et al. *Lancet.* 2020;396:839–52.

What are the key safety data for the anti-CD19 CAR T-cell therapies in the clinical trial setting?

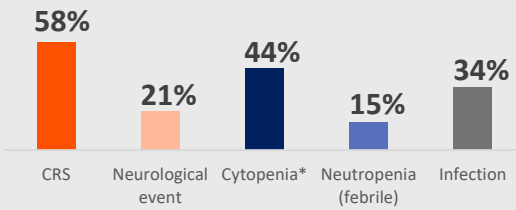
Anti-CD19 CAR T-cell therapies: Safety in B-cell malignancies

JULIET[1]

tisa-cel in adult R/R DLBCL

AE suspected to be related to study drug (any grade) **89%**

AEs (any grade) starting week ≤8 post-infusion



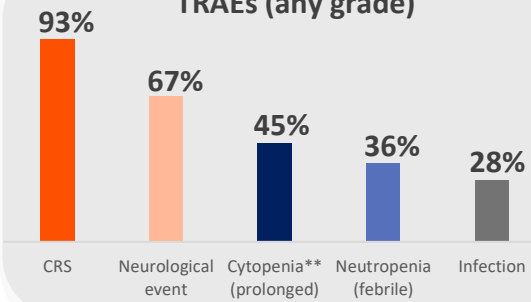
n=111

ZUMA-1[2]

axi-cel in adult R/R LBCL

AE (any grade) **100%**

TRAEs (any grade)



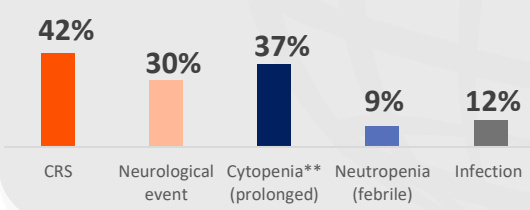
n=108

TRANSCEND-001[3]

liso-cel in adult R/R LBCL

Treatment-emergent AE (any grade) **99%**

TRAEs (any grade)



n=269

*Cytopenia not resolved by day 28. **Prolonged cytopenia defined as follows: cytopenia lasting ≥30 days and occurring within 3 months of treatment in ZUMA-1;[2] cytopenia not resolved at day 29 study visit in TRANSCEND-001.[3]
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; R/R, relapsed or refractory; tisa-cel, tisagenlecleucel; TRAE, treatment-related AE.

1. Schuster SJ, et al. *N Engl J Med.* 2019;380:45–56; 2. Locke FL, et al. *Lancet Oncol*. 2019;20:31–42; 3. Abramson JS, et al. *Lancet.* 2020;396:839–52.

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How safe and effective are CD19-targeting CAR T-cell therapies for B-cell malignancies in the real-world?

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CAR T-cell therapy: The UK NCCP real-world experience

Broadly confirms pivotal trial data suggesting 35–40% patients receiving CAR T-cell therapy may have long-term benefit

UK NCCP

Dec 2018 to Jan 2020

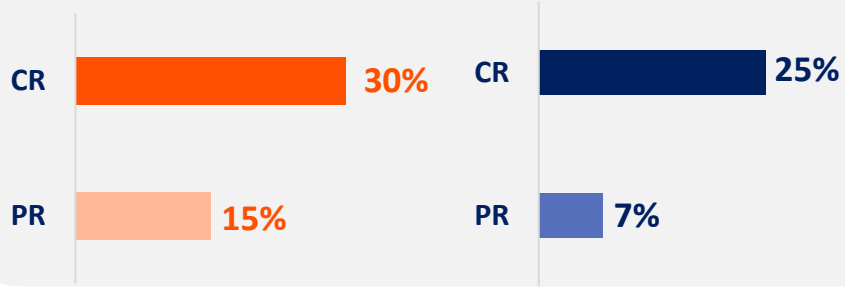
CAR T-cell infused N=183

- axi-cel n=133
- tisa-cel n=50

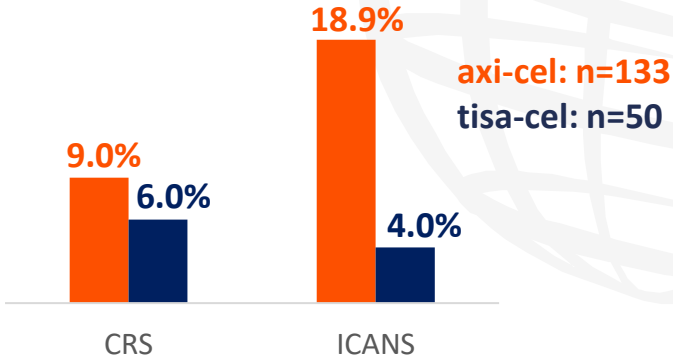
Treatment response at 3 months

axi-cel n=112 ▶ ORR 45%

tisa-cel n=44 ▶ ORR 32%



Safety (grade ≥3 events)



Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, objective response rate; PR, partial response; tisa-cel, tisagenlecleucel; UK NCCP, United Kingdom National CAR-T Clinical Panel.
Kuhnl A, et al. EHA25 Virtual 2020 [Oral presentation p42804; abstract S243].

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CAR T-cell therapy: The LYSA real-world experience

Early relapse is associated with high TMTV at time of treatment

LYSA

June 2018 to Jan 2020

CAR T-cell infused N=116

- axi-cel n=49
- tisa-cel n=67

Treatment response

Median follow-up **8.2** months

Estimated median 12-month:

PFS 47.2%
95% CI 38.0–58.6%

OS 67.0%
95% CI 57.0–79.0%

Risk factors for early relapse (within 1 month)

At day 0 (time of treatment):*

- TMTV >80 mL
- ≥2 extranodal sites
- Elevated CRP

*Day 0 (time of treatment) with lymphodepletion and CAR T-cell infusion.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CI, confidence interval; CRP, C-reactive protein; LYSA, French Lymphoma Study Association; OS, overall survival; PFS, progression-free survival; tisa-cel, tisagenlecleucel; TMTV, total metabolic tumour volume.
Vercellino L, et al. *Blood Adv.* 2020;4:5607–15.

