

RESEARCH ARTICLE

Who Benefits Most? Patient Selection Frameworks for CAR T-Cell Therapy in Non-Hodgkin Lymphoma

Victoria A. Shestakova^{1,2a}, Ekaterina I. Smirnova^{1,2}, Victoria A. Rybachuk¹, Ilya D. Klabukov^{2,3}, Peter V. Shegay¹, Andrey D. Kaprin^{1,4}, Denis S. Baranovskii^{5,6,7,8}

¹ Department of Regenerative Medicine, National Medical Research Radiological Center of the Ministry of Health of the Russian Federation, Obninsk, Russia,

² Department of Biotechnology, Obninsk Institute for Nuclear Power Engineering of the National Research Nuclear University MEPhI, Obninsk, Russia,

³ Department of Regenerative, National Medical Research Radiological Center of the Ministry of Health of the Russian Federation, Obninsk, Russia,

⁴ Department of Urology and Operative Nephrology, Patrice Lumumba Peoples Friendship University of Russia (RUDN University), Moscow, Russia, ⁵ Research and Educational Resource Center for Cellular Technologies, Patrice Lumumba Peoples Friendship University of Russia (RUDN University), Moscow, Russia,

⁶ University of Basel, Basel, Switzerland, ⁷ K.E.Tsiolkovski's Kaluga State University, Kaluga, Russia, ⁸ FSBEI HE "Rosunimed" of the Ministry of Health of the Russian Federation, Moscow, Russia

Keywords: cell therapy, non-Hodgkin's lymphoma, CAR T-cell therapy, chimeric antigen receptor, immunotherapy

<https://doi.org/10.36000/HBT.OH.2025.25.190>

healthbook TIMES Oncology Hematology

Vol. 25, Issue 3, 2025

Non-Hodgkin's lymphoma (NHL) is a generic name for a diverse group of malignancies arising from lymphocytes and primarily affecting the lymph nodes, but also involving other organs. Chimeric antigen receptor (CAR) T-cell therapy has emerged as a groundbreaking treatment for patients with NHL, offering hope for those who have relapsed or are refractory to conventional therapies. However, due to the risk of toxicities such as cytokine release syndrome and neurotoxicity, the efficacy and safety of CAR T-cell therapy are highly dependent on patient selection criteria. This article outlines the most important considerations that clinicians need to make when evaluating candidates for CAR T-cell therapy. Key parameters for the optimal patient selection scale were categorized into four domains: disease biology, tumor burden and microenvironment, patient factors and risk mitigation. A 100-point scoring scale was created and patients were stratified into three prognostic groups: ideal candidates (≥ 70 points), conditional approval (40–69 points) and non-recommended (< 40 points). By integrating tumor-, host- and risk-mitigation-specific parameters, the novel score provides a practical and systematic approach to clinical decision-making in the field of cellular immunotherapy for NHL.

Received on July 07, 2025; accepted after peer review on October 02, 2025; published on October 10, 2025.

PEER REVIEWED ARTICLE

Peer reviewers:

Two anonymous peer reviewers

^a Corresponding author:

Victoria A. Shestakova, M.Sc.

Department of Regenerative Medicine

National Medical Research Radiological Center of the Ministry of Health of the Russian Federation

249036 Obninsk

Russia

Email: schestakova.vika2017@yandex.ru

Introduction

Non-Hodgkin's lymphoma (NHL) is a group of heterogeneous hematologic malignancies characterized by uncontrolled proliferation of lymphoid cells, with B-cell lymphomas accounting for approximately 90% of cases¹ and GLOBOCAN estimating 553,010 new cases and 250,475 deaths worldwide in 2022.² Currently, radiation therapy remains a potent intervention for NHL. It is a standard monotherapy for many indolent subtypes and is used as a consolidative treatment following chemoimmunotherapy in aggressive lymphomas, such as diffuse large B-cell lymphoma (DLBCL), especially in cases of bulky disease or partial response.^{3,4} In early-stage NHL, radiation therapy is the mainstay of treatment, especially for localized follicular and mucin-associated lymphoid tissue-derived lymphoma. Patients with late-stage large-cell and highly malignant lymphomas typically undergo chemotherapy.^{5,6} However, despite the usually good initial response to treatment, relapses occur frequently, requiring additional therapies. New therapies focus mainly on epigenetic regulation and immunomodulation. Epigenetic dysregulation plays a crucial role in lymphomagenesis, leading to the development of various epigenetic-modifying agents.⁷ These include inhibitors targeting histone deacetylases (HDACs),⁸ DNA methyltransferases (DNMTs),⁹ enhancer of zeste homolog 2 (EZH2),¹⁰ extra-terminal domain proteins (BETs),¹¹ protein arginine N-methyltransferases (PRMTs)¹² and isocitrate dehydrogenase (IDH).¹³ Immunotherapy strategies, including the use of monoclonal antibodies,¹⁴ antibody-drug conjugates,¹⁵ immune checkpoint inhibitors¹⁶ and chimeric antigen receptor (CAR) T-cell therapy,¹⁷⁻¹⁹ have shown promising results in relapsed or refractory NHL.

CAR T-cell therapy has emerged as a promising treatment for relapsed/refractory aggressive B-cell NHL, providing overall response rates (ORR) ranging from 40% to 83%,²⁰ 12-month progression-free survival (PFS) rates ranging from 33% to 42% and 12-month overall survival (OS) rates ranging from 54% to 73%.^{21,22} However, in three large-scale multicenter phase III clinical trials, CAR T-cell therapy was associated with notable side effects. Specifically, the most common side effect of CAR T-cell therapy was moderate-to-severe cytokine release syndrome (CRS), which was observed in all three trials. In addition, side effects also included neurotoxicity, prolonged cytopenias and hypogammaglobulinemia.^{17,23} Other potential complications included B-cell aplasia and hemophagocytic lymphohistiocytosis.²⁴ Differences in patient selection largely explain the wide range of efficacy rates observed in CAR T-cell therapy trials. Notably, the efficacy of CAR T-cell therapy depends not only on the treatment regimen itself, but also on the appropriate selection of patients. Proper patient selection for CAR T-cell therapy is important to ensure an optimal therapeutic effect with minimal risk of potential side effects. Various parameters, including diagnosis, disease stage, number of lesions, tumor diameter, metabolic tumor volume,

circulating tumor DNA, prior treatments, CD19 antigen density, molecular markers, T-cell fitness, programmed death-ligand 1 (PD-L1) expression, performance status, hematological parameters, organ function and comorbidities, should be considered.

To address this issue, we developed a rating scale based on studies from [ClinicalTrials.gov](https://clinicaltrials.gov), PubMed and Google Scholar to guide clinicians in selecting patients for CAR T-cell therapy for NHL.

Materials and Methods

A comprehensive analysis of the extant literature was conducted using electronic databases including [ClinicalTrials.gov](https://clinicaltrials.gov), PubMed and Google Scholar. A search strategy was meticulously devised utilizing pertinent Medical Subject Heading terminology and keywords, namely “B-cell non-Hodgkin’s lymphoma”, “B-cell lymphoma”, “CAR-T”, “CD19 CAR T-Cells”, “Chimeric antigen receptor T cells”, “CAR-T cell therapy”, “Patient selection”, “Immunotherapy”. A bespoke search filter was configured to display publications exclusively from the specified timeframe of 2015-2025. The following criteria were used to screen the papers: 1) utilization of CAR T-cell therapy for B-cell NHL as a stand-alone therapy; 2) disease-specific biological factors, tumor burden characteristics, patient factors related to the host and risk reduction parameters; 3) clinical trial (phase I-IV), systematic review/meta-analysis and research articles; 4) toxicity and survival outcomes.

