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Clinical comparison of the efficacy and toxicity of axicabtagene ciloleucel and lisocabtagene maraleucel in relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma

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BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**CLINICAL COMPARISON OF THE EFFICACY AND TOXICITY OF
AXICABTAGENE CILOLEUCEL AND LISOCABTAGENE MARALEUCEL IN
RELAPSED OR REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN'S
LYMPHOMA**

by

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ABSTRACT

Background: Patients with relapsed or refractory large B-cell lymphoma (LBCL) who have relapsed after at least 2 lines of therapy had a poor prognosis before the introduction of chimeric antigen receptor (CAR) T-cell therapy. The FDA approved three CD19 CAR T-cell products, axicabtagene ciloleucel (axi-cel), tisagenlecleucel, and lisocabtagene maraleucel (liso-cel), based on the results of pivotal phase 2 clinical trials. High response rates and long-term remissions in these multiply relapsed patients led to randomized trials as a second-line therapy against the current standard of care for primary refractory and early relapsing LBCL. Axi-cel and liso-cel are now approved as second-line treatments for patients with relapsed or refractory large B-cell lymphoma based on these trials, while tisagenlecleucel failed to improve upon second-line standard of care. This has led to greater axi-cel and liso-cel usage as compared with tisagenlecleucel. Clinical trials and real-world trials show a higher toxicity profile for axi-cel as compared to liso-cel with similar efficacy outcomes, leading to selection of liso-cel for older patients with more medical comorbidities. However, axi-cel manufacturing is faster and more reliable making it a preferred choice for rapidly progressive lymphomas. No direct comparison has been made between the two in order to optimally inform product selection.

Objective: We aimed to compare the toxicity profile and efficacy outcomes between two cohorts, one treated with axi-cel and the other with liso-cel, ideally well matched, during the same period of time.

Methods: We retroactively gathered patient data for patients treated between June 2021 to September 2022 with both products. We compared the cohorts for patient characteristics that are proven to affect the toxicity and efficacy in order to identify significant differences that could influence our results and to increase the likelihood that the two cohorts were well matched. We then assessed associated toxicities and long-term efficacy outcomes.

Results: The two cohorts were comparable for all patient and disease variables other than age (median age of 62 years old in axi-cel compared to 71 years old liso-cel [$p < 0.001$]). There was no significant difference between high-grade cytokine release syndrome (CRS) (