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Who is eligible for CAR T-cell therapy, and why is early referral essential?

Prof. Dr. Marion Subklewe

Attending Physician, Hematology/Oncology,
Head of the CAR T-cell therapy programme,
University Hospital of Munich (LMU),
Munich, Germany

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Which patients are currently eligible for anti-CD19 CAR T-cell therapies?

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Eligibility criteria in key trials

	JULIET: tisagenlecleucel in DLBCL[1,3]	**ZUMA-1:** axicabtagene-ciloleucel in LBCL[2,3]
Disease status	Relapsed or refractory disease; previously received ≥2 lines of therapy	
Age	≥18 years	
Performance status	ECOG performance status 0 or 1	
History of CNS disease	Active CNS involvement due to malignancy excluded	Excluded if detectable malignant cells in cerebrospinal fluid or brain metastases, or a history of either
Prior allo-SCT	Excluded	
Systemic immunosuppressants	Immunosuppressive medication to be stopped >4 weeks prior to enrolment	
History of autoimmune disease	Not an exclusion criterion	
History of malignancy	No previous or concurrent malignancy except basal or squamous cell carcinoma, *in situ* breast or cervical cancer adequately treated and recurrence-free for ≥3 years, primary malignancy resected and in remission ≥5 years	No previous malignancy other than non-melanoma skin cancer or *in situ* carcinoma (e.g. cervical, bladder, breast) or follicular lymphoma, unless disease-free for ≥3 years
Previous CAR T-cell therapy	Not applicable in trials	Excluded
Prior anti-CD19/CD-3 BiTE antibody or any CD19 therapy	Excluded	Excluded if prior CD19-targeted therapy
Existing or suspected infection	Excluded if: uncontrolled active or latent HBV or active HCV; uncontrolled acute active life-threatening bacterial, viral or fungal infection	Excluded if: known history of HIV, HBV or HCV; clinically significant active infection or currently receiving intravenous antibiotics or within 7 days of enrolment

Allo-SCT, allogeneic stem cell transplant; BiTE, bi-specific T-cell engager; CAR, chimeric antigen receptor; CD, cluster of differentiation; CNS, central nervous system; DLBCL, diffuse LBCL; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LBCL, large B-cell lymphoma.

1. Schuster SJ, et al. *N Engl J Med.* 2019;380:45–56; 2. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531–44; 3. Yakoub-Agha I, et al. *Haematologica*. 2018;105:297–316.

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Eligibility considerations for CAR T-cell therapy

Patient medical history, physical condition, current and prior therapies are important guiding factors

Patient age	• Physical condition more informative than age
Performance status	• Prognosis may be less poor if declining PS due to active disease
Disease history	• Caution necessary with history of CNS disease due to higher risk of neurological toxicity • Individualized risk–benefit assessment required if history of autoimmune disease
Active GvHD or infection	• Active GvHD may indicate reason to delay treatment • Active infection(s) controlled and on treatment prior to leukapheresis

CAR, chimeric antigen receptor; CNS, central nervous system; GvHD, graft-versus-host-disease; PS, performance status.

Yakoub-Agha I, et al. *Haematologica*. 2018;105:297–316.

What factors may influence the decision to treat a patient with CAR T-cell therapy?

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Treatment decisions require a multifaceted approach

Factors guiding decisions to treat with CAR T-cell therapy[1–4]

Patient status

- Age
- Fitness
- Performance status
- Co-morbidities
- Organ function
- Inflammatory markers

Disease status

- NHL histology
- Non-FL transformation
- CNS involvement
- Tumour volume

Other

- CAR T-cell fitness
- Need for urgent therapy
- Logistics of treatment
- Psychosocial factors
- Financial/reimbursement

Collective MDT decision making in a designated centre for CAR T-cell therapy is advised

Allo-SCT, allogeneic stem cell transplant; CAR, chimeric antigen receptor; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MDT, multidisciplinary team; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; tFL, transformed FL.

1. Smith S, et al. *Am J Hematol.* 2019;94:E117–20; 2. Yakoub-Agha I, et al. *Haematologica*. 2018;105:297–316; 3. Locke FL, et al. *Blood Adv.* 2020;4:4898–911; 4. Kansagara A, et al. *Am Soc Clin Oncol Educ Book.* 2020;40:e27–34.