The exclusion criteria encompassed instances of incomplete or insufficient data, as well as the presence of significant comorbidities that could potentially influence the outcomes. Consequently, the following sources were analyzed: 28 research articles, six review articles and 10 protocols on the specified topic.

Results

The [ClinicalTrials.gov](https://clinicaltrials.gov) website currently lists 55 completed studies on CAR T-cell therapy for the treatment of NHL and its subtypes. However, the majority of these studies utilized combination treatment based on CAR T-cell therapy with chemotherapy or allogeneic hematopoietic stem cell transplantation (allo-HSCT). These combination therapies are designed to capitalize on the potential synergistic effects of multiple treatment modalities. For example, chemotherapy may enhance the function of CAR T cells by creating a pro-inflammatory tumor environment that maximizes CAR T-cell recruitment and activity.²⁵ However, the efficacy of these combinations faces some challenges and limitations. The dose and timing of the combination therapy are critical considerations that can significantly influence treatment responses.²⁶

One of the primary concerns in combining CAR T-cell therapy and allo-HSCT is the risk of antigen overlap. This occurs when target antigens are expressed not only on malignant cells but also on normal hematopoietic stem

cells and progenitor cells.^{27,28} This kind of overlap can lead to on-target/off-tumor toxicity, graft rejection and an increased risk of acute or chronic graft-versus-host disease (GVHD).²⁹ Additionally, patients may experience side effects of these combination regimens, such as infections, prolonged cytopenias, neurotoxicity and CRS. These are added to the extremely high risk of disease recurrence and persistence following allo-HSCT.³⁰ Moreover, the selection criteria for patients receiving combination therapy are far from similar to those for patients receiving CAR T-cell monotherapy. Candidates must be evaluated for overall fitness, prior treatment history (e.g., resistance to chemotherapy or prior HSCT), and disease-specific features (e.g., tumor mutational burden and antigen expression heterogeneity).³¹

Keeping these nuances in mind, we decided to focus our analysis on studies that employed CAR T-cell therapy as monotherapy against CD19 or CD20 antigens. Upon reviewing the [ClinicalTrials.gov](https://clinicaltrials.gov) database, we identified ten clinical studies that met these parameters. We also conducted a systematic literature review of 34 relevant articles to determine the efficacy and outcomes of CAR T-cell monotherapy in NHL, untainted by confounding factors inherent in combination regimens.

Through our comprehensive review of clinical trials, systematic reviews and peer-reviewed research articles, we have identified the critical criteria for optimal patient selection when considering CAR T-cell monotherapy for NHL ([Table 1](#)).

Having identified the key parameters that significantly affect the efficacy and safety of CAR T-cell therapy for NHL, we developed a comprehensive assessment scale designed to facilitate optimal patient selection. This scale assigns the highest number of points to criteria that play a significant role in treatment outcomes, as supported by the weight of evidence from published literature and clinical studies. Points were allocated based on the relative strength of each parameter's association with efficacy (e.g., ORR or PFS) and safety (e.g., incidence and severity of CRS and immune effector cell-associated neurotoxicity syndrome [ICANS]). Parameters with the most substantial and consistent impact, such as specific histological subtypes, CD19/CD20 antigen density, prior treatment lines etc., received the highest scores to ensure that the system accurately reflects their prognostic importance.

The scale classifies key factors into four main groups of parameters (systematically presented in [Table 2](#)): disease-specific biological factors, including histological subtype and CD19/CD20 antigen density; tumor burden characteristics, such as MTV and extranodal involvement; patient factors, including performance status, hematologic parameters and T-cell status; and risk reduction parameters, including CRS/ICANS risk profiling. By combining these parameters, this scale offers a standardized and objective framework that will enable physicians to more accurately assess patients' suitability for CAR T-cell therapy, providing a balanced assessment that takes

Table 1. Criteria for optimal patient selection for CAR-T therapy for non-Hodgkin lymphoma.

Parameter	Criteria	References
Diagnosis	Relapsed or refractory CD19/CD20 positive B-cell lymphoma, DLBCL - <i>de novo</i> or transformed, FL or tFL, MCL, PMBCL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma), CLL, SLL	32-41
Disease stage	III-IV (for all diagnoses, except refractory CD19/CD20-positive B-cell lymphoma)	32,39,41
Number of lesions	At least one measurable lesion	33-35,39
Maximum tumor diameter	≥1.5 cm	33-35,40
Prior treatments	Chemotherapy or allogeneic stem cell transplant	32-36,39,40
Time since prior treatment	Minimum of two weeks elapsed from the conclusion of the final treatment and less than 12 months after first-line therapy. The ORR with CAR T-cell therapy was observed to be associated with poorer outcomes in patients who had received >4 lines of therapy	34,35
CD19 antigen density	The optimal range for durable responses is 5,000–10,000 CD19 molecules/cell	42,43
Molecular markers	<i>TP53</i> and <i>B2M</i> mutations can impact the effectiveness of the treatment. <i>TP53</i> mutations in tumor cells can lead to T-cell exhaustion and resistance to CAR T-cell therapy, while <i>B2M</i> mutations are known to correlate with poorer outcomes in certain cancers	44-46
MTV	MTV exceeding 80 cm ³ on baseline PET-CT is associated with heightened risks of CRS and ICANS	47-49
Extranodal involvement	Extranodal involvement, especially at certain sites like liver and adrenal glands, is associated with reduced efficacy of CAR T-cell therapy in large B-cell lymphoma patients	50-52
ctDNA	ctDNA dynamics offer early response assessment, with clearance by day 7 post-infusion correlating with durable remission	53-55
T-cell fitness	The presence of markers of T-cell depletion (PD-1, TIM-3, LAG-3) indicates poor CAR T-cell persistence	56-58
PD-L1 expression	PD-L1 is expressed on tumor cells and in the tumor microenvironment of some NHL patients, potentially limiting CAR T-cell efficacy	59,60
Performance status	ECOG score 0–2.	32,36,38,39
Hematological parameters	Hemoglobin: >8.0 g/dL Platelets: >50 × 10 ⁹ /L Neutrophils: 1 × 10 ⁹ /L Serum albumin: >30 g/L Serum LDH level: <400 U/L Serum bilirubin: <1.5 × ULN Serum creatinine: <ULN or <1.5 × ULN ALT/AST: ≤2 × ULN or ≤2.5 × ULN or <3 × ULN Lymphocytes: >2 × 10 ⁸ /L Creatinine clearance: ≥30–60 mL/min GFR: <60 mL/min Hematocrit: ≥28–32%	61-64
LVEF	≥50%	34,37,40
Oxygen saturation	≥90–92% on room air	34,41
Apheresis	No contraindications	33,35,40
Concomitant diseases	Absence of: 1. Active HIV, HBV and HCV infection 2. Damage to CNS, altered mental status (confusion, delirium, GCS ≤12), seizures, focal neurological deficits (aphasia, hemiparesis) 3. Impaired cardiac function Class III or IV according to NYHA 4. Cardiovascular instability manifested by the presence of: a. hypotension (SBP <90 mmHg or MAP <65 mmHg) b. tachycardia (HR >120 bpm) c. arrhythmias (AF, VT/VF) 5. Respiratory distress manifested by the presence of: a. tachypnea (RR >24–30/min)	32-37,39-41, 65-75

