ICANS mitigation in high-risk elderly patients treated with CD28 co-stimulatory anti-CD19 CAR-T cells using a standardization protocol: a pilot study

Gil Fridberg,[1,2] Odelia Amit,[1,2] Yehonathan Sherf,[3] Chava Perry,[1,2] Yair Herishanu,[1,2] Erel Joffe,[1,2] Tamir Shragai,[1,2] Roy Vitkon,[1,2] Meir Preis,[4] Shoshan Perk,[4] Nadav Sarid,[5,2] Sharon Ben Barouch,[6] Ronit Gold,[1] Chen Glait-Santar,[1] Irit Avivi[1,2] and Ron Ram[1,2]

[1]BMT and Cellular Therapy Unit, Hematology Division, Tel Aviv Sourasky Medical Center, Tel Aviv; [2]Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv; [3]Hematology Department, Soroka University Medical Center, Affiliated with Ben Gurion University of the Negev, Beer Sheva; [4]Institute of Hematology, Lady Davis Carmel Medical Center, Haifa; [5]Department of Hematology, The Edith Wolfson Medical Center, Holon and [6]Institute of Hematology, Assuta Ashdod Medical Center, Ashdod, Israel

Correspondence: G. Fridberg
gilfr@tlvmc.gov.il

Received: August 19, 2025.
Accepted: February 3, 2026.
Early view: February 12, 2026.

https://doi.org/10.3324/haematol.2025.288954

Abstract

Chimeric antigen receptor T-cell therapy (CAR-T) has transformed the treatment of relapsed/refractory large B-cell lymphoma (LBCL), with CD28-based products yielding rapid responses but higher rates of immune effector cell-associated neurotoxicity syndrome (ICANS). With axicabtagene-ciloleucel and brexucabtagene-autoleucel, overall and severe ICANS reach 78% and 35%, respectively. Older adults are vulnerable, yet mitigation strategies are still lacking. To address this critical gap, we aimed to develop and implement a standardized ICANS mitigation protocol for older adults receiving CD28-based anti-CD19 CAR-T. We conducted a single-arm prospective pilot study in patients ≥75 or ≥65 years with additional risk factor receiving CD28-based CAR-T. The protocol included levetiracetam and thiamine prophylaxis, early grade-based corticosteroids and anakinra for grade ≥3 and refractory ICANS, which was defined as no improvement within 24 hours. Endpoints were ICANS duration, refractoriness, response, and toxicity. Forty-five patients met eligibility criteria. Median age was 75 years (range: 65-86 years); 78% had Eastern Cooperative Oncology Group (ECOG) ≥2 and 42% had neurologic comorbidity. Grade ≥3 and refractory ICANS developed in 67% overall, with grade ≥3 in 31%, and refractory ICANS in 20%. Median ICANS duration was four days, which was shorter than previous cohorts. Disease and patients' characteristics did not predict ICANS metrics, excluding lactate dehydrogenase which showed a trend for severe ICANS (P=0.07). modified Endothelial Activation and Stress Index (mEASIX) and ICANS-Prognostic Scoring System (PSS) scores were not predictive and expansion was not compromised. Cumulative steroids associated with infections (P=0.002) and non-relapse mortality (P<0.0001). Six-month progression-free survival and overall survival were 46% and 59%, respectively. In this high-risk cohort, the ICANS mitigation protocol using anakinra in a graded approach (*vs*. prophylaxis or salvage therapy) and a pragmatic definition of refractory disease was associated with shorter ICANS duration, despite severe event rates. Steroid-related toxicity remains a concern, and future efforts should focus on steroid-sparing mitigation to optimize outcomes in older adults undergoing CAR-T.

Introduction

Chimeric antigen receptor T-cell therapy (CAR-T) has revolutionized the treatment landscape of large B-cell lymphoma (LBCL), offering a curative option for patients with relapsed or refractory LBCL with impressive overall and complete response rates.[1-3] A key distinction between available CAR-T products lies in the co-stimulatory domain: CD28 (e.g., axicabtagene-ciloleucel [axi-cel], brexucabtagene-autoleucel [brexu-cel]) *versus* 4-1BB (e.g., tisagenlecleucel [tisa-cel], lisocabtagene-maraleucel [liso-cel]).[1-6] CD28-based CAR-T constructs are associated with a rapid T-cell expansion and earlier onset of clinical responses, but this comes at the cost of higher toxicity, particularly increased incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[4,7-9] The early pivotal trials of axi-cel and brexu-cel reported any grade of ICANS in up to 64% and 78%, respectively, and grade ≥3 in 28% and 38%, respectively.[1,5,6] These high rates of ICANS were observed in both clinical trials and real-world settings,[10,11] while parallel studies of non-CD28-based anti-CD19 CAR constructs have demonstrated mark-

edly lower rates and severity across different indications and treatment settings,[2,3] highlighting the impact of the co-stimulatory domain on ICANS development.[7]

Incidence of ICANS is further increased among older patients.[12] In both the ZUMA-1 and ZUMA-7 trials, older age (≥65 years) was associated with increased incidence and severity of ICANS. Available data from ZUMA-7 suggested an age-dependent pattern, with patients aged ≥70 years experiencing higher ICANS rates than those aged ≥65 years.[1,13] Furthermore, several additional risk factors for ICANS are more prevalent in older age patients. These include advanced stage malignancy and high disease burden at lymphodepletion (LD) (potentially influenced by reduced tolerance to bridging therapy), as well as pre-existing neurologic comorbidities and poor performance status.[7,12,14-16] While risk factors are assessed when considering candidates for CAR-T, formal eligibility criteria, particularly regarding age and comorbidities, still remain undefined, reflecting the complexity of using age and comorbidities as strict criteria for withholding an effective and life-saving treatment.[17,18]

ICANS management is guided by a consensus-based protocol and is mainly based on administration of steroids;[19] however, this is not specified for elderly patients who, if severe ICANS develops, are prone to longer recovery periods. Similarly, management of prolonged and refractory ICANS is also not universally defined, and is guided primarily by case series, some describing the off-label use of adjunctive agents such as thiamine, based on biological plausibility in similar scenarios.[20] These case series are limited in their ability to evaluate efficacy and generalizability, particularly in elderly patients.

These factors expose older patients to both an unacceptable risk for ICANS and for treatment-associated deconditioning, with potentially prolonged functional recovery and hospitalization, posing additional risk for complications or, in some cases, limiting patients' access to CAR-T due to toxicity concerns.[18]

Considering the unmet-need for ICANS mitigation and the lack of standardized treatment, we aimed to develop and implement a prospectively predefined protocol for ICANS mitigation in elderly patients treated with CD28-based anti-CD19 CAR-T.