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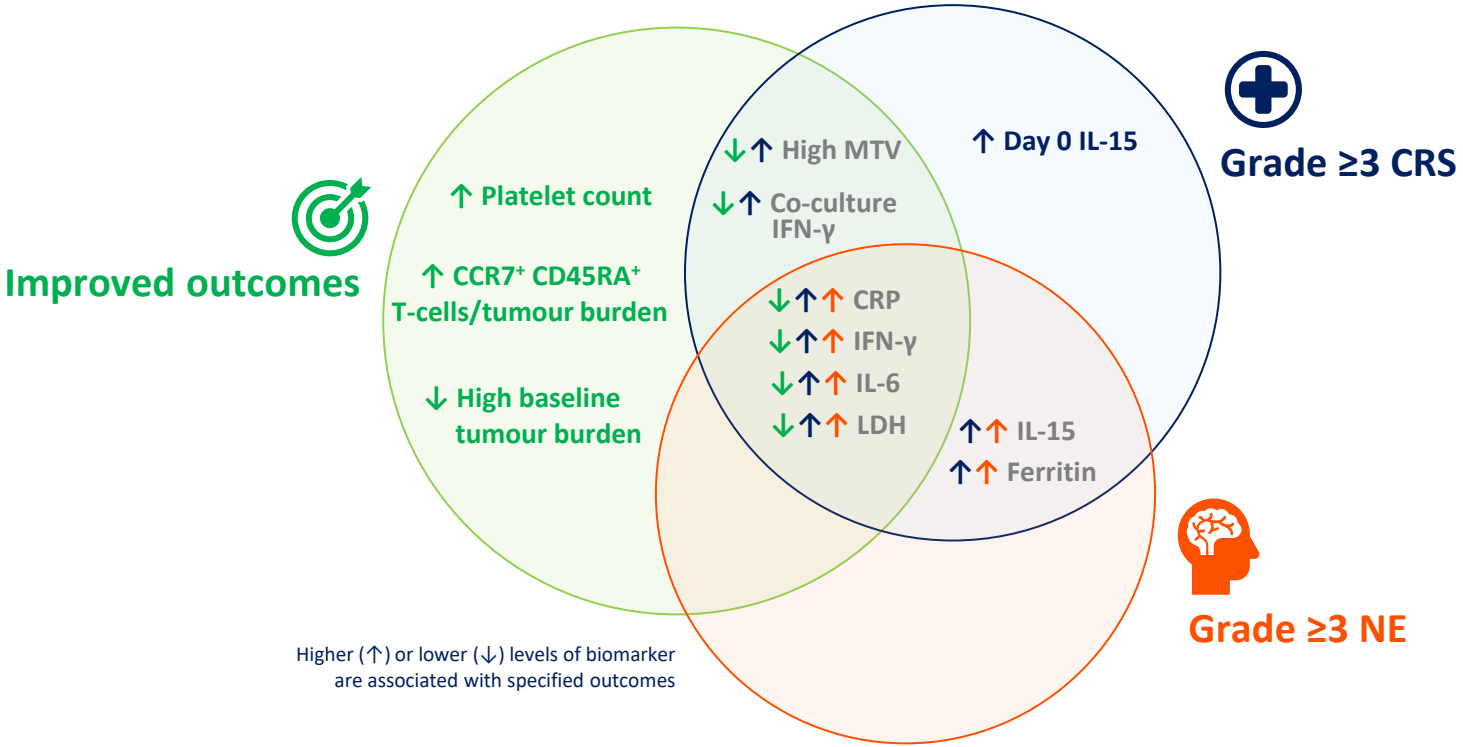
What possible biomarkers could be used in the future to better identify patients who may benefit from CAR T-cell therapies?

Emerging biomarkers require further validation[1–5]



CC, chemokine; CD, cluster of differentiation; CRP, C-reactive protein; CRS, cytokine release syndrome; IFN, interferon; IL-interleukin; LD, lymphodepletion; LDH, lactate dehydrogenase; MTV, metabolic tumour volume; NE, neurological event.

1. Dean EA, et al. *Blood Adv.* 2020;4:3268–76; 2. Vercellino L, et al. *Blood Adv.* 2020;4:5607–15; 3. Locke FL, et al. *Blood Adv.* 2020;4:4898–911; 4. Turtle CJ, et al. *Sci Transl Med.* 2016;8:355ra116; 5. Du M, et al. *Biomark Res.* 2020;8:13.

When should a patient be referred for assessment for treatment with CAR T-cell therapy?

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Early and broad referral for timely treatment is advised

Optimizing access to CAR T-cell therapy in eligible patients requires early consideration

When should we refer?

- Where primary refractory disease is suspected
- Following first-line relapse as patient commences salvage chemotherapy with a plan for auto-SCT but consider CAR T-cell therapy if inadequate response or disease progression following ≤2 cycles

Why early and broad referral?

- Patient condition and PS more suited to therapy
- Avoid toxicities from ineffective chemotherapies
- Facilitates coordination of treatment logistics to avoid unnecessary delays, such as:
  - Referral to expert centre
  - MDT assessment(s)
  - Collection, work-up and manufacture

Auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; MDT, multidisciplinary team; PS, performance status.

Kansagara A, et al. *Am Soc Clin Oncol Educ Book.* 2020;40:e27–34.

How are the toxicities associated with CAR T-cell therapy best managed?

Dr Maeve O'Reilly

Consultant Haematologist,
University College Hospital,
London, UK

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What are the short-term safety considerations associated with CAR T-cell therapy, and how are they best managed?

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Cytokine release syndrome

Incidence[1]

30–100%

10–30% grade 3/4

1–14 days
to onset post-infusion

Symptoms can last
1–10 days

Clinical features[2]

- Fever
- Hypoxia
- Vasodilatory shock
- Capillary leak
- End-organ dysfunction

Risk factors[1]

- Tumour burden
- CAR T-cell dose and construct
- Active infection at infusion
- Lymphodepletion regimen

CAR, chimeric antigen receptor.

1. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316; 2. Frey N, Porter D. *Biol Blood Marrow Transplant.* 2019;25:e123–7.

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CRS: Assessment, grading and safety management

ASTCT consensus grading system for CRS[1]

Grade 1	Grade 2	Grade 3	Grade 4
Temperature ≥38°C *with:*			
No hypotension	**Hypotension** Not requiring vasopressors	**Hypotension** Vasopressor ± vasopressin	**Hypotension** Multiple vasopressors (excluding vasopressin)
	and/or	***and/or***	***and/or***
No hypoxia	**Hypoxia** Low-flow nasal cannula/blow-by	**Hypoxia** High-flow nasal cannula, face mask, nonrebreather mask or Venturi mask	**Hypoxia** Requiring positive pressure

Grade 2 CRS: Alert ICU if no response to tocilizumab

In addition to symptomatic measures, tocilizumab or corticosteroids may be administered[2]

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICU, intensive care unit.

1. Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625–38; 2. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316.

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Neurological toxicity (ICANS)

Incidence[1–3]

21–64%

12–33% grade 3/4

May progress over **hours or days[4]**

Symptoms can last **2–9 days[5]**

Clinical features[5,6]

- Non-specific, ranging in severity from mild confusion to coma
- Early manifestations include:
  - Tremor
  - Dysgraphia
  - Expressive speech difficulties

Risk factors include:[5]

- Tumour burden
- Prior CNS-directed therapies
- Previous meningeal involvement
- ALL

ALL, acute lymphoblastic leukaemia; CNS, central nervous system; ICANS, immune effector cell-associated neurotoxicity syndrome.