	6. Fever and hyperinflammatory state manifested by the presence of: - persistent high fever ($\geq 39^{\circ}\text{C}$ or 102.2°F) - hypothermia ($< 36^{\circ}\text{C}$) 7. Hemodynamic or metabolic instability manifested by the presence of: - lactate > 2 mmol/L - oliguria/anuria (urine output < 0.5 mL/kg/h) - severe metabolic acidosis ($\text{pH} < 7.2$, $\text{HCO}_3^- < 15$)	
--	--	--

AF, new-onset atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B2M, beta-2-microglobulin; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CRS, cytokine release syndrome; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, heart rate; ICANS, immune effector cell-associated neurotoxicity syndrome; LAG3, lymphocyte-activation gene 3; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MCL, mantle cell lymphoma; MTV, metabolic tumor volume; NYHA, New York Heart Association; ORR, objective response rate; PD-L1, programmed death-ligand 1; PET-CT, positron emission tomography and computed tomography; PMBCL, primary mediastinal B-cell lymphoma; RR, respiratory rate; SBP, systolic blood pressure; SLL, small lymphocytic lymphoma; tFL, transformed follicular lymphoma; TIM-3, T-cell immunoglobulin and mucin domain 3; TP53, tumor protein p53; ULN, upper limit of normal; VF, ventricular fibrillation; VT, ventricular tachycardia.

into account important predictors of therapeutic efficacy, such as disease stage and antigen expression, along with risk factors that may compromise treatment safety, including comorbidities and organ function.

Table 3 provides an evidence-based interpretive framework for the total scores derived from our comprehensive patient selection scale for CAR T-cell therapy. This stratification system classifies NHL patients into three distinct prognostic categories based on their cumulative evaluation across clinical, biological and risk-mitigation parameters.

Discussion

CAR T-cell therapy has emerged as a groundbreaking treatment for relapsed/refractory NHL, demonstrating impressive response rates and durable remissions in patients who have exhausted traditional options.²⁰ However, careful patient selection is critical to optimize outcomes and minimize the risks associated with toxicities, such as cytokine release syndrome and neurotoxicity.⁷⁶ This study consolidates evidence from clinical trials and systematic reviews to develop a structured patient selection scale, optimizing therapeutic outcomes while minimizing risks.

The proposed scale evaluates four key domains: disease biology, tumor burden, host factors and risk mitigation. In our opinion, disease biology parameters, such as histologic subtype and CD19/CD20 antigen density, are pivotal for predicting CAR T-cell efficacy. For instance, patients with DLBCL or primary mediastinal B-cell lymphoma (PMBCL) exhibited higher response rates. In particular, a 68.1% complete response (CR) rate and 73.8% 2-year OS rate were reported in patients with PMBCL.⁷⁷ For DLBCL, a meta-analysis found an ORR of 68% and a CR rate of 46%.⁷⁸ Another study observed complete remission in 43% of DLBCL patients and 71% of follicular lymphoma patients.⁷⁹ These data confirm the correlation with the rating scale system. However, low antigen density or *TP53/B2M* mutations are usually associated with poorer outcomes, underscoring the importance of

Table 2. Optimal patient selection scale for CAR T-cell therapy in non-Hodgkin lymphoma.

Parameter	Score	Criteria
1. Disease biology (max: 31 points)		
Histologic subtype	0-7	7 = DLBCL/PMBCL 5 = MCL/FL3B 3 = FL/tFL 1 = CLL/SLL 0 = other
Disease stage	0-1	1 = stage III or IV 0 = stage I-II
Measurable lesions	0-1	1 = ≥ 1 lesion with tumor diameter ≥ 1.5 cm 0 = no measurable lesions
Molecular markers	0-5	5 = no <i>TP53/B2M</i> mutations 3 = single mutation 0 = double-hit
CD19/CD20 antigen density	0-8	8 = 5,000–10,000 molecules/cell 4 = 3,000–5,000 molecules/cell 0 = $< 3,000$ molecules/cell
Prior treatment lines	0-8	8 = 2 lines 4 = 3 lines 2 = 4 lines 0 = ≥ 5 lines
Time since prior treatment	0-1	1 = ≥ 2 weeks from prior treatment and < 12 months after first-line therapy 0 = < 2 weeks from prior treatment or ≥ 2 months after first-line therapy
2. Tumor burden and microenvironment (max: 21 points)		
MTV	0-8	8 = < 50 cm ³ 5 = 50–80 cm ³ 1 = 80–120 cm ³ 0 = ≥ 120 cm ³
Extranodal involvement	0-5	5 = 0–1 site 2 = 2 sites 0 = ≥ 3 sites
PD-L1 expression	0-5	5 = low ($< 10\%$) 3 = intermediate (10–50%) 0 = high ($> 50\%$)
ctDNA	0-3	3 = undetectable 2 = low 0 = high
3. Patient factors (max: 43 points)		
Performance status	0-5	5 = ECOG 0-1 2 = ECOG 2 0 = ECOG ≥ 3
Hematological parameters	0-8	8 = optimal values as per Table 1 4 = suboptimal 0 = unfit
LVEF	0-5	5 = $\geq 50\%$ 0 = $< 50\%$
Oxygen saturation	0-5	5 = $\geq 92\%$ 0 = $< 90\%$
Apheresis	0-1	1 = no contraindications 0 = there are contraindications*
Organ function	0-6	6 = normal heart, lung, kidney, liver and nervous system function and normal body temperature; absence of concomitant diseases listed in Table 1 3 = mild impairment 0 = severe impairment
Infection risk	0-5	5 = no history 0 = controlled or active

T-Cell fitness	0-8	8 = low PD-1/TIM-3 3 = moderate exhaustion 0 = high exhaustion
4. Risk mitigation (max: 5 points)		
CRS/ICANS risk	0-5	5 = low (IL-6 <10 pg/mL) 2 = intermediate 0 = high
Maximum total points: 100		

B2M, beta-2-microglobulin; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IL-6, interleukin 6; LVEF, left ventricular ejection fraction; MCL, mantle cell lymphoma; MTV, metabolic tumor volume; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PMBCL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma; tFL, transformed follicular lymphoma; TIM-3, T-cell immunoglobulin and mucin domain 3; TP53, tumor protein p53.

* Absolute contraindications to apheresis for CAR T-cell therapy include sepsis or active bloodstream infection, severe thrombocytopenia (usually <20,000–50,000/ μ L), severe anemia with hemoglobin below 7–8 g/dL, uncontrolled bleeding or coagulopathy, hemodynamic instability such as hypotension or significant arrhythmias, metabolic disturbances, especially severe hypocalcemia or electrolyte imbalance, severe respiratory failure requiring oxygen support and failure to establish adequate vascular access. Relative contraindications include a low absolute lymphocyte count (ALC), recent use of chemotherapy or corticosteroids (usually within the past two weeks), poor performance status or advanced frailty, ongoing localized infections, severe anemia that may require transfusion prior to the procedure and underlying autoimmune or bone marrow disorders such as systemic lupus erythematosus (SLE) or myelodysplastic syndrome (MDS).

