Real-World Insights into CAR T-Cell Therapy: Efficacy and Safety of Kymriah in B-ALL and NHL

Harish Jaiswal [1*], Aayush Vaishnaw [1]

Abstract

Background: Chimeric Antigen Receptor (CAR) T-cell therapy has emerged as a revolutionary treatment for certain cancers, particularly B-cell malignancies. This study focused on the real-world outcomes of Kymriah (tisagenlecleucel), a CAR T-cell therapy targeting CD19, by analyzing data from the Cellular Immunotherapy Data Resource (CIDR). A total of 410 patients with relapsed or refractory B-cell Acute Lymphoblastic Leukemia (B-ALL) and Non-Hodgkin Lymphoma (NHL) were included. Methods: Data were collected from 73 treatment centers across the U.S. and Canada. Key outcomes measured included Cytokine Release Syndrome (CRS), Immune-effector Cell-Associated Neurotoxicity Syndrome (ICANS), overall response rate (ORR), duration of response (DOR), and survival rates. Statistical analyses were performed using descriptive statistics, Kaplan-Meier methods, and logistic regression. Results: CRS was observed in 54.3% of B-ALL patients, with severe cases in 16.1%. The complete remission rate in B-ALL patients was 85.5%, with a 12-month overall survival rate of 76.4%. In NHL patients, the overall response rate was 62.4%, with 38.2% achieving complete remission. Severe CRS and ICANS were less frequent in NHL patients. Conclusion: Kymriah demonstrated high efficacy in both B-ALL and NHL, with manageable side effects. However, ongoing monitoring is essential to optimize outcomes and reduce adverse events. This study provides valuable real-world data, contributing to the growing understanding of CAR T-cell therapy's potential in clinical practice.

Keywords: CAR T-cell therapy, Kymriah, B-cell acute lymphoblastic leukemia, Cytokine release syndrome, Non-Hodgkin lymphoma

Significance | This study provides extensive real-world data on Kymriah's efficacy and safety, revealing valuable insights into its use in B-ALL and NHL.

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1. Introduction

Chimeric Antigen Receptor (CAR) T-cell therapy represents a significant advancement in immunotherapy, harnessing genetic engineering to improve the body's immune response against cancer cells. Unlike traditional treatments that rely on small molecules or antibodies, CAR-T cells, often referred to as "living drugs," possess the unique ability to persist in the body for extended periods, proliferating and remaining effective months or even years after treatment (Qu et al., 2021). Understanding the cellular mechanisms behind CAR-T cells, such as their pharmacokinetics and the variables influencing their effectiveness, is crucial for maximizing their potential in clinical practice.

One of the pioneering CAR-T cell therapies is Tisagenlecleucel, marketed as Kymriah. Kymriah targets the CD19 protein on B-cells, making it effective against certain B-cell malignancies, particularly in cases where other treatments have failed. The engineering process involves extracting T cells from the patient, modifying them in the laboratory via lentiviral transduction to express a CD19-targeted CAR, and then reinfusing them into the patient (Awasthi et al., 2023). This CAR consists of a single-chain fragment derived from a mouse antibody that specifically binds to CD19, combined

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with the the signaling domains CD3ζ and 4-1BB, which activate the T-cell response and promote long-term cell persistence (Wu et al., 2020). The ability of Kymriah to survive and expand in the body after infusion enhances its potential for sustained antitumor activity.

Kymriah has demonstrated remarkable efficacy in patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) and chronic lymphocytic leukemia (CLL). Early clinical trials revealed that Kymriah cells proliferated more in patients who responded positively to treatment than in those who did not. This proliferation correlated with improved outcomes and long-term remission, especially in cases where patients presented with high tumor burdens (Ramakrishnan et al., 2019). However, the treatment is not without risks. One of the significant side effects is Cytokine Release Syndrome (CRS), a condition characterized by an excessive immune response that can lead to severe symptoms and even be life-threatening. CRS severity is often associated with the patient's tumor load and the degree of CAR-T cell expansion (Que et al., 2022).

Studies focusing on the pharmacology and cellular kinetics of CAR-T cells have revealed valuable insights into the therapy's effectiveness and safety. The proliferation and persistence of CAR-T cells are key factors in determining patient outcomes. The durability of Kymriah's response has been especially notable in B-ALL patients, where long-term survival often depends on sustained CAR-T cell activity. The persistence of Kymriah cells in the bloodstream was critical to maintaining remission in both pediatric and adult patients (Fallati et al., 2022).