1. Schuster SJ, et al. *N Engl J Med.* 2019;380:45–56; 2. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531–44; 3. Locke FL, et al. *Lancet Oncol.* 2019;20:31–42;
4. Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625–38; 5. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316;
6. Siegler EL, Kenderian SS. *Front Immunol.* 2020;11:1973.

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ICANS: Grading and safety management

ASTCT consensus grading system for ICANS[1]

Grade 1 ICE 7–9	Grade 2 ICE 3–6	Grade 3 ICE 0–2	Grade 4 ICE 0
• Drowsiness but patient awakens spontaneously	• Drowsiness but awakens to voice	• Awakens only to tactile stimulus • Clinical or electrographic seizure • Focal or local oedema on neuroimaging	• Unable to rouse patient • Unable to ICE-assess • Prolonged or repetitive electrographic seizures • Deep focal motor weakness • Diffuse cerebral oedema on neuroimaging

⚠ ALERT ICU with rapid access to neurological expertise[1,2] (grades 3–4, transfer to ICU)[3*]

Management may require cross-sectional imaging, electroencephalography, and CSF examination[2]

*Hospital capacity and policies governing escalating care for patients experiencing serious complications of CAR T-cell therapy may vary locally.[1]

ASTCT, American Society for Transplantation and Cellular Therapy; ATMP, advanced therapy medicinal products; CSF, cerebrospinal fluid; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune Effector Cell-Associated Encephalopathy; ICU, intensive care unit; NHS SPS, National Health Service (UK) Specialist Pharmacy Service.

1. Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625–38; 2. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316; 3. NHS SPS Pan UK Working Groups for ATMPs. Diagnosis and Management of Acute CAR-T Cell Toxicities in Adults Version 1.0, December 2020. Available at: www.sps.nhs.uk/wp-content/uploads/2020/12/Diagnosis-and-medical-management-of-acute-CAR-T-cell-toxicities-in-Adults-V1.pdf (accessed 08 January 2021).

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Infection risk associated with CAR T-cell therapy

Bacterial
infections are most common[1]

Present within
30 days[1]

Beyond 30 days respiratory viral infections predominate[1]

Risk factors[1–4]

- CRS
- Combined effects of prior therapies
- ALL diagnosis
- Prolonged cytopenias
- CAR T-cell dose
- Steroid use

ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

1. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316; 2. Vora SB, et al. *Open Forum Infect Dis.* 2020;7:ofaa121; 3. Wudhikarn K, et al. *Blood Cancer J.* 2020;10:79; 4. Hill JA, et al. *Blood.* 2018;131:121–30.

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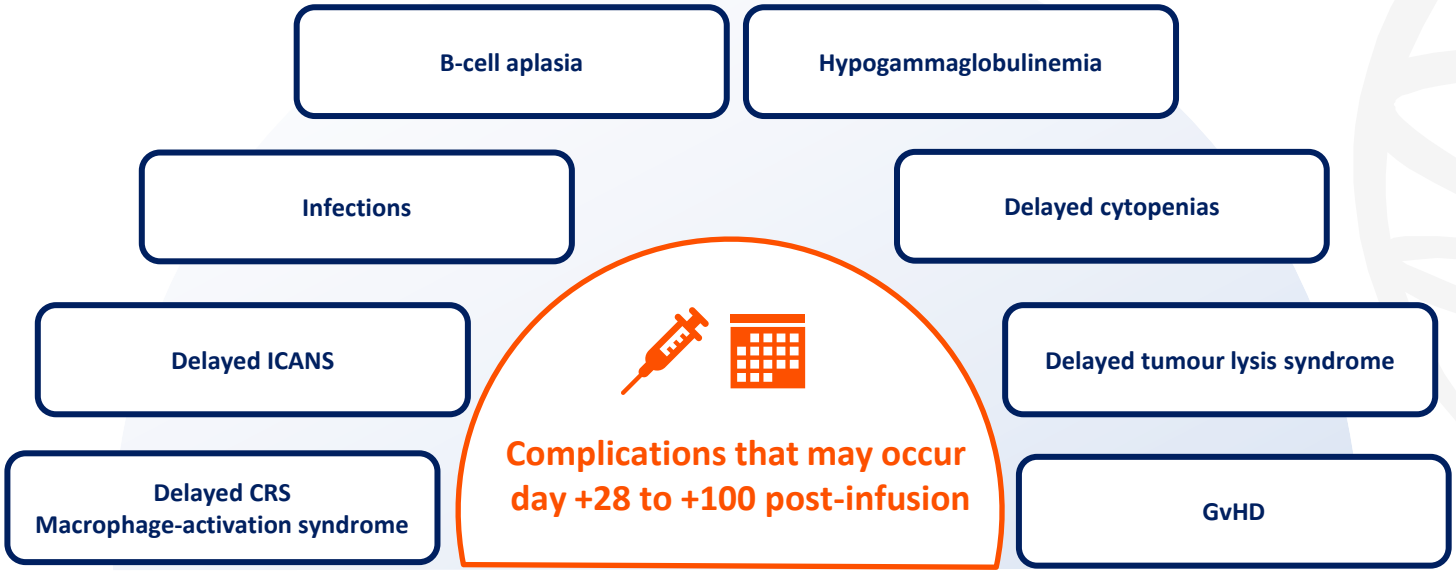
What medium-term safety considerations do HCPs need to be aware of and how can they be optimally managed?

CAR T-cell therapy: Medium-term complications

Vigilance through monitoring of patients during medium-term follow-up



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; GvHD, graft versus host disease; ICANS, immune effector cell-associated neurotoxicity syndrome.
Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316.

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What are the key long-term safety considerations associated with CAR T-cell therapy, and how are they best managed?