Table 3. Interpretation of the total score.

Score Range	Recommendation	Rationale
≥70 points	Ideal candidate	Excellent candidate for CAR T-cell monotherapy. These patients demonstrate optimal characteristics for CAR T-cell monotherapy, including favorable tumor biology (e.g., high CD19 antigen density), limited disease burden and excellent biochemical parameters. In this case, the use of CAR T-cell therapy will ensure a high probability of a sustained response with manageable toxicity.
40–69 points	Conditional approval	Good candidate. Despite signs of potential efficacy of CAR T-cell therapy for these patients, careful assessment of the benefit-risk ratio is required due to clinically significant risk factors, such as moderate tumor burden or suboptimal T-cell function. Therefore, additional optimization of therapy or modification of the protocol should be considered, including alternative or combination therapies, or additional PD-1 inhibition.
<40 points	Not recommended	Poor candidate. Patients in this group are likely to have multiple adverse prognostic factors that complicate CAR T-cell therapy, including extensive tumor, low target antigen expression, or significant comorbidities. High risk of adverse events or poor CAR T-cell efficacy, the treatment strategy should be reconsidered.

CAR, chimeric antigen receptor; PD-1, programmed cell death protein 1.

molecular profiling for patient selection. It has been noted that low CD19 antigen density (<2,000 molecules/cell) significantly reduces the likelihood of clinical response to CD19-targeting CAR T-cell therapy.⁴² Similarly, a threshold of approximately 200 CD20 molecules per cell is required for CAR T-cell lysis, while cytokine production necessitates a higher density of a few thousand molecules per cell.⁸⁰ Furthermore, *TP53* mutations were associated with inferior CR and OS rates in large B-cell lymphoma patients treated with CD19-CAR T cells.⁸¹ Moreover, *TP53*-mutated circulating tumor DNA (ctDNA) levels correlated with PFS in non-Hodgkin's lymphoma patients after CAR T-cell therapy.⁸²

Tumor burden, assessed using metabolic tumor volume (MTV) and extranodal involvement, impacts both toxicity and response. Higher MTV ($>80 \text{ cm}^3$) and total lesion glycolysis (TLG), as measured by fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), were associated with an increased risk of severe CRS and ICANS.^{47,48} However, baseline MTV and TLG were not significantly correlated with OS or response rates.⁴⁷ At the same time, extranodal involvement, particularly in the liver or adrenal glands, further diminished CAR T-cell efficacy, highlighting the need for thorough baseline imaging and risk stratification.^{50,52}

Equally important are host factors, including performance status, hematological parameters, and T-cell status. Patients with an Eastern Cooperative Oncology Group (ECOG) score of 0–1 and optimal hematological parameters (e.g., hemoglobin $>8.0 \text{ g/dL}$, platelets $>50 \times 10^9/\text{L}$) were more likely to tolerate therapy successfully and achieve a sustained response.^{83–85} Conversely, markers of T-cell exhaustion (e.g., programmed cell death protein 1 [PD-1] or T-cell immunoglobulin and mucin domain 3 [TIM-3]) predicted poor CAR T-cell persistence, emphasizing the need for functional assessment of T cells prior to therapy initiation.^{58,86}

Recent studies have also highlighted the importance of risk reduction strategies and biomarker monitoring in CAR T-cell therapy for patients with NHL. Elevated levels of interleukin (IL)-6 and other cytokines have been associated with severe CRS and ICANS.^{87,88} Researchers have identified specific cut-off points for IL-3, IL-6, IL-8 and IL-10 that may predict CRS and ICANS, regardless of the CAR T-cell product used.⁸⁸ Additionally, the exclusion of patients with active infections or significant comorbidities (e.g., New York Heart Association [NYHA] Class III/IV cardiac dysfunction) further enhances safety.^{89,90}

Despite its remarkable efficacy, CAR T-cell therapy still encounters difficulties in its implementation, including manufacturing logistics, high costs and the necessity of specialized care. The cost of a CAR T-cell product approved by the U.S. Food and Drug Administration (FDA) ranges from \$373,000 to \$475,000 per infusion, with no extra costs for patient management and monitoring of adverse events.⁹¹ The proposed scale provides a standardized framework to identify ideal candidates (score ≥ 70) who are most likely to achieve durable remissions, while conditional approval (score 40–69) or non-recommendation (score <40) guides clinicians in balancing benefits and risks for marginal candidates. In order to ensure the most efficient use of medical resources, it is crucial to offer CAR T-cell therapy in cases with the highest probability of success. For patients for whom CAR T-cell therapy is not

the optimal treatment option, alternative treatments should be considered in order to avoid adverse outcomes. Creating a patient selection scale is crucial for achieving optimal results and mitigating the risks of CAR T-cell therapy.

However, there are limitations to the use of the developed scale. The scale is based on retrospective data and expert consensus, thus requiring prospective validation in various clinical settings. Furthermore, the relevance of certain parameters of the scale may change in the context of CAR T-cell technology development, necessitating continuous updates in the future.

In conclusion, it should be noted that the developed patient selection scale enhances the accuracy of CAR T-cell therapy for NHL. It reduces risks and simplifies the identification of patients who will benefit the most with minimal exposure for clinicians. The integration of this scale with artificial intelligence algorithms, with subsequent validation against large, multicenter real-world data registries, has the potential to yield powerful predictive insights and facilitate continuous automated refinement. Future research should focus on validating and improving this scale in prospective trials. Adapting this scale to new innovative CAR T-cell therapies will ensure its continued relevance in the rapidly evolving field of cellular immunotherapy.

Conclusion

CAR T-cell therapy has transformed the treatment of NHL. Recent studies show significant response rates and durable remissions in patients who fail conventional therapies. However, the efficacy and safety of CAR T-cell therapy are highly dependent on appropriate patient selection based on tumor biology, host factors and individual risk profiles for treatment-related toxicity. This study developed a comprehensive patient selection assessment that can provide a foundation for integrating critical prognostic factors to stratify patients into distinct groups and identify optimal candidates who are most likely to achieve durable responses with manageable toxicity.

While this score offers a valuable tool for optimizing CAR T-cell therapy in NHL, prospective validation is needed to confirm its predictive accuracy in a variety of clinical settings. Furthermore, as CAR T-cell technology evolves—using next-generation constructs targeting alternative antigens or incorporating safety switches—this scoring system will require periodic refinement to maintain its clinical relevance. Ultimately, the implementation of evidence-based patient selection criteria will improve therapeutic outcomes, minimize unnecessary risks and ensure the most efficient allocation of this transformative but resource-intensive therapy. By integrating tumor-, host- and risk-mitigation-specific parameters, this score provides a practical and systematic approach to clinical decision-making in the rapidly evolving field of cellular immunotherapy for NHL.

.....

Conflict of interest

The authors have declared that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

All authors have declared that no financial support was received from any organization for the submitted work.

Author contributions

Conceptualization, V.A.S., E.I.S. and D.S.B.; investigation, V.A.S. and E.I.S.; data curation, V.A.S. and E.I.S.; writing—original draft preparation, V.A.S., E.I.S. and D.S.B.; writing—review and editing, V.A.R., D.S.B., I.D.K., P.V.S., A.D.K.; supervision, V.A.S., D.S.B., I.D.K., P.V.S., A.D.K. All authors contributed to and approved the final manuscript.