Methods

Patients and investigational protocol

We conducted a single arm prospective pilot study in the Tel Aviv Sourasky Medical Center. The study was performed in accordance with the principles of the Declaration of Helsinki. All patients gave informed consent to the planned treatment schedule and for the reporting of treatment outcomes. The study was approved by the local institutional review board.

Eligible patients were aged ≥75 or ≥65 years with ≥1 additional risk factor: pre-existing neurologic comorbidity, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, high disease burden at LD (stable/progressive disease and/or lactate dehydrogenase [LDH] > upper limit of normal) who received CD28-based CAR-T treatment.

The protocol comprised three components: prophylaxis, first-line treatment, and second-line treatment for refractory ICANS (see Table 1).

Prophylaxis - All patients received oral (PO) levetiracetam and PO thiamine from day 0. For ICANS grade ≥2, both were converted to intravenous (IV) administration.

First-line treatment - Corticosteroids was administrated at grade-specific starting dose (Table 1), using higher initial once-daily doses to mitigate toxicity of prolonged courses. Anakinra was initiated for grade ≥3 ICANS. With concurrent CRS indicating tocilizumab, dexamethasone was co-administrated with each dose.

Refractory ICANS – Defined as no clinical improvement or worsening within 24 hours (hr) of treatment initiation. Managed by escalating steroids to the next grade and adding anakinra if not already used.

Table 1. Study protocol.

	Steroids	Anakinra†	Seizure prophylaxis	Supportive care
No ICANS	NA	NA	PO Levetiracetam 750 mg BID	PO Thiamine 1 Tab OD
Grade 1	IV Dexamethasone 20 mg OD	NA	PO Levetiracetam 750 mg BID	PO Thiamine 1 Tab OD
Grade 2	IV Dexamethasone 20 mg QD	NA	IV Levetiracetam 1,000 mg BID	IV Thiamine 500 mg TID
Grade 3	IV Methylprednisolone 1 g OD	SC Anakinra 100 mg BID	IV Levetiracetam 1,000 mg BID	IV Thiamine 500 mg TID
Grade 4	IV Methylprednisolone 2 g OD	SC Anakinra 100 mg BID	IV Levetiracetam 1,000 mg BID	IV Thiamine 500 mg TID
Refractory ICANS	Dose escalation to subsequent grade	SC Anakinra 100 mg BID	IV Levetiracetam 1,000 mg BID	IV Thiamine 500 mg TID
Concurrent CRS	Dexamethasone 20 mg with each dose of tocilizumab			

Refractory immune effector cell-associated neurotoxicity syndrome (ICANS) defined as no clinical improvement within 24 hours (hr) of treatment initiation and/or worsening to a higher grade within 24 hr under active treatment. †Anakinra administration until ICANS grade reaches ≤1. BID: twice a day; CRS: cytokine release syndrome; IV: intravenous; NA: not applicable; OD: once a day; PO: oral administration; SC: subcutaneous inection; Tab: Thiamine 1 Tab 100 mg; TID: three times a day.

Additional work up and management – Patients were routinely evaluated by immune effector cell-associated encephalopathy (ICE) score once a day and, in case of grade ≥2 ICANS, every 8 hr. All ICANS events were graded and evaluated for reversible causes (medications, electrolytes, etc.). CRS was defined and graded as per ASTCT 2019 and ASCO 2021 guidelines, as were imaging and electroencephalogram (EEG) studies for grade >2 and refractory ICANS.[19,21] Lumbar puncture was performed when central nervous system (CNS) involvement or infection was suspected.

Preparative regimen and supportive care

All patients received ≥1 prior therapy before anti-CD19 CAR-T. Patients were admitted to the Bone Marrow Transplantation ward in designated HEPA-filtered rooms (high efficiency particulate air filters). LD consisted of cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) for three days (days –5 to –3). Prophylaxis included acyclovir from LD start, and ciprofloxacin and fluconazole during neutropenia (<500/µL). Red blood cell and platelet transfusions were given for hemoglobin <7 g/dL and platelets <10x10^9/L, respectively. Premedication for infusion included IV promethazine 6.25 mg and PO paracetamol 1,000 mg. Cells were thawed and infused according to the manufacturer's recommendations.[22,23]

Primary and secondary endpoints

Primary endpoints were ICANS duration and refractory ICANS. Secondary outcomes included length of hospital stay, cumulative corticosteroid dose (dexamethasone equivalents), disposition (home *vs*. rehabilitation), CAR-T expansion, and 3-month complete response (CR) rates. Safety endpoints included non-relapse mortality (NRM) and early/late toxicities (infections, immune effector cell-associated hematotoxicity [ICAHT] and immune effector cell-associated hemophagocytic syndrome [IEC-HS]).

Assessment

CAR-T expansion was measured by flow cytometry based on median time to peak expansion (day +7 for axi-cel and day +14 for brexu-cel), as reported in pivotal trials[1,5,6] and following additional in-house validation of expansion kinetics, and as previously published by our group.[24] Disease was evaluated with PET-CT and bone marrow biopsy (if indicated) before LD, with response evaluated according to Lugano criteria.[25] ECOG performance status[26] was recorded. Cytopenias were scored using ICAHT; IEC-HS was defined as per ASTCT 2023.[27,28] Prediction models (day 3+ modified Endothelial Activation and Stress Index [mEASIX][29] and ICANS-Prognostic Scoring System [PSS][30] scores) were applied for severe ICANS risk.

Statistical analysis

Mann-Whitney U test was used for two-group comparisons of continuous variables, ordinal logistic regression for ordered categorical outcomes, Kendall's tau for ordinal correlations, logistic regression and ROC analysis for predictive scores, and Kaplan-Meier with log-rank tests for time-to-event data. NRM was calculated using a competing risks approach with relapse as a time-dependent covariate in the Fine-Gray model. P<0.05 was considered statistically significant. Analyses were performed in R v.4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Between April 2023 and December 2024, 95 patients were referred for evaluation of anti-CD19 CAR-T treatment. Four patients were either not eligible or decided not to proceed to CAR-T. Two patients underwent lymphopheresis but had a rapid disease progression and did not receive the product. Eighty-seven (92%) patients received lymphodepletion; among these, 45 (52%) met eligibility criteria. Median age in the cohort was 75 years (range: 65-86 years), 78% of patients had ECOG performance score >2, 42% of patients had a neurologic comorbidity, and 22% had active CNS involvement. Twenty-four (53%) patients had progressive disease at lymphodepletion.

Comparisons of other characteristics and populations to those in clinical trials and real-world data are outlined in Table 2. Overall, there was a high proportion of individuals with poor performance status (ECOG) and a significant percentage with progressive disease at the time of lymphodepletion. In 23 (82%) patients, CRS preceded ICANS (median time from CRS to ICANS: 4 days; range: 1-16 days), while in 5 patients (18%), CRS occurred concomitantly. Any grade CRS was observed in 98% of patients, of which 20% was grade ≥3. A median of 2 (range: 0-4) tocilizumab doses were given for CRS management.