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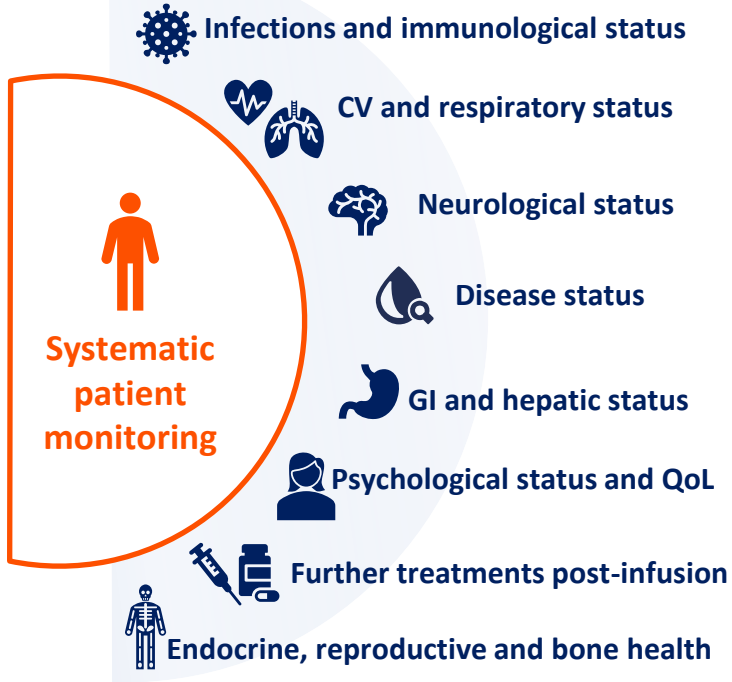
CAR T-cell therapy: Long-term safety considerations

Main complications include prolonged cytopenias and hypogammaglobulinemia



'Late-effects' monitoring
in stable patients in ongoing remission

- Attentive and regular follow-up tailored to individual patient*
- Monitoring could be performed by CAR T-cell therapy specialist centre or referring clinician

*Follow-up schedule may vary according to local policies and practice guidelines.
CAR, chimeric antigen receptor; CV, Cardiovascular; GI, gastrointestinal; QoL, quality of life.
Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316.

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How can we safely and effectively manage our patients in the community setting?

Effective communication and an MDT approach are key

CAR T-cell specialist centre

Complete documentation
- Discharge notes and clinical records
- Follow-up protocol and policies

Referring healthcare centre

Outpatient management
- Patient/caregiver awareness of CRS/ICANS
- Rapid access to specialist treatment/readmission

Long-term MDT follow-up

Review disease status and late-effects of CAR T-cell therapy and prior treatments

- **CAR T-cell therapy treating physician**
- **Nurse specialists**
- **Other specialists**
- **Clinical trial staff**
- **Data managers**

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome; MDT, multidisciplinary team.
Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316.

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CAR T-cell therapy in B-cell ALL: Where are we now?

Prof. Adriana Balduzzi

Associate Professor of Pediatrics,
Pediatric Department,
University of Milano Bicocca,
Monza, Italy

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What is the current status of CAR T-cell therapies in the clinical management of B-cell ALL?

Expanding options for CAR T-cell therapies in B-cell ALL

Brexucabtagene autoleucel

Trial in progress

ZUMA-4: paediatric and young adult patients aged ≤21 years[1]

Lisocabtagene maraleucel

Trial in progress

NCT03743246: paediatric and young adult patients aged ≤25 years[7]

Tisagenlecleucel

Approved in paediatric and young adult patients aged ≤25 years with B-cell ALL that is:

- refractory, in relapse post-transplant or, in second or later relapse[2]
- refractory or in second or later relapse[3]

Trials in progress

CASSIOPEIA: high-risk paediatric and young adult patients; first-line in MRD+ after EOC[4]

NCT04225676: paediatric and young adult patients; reinfusion in patients experiencing loss of B-cell aplasia[5]

NCT04156659: Chinese cohort aged ≤25 years[6]

Multiple ongoing academic trials: CARPALL: paediatric and adult patients aged ≤24 years;[8] **CART19-BE-01:** paediatric and adult;[9] **CARCIK:** paediatric and adult post-HSCT[10]

ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; EOC, end of consolidation therapy; HSCT, haematopoietic stem cell transplant; MRD+, minimal residual disease positive; R/R, relapsed or refractory.

1. NCT02625480; 2. EMA SmPC: tisagenlecleucel; 3. FDA PI: tisagenlecleucel; 4. NCT03876769; 5. NCT04225676; 6. NCT04156659; 7. NCT03743246; 8. Ghorashian S, et al. *Nat Med*. 2019;25:1408–14; 9. Ortíz-Maldonado V, et al. *Mol Ther*. 2020;S1525-0016(20)30484-6 [online ahead of print]; 10. Magnani CF, et al. *J Clin Invest*. 2020;130:6021–33. EMA SmPC and FDA PI available at: www.ema.europa.eu/ and www.fda.gov/ (accessed 11 January 2021). NCT information available at: https://clinicaltrials.gov/ (accessed 11 January 2021).

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How effective are CAR T-cell therapies for B-cell ALL?