Submitted: July 07, 2025 CET. Accepted: October 02, 2025 CET. Published: October 10, 2025 CET.



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-NC-SA-4.0). View this license's legal deed at <https://creativecommons.org/licenses/by-nc-sa/4.0> and legal code at <https://creativecommons.org/licenses/by-nc-sa/4.0/legalcode> for more information.

REFERENCES

1. Ansell SM. Non-Hodgkin Lymphoma: Diagnosis and Treatment. *Mayo Clin Proc.* 2015;90(8):1152-1163. doi:[10.1016/j.mayocp.2015.04.025](https://doi.org/10.1016/j.mayocp.2015.04.025)
2. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263. doi:[10.3322/caac.21834](https://doi.org/10.3322/caac.21834)
3. Imber BS, Yahalom J. Radiotherapy for Non-Hodgkin Lymphomas. *Cancer J.* 2020;26(3):217-230. doi:[10.1097/ppo.0000000000000453](https://doi.org/10.1097/ppo.0000000000000453)
4. Jones G, Plastaras JP, Ng AK, Kelsey CR. The Evolving Role of Radiation Therapy in DLBCL: From Early-Stage to Refractory Disease. *Oncology (Williston Park).* 2022;36(12):718-727. doi:[10.46883/2022.25920980](https://doi.org/10.46883/2022.25920980)
5. Kirsch BJ, Chang SJ, Le A. Non-Hodgkin Lymphoma Metabolism. *Adv Exp Med Biol.* 2018;1063:95-106. doi:[10.1007/978-3-319-77736-8_7](https://doi.org/10.1007/978-3-319-77736-8_7)
6. Kirsch BJ, Chang SJ, Betenbaugh MJ, Le A. Non-Hodgkin Lymphoma Metabolism. In: *The Heterogeneity of Cancer Metabolism.* ; 2021:103-116. doi:[10.1007/978-3-030-65768-0_7](https://doi.org/10.1007/978-3-030-65768-0_7)
7. Sermer D, Pasqualucci L, Wendel HG, Younes A. Emerging epigenetic-modulating therapies in lymphoma. *Nat Rev Clin Oncol.* 2019;16(8):494-507. doi:[10.1038/s41571-019-0190-8](https://doi.org/10.1038/s41571-019-0190-8)
8. Apuri S, Sokol L. An overview of investigational Histone deacetylase inhibitors (HDACis) for the treatment of non-Hodgkin's lymphoma. *Expert Opin Investig Drugs.* 2016;25(6):687-696. doi:[10.1517/13543784.2016.1164140](https://doi.org/10.1517/13543784.2016.1164140)
9. Zhou Z, Li HQ, Liu F. DNA Methyltransferase Inhibitors and their Therapeutic Potential. *Curr Top Med Chem.* 2018;18(28):2448-2457. doi:[10.2174/1568026619666181120150122](https://doi.org/10.2174/1568026619666181120150122)
10. Eich ML, Athar M, Ferguson JE 3rd, Varambally S. EZH2-Targeted Therapies in Cancer: Hype or a Reality. *Cancer Res.* 2020;80(24):5449-5458. doi:[10.1158/0008-5472.Can-20-2147](https://doi.org/10.1158/0008-5472.Can-20-2147)
11. Dickinson M, Kamdar M, Huntly BJP, et al. A Phase I Study of Molibresib (GSK525762), a Selective Bromodomain (BRD) and Extra Terminal Protein (BET) Inhibitor: Results from Part 1 of a Phase I/II Open Label Single Agent Study in Subjects with Non-Hodgkin's Lymphoma (NHL). *Blood.* 2018;132:1682. doi:[10.1182/blood-2018-99-117089](https://doi.org/10.1182/blood-2018-99-117089)
12. Sloan SL, Renaldo KA, Long M, et al. Validation of protein arginine methyltransferase 5 (PRMT5) as a candidate therapeutic target in the spontaneous canine model of non-Hodgkin lymphoma. *PLoS One.* 2021;16(5):e0250839. doi:[10.1371/journal.pone.0250839](https://doi.org/10.1371/journal.pone.0250839)
13. Fujii T, Khawaja MR, DiNardo CD, Atkins JT, Janku F. Targeting isocitrate dehydrogenase (IDH) in cancer. *Discov Med.* 2016;21(117):373-380. <https://www.discoverymedicine.com/Takeo-Fujii/2016/05/targeting-isocitrate-dehydrogenase-idh-in-cancer/>
14. Engelhard M. Anti-CD20 antibody treatment of non-Hodgkin lymphomas. *Clin Immunol.* 2016;172:101-104. doi:[10.1016/j.clim.2016.08.011](https://doi.org/10.1016/j.clim.2016.08.011)
15. Thapa B, Caimi PF, Ardeshtna KM, et al. CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy. *Blood Adv.* 2020;4(16):3850-3852. doi:[10.1182/bloodadvances.2020002587](https://doi.org/10.1182/bloodadvances.2020002587)
16. Matsuki E, Younes A. Checkpoint Inhibitors and Other Immune Therapies for Hodgkin and Non-Hodgkin Lymphoma. *Curr Treat Options Oncol.* 2016;17(6):31. doi:[10.1007/s11864-016-0401-9](https://doi.org/10.1007/s11864-016-0401-9)
17. Giraudo MF, Jackson Z, Das I, Abiona OM, Wald DN. Chimeric Antigen Receptor (CAR)-T Cell Therapy for Non-Hodgkin's Lymphoma. *Pathog Immun.* 2024;9(1):1-17. doi:[10.20411/pai.v9i1.647](https://doi.org/10.20411/pai.v9i1.647)