ICANS metrics and management

Any grade ICANS developed in 67% of patients; median onset was five days (range: 0-15 days) post CAR-T, and median duration was four days (range: 1-15 days). Grade ≥3 ICANS developed in 31% of patients. Among patients who developed any grade ICANS, the presenting signs were writing abnormality in 73%, inattention in 47%, naming in 33%, orientation in 30%, and inability to follow commands in 17%. Two patients were not able to perform the full ICE score components and one patient presented with seizure. Refractory ICANS was observed in 9 patients (20%) and this developed in a median of six days (range: 4-16 days) post CAR-T.

In univariate analysis, no significant association was found between age, disease status at LD, neurologic comorbidity, CRS grade, day of CRS onset, day 7+ expansion and tocilizumab use, or the occurrence of refractory ICANS. Figures 1, 2 and 3 depict ICANS-related metrics and temporal trends. Median cumulative steroid dose was 160 mg

(interquartile range [IQR]: 20-530 mg); anakinra was used in 11 (24%) patients. Median length of hospital stay was 22 days (range: 15-86 days) and 7 patients (15%) required in-patient rehabilitation after their initial discharge.

Electroencephalogram was performed in 13 patients. Abnormal activity was recorded in 85% of cases. In 7 patients, the findings were interpreted as generalized abnormal discharges. In 2 patients, the abnormal activity was restricted to the left temporal lobe and localized to the right parietal and right frontal lobes in one patient each. No epileptiform activity was recorded. Imaging was performed in 15 patients (33%) (MRI: N=10; CT scan: N=5). The most common finding in MRI was T2/ fluid-attenuated inversion recovery (FLAIR) hyperintensities found in 9 of 10 MRI scans. Most commonly located in the white matter (periventricular, subcortical), brainstem (pons, midbrain), thalami, and cerebellum. One patient had a small microhemorrhage on susceptibility-weighted imaging (SWI) sequence, located at the frontal lobe. No leptomeningeal enhancement, cerebral edema or restricted diffusion was identified. *Online Supplementary Table S1* summarizes the characteristics of MRI and EEG findings.

Predictors for severity and duration of ICANS

Early onset CRS (≤ day 3+) was not associated with ICANS duration (P=0.57). Similarly, peak expansion of CAR-T cells was also not associated with ICANS duration (Spearman correlation (P): 0.01 P value=0.96) or severity (121 cells/microL in patients who did not develop severe ICANS *vs.* 48 cells/microL in patients who did; P=0.15).

Disease status at lymphodepletion was not associated with

Table 2. Patients and disease characteristics.

Characteristic	Study protocol N=45	ZUMA 7 N=180	ZUMA 7 ≥65 yr N=51	ALYCANTE N=62	CIBMTR Registry N=446
Age, yr					
Median (range)	75 (65-86)	58 (21-80)	70 (65-81)	70 (49-81)	64 (19-86)
Age ≥65, N (%)	45 (100)	51 (28)	51 (100)	55 (88)	NR
Age ≥75, N (%)	23 (49)	NR	24 (47)	7 (11)	NR
Female sex, N (%)	20 (44)	70 (39)	NR	15 (24)	160 (36)
ECOG ≥2, N (%)	35 (78)	0 (0)*	0 (0)*	1 (2)	13 (3)
Neurologic comorbidity, N (%)	19 (42)	0 (0)	0 (0)	NR	NR
Disease characteristics, N (%)					
DLBCL	36 (80)	110 (61)	51 (100)	52 (84)	347 (78)
MCL	8 (18)	0 (0)	0 (0)	0 (0)	0 (0)
ALL	1 (2%)	0 (0)	0 (0)	0 (0)	0 (0)
CNS involvement	10 (22)	0 (0)	0 (0)	0 (0)	NR
Primary refractory/early relapse	19 (53)/13 (36)	133 (74)/47 (26)	36 (70)/15 (30)	NR	NR
Received bridging therapy	44 (98)	0 (0)	0 (0)	52 (84)	294 (66)
SD\PD at lymphodepletion	27 (60)	NR	NR	7 (11)	NR
LDH >ULN lymphodepletion	27 (62)	101 (56)	31 (61)	7 (11)	214 (48)
Non-ICANS toxicities					
CRS any grade, N (%)	44 (98)	157 (92)	48 (98)	58 (93)	388 (87)
CRS Grade ≥3, N (%)	9 (20)	11 (6)	4 (8)	5 (8)	13 (3)
ICAHT, N (%)†	21 (47)	43 (24)	NR	62 (27)	95 (21)
Infections, N (%)	19 (42)	NR	NR	17 (27)	143 (32)
IEC-HS, N (%)	15 (33)	0 (0)	0 (0)	NR	NR
Cumulative steroid, median (IQR)‡	160 (20-530)	NR	NR	NR	NR
Patients received Anakinra, N (%)	11 (24)	0 (0)	NR	0 (0)	80 (18)
Median N of days in hospital (range)	22 (15-86)	NR	NR	NR	NR
Response, N (%)					
ORR	21 (47)	149 (83)	25 (75)	47 (76)	353 (79)
CR	20 (44)	117 (65)	38 (75)	44 (71)	285 (64)
PFS§	19 (43)	86 (48)	22 (42)	30 (49)	236 (53)
OS§	21 (46)	135 (75)	33 (64)	49 (78)	317 (71)

ALL: acute lymphoblastic leukemia; CIBMTR: Center for International Blood and Marrow Transplantation Research; CNS: central nervous system; CR: complete response; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; ICAHT: immune effector cell-associated hematotoxicity; ICANS: immune effector cell-associated neurotoxicity syndrome; IEC-HS: immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; IQR: interquartile range; LDH: lactate dehydrogenase; MCL: mantle cell lymphoma; N: number; NR: not reported; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; SD: stable disease; ULN: upper limit of normal; yr: years. *Exclusion criteria. †Early (≤30 days). ‡Dexamethasone equivalent. §At 12 months.

severe ICANS: 4/10 patients (40%) with low disease burden (CR/partial response [PR]) developed severe ICANS, compared to 10/20 (50%) with high disease burden (*P*=0.89). Similarly, LDH levels at lymphodepletion showed no significant correlation with ICANS severity or duration, though a positive trend was noted. LDH levels correlated with ICANS duration (Spearman *P*=0.33, *P*=0.07), and patients who developed grade ≥3 ICANS had a higher median LDH (488 U/L) than those who did not (389 U/L) (*P*=0.07). Baseline neurologic comorbidity was not associated with high grade CRS but was, however, associated with duration of ICANS (median 7 days for those patients with neurologic comorbidity *vs*. 3 days in patients without; *P*=0.02). Nevertheless, no association was observed between baseline CNS involvement and severe ICANS (*P*=0.47) or ICANS duration (*P*=0.36).