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CAR T-cell therapies: Efficacy in B-cell ALL

ELIANA (updated analysis)[1,2]

tisa-cel

- Aged between ≥3 and ≤21 years
- No prior anti-CD19 therapy
- 113 patients screened, 97 enrolled, 79 infused

- Median age: 11 years (range 3–24)
- Median prior lines of therapy: 3 (range 1–8)
- Prior SCT: 61%
- Median follow-up: 24.2 months (range 4.5–35.1)

ORR 82%
95% CI 72–90%

64/65 responders achieved MRD-negative bone marrow

Probability at 24 months of:

RFS 62%
95% CI 47–75% in responders (N=65)

OS 66%
95% CI 54–76% in all patients (N=79)

Relapses: 73.7% CD19-negative

B2001X[3,4]

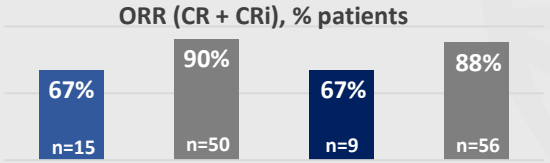
tisa-cel

- Aged up to 25 years
- ≥2 relapses, refractory or post-alloSCT relapse
- Prior anti-CD19/CD22 therapy permitted: **BLINA exposure (n=15)** or **INO as BT (n=9)**
- 80 screened, 73 enrolled, 67 infused

- Median age: 10 years (range 2–33)
- Median follow-up: 9.6 months (range 0.2–16.5)

ORR 85%
95% CI 74–92%

12-month OS 83%
95% CI 69–92%



	Prior BLINA	No prior BLINA	INO as BT	No INO as BT
12-month OS, % (95% CI)	53 (19–78)	91 (74–97)	71 (23–92)	85 (69–93)

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; BLINA, blinatumomab; BT, bridging therapy; CAR, chimeric antigen receptor; CD, cluster of differentiation; CI, confidence interval; CR, complete response; CRi, CR with incomplete haematological recovery; EFS, event-free survival; INO, inotuzumab; MRD, minimal residual disease; ORR, overall remission rate; OS, overall survival; RFS, relapse-free survival; SCT, stem cell transplant; tisa-cel, tisagenlecleucel.

1. Grupp SA, et al. *Blood.* 2018;132(Suppl. 1):895; 2. Grupp SA, et al. *Biol Blood Marrow Transplant.* 2019;25(Suppl):S126–7; 3. Krueger J, et al. *J Clin Oncol.* 2020;38(Suppl. 15):10518; 4. NCT03123939. Available at: https://clinicaltrials.gov/ct2/show/NCT03123939 (accessed 11 January 2021).

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What have we learned so far about CAR T-cell therapies for B-cell ALL in the real-world setting?

CAR T-cell therapy in B-cell ALL: UK NCCP experience

Greater proportion of CD19^{+} vs CD19^{-} relapses observed compared with ELIANA trial

In first 90 days

CR/CRi 95%

MRD^{-} 78.9%

ITT population — **CR/CRi 84.8%**

Relapses: 40% CD19-negative

Composite EFS, including:

- Molecular or frank relapse
- Death
- Further therapy
- B-cell recovery
- Treatment failure

All infused — **6-month EFS 47.6%**
12-month EFS 33.6%

ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; CRi, CR with incomplete haematological recovery; EFS, event-free survival; ITT, intention-to-treat; MRD, minimal residual disease; OS, overall survival; tisa-cel, tisagenlecleucel; UK NCCP, United Kingdom National CAR T-cell Clinical Panel.

Ghorashian S, et al. *Blood.* 2020;136(Suppl. 1):1016.

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CAR T-cell therapy in B-cell ALL: PRWCC experience

Real-world effectiveness of tisa-cel is comparable with ELIANA trial results

Treatment response

Median follow-up 11.2 months (0.2–28.8)

CRR
ITT: 79%
Infused: 85%

35% relapsed responders
41% CD19⁻

	6 months	12 months
DoR	75%	63%
OS	85%	72%
EFS	64%	51%

Response by disease burden

	12-month OS (p<0.0001)	12-month EFS (p<0.0001)
High disease burden	58%	34%
Low disease burden	85%	69%
No detectable disease	95%	72%

ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CD, cluster of differentiation; CD19⁻, CD19 negative; CRR, complete response rate; DoR, duration of response; EFS, event-free survival; ITT, intention-to-treat; OS, overall survival; PRWCC, Pediatric Real World CAR Consortium; tisa-cel, tisagenlecleucel.

Schultz LM, et al. *Blood*. 2020;136(Suppl. 1):14–15.

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How can we identify patients with B-cell ALL who may benefit from CAR T-cell therapy?

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Baseline MDT assessment may guide patient selection[1,2]

Timely referral of patients eligible for CAR T-cell therapy is needed to optimize outcomes

Indications
Approved indications and pivotal trial eligibility criteria inform patient selection

Patient-related factors
Acceptable PS according to thresholds defined in treatment protocols and/or institutional guidelines

Disease-specific factors
Consider sites of active disease within the context of possible tumour flare following immune activation that may compromise vital organ function

Contraindications
Preclusions to treatment may include recent:
- DLI therapy
- Uncontrolled infection(s)
- Active grade II–IV acute or extensive chronic GvHD

Informed consent for CAR T-cell therapy must be obtained from the patient and/or their guardians and, where appropriate, child assent should be given

CAR, chimeric antigen receptor; DLI, donor-lymphocyte infusion; GvHD, graft-versus-host disease; MDT, multidisciplinary team; PS, performance status.
1. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316; 2. Mahadeo KM, et al. *Nat Rev Clin Oncol.* 2019;16:45–63.

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What are the possible adverse events with CAR T-cell therapy in patients aged under 25 years, and how can they be optimally managed?

CAR T-cell therapies: Safety in B-cell ALL

ELIANA (updated analysis)[1]

tisa-cel

N=79

CRS 77% (49% grade 3/4)

Median time to onset: 3 days (range 1–22)
Median duration: 8 days (range 1–36)

NEs 39% (13% grade 3/4)

Median time to onset: 7 days

CRS management

ICU admission 48%
Intubation 15%

Tocilizumab 39%
Corticosteroids 20%
High-dose vasopressors 24%

B2001X[2]

tisa-cel

N=67

CRS 64% (28% grade 3/4)

Median time to onset: 5 days (range 1–13)
Median duration: 7 days (range 1–27)

NEs 24% (11% grade 3/4)

CRS management

ICU admission 28%
Intubation 7%

Tocilizumab 27%
Corticosteroids 6%
Siltuximab 3%
High-dose vasopressors 22%

ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICU, intensive care unit; NE, neurological event; tisa-cel, tisagenlecleucel.