18. Klabukov I, Kabakov AE, Yakimova A, et al. Tumor-Associated Extracellular Matrix Obstacles for CAR-T Cell Therapy: Approaches to Overcoming. *Curr Oncol*. 2025;32(2):79. doi:[10.3390/curroncol32020079](https://doi.org/10.3390/curroncol32020079)
19. Rybachuk V, Evstratova E, Klabukov I, et al. A Bright Future for Immunotherapy: CAR T-Cell Therapy Promises Revolutionary Changes. *healthbook TIMES Onco Hema*. 2024;22:71-84. doi:[10.36000/HBT.OH.2024.22.164](https://doi.org/10.36000/HBT.OH.2024.22.164)
20. St-Pierre F, Gordon LI. CAR T-cell therapy for relapsed/refractory non-Hodgkin's lymphoma: a comprehensive review. *Clin Adv Hematol Oncol*. 2022;20(5):309-318. <https://www.hematologyandoncology.net/archives/may-2022/car-t-cell-therapy-for-relapsed-refractory-non-hodgkins-lymphoma-a-comprehensive-review/>
21. Di Blasi R, Le Gouill S, Bachy E, et al. Outcome of Relapsed/Refractory Aggressive B-Cell Lymphoma Patients Relapsing after Anti-CD19 CAR T-Cells and Enrolled in the Descar-T French National Registry. *Blood*. 2021;138(suppl_1):885. doi:[10.1182/blood-2021-150994](https://doi.org/10.1182/blood-2021-150994)
22. Yu M, Zhang Q, Kong F, et al. Efficacy and Safety of Dual-Targeting Chimeric Antigen Receptor-T Therapy for Relapsed or Refractory B Cell Lymphoid Malignancies: A Systematic Review and Meta-Analysis. *Hum Gene Ther*. 2023;34(5-6):192-202. doi:[10.1089/hum.2022.183](https://doi.org/10.1089/hum.2022.183)
23. Munshi PN, Ujjani C. The acceleration of CAR-T therapy in non-Hodgkin lymphoma. *Hematol Oncol*. 2019;37(3):233-239. doi:[10.1002/hon.2568](https://doi.org/10.1002/hon.2568)
24. Oluwole OO. Clinical experience of CAR T cell therapy in lymphomas. *Best Pract Res Clin Haematol*. 2021;34(3):101281. doi:[10.1016/j.beha.2021.101281](https://doi.org/10.1016/j.beha.2021.101281)
25. Wang AX, Ong XJ, D'Souza C, Neeson PJ, Zhu JJ. Combining chemotherapy with CAR-T cell therapy in treating solid tumors. *Front Immunol*. 2023;14:1140541. doi:[10.3389/fimmu.2023.1140541](https://doi.org/10.3389/fimmu.2023.1140541)
26. Khurana A, Hathcock M, Habermann TM, et al. Lines of therapy before autologous stem cell transplant and CAR-T affect outcomes in aggressive Non-Hodgkin's lymphoma. *Am J Hematol*. 2021;96(10):E386-E389. doi:[10.1002/ajh.26293](https://doi.org/10.1002/ajh.26293)
27. Liu J, Zhang X, Zhong JF, Zhang C. Use of chimeric antigen receptor T cells in allogeneic hematopoietic stem cell transplantation. *Immunotherapy*. 2019;11(1):37-44. doi:[10.2217/imt-2018-0089](https://doi.org/10.2217/imt-2018-0089)
28. Hombach AA, Abken H. Shared target antigens on cancer cells and tissue stem cells: go or no-go for CAR T cells? *Expert Rev Clin Immunol*. 2017;13(2):151-155. doi:[10.1080/1744666x.2016.1221763](https://doi.org/10.1080/1744666x.2016.1221763)
29. Zhang Y, Li Y, Cao W, et al. Single-Cell Analysis of Target Antigens of CAR-T Reveals a Potential Landscape of "On-Target, Off-Tumor Toxicity." *Front Immunol*. 2021;12:799206. doi:[10.3389/fimmu.2021.799206](https://doi.org/10.3389/fimmu.2021.799206)
30. Al-Haideri M, Tondok SB, Safa SH, et al. CAR-T cell combination therapy: the next revolution in cancer treatment. *Cancer Cell Int*. 2022;22(1):365. doi:[10.1186/s12935-022-02778-6](https://doi.org/10.1186/s12935-022-02778-6)
31. Ernstoff MS, Gandhi S, Pandey M, et al. Challenges faced when identifying patients for combination immunotherapy. *Future Oncol*. 2017;13(18):1607-1618. doi:[10.2217/fon-2017-0218](https://doi.org/10.2217/fon-2017-0218)
32. CD19 CAR T Cells in Patients With Relapsed or Refractory CD19 Positive B-cell Lymphoma. ClinicalTrials.gov identifier: NCT03029338. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT03029338>
33. A Study of C-CAR066 in Subjects With r/r B Cell Lymphoma Who Received CD19 CAR-T Therapy. ClinicalTrials.gov identifier: NCT04036019. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT04036019>

34. A Phase Ib Study Evaluating Safety and Efficacy of C-CAR011 Treatment in B- NHL Subjects. ClinicalTrials.gov identifier: NCT03483688. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT03483688>
35. A Study of C-CAR066 in Subjects With r/r Diffuse Large B Cell Lymphoma Who Received CD19 CAR-T Therapy. ClinicalTrials.gov identifier: NCT04316624. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT04316624>
36. Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-PILOT-017006). ClinicalTrials.gov identifier: NCT03483103. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT03483103>
37. Safety of MB-CART2019.1 in Lymphoma Patients (MB-CART2019.1 Lymphoma / DALY 1). ClinicalTrials.gov identifier: NCT03870945. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT03870945>
38. MB-CART20.1 Lymphoma. ClinicalTrials.gov identifier: NCT03664635. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT03664635>
39. Treatment of Relapsed and/or Chemotherapy Refractory B-cell Malignancy by Tandem CAR T Cells Targeting CD19 and CD20. ClinicalTrials.gov identifier: NCT03097770. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT03097770>
40. A Phase 1 Study Evaluating Safety and Efficacy of C-CAR011 Treatment in DLBCL Subjects (C-CAR011). ClinicalTrials.gov identifier: NCT02976857. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT02976857>
41. Study of CAR-20/19-T Cells in Patients With Relapsed Refractory B Cell. ClinicalTrials.gov identifier: NCT03019055. Accessed July 1, 2025. <https://www.clinicaltrials.gov/study/NCT03019055>
42. Majzner RG, Rietberg SP, Labanieh L, et al. Low CD19 Antigen Density Diminishes Efficacy of CD19 CAR T Cells and Can be Overcome By Rational Redesign of CAR Signaling Domains. *Blood*. 2018;132(suppl_1):963. doi:[10.1182/blood-2018-99-115558](https://doi.org/10.1182/blood-2018-99-115558)
43. Majzner RG, Rietberg SP, Sotillo E, et al. Tuning the Antigen Density Requirement for CAR T-cell Activity. *Cancer Discov*. 2020;10(5):702-723. doi:[10.1158/2159-8290.Cd-19-0945](https://doi.org/10.1158/2159-8290.Cd-19-0945)
44. Li L, Muftuoglu M, Ayoub E, et al. TP53 Mutations within T Cells Induce T-Cell Exhaustion and Functional Impairment in TP53 Mutant AML. *Blood*. 2024;144(suppl_1):330. doi:[10.1182/blood-2024-210412](https://doi.org/10.1182/blood-2024-210412)
45. Mirgayazova R, Khadiullina R, Filimonova M, et al. Impact of TP53 mutations on the efficacy of CAR-T cell therapy in cancer. *Explor Immunol*. 2024:837-852. doi:[10.37349/ei.2024.00176](https://doi.org/10.37349/ei.2024.00176)
46. Gao F, Hu K, Zheng P, Shi H, Ke X. Characteristics and prognosis of rrDLBCL with TP53 mutations and a high-risk subgroup represented by the co-mutations of DDX3X-TP53. *Cancer Med*. 2023;12(9):10267-10279. doi:[10.1002/cam4.5756](https://doi.org/10.1002/cam4.5756)
47. Wang J, Hu Y, Yang S, et al. Role of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Predicting the Adverse Effects of Chimeric Antigen Receptor T Cell Therapy in Patients with Non-Hodgkin Lymphoma. *Biol Blood Marrow Transplant*. 2019;25(6):1092-1098. doi:[10.1016/j.bbmt.2019.02.008](https://doi.org/10.1016/j.bbmt.2019.02.008)
48. Hong R, Tan Su Yin E, Wang L, et al. Tumor Burden Measured by 18F-FDG PET/CT in Predicting Efficacy and Adverse Effects of Chimeric Antigen Receptor T-Cell Therapy in Non-Hodgkin Lymphoma. *Front Oncol*. 2021;11:713577. doi:[10.3389/fonc.2021.713577](https://doi.org/10.3389/fonc.2021.713577)