Poor performance status showed a statistically significant moderate positive correlation with ICANS severity (*P*=0.38, *P*=0.04), with a non-statistically significant trend toward ICANS duration (*P*=0.33, *P*=0.07). In contrast, no association was observed between age and ICANS duration or severity. Higher mEASIX score was associated with a trend toward increased risk of ICANS ≥3 but this did not reach statistical significance (*P*=0.11); the model discriminative performance was moderate (AUC=0.68). In contrast, the ICANS-PSS score was not associated with high grade ICANS (odds ratio [OR]=0.99, 95% Confidence Interval [CI]: 0.39-2.49; *P*=0.98) and demonstrated poor discriminative ability (AUC=0.50).

Non-ICANS CAR-T-associated toxicities

Twenty-one patients (47%) developed early ICAHT (≤30 days),

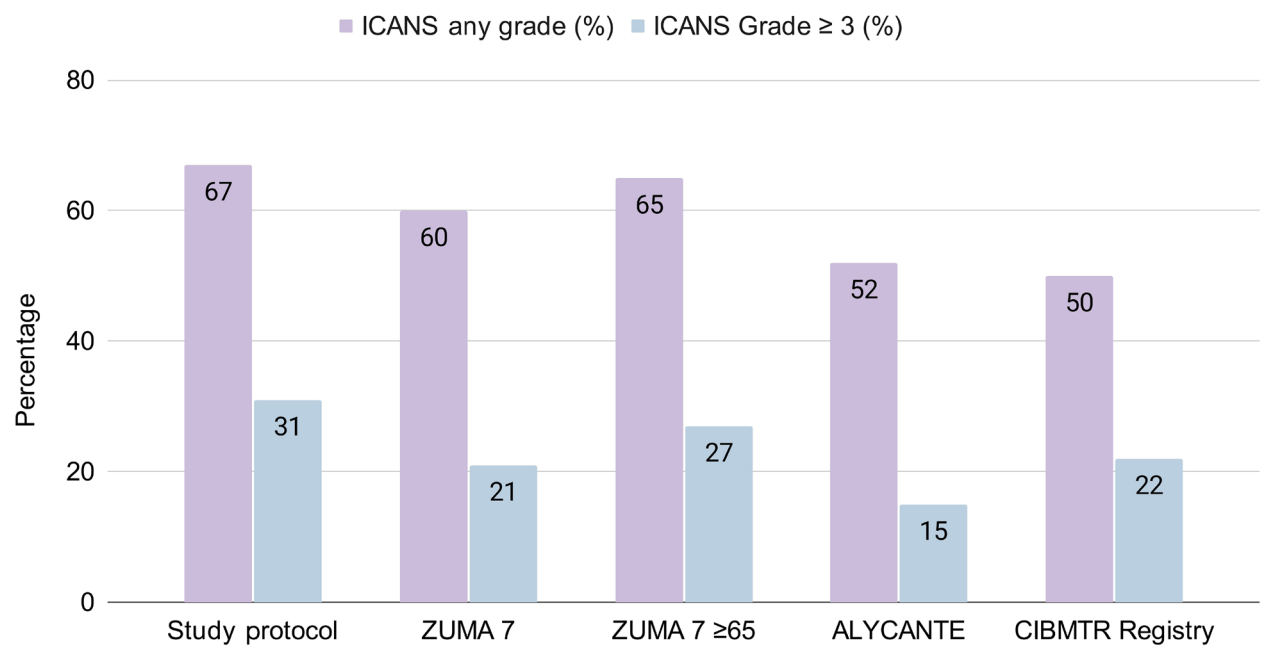

Figure 1. Incidence of immune effector cell-associated neurotoxicity syndrome. CIBMTR: Center for International Blood and Marrow Transplantation Research; ICANS: immune effector cell-associated neurotoxicity syndrome.

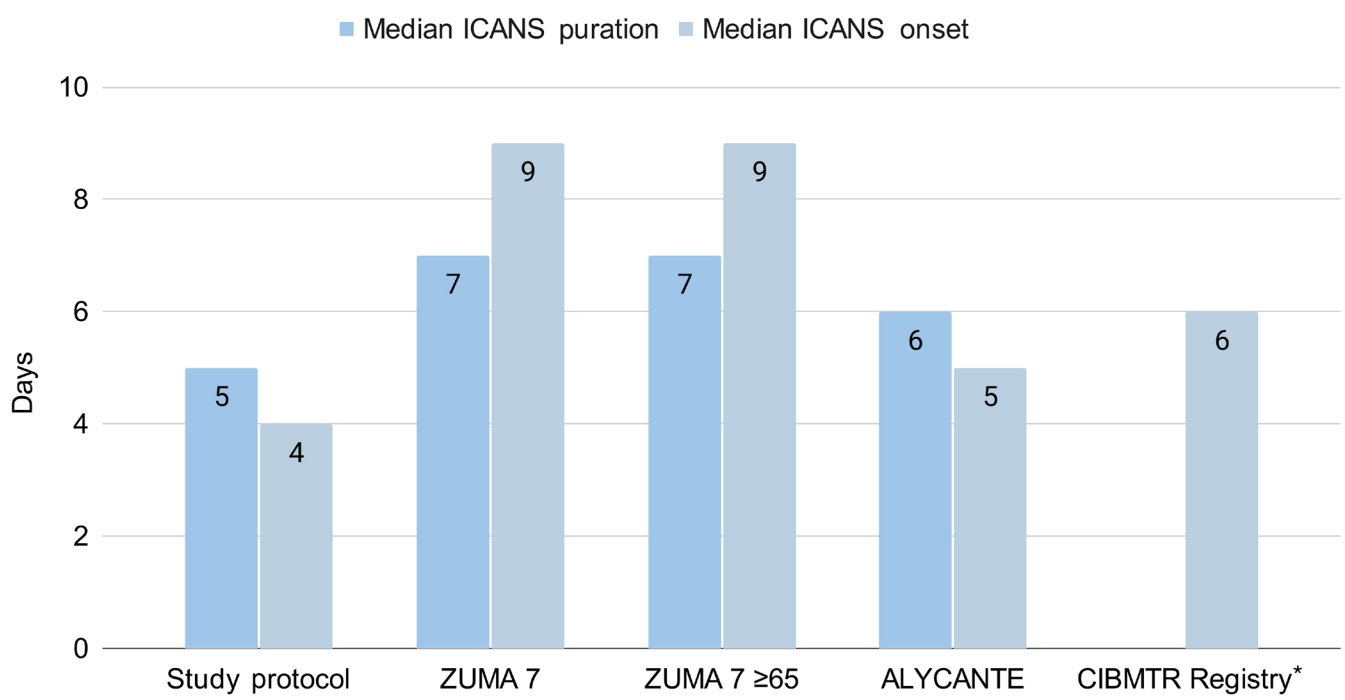

Figure 2. Immune effector cell-associated neurotoxicity syndrome metrics comparison. *Onset of immune effector cell-associated neurotoxicity syndrome (ICANS) was not specified in the publication of the Center for International Blood and Marrow Transplantation Research Registry (CIBMTR) Registry. IQR: interquartile range.