1. Grupp SA, et al. *Blood.* 2018;132(Suppl. 1):Abstract 895; 2. Krueger J, et al. *J Clin Oncol.* 2020;38:10518.

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Real-world safety: UK NCCP and PRWCC experiences

UK NCCP[1]

- Grade ≥3 CRS 20.4%
- Grade ≥3 NEs 10.2%
- Tocilizumab administered 44.9%
- ICU managed 22.0%

PRWCC[2]

- Grade ≥3 CRS 19.0%
- Grade ≥3 NEs 7.0%
- Tocilizumab administered 26.0%
- Steroids administered 14.0%

CRS, cytokine release syndrome; ICU, intensive care unit; NE, neurological event; PRWCC, Pediatric Real World CAR Consortium; UK NCCP, United Kingdom National CAR T-cell Clinical Panel.

1. Ghorashian S, et al. *Blood.* 2020;136(Suppl. 1):1016; 2. Schultz LM, et al. *Blood*. 2020;136(Suppl. 1):14–15.

What are the new and emerging indications for CAR T-cell therapy?

Dr Michael Dickinson

Consultant Haematologist and Lead of the Aggressive Lymphoma disease group,
Peter MacCallum Cancer Centre and Royal Melbourne Hospital,
Melbourne, Australia

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For which new indications are CD19-targeting CAR T-cell therapies being explored and why are additional treatment options needed for these patients?

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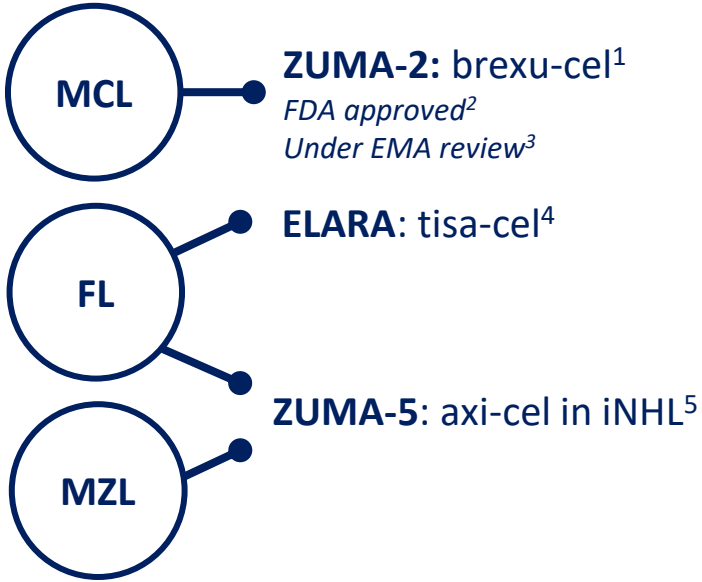
CAR T-cell therapy: Clinical potential in MCL, FL and MZL

Potential for CAR T-cell therapies to address existing challenges and unmet needs



ZUMA-2: brexu-cel[1]
FDA approved[2]
Under EMA review[3]

ELARA: tisa-cel[4]

ZUMA-5: axi-cel in iNHL[5]

MCL, FL and MZL are incurable with current treatments and patients inevitably relapse [6,7]

CAR T-cell therapy may be able to induce durable complete remissions in patients with MCL, FL and MZL[1,5,8]

Axi-cel, axicabtagene ciloleucel; brexu-cel, brexucabtagene autoleucel; CAR, chimeric antigen receptor; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PI, prescribing information; tisa-cel, tisagenlecleucel.

1. Wang M, et al. *N Engl J Med.* 2020;382:1331–42; 2. FDA PI: brexucabtagene autoleucel, July 2020; 3. EMA Proceedings of CHMP Meeting 12–15 October 2020. Available at www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-12-15-october-2020; 4. Dickinson M, et al. *J Clin Oncol.* 2019;37:TPS7573; 5. Jacobson C, et al. *J Clin Oncol.* 2020;38:8008; 6. Abramson JS, et al. *Am Soc Clin Oncol Educ Book.* 2020;40:302–13; 7. Denlinger NM, et al. *Cancer Manag Res.* 2018;10:615–24; 8. Fowler NH, et al. *Blood.* 2020;136:DOI:10.1182/blood-2020-138983.

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How safe and effective are CAR T-cell therapies in indolent NHL in the clinical trial setting?

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ZUMA-5: Phase II evaluation of axi-cel in iNHL

R/R iNHL
FL or MZL after ≥2 prior lines

N=140

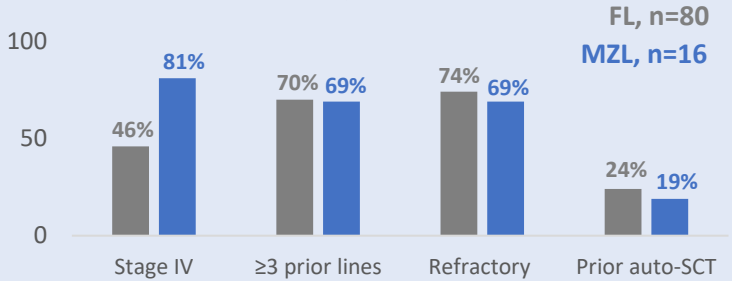
axi-cel
2 x 10^6 CAR T-cells/kg

ORR

FL
Grade 1–3a
n=124

MZL
[extra]nodal
n=16

Baseline disease characteristics, % patients

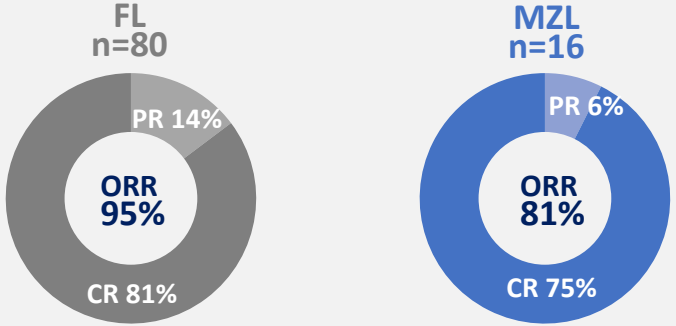


Efficacy

Median follow-up: 15.3 months

Overall ORR 93%
95% CI 86–97%

Overall CR 80%
95% CI 71–88%



68% of patients with FL had an ongoing response (80% CR)

Safety*

Median follow-up: 12.8 months

	Any grade		Grade ≥3	
	FL, n=124	MZL, n=16	FL, n=124	MZL, n=16
CRS	77%	100%	7%	13%
NE	55%	81%	15%	38%

Auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; NE, neurological event; PR, partial response; ORR, objective response rate; R/R, relapsed or refractory.