49. Galli E, Guarneri A, Sorà F, et al. Baseline Tumor Burden Assessed With AI-Guided PET/CT Total Metabolic Tumor Volume (TMTV) and LDH Levels Predict Efficacy of CAR-T in Aggressive B-Cell Lymphoma. *Hematol Oncol*. 2025;43(1):e70029. doi:[10.1002/hon.70029](https://doi.org/10.1002/hon.70029)
50. Iacoboni G, Rejeski K, Navarro V, et al. Site-specific analysis of extranodal involvement in large B-cell lymphoma reveals distinct efficacy with chimeric antigen receptor T-cell therapy. *Leukemia*. 2025;39(5):1196-1205. doi:[10.1038/s41375-025-02582-x](https://doi.org/10.1038/s41375-025-02582-x)
51. Luna A, Corona M, Flynn J, et al. Site-Specific Response Rates in Large B-Cell Lymphomas Treated with CD19-CART Therapy. *Transplant Cell Ther*. 2024;30(suppl_2):S217. doi:[10.1016/j.jtct.2023.12.282](https://doi.org/10.1016/j.jtct.2023.12.282)
52. Luna A, Devlin SM, Rejeski K, et al. CAR T-cell therapy response varies by extranodal disease site in large B-cell lymphoma. *Blood Cancer J*. 2025;15(1):64. doi:[10.1038/s41408-025-01273-1](https://doi.org/10.1038/s41408-025-01273-1)
53. Hesong Z, Wei L, Xiaojuan W, et al. Dynamic monitoring of circulating tumor DNA reveals outcomes and genomic alterations in patients with relapsed or refractory large B-cell lymphoma undergoing CAR T-cell therapy. *J Immunother Cancer*. 2024;12(3):e008450. doi:[10.1136/jitc-2023-008450](https://doi.org/10.1136/jitc-2023-008450)
54. Delfau-Larue MH, Gomes L, Cartron G, et al. P1123: EARLY CTDNA CLEARANCE AFTER CAR T-CELL INFUSION PREDICTS OUTCOME IN PATIENTS WITH LARGE B-CELL LYMPHOMA: RESULTS FROM ALYCANTE, A PHASE 2 LYSA STUDY. *HemaSphere*. 2023;7(S3):e5262795. doi:[10.1097/01.HS9.0000971388.52627.95](https://doi.org/10.1097/01.HS9.0000971388.52627.95)
55. Xi L, Pham TH, Payabyab EC, Sherry RM, Rosenberg SA, Raffeld M. Circulating Tumor DNA as an Early Indicator of Response to T-cell Transfer Immunotherapy in Metastatic Melanoma. *Clin Cancer Res*. 2016;22(22):5480-5486. doi:[10.1158/1078-0432.Ccr-16-0613](https://doi.org/10.1158/1078-0432.Ccr-16-0613)
56. Chow A, Perica K, Klebanoff CA, Wolchok JD. Clinical implications of T cell exhaustion for cancer immunotherapy. *Nat Rev Clin Oncol*. 2022;19(12):775-790. doi:[10.1038/s41571-022-00689-z](https://doi.org/10.1038/s41571-022-00689-z)
57. Kong Y, Tang L, You Y, Li Q, Zhu X. Analysis of causes for poor persistence of CAR-T cell therapy in vivo. *Front Immunol*. 2023;14:1063454. doi:[10.3389/fimmu.2023.1063454](https://doi.org/10.3389/fimmu.2023.1063454)
58. Funk CR, Petersen CT, Jagirdar N, et al. Oligoclonal T Cells Transiently Expand and Express Tim-3 and PD-1 Following Anti-CD19 CAR T Cell Therapy: A Case Report. *Int J Mol Sci*. 2018;19(12):4118. doi:[10.3390/ijms19124118](https://doi.org/10.3390/ijms19124118)
59. Larson RP, Ports M, Jessup H, et al. Preclinical Analyses Support Clinical Investigation of Combined PD-L1 Blockade and Anti-CD19 CAR T Cell Therapy for the Treatment of NHL. *Blood*. 2015;126(23):5430. doi:[10.1182/blood.V126.23.5430.5430](https://doi.org/10.1182/blood.V126.23.5430.5430)
60. Liu G, Rui W, Zhao X, Lin X. Enhancing CAR-T cell efficacy in solid tumors by targeting the tumor microenvironment. *Cell Mol Immunol*. 2021;18(5):1085-1095. doi:[10.1038/s41423-021-00655-2](https://doi.org/10.1038/s41423-021-00655-2)
61. Kinoshita H, Bollard CM, Toner K. CD19 CAR-T cell therapy for relapsed or refractory diffuse large B cell lymphoma: Why does it fail? *Semin Hematol*. 2023;60(5):329-337. doi:[10.1053/j.seminhematol.2023.11.007](https://doi.org/10.1053/j.seminhematol.2023.11.007)
62. Tan JY, Low MH, Chen Y, Lim FLWI. CAR T Cell Therapy in Hematological Malignancies: Implications of the Tumor Microenvironment and Biomarkers on Efficacy and Toxicity. *Int J Mol Sci*. 2022;23(13):6931. doi:[10.3390/ijms23136931](https://doi.org/10.3390/ijms23136931)
63. Liao CF, Lai HR, Li J. [Research Progress on the Influence of Blood Tumor Microenvironment on the Efficacy and the Adverse Reactions of CAR-T Cell Immunotherapy--Review]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2024;32(4):1290-1294. <https://pubmed.ncbi.nlm.nih.gov/39192433/>

64. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J.* 2021;11(4):69. doi:[10.1038/s41408-021-00459-7](https://doi.org/10.1038/s41408-021-00459-7)
65. Dalal P, Patel N, Cascino G, et al. Abstract 14394: Cardiovascular Toxicities After Chimeric Antigen Receptor T-cell (CAR-T) Therapy: A Single Center Experience. *Circulation.* 2021;144(suppl_1):A14394. doi:[10.1161/circ.144.suppl_1.14394](https://doi.org/10.1161/circ.144.suppl_1.14394)
66. Brammer JE, Braunstein Z, Katapadi A, et al. Cardiovascular Toxicity and Clinical Outcomes Following Chimeric Antigen Receptor T-Cell Infusion (CART) for Lymphoid Malignancies. *Bio Blood Marrow Transplant.* 2020;26(suppl_3):S270. doi:[10.1016/j.bbmt.2019.12.438](https://doi.org/10.1016/j.bbmt.2019.12.438)
67. Terwindt LE, Schuurmans J, van der Ster BJP, et al. Incidence, Severity and Clinical Factors Associated with Hypotension in Patients Admitted to an Intensive Care Unit: A Prospective Observational Study. *J Clin Med.* 2022;11(22):6832. doi:[10.3390/jcm11226832](https://doi.org/10.3390/jcm11226832)
68. Totzeck M, Michel L, Lin Y, Herrmann J, Rassaf T. Cardiotoxicity from chimeric antigen receptor-T cell therapy for advanced malignancies. *Eur Heart J.* 2022;43(20):1928-1940. doi:[10.1093/eurheartj/ehac106](https://doi.org/10.1093/eurheartj/ehac106)
69. Simbaqueba CC, Aponte MP, Kim P, et al. Cardiovascular Complications of Chimeric Antigen Receptor T-Cell Therapy: The Cytokine Release Syndrome and Associated Arrhythmias. *J Immunother Precis Oncol.* 2020;3(3):113-120. doi:[10.36401/jipo-20-10](https://doi.org/10.36401/jipo-20-10)
70. Jatiani SS, Aleman A, Madduri D, et al. Myeloma CAR-T CRS Management With IL-1R Antagonist Anakinra. *Clin Lymphoma Myeloma Leuk.* 2020;20(9):632-636.e1. doi:[10.1016/j.clml.2020.04.020](https://doi.org/10.1016/j.clml.2020.04.020)
71. Davis JA, Gaffney KJ, McGann M, et al. Fever Characteristics and Impact on Safety and Efficacy of Chimeric Antigen Receptor T-Cell Therapy. *Clin Lymphoma Myeloma Leuk.* 2023;23(1):e14-e18. doi:[10.1016/j.clml.2022.09.005](https://doi.org/10.1016/j.clml.2022.09.005)
72. Kushimoto S, Abe T, Ogura H, et al. Impact of Body Temperature Abnormalities on the Implementation of Sepsis Bundles and Outcomes in Patients With Severe Sepsis: A Retrospective Sub-Analysis of the Focused Outcome Research on Emergency Care for Acute Respiratory Distress Syndrome, Sepsis and Trauma Study. *Crit Care Med.* 2019;47(5):691-699. doi:[10.1097/ccm.0000000000003688](https://doi.org/10.1097/ccm.0000000000003688)
73. Vallet N, Drieu Larochelle L, Santiago-Ribeiro MJ, et al. Glycolytic activity following anti-CD19 CAR-T cell infusion in non-Hodgkin lymphoma. *Eur J Clin Invest.* 2025;55(2):e14342. doi:[10.1111/eci.14342](https://doi.org/10.1111/eci.14342)
74. Wood AC, Perez AP, Arciola B, et al. Outcomes of CD19-Targeted Chimeric Antigen Receptor T Cell Therapy for Patients with Reduced Renal Function Including Dialysis. *Transplant Cell Ther.* 2022;28(12):829.e1-829.e8. doi:[10.1016/j.jtct.2022.09.009](https://doi.org/10.1016/j.jtct.2022.09.009)
75. Shi T, Sun M, Tuerhong S, et al. Acidity-targeting transition-aided universal chimeric antigen receptor T-cell (ATT-CAR-T) therapy for the treatment of solid tumors. *Biomaterials.* 2024;309:122607. doi:[10.1016/j.biomaterials.2024.122607](https://doi.org/10.1016/j.biomaterials.2024.122607)
76. Cahill KE, Leukam MJ, Riedell PA. Refining patient selection for CAR T-cell therapy in aggressive large B-cell lymphoma. *Leuk Lymphoma.* 2020;61(4):799-807. doi:[10.1080/10428194.2019.1691201](https://doi.org/10.1080/10428194.2019.1691201)
77. Galtier J, Mesguich C, Sesques P, et al. Outcomes of patients with relapsed or refractory primary mediastinal B-cell lymphoma treated with anti-CD19 CAR-T cells: CARTHYM, a study from the French national DESCAR-T registry. *Hemasphere.* 2025;9(2):e70091. doi:[10.1002/hem3.70091](https://doi.org/10.1002/hem3.70091)
78. Al-Mansour M, Al-Foheidi M, Ibrahim E. Efficacy and safety of second-generation CAR T-cell therapy in diffuse large B-cell lymphoma: A meta-analysis. *Mol Clin Oncol.* 2020;13(4):33. doi:[10.3892/mco.2020.2103](https://doi.org/10.3892/mco.2020.2103)

79. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N Engl J Med*. 2017;377(26):2545-2554. doi:[10.1056/NEJMoa1708566](https://doi.org/10.1056/NEJMoa1708566)
80. Watanabe K, Terakura S, Martens AC, et al. Target antigen density governs the efficacy of anti-CD20-CD28-CD3 ζ chimeric antigen receptor-modified effector CD8⁺ T cells. *J Immunol*. 2015;194(3):911-920. doi:[10.4049/jimmunol.1402346](https://doi.org/10.4049/jimmunol.1402346)
81. Shouval R, Alarcon Tomas A, Fein JA, et al. Impact of TP53 Genomic Alterations in Large B-Cell Lymphoma Treated With CD19-Chimeric Antigen Receptor T-Cell Therapy. *J Clin Oncol*. 2022;40(4):369-381. doi:[10.1200/jco.21.02143](https://doi.org/10.1200/jco.21.02143)
82. Chen L, Mu W, Gu J, et al. TP53-Mutated Circulating Tumor DNA for Disease Monitoring in Lymphoma Patients after CAR T Cell Therapy. *Diagnostics (Basel)*. 2021;11(5):844. doi:[10.3390/diagnostics11050844](https://doi.org/10.3390/diagnostics11050844)
83. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. *Blood Adv*. 2020;4(19):4898-4911. doi:[10.1182/bloodadvances.2020002394](https://doi.org/10.1182/bloodadvances.2020002394)
84. Cunningham K, DiFilippo H, Henes K, Irwin LL, Napier E, Weber E. Tisagenlecleucel Therapy: Nursing Considerations for the Outpatient Setting. *Semin Oncol Nurs*. 2021;37(4):151178. doi:[10.1016/j.soncn.2021.151178](https://doi.org/10.1016/j.soncn.2021.151178)
85. Jain T, Knezevic A, Pennisi M, et al. Hematological Count Recovery in Patients Undergoing Treatment with Chimeric Antigen Receptor T Cells (CAR T). *Blood*. 2019;134(suppl_1):4455. doi:[10.1182/blood-2019-127480](https://doi.org/10.1182/blood-2019-127480)
86. Su G, Wu T. Exploratory Analysis of Biomarkers for Quality Control of Cell Cultures and Prediction of Response to CART Cell Therapy. *Blood*. 2024;144:7271. doi:[10.1182/blood-2024-212218](https://doi.org/10.1182/blood-2024-212218)
87. Teachey DT, Lacey SF, Shaw PA, et al. Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia. *Cancer Discov*. 2016;6(6):664-679. doi:[10.1158/2159-8290.Cd-16-0040](https://doi.org/10.1158/2159-8290.Cd-16-0040)
88. Kewan T, Mirza S, Pine AB, et al. CAR T-Related Toxicities Based on Dynamic Proteomic Profiles Identifies Risk Factors for Cytokine Release Syndrome (CRS) and Immune Effector Cell -Associated Neurotoxicity Syndrome (ICANS). *Blood*. 2023;142:2132. doi:[10.1182/blood-2023-187295](https://doi.org/10.1182/blood-2023-187295)
89. Styczynski J. Infections following CAR-T cells therapy: current state-of-the-art review and recommendations. *Acta Haematol Pol*. 2020;51:11-16. doi:[10.2478/ahp-2020-0004](https://doi.org/10.2478/ahp-2020-0004)
90. Bupha-Intr O, Haeusler G, Chee L, Thursky K, Slavin M, Teh B. CAR-T cell therapy and infection: a review. *Expert Rev Anti Infect Ther*. 2021;19(6):749-758. doi:[10.1080/14787210.2021.1855143](https://doi.org/10.1080/14787210.2021.1855143)
91. Abou-el-Enein M, Gauthier J. The Value of CAR-T-cell Immunotherapy in Cancer. In: *The EBMT/EHA CAR-T Cell Handbook*. ; 2022:231-234. doi:[10.1007/978-3-030-94353-0_46](https://doi.org/10.1007/978-3-030-94353-0_46)