of whom 12 (26%) had grade ≥3 events. Among patients who developed ICAHT, 71.4% experienced thrombocytopenia (T-ICAHT), 85.7% developed neutropenia (N-ICAHT), and 57.1% had both T-ICAHT and N-ICAHT. Steroid exposure was numerically higher in patients who developed ICAHT compared with those who did not (250 *vs*. 74 mg; *P*=0.12). Granulocyte colony-stimulating factor was given to 37.8% of patients for early neutropenia and was not associated with cumulative steroid dose (OR=1.001; 95%CI: 0.999-1.003; *P*=0.19). Similarly, there was no association between cumulative steroid exposure and patients who developed (N=10, 22%) or did not develop hypogammaglobulinemia (median 117.0 *vs*. 160.5 mg, respectively; *P*=0.27). This was also true between patients who developed (N=15, 34%) or did not develop IEC-HS (median 250 *vs*. 138 mg, respectively; *P*=0.484). No post-CAR-T secondary malignancy was documented.

Cytomegalovirus (CMV) reactivation requiring treatment occurred in 5 patients (11%). The median cumulative steroid dose was numerically higher among patients who developed CMV reactivation compared to those who did not (358.5 mg [IQR: 320.0-380.0] *vs*. 138.0 mg [IQR: 20.0-536.2], respectively; *P*=0.133).

Documented infections occurred in 19 of 45 patients (42%), including 14 bacterial infections, 4 invasive fungal infections, and 2 cases of COVID-19. In univariate analysis, patients who experienced infections had a significantly higher cumulative steroid dose compared to those who did not (median: 380 *vs*. 77.5 mg, respectively; *P*=0.002).

Anakinra use was not associated with infectious complications. Infections occurred in 10 out 18 patients (55.6%) who received anakinra compared with 13 out of 27 (48.1%) who did not (*P*=0.16). When analyzed by cumulative anakinra dose, we observed a non-significant trend toward higher infection rate with greater exposure (*P*=0.06). We did not observe any other adverse effect that can directly be attributed to anakinra use.

Incidences of NRM at 1- and 3-months post CAR-T were 8.7% (95%CI: 0-20.2%) and 26.1% (95%CI: 8.1-44%), respectively. The causes of NRM were: simultaneous ICAHT and infection (N=5), infection (N=2), ICAHT (N=1), and refractory ICANS (N=1). In 2 patients, the cause of death remained undetermined. Higher steroid dose was significantly associated with higher NRM; the median cumulative steroids exposure was 850 mg (IQR: 532.5-1,020.6) among NRM patients *versus* 77.5 mg (IQR: 20-239.4) among non-NRM patients (*P*=0.02).

Efficacy of CAR-T

Median follow-up of surviving patients was 5.9 months (range: 0.5-19.4 months). Nineteen patients (42%) were alive at data extraction. Median peak expansion of CAR-T was 72 cells/microL (range: 0-1,725 cells/microL). There was no association between the cumulative steroid dose and CAR-T expansion on day 7+ (τ [Kendall's tau]=0.0857; *P*=0.415). At three months post CAR-T, 20 patients (44%) achieved CR and one achieved PR. Cumulative incidences of progression-free survival (PFS) at 6 and 12 months were 46% (95%CI: 30.0-59.7) and 42.9% (95%CI: 26.9-56.8), respectively. Cumulative incidences of overall survival at six and 12 months were 59% (95%CI: 43.5-73.0) and 46.1% (95%CI: 29.3-56.8), respectively (Figure 4).

Discussion

To our knowledge, this is the first attempt to implement a specified ICANS treatment protocol for older patients treated with CAR-T, together with a pragmatic and short-interval

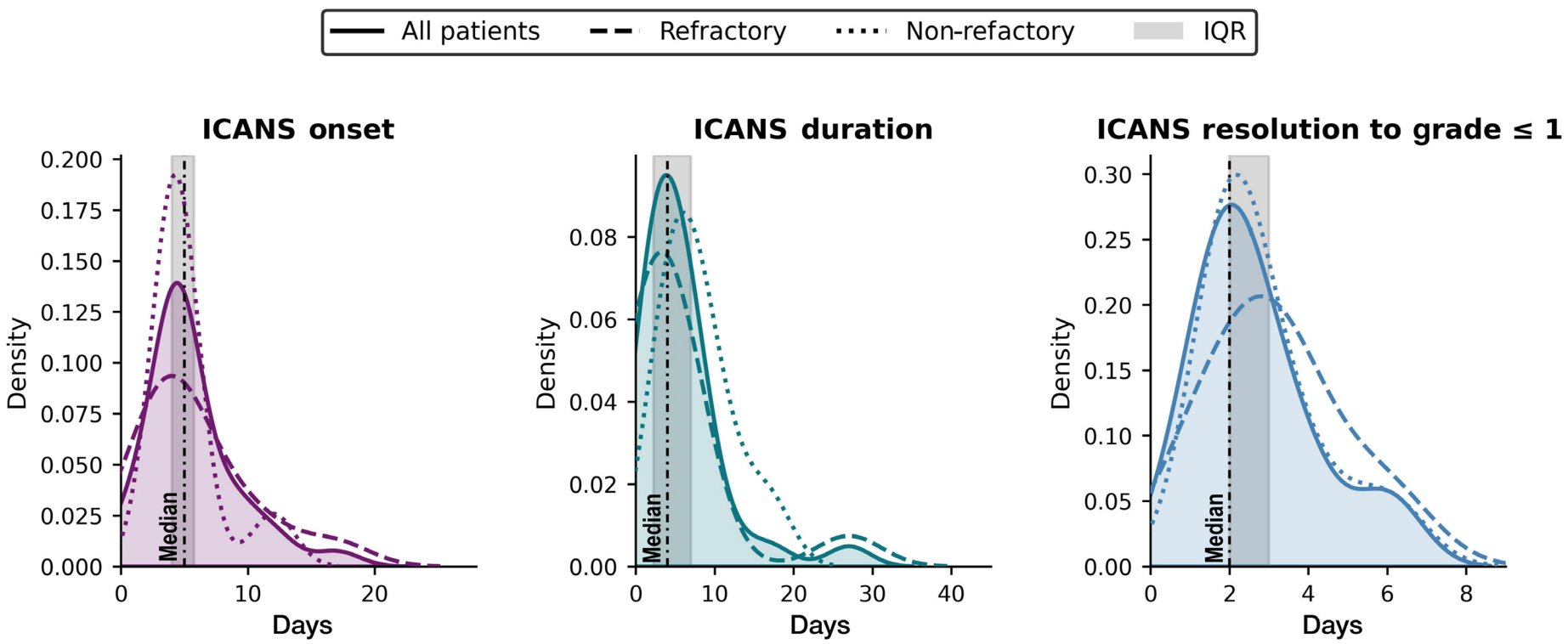

Figure 3. Immune effector cell-associated neurotoxicity syndrome metrics trends for refractory and non-refractory patients. ICANS: immune effector cell-associated neurotoxicity synrdome; IQR: interquartile range.

definition of refractoriness, treatment escalation, and early integration of anakinra (rather than prophylactic or salvage therapy). Taken together, our findings suggest that this protocol may mitigate ICANS duration in an extremely high-risk population of patients treated with a CD28-based co-stimulatory CAR-T, to levels comparable to those observed in standard-risk cohorts, with no sign of compromising CAR-T expansion or efficacy.