As CAR-T therapies like Kymriah continue to evolve, understanding their cellular behavior and patient-specific factors will be essential for optimizing their use. Further studies are needed to explore the therapy's efficacy in diverse patient populations and its potential application in other types of cancer. Future research will likely focus on refining dosing strategies, improving safety profiles, and expanding the therapeutic use of CAR-T cells to offer hope to more patients battling difficult-to-treat cancers (Alamer et al., 2023).

2. Materials and Methods

2.1 Data Sources

The data sources for this study were based on information from the Center for International Blood and Marrow Transplant Research (CIBMTR), a collaborative initiative between the Medical College of Wisconsin and the National Marrow Donation Program (Zinter et al., 2020). The CIBMTR collects data on various cellular therapies beyond Hematopoietic Cell Transplantation (HCT), including Chimeric Antigen Receptor (CAR) T-cell therapies. The primary goal of the CIBMTR is to gather, analyze, and distribute data related to these therapies, providing valuable insights for advancing cancer treatments (D'Souza et al., 2020).

This collaboration is supported by the National Cancer Research Fund, which finances the Cellular Immunotherapy Data Resource (CIDR). The CIDR's purpose is to facilitate the systematic collection and analysis of data on cellular treatments used to treat cancer patients (Awasthi et al., 2023). The data gathered by the CIDR is crucial for monitoring the safety, effectiveness, and long-term outcomes of cellular therapies, enabling researchers to optimize treatment strategies and improve patient outcomes.

Data on cellular therapies, such as CAR T-cell therapy, are collected from 130 collaborating facilities across the United States and Canada. This ensures a large and diverse dataset, covering a wide range of patient populations and treatment settings. To maintain the quality and integrity of the data, the CIBMTR employs a rigorous system of error checking, on-site audits, and monitoring the timely submission of data by participating centers (Zinter et al., 2020). These measures help ensure that the data collected is accurate and reliable, making it a valuable resource for clinical research.

Before data can be used in research studies, it must undergo a comprehensive data-sharing procedure. This process involves review and approval by local ethical boards to ensure that patient privacy and confidentiality are protected (Guarini et al., 2023). In addition, every patient included in the CIBMTR registry provides explicit permission for their data to be shared with the CIBMTR, ensuring compliance with ethical standards for data use.

For the Kymriah Post-Marketing Requirement (PMR) trial, which is a key focus of this study, the trial design underwent rigorous scrutiny and received approval from institutional review boards. This ensures that the trial adhered to the highest ethical standards in patient care and data management (Zhang et al., 2023). As part of the trial, data on the manufacturing characteristics of Kymriah, such as cell dosage and viability, were collected from the Novartis manufacturing database. This information was linked to patient outcomes using a unique Kymriah batch identifier, enabling researchers to assess the relationship between manufacturing characteristics and clinical efficacy.

2.2 Patients and Study Design

This study utilized an observational design to evaluate the outcomes of patients who received Kymriah for approved indications in the United States or Canada. Treatment centers that administered Kymriah submitted detailed clinical data to the CIBMTR, while Novartis provided additional information on the manufacturing characteristics of the therapy (Awasthi et al., 2023). This allowed for a comprehensive analysis of the safety and efficacy of Kymriah across diverse patient populations.

The study focused on several key outcomes, including the occurrence and severity of Cytokine Release Syndrome (CRS) and Immune-effector Cell-Associated Neurotoxicity Syndrome (ICANS), both of which are common side effects of CAR T-cell therapy. Other outcomes included the incidence of Serious Adverse