Jacobson C, et al. *J Clin Oncol.* 2020;38(Suppl 15):8008 (Presented at ASCO20 Virtual Scientific Program; 29–31 May 2020).

ELARA: Phase II evaluation of tisa-cel in FL

R/R FL
Grade 1–3A after ≥2 prior lines

N=98

n=97 received tisa-cel

tisa-cel
0.6–6 x 10^8 CAR T-cells

CRR

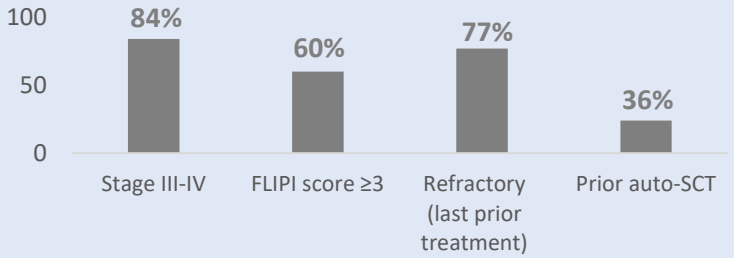
Median follow-up
9.9 months (efficacy)

ITT n=52

ORR 82.7%
95% CI 69.7–91.8%

CR 65.4%
95% CI 45.1–82.4%

Baseline disease characteristics, % patients



Safety
n=97

	CRS (Lee scale)	NE (CTCAE v4.03)
Any grade	48%	10%
Grade 1	29%	NS
Grade 2	20%	NS
Grade ≥3	0%	2%

Auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; CRR, complete response rate; CRS, cytokine release syndrome; CTCAE, Common Terminology for Adverse Events; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ITT, intention-to-treat (population); NE, neurological event; ORR, objective response rate; NS, not specified; R/R, relapsed or refractory; tisa-cel, tisagenlecleucel.

Fowler NH, et al. *Blood.* 2020;136:DOI:10.1182/blood-2020-138983.

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How safe and effective are CAR T-cell therapies in MCL in the clinical trial setting?

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ZUMA-2: Brexu-cel (KTE-X19) in MCL

R/R MCL
≤5 prior lines
Including previous BTKi

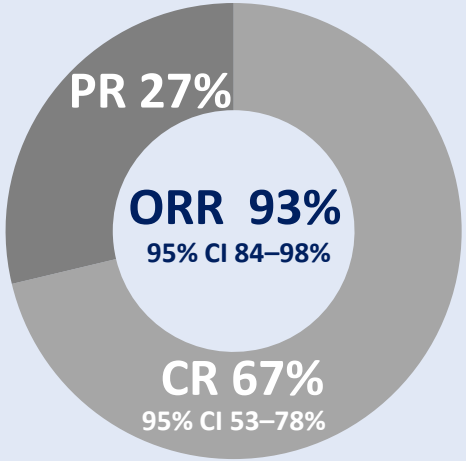
N=68

KTE-X19
2 x 10^6
CAR^+ T cells/kg

ORR
IRRC-assessed

Median follow-up **12.3 months**
7.0–32.3*

Patients with ≥7 months of follow-up

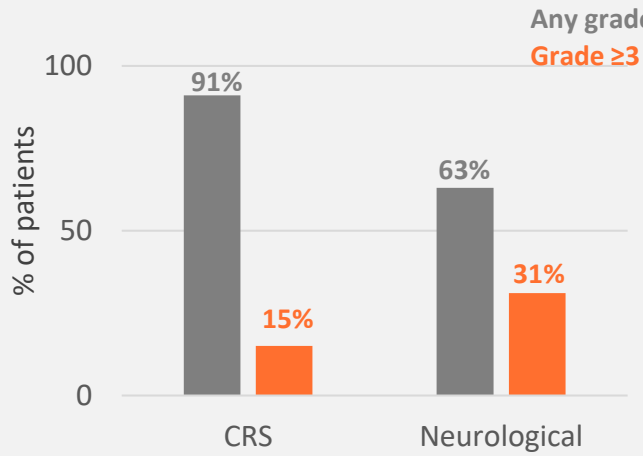


At 12 months (estimated)

OS 83% **PFS 61%**

n=60

AEs of special interest



n=68

*Range. AE, adverse event; brexu-cel, brexucabtagene autoleucel; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; IRRC, independent radiologic review committee; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed or refractory.

Wang M, et al. *N Engl J Med.* 2020;382:1331–42.

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How will CD19-targeting CAR T-cell therapies influence future practice in the clinical management of B-cell malignancies?

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CAR T-cell therapy: New horizons in emerging indications

Recent approval for CAR T-cell therapy in MCL (FDA)[1]

Promising early data for CAR T-cell therapy in FL and MZL[2,3]

CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; FL, follicular lymphoma; MCL, mantle-cell lymphoma; MZL, marginal zone lymphoma.

1. FDA. FDA approves first cell-based gene therapy for patients with relapsed or refractory MCL. Available at: www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-relapsed-or-refractory-mcl. Accessed November 2020; 2. Jacobson C, et al. *J Clin Oncol.* 2020;38:8008;
3. Fowler NH, et al. *Blood.* 2020;136:DOI:10.1182/blood-2020-138983.

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