Treatment components and dosing were adapted from current consensus guidelines and case reports of refractory ICANS management[19,20] with adaptation to a high-risk population with steroids as the backbone of ICANS management. Previous attempts in safety cohorts of the ZUMA1 used prophylactic steroids and showed reduction in CRS incidence and severity in cohort 4,[31] although there was no benefit to ICANS development or grade in a matched analysis of cohort 6 of ZUMA1.[32] ICANS management in cohort 6 included steroid treatment from grade 1, and long-term data showed no compromise of either expansion or outcomes.[31,32] Based on this, we decided to integrate steroids early and in an intensive manner in the protocol. (See Table 1 for an outline of the study protocol.)

In cohort 3 of the ZUMA 1, prophylactic levetiracetam was given with tocilizumab and failed to reduce ICANS rates.[33] Considering the scarcity of data, extremely high-risk patients and favorable toxicity profile of the drug, we decided to give all patients seizure prophylaxis coverage with levetiracetam. The use of thiamine in the protocol is primarily supported by observational data, biological plausibility, and indirect evidence from analogous clinical scenarios. Such scenarios include thiamine deficiency observed in patients with CRS and ICANS, imaging studies of ICANS patients mimicking Wernicke's encephalopathy, and sepsis patients who are often thiamine-depleted, which is associated with damage to the blood brain barrier.[34-36]

Anakinra use is based on several retrospective studies and case reports showing its potential as a rescue therapy for steroid refractory ICANS,[20,37-39] and from early studies showing promising results of its effectiveness as a prophylactic agent.[40,41] Both scenarios showed a good safety profile with its use in this setting. Considering that the timing and grade of CRS along with tocilizumab use are associated with developing ICANS,[12,31] each tocilizumab dose was given together with dexamethasone.

There is no uniform definition of refractory ICANS and previous descriptions across studies have been inconsistent.[20,37,39] Our aim was to create a standardized treatment for this extremely high-risk population in whom high rates of ICANS were expected. Given the population's low physiological reserve and potentially consequential effects of

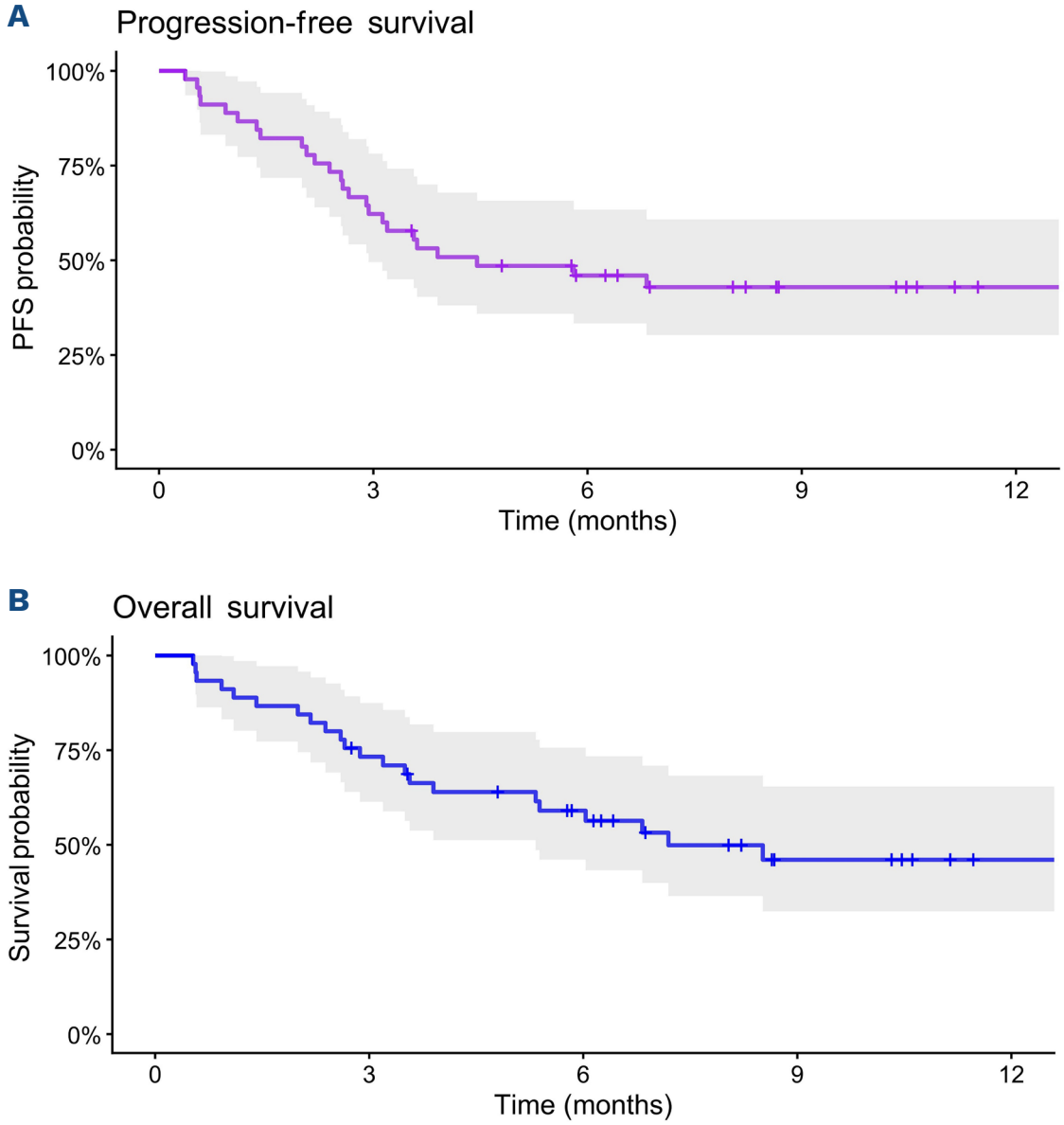

Figure 4. Kaplan-Meier survival curves. (A) Progression-free survival (PFS). (B) Overall survival.

prolonged and severe ICANS, we defined refractoriness as escalating or lack of improvement within 24 hr of treatment initiation. We observed a different and more severe ICANS trajectory with patients who met the refractory definition in our cohort. Though clinically coherent and in some way expected, the lack of a uniform and time-bound definition makes the observation that a 24 hr time frame for lack of improvement might be sufficient to suggest escalation of treatment, and perhaps even before when high-risk features are present.