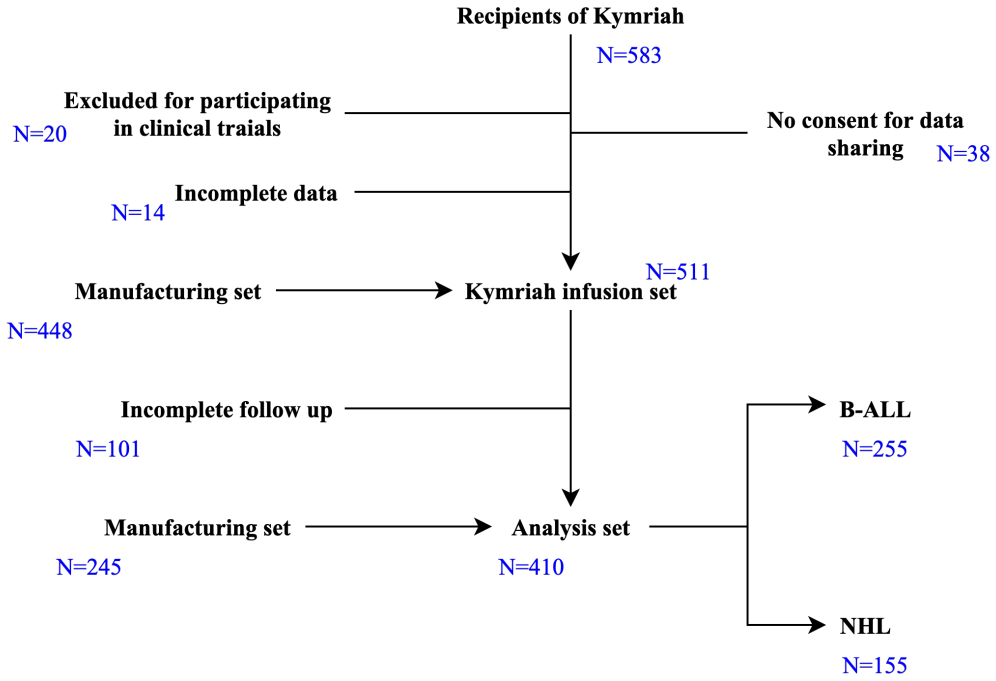

Figure 1. Workflow of the research

Table 1. Demographic details

Details	B-ALL		NHL	
	Count	Percentage	Count	Percentage
Gender				
Men	150	58.82	91	58.71
Women	105	41.18	64	41.29
Disease status				
Main refractory / relapsed	159	62.35	147	94.84
CR	95	37.25	7	4.52
Unknown	1	0.39	1	0.65
Previous HCT				
Allogeneic	71	27.84	5	3.23
Autologous	1	0.39	40	25.81
Both	1	0.39	1	0.65
Performance status				
90 to 100	174	68.24	57	36.77
80	37	14.51	49	31.61
Less than 80	31	12.16	30	19.35
Not reported	13	5.1	19	12.26
Time of acceptance				
Mean	32		31.4	
Range	20-90		21-135	
Time of follow-up				
Mean	12.8		11.2	
Range	3.8-28.3		3.6-19.2	

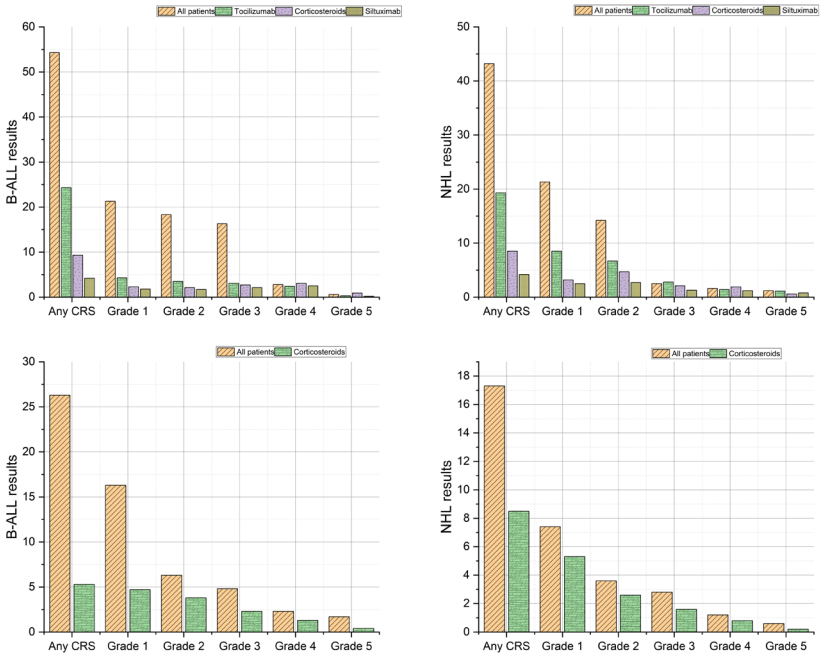

Figure 2. B-ALL and NHL result analysis

Events (SAEs), recovery of blood cell counts (specifically neutrophils and platelets), and measures of treatment efficacy such as the Overall Response Rate (ORR), Duration of Response (DOR), Event-Free Survival (EFS), Progression-Free Survival (PFS), and Overall Survival (OS) (Fallati et al., 2022).