A key finding in our cohort was a markedly short median duration of ICANS of four days (range: 1-15 days); this is favorable when compared with the median of 5-9 days observed in the ALYCANTE trial,[42] real-word data,[11,43] and the ZUMA-7 trial,[1,44] all of which included markedly less predisposed populations. This shorter duration was achieved despite a substantial incidence of ICANS (overall and severe in 67% and 31%, respectively). Interestingly, although there were more higher risk patients in our cohort, grade ≥3 ICANS incidence was comparable to that observed in the most elderly subgroups of the ZUMA-7 (27% for patients ≥65 years and 33% for patients ≥70 years), underscoring the potential of the current protocol to mitigate further neurologic deterioration.

In order to examine the effectiveness of the protocol with the caveat of a single arm design, we evaluated several surrogates that are known to be associated with ICANS severity. Several studies of both CD28 and 41-BB established an association between CAR-T expansion and ICANS severity,[4,7,9] which was not shown in our cohort of high-risk patients. Similarly, previously reported factors such as disease status at lymphodepletion and CRS onset were also not associated either with higher incidence of grade ≥3 ICANS or with longer duration.[7,12,14] Interestingly, neurological comorbidities, which were widely defined, were associated with duration but not severity of ICANS, perhaps suggesting a distinct mechanism for ICANS pathogenesis and recovery; this might further guide management of such patients. The lack of a predictive value of both the mEASIX score[29] at day +3 and the ICANS-PSS[30] score in our high-risk cohort may suggest that the prospective protocol effectively attenuated the clinical and biological factors captured by these models. It could also reflect the fact that these models have limited applicability in populations with an inherently elevated risk for ICANS, as they were not originally validated in such settings. On the other hand, the lack of a predictive value may also have been due to the relatively small sample size. Consistent with previous observation, our cohort demonstrated a distinct time gap between CRS and ICANS. The findings that ICANS duration was short and not associated with the timing of CRS onset support using this intervening period for pre-emptive mitigation strategy. This could be considered when designing future trials.

Considering this, anakinra has been utilized in ICANS management at both ends of the clinical spectrum: prophylactically and in refractory cases.[20,39-41] To our knowledge, we are the first to demonstrate that early integration of anakinra, initiated upon lack of rapid improvement or escalation within 24 hr, may offer additional clinical benefit.

Non-relapse mortality and increased infectious complications (similar to other reports[45]) were notable in this protocol. Importantly, the majority of NRM cases in our cohort occurred in the context of concurrent cytopenia presumed to be related to ICAHT and to the clinical vulnerability of our patient population. Nevertheless, risk might be minimized with a preventive approach stratified by steroid exposure, use of anakinra, and satisfying the definition of refractory ICANS.

We acknowledge several limitations to our study. First, this was a single arm pilot study design with a relatively small sample size (with an under-representation of acute lymphoblastic leukemia and mantle cell lymphoma). Nevertheless, a comparison (even though indirect) of our extreme high-risk population cohort and ICANS metrics to previous studies, alongside several surrogates to assess efficacy and safety, offers valuable information on ICANS management in this population with a novel standardized approach. Both axi-cel and liso-cel are available as second-line therapies, joined by tisa-cel for later lines; all have demonstrated comparable efficacy in parallel studies, although with a higher toxicity profile for axi-cel.[1-3] This protocol may serve as a backbone in cases in which 4-1BB based-anti CD-19 CAR-T is not available and axi-cel is chosen for these vulnerable populations.[46,47]

In summary, we demonstrate that, since most risk factors for ICANS both pre- and post-infusion are unmodifiable, a mitigation-based approach may offer a compelling alternative to safely extend CAR-T therapy to high-risk elderly patients. Future studies should focus on decreasing steroid dose and incorporate steroid-sparing agents (i.e., anakinra, JAK inhibitors,[48] siltuximab[49]) early in the treatment course to further mitigate ICANS and the associated comorbidity burden.

Disclosures

RR reports honoraria from Novartis, Gilead, Takeda, BMS, MDS and Sanofi; YH reports honoraria from Abbvie, Astra-Zeneca, Medison, Lily and Roche, a research grant from Janssen, and advisory board for Beigene, Ascentage and Lily. All of the other authors have no conflicts of interest to disclose.

Contributions

GF, OA and RR designed the study, collected and analyzed the data, interpreted the results, and wrote the first draft of the manuscript; YS, RG, CGS, CP, YH, EJ, TS, RV, MP, SP, NS, SBB and IA collected data and interpreted the results. All authors critically revised the manuscript for important intellectual content.