CRS was graded using guidelines established by the American Society for Transplantation and Cellular Therapy (ASTCT). The grading was based on the most severe symptoms experienced by the patient during the reporting period. ICANS was also graded according to ASTCT criteria, which focus on the neurological symptoms associated with CAR T-cell therapy (Qu et al., 2021).

For patients with B-cell Acute Lymphoblastic Leukemia (B-ALL), the study defined Complete Remission (CR) as achieving a full morphologic response with less than 5% blasts. In addition, the Minimal Residual Disease (MRD) status of these patients was evaluated to determine the presence of any remaining leukemia cells after treatment. For patients with Non-Hodgkin Lymphoma (NHL), disease response was assessed using Computed Tomography (CT) or Positron Emission Tomography (PET) scans, with PET scans preferred when available (Awasthi et al., 2023).

Duration of Response (DOR) was defined as the time from the initial achievement of CR or Partial Response (PR) until disease progression, relapse, or death from the underlying illness. In contrast, Event-Free Survival (EFS) for B-ALL patients was measured as the time from Kymriah infusion to the first event of relapse, death, or failure to achieve remission. Progression-Free Survival (PFS) for NHL patients was defined as the time from Kymriah infusion to disease progression or death (Wu et al., 2020).

Neutrophil and platelet recovery were assessed based on the absolute neutrophil count, with prolonged cytopenia defined as the failure to recover platelet counts within 30 days post-infusion. Cell viability, defined as the percentage of living T cells in the final product, was a key variable, with the U.S. release standard set at 82.5%. The cell dose, which refers to the total number of viable T cells expressing the CAR construct, was also documented and analyzed (Guarini et al., 2023).

2.3 Analysis Set

The analysis set for this study consisted of patients with varying follow-up durations, due to the ongoing recruitment of participants. The Cellular Therapy Registry collects data on both safety and efficacy in separate formats, meaning that the number of patients with complete data may vary between different analyses (D'Souza et al., 2020). A CONSORT diagram was used to detail the flow of patients through the study, including those who were excluded from the analysis due to missing data or other factors.

For the efficacy analysis, only patients who had completed a three-month follow-up form post-Kymriah infusion were included. This accounted for approximately 72.5% of the total recipients of Kymriah (Ramakrishnan et al., 2019). The production dataset was limited to patients with recorded batch information, allowing for an analysis of the relationship between Kymriah's manufacturing characteristics and clinical outcomes.

2.4 Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and disease characteristics. Adverse events following the first Kymriah infusion were reported using counts and percentages. Response rates were evaluated as the proportion of patients who achieved CR for B-ALL or CR/PR for NHL, with these outcomes tracked from the time of infusion until disease progression or the initiation of new anticancer therapy (Zhang et al., 2023). Odds ratios (ORs) were calculated for key outcomes, such as the best disease response and the incidence of adverse events, with 95% confidence intervals (CIs) provided.

To estimate Overall Survival (OS), Event-Free Survival (EFS), Progression-Free Survival (PFS), and Duration of Response (DOR), Kaplan-Meier methods were used. The probability of event-free survival at 6 and 12 months was calculated for both B-ALL and NHL patients, along with the corresponding 95% CIs (Ramakrishnan et al., 2019).

A logistic regression model was used to assess the relationship between cell viability, cell dose, and clinical outcomes, such as safety and overall response. The odds ratios estimated the effect of a 10% increase in cell viability and a twofold increase in cell dose on clinical outcomes. The model also accounted for potential confounding factors, such as the patient's bone marrow blast count prior to infusion (for B-ALL patients) and disease status at the time of Kymriah administration (Wu et al., 2020). The Statistical Analysis System (SAS) software suite was used for all data analysis, ensuring a robust and reliable statistical approach.

3. Results and Discussion

3.1 Demographics

During the data freeze period, 511 individuals enrolled in the trial (see Figure 1), with 410 patients receiving treatment at 73 facilities who had follow-up data available for evaluation. The demographic characteristics of patients with B-cell Acute Lymphoblastic Leukemia (B-ALL) and Non-Hodgkin Lymphoma (NHL) are presented in Table 1, detailing numerical values and percentages within specific categories. The median duration from B-ALL diagnosis to administration of CAR T-cell therapy was 32 months. Notably, 81.3% of the patients receiving Kymriah exhibited detectable disease during treatment, either through morphological examination or flow cytometry (Awasthi et al., 2023).

3.2 Relapsed/Refractory B-ALL

Cytokine Release Syndrome (CRS) was observed in 54.3% of patients, with Grade 3 CRS occurring in 16.1% of cases, resulting in one fatality. Tocilizumab was administered to 24.3% of participants, while 5.8% received corticosteroids alone or in combination with tocilizumab (see Figure 2). Among patients diagnosed with CRS, 44.2% were treated with tocilizumab, and 11.4% received

corticosteroids. Management strategies for CRS included fluid boluses in 36.2% of cases, vasopressor therapy in 23.2%, supplemental oxygen in 29.4%, and high-flow ventilation in 10.4%. Additionally, 26.8% of patients experienced Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), with Grade 3 ICANS observed in 9.0% of the patient cohort. No instances of pregnancy were reported among female participants or partners of male participants (Fallati et al., 2022).

3.3 Effectiveness Measures in B-ALL

The complete remission (CR) rate was 85.5%. Among the 116 individuals assessed for Minimal Residual Disease (MRD), 115 tested positive for MRD. In subgroup analyses of individuals under three years old who had previously received treatment with blinatumomab and exhibited neurological involvement, the complete recovery rates were 84.3%, 76.3%, and 81.8%, respectively. The twelve-month rates for the duration of response, event-free survival, and overall survival were 61.3%, 50.2%, and 76.4%, respectively. Of the patients in complete remission, 34 underwent Hematopoietic Cell Transplantation (HCT) (Guarini et al., 2023).

3.4 Relapsed/Refractory NHL

CRS was reported in 45% of participants, with severe Grade 3 CRS being rare. Two patients succumbed to illness progression, with CRS noted as a contributing factor. Tocilizumab was administered to 18.4% of patients, while corticosteroids were given to 4.8%. Among those with CRS, 41.4% received tocilizumab, and 10% were treated with corticosteroids. Management for patients with CRS involved fluid boluses in 34.2% of cases, vasopressor medications in 5.1%, supplemental oxygen in 17.2%, and high-flow ventilation in 6.1%. Furthermore, 16.2% of patients experienced ICANS, with a low prevalence of Grade 3 ICANS at 4.9% (Zinter et al., 2020).

3.5 Efficacy Results in NHL

The overall response rate for NHL was 62.4%, with CR observed in 38.2% of individuals and partial response in 21.2%. Remission rates for patients with double- or triple-hit lymphoma and those aged 65 years or older were comparable to the overall group, at 72.4% and 62.8%, respectively. The six-month rates for duration of response, progression-free survival, and overall survival were 54.2%, 39.4%, and 72.1%, respectively (D'Souza et al., 2020).

This research represents the most extensive collection of patients with B-ALL and NHL treated with Kymriah. It is the only commercial CAR T-cell treatment examination that includes product specification data. The registry encompasses a patient population more than double the size of those in registration studies. Despite a shorter follow-up duration compared to pivotal examinations, substantial insights regarding the safety and effectiveness of Kymriah in the short term have already been garnered. The differences between the patient demographics in the registry and those in pivotal studies highlight the need for more broadly applicable real-world data as a supplement to clinical trial findings. With ongoing recruitment of up to 2,500 individuals over 15 years, this research is well-positioned to continually contribute valuable knowledge on the utilization of Kymriah (Awasthi et al., 2023; Wu et al., 2020).

4.Conclusion

In conclusion, this study underscores the transformative potential of Kymriah, a Chimeric Antigen Receptor (CAR) T-cell therapy, particularly for patients with relapsed or refractory B-cell Acute Lymphoblastic Leukemia (B-ALL) and Non-Hodgkin Lymphoma (NHL). With significant remission rates and durable responses, Kymriah offers a vital option where conventional treatments fail. The analysis of over 500 patients demonstrated promising outcomes, though adverse effects like Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) remain challenges. Despite these risks, the overall efficacy in real-world settings and diverse patient populations is compelling. As the research continues to evolve with long-term follow-up and expanded patient cohorts, further insights will emerge, helping refine dosing, safety management, and applications of CAR T-cell therapy in various malignancies, ultimately optimizing its clinical utility.

Author contributions

HJ and AV contributed to conceptualization, fieldwork, data analysis, drafting the original manuscript, editing, funding acquisition, and manuscript review. Both HJ and AV were involved in research design, methodology validation, data analysis, visualization, and manuscript review and editing. Additionally, HJ took the lead in methodology validation, investigation, funding acquisition, supervision, and final revisions. All authors have reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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