Data-sharing statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

1. Locke FL, Ghobadi A, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.
2. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplant in relapsed or refractory large B-cell lymphoma (TRANSFORM): a randomised, open-label, phase 3 trial. Lancet. 2022;399(10343):2294-2308.
3. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.
4. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 2021;11(4):69.
5. Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. J Clin Oncol. 2023;41(3):555-567.
6. Shah BD, Cassaday RD, Park JH, et al. Three-year analysis of adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with brexucabtagene autoleucel in ZUMA-3. Leukemia. 2025;39(6):1058-1068.
7. Lin X, He Y, Zhao M, Wu Y, Li Z, Liu J. Mechanisms and management of CAR T-cell-related neurotoxicity and cytokine release syndrome in CD19-directed therapy. J Hematol Oncol. 2021;14(1):47.
8. Looka A, Sbeitan O, Campbell S, et al. A real-world comparison of commercial-use axicabtagene ciloleucel and lisocabtagene maraleucel in large B-cell lymphoma. Blood Adv. 2025;9(3):455-462.
9. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145-2154.
10. Pasquini MC, Locke FL, Herrera AF, et al. Real-world outcomes of axicabtagene ciloleucel for large B-cell lymphoma from the CIBMTR: impact of patient characteristics and prior therapies. J Clin Oncol. 2022;40(36):3938-3948.
11. Lee DC, Jacobson CA, Kittai AS, et al. Real-world early outcomes of second-line axicabtagene ciloleucel (axi-cel) therapy in patients (pts) with relapsed or refractory (R/R) large B-cell lymphoma (LBCL). Blood. 2024;144(Suppl 1):526.
12. Grant SJ, Grimshaw A, Mian H, et al. Clinical presentation, risk factors, and outcomes of immune effector cell-associated neurotoxicity syndrome following chimeric antigen receptor T cell therapy: a systematic review. Transplant Cell Ther. 2022;28(6):294-302.
13. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
14. Ucpinar BA, Brown S, Bedmutha A, et al. PET-based biomarkers for toxicity prediction in CAR T-cell therapy for aggressive lymphoma: evidence from a large-scale retrospective analysis. J Nucl Med. 2025;66(Suppl 1):251586.
15. Rubin DB, Al-Homsi AS, Mehta-Shah N, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. Brain. 2020;143(5):1334-1348.
16. Nair NM, Lulla P, Lulla A, et al. Physical function measures identify non-Hodgkin lymphoma patients at high risk of immune effector cell-associated neurotoxicity syndrome (ICANS) and 1-year mortality after chimeric antigen receptor T (CAR-T) cell therapy. Transplant Cell Ther. 2025;31(2 Suppl):S46.
17. Haslam A, Hoeg TB, Prasad V. Estimation of eligibility for and response to CAR-T therapy in the United States. Blood Adv. 2024;8(4):1032-1036.
18. Jaggers JL, Gries M, Blalock J, et al. Characterizing inclusion and exclusion criteria in clinical trials for chimeric antigen receptor (CAR) T-cell therapy among adults with hematologic malignancies. J Geriatr Oncol. 2021;12(2):235-238.
19. Santomasso BD, Nastoupil LJ, Crombie JL, et al. Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO guideline. J Clin Oncol. 2021;39(35):3978-3992.
20. Santomasso BD, Gust J, Perna F. How I treat unique and difficult-to-manage cases of CAR T-cell therapy-associated neurotoxicity. Blood. 2023;141(20):2443-2451.
21. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
22. Yescarta (axicabtagene ciloleucel) [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2024. https://www.fda.gov/media/108377/download Accessed August 18, 2025.
23. Tecartus (brexucabtagene autoleucel) [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2024. https://www.fda.gov/media/140409/download Accessed August 18, 2025.
24. Ram R, Amit O, Wolf I, et al. Addition of nivolumab tailored by expansion of CAR-T cells in patients with stable/progressive large B cell lymphoma at lymphodepletion-a phase 2, prospective interventional study. Transplant Cell Ther. 2024;30(12):1178-1188.
25. Cheson BD, Fisher RI, Barrington SF, et al. Refinement of the Lugano classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128(21):2489-2496.
26. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.
27. Rejeski K, Perez A, Kase J, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. Blood. 2023;142(10):865-877.
28. Hines MR, Caimi PF, Keng M, et al. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. Transplant Cell Ther. 2023;29(7):438.e1-438.e7.
29. Pennisi M, Jain T, Santomasso BD, et al. Easix and modified-Easix are early predictors of severe cytokine release syndrome and neurotoxicity in patients treated with chimeric antigen receptor T cells. Blood. 2019;134(Suppl 1):1947.
30. Kirkwood AA, Au-Yeung R, Salles G, et al. Novel prognostic scoring systems for severe CRS and ICANS after anti-CD19 CAR T cells in large B-cell lymphoma. eClinicalMedicine. 2024;70:102521.
31. Topp MS, van Meerten T, Houot R, et al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021;195(3):388-398.
32. Oluwole OO, Forcade E, O'Leary D, et al. Long-term outcomes of patients with large B-cell lymphoma treated with axicabtagene ciloleucel and prophylactic corticosteroids. Bone Marrow Transplant. 2024;59(3):366-372.
33. Locke FL, Jacobson CA, Westin JR, et al. Tocilizumab prophylaxis following axicabtagene ciloleucel in relapsed or

refractory large B-cell lymphoma. Transplant Cell Ther. 2024;30(11):1065-1079.
34. Santomasso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018;8(8):958-971.
35. Costa NA, de Souza IC, de Souza JV, da Silva A Jr, Pinheiro M Jr, Zamos F. Serum thiamine concentration and oxidative stress as predictors of mortality in patients with septic shock. J Crit Care. 2014;29(2):249-252.
36. Hazell AS, Butterworth RF. Region-selective permeability of the blood-brain barrier to α-aminoisobutyric acid during thiamine deficiency and following its reversal. Metab Brain Dis. 2021;36(2):239-246.
37. Gazeau N, El-Murr T, Vey N, et al. Anakinra for refractory cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome after chimeric antigen receptor T cell therapy. Transplant Cell Ther. 2023;29(7):430-437.
38. Wehrli M, Galli S, Bacher U, et al. Single-center experience using anakinra for steroid-refractory immune effector cell-associated neurotoxicity syndrome (ICANS). J Immunother Cancer. 2022;10(1):e003847.
39. Jain MD, Smith M, Shah NN. How I treat refractory CRS and ICANS after CAR T-cell therapy. Blood. 2023;141(20):2430-2442.
40. Strati P, Ahmed S, Furqan F, et al. A phase 1 study of prophylactic anakinra to mitigate ICANS in patients with large B-cell lymphoma. Blood Adv. 2023;7(21):6785-6789.
41. Park JH, Park S, Tashiro H, et al. CD19 CAR T-cell therapy and prophylactic anakinra in relapsed or refractory lymphoma: phase 2 trial interim results. Nat Med. 2023;29(7):1710-1717.
42. Houot R, Bachy E, Cartron G, et al. Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial. Nat Med. 2023;29(10):2593-2601.
43. Kwon M, Iacoboni G, Reguera JL, et al. Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of aggressive B-cell lymphoma. Haematologica. 2023;108(1):110-121.
44. Kersten MJ, Miklos D, Locke FL, et al. Improved overall survival with axicabtagene ciloleucel vs standard of care in second-line large B-cell lymphoma among the elderly: a subgroup analysis of ZUMA-7. Blood. 2023;142(Suppl 1):1761.
45. Wudhikarn K, Palomba ML, Pennisi M, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. Blood Cancer J. 2020;10(8):79.
46. Hu B, Lin RJ, Lazaryan A, et al. Real-world analysis of barriers to timely administration of chimeric antigen receptor T cell (CAR T) therapy in diffuse large B-cell lymphoma. Transplant Cell Ther. 2024;30(11):1082.e1-1082.e7.
47. Novak U, Einsele H, Casadei B, et al. Choice of commercially available CAR-T cell products for r/r DLBCL & PMBCL in Europe: a survey on behalf of the cellular therapy & immunobiology working party (CTIWP) of the EBMT. Bone Marrow Transplant. 2024;59(11):1631-1634.
48. Diamond A, Luznik L. Inhibiting JAK1: lowering CRS, CAR stays on track. Blood. 2025;146(4):399-400.
49. Bajwa A, Zayac AS, Caimi PF, et al. Siltuximab for chimeric antigen receptor T-cell therapy-related CRS and ICANS: a multicenter retrospective analysis. Blood Adv. 2025;9(1):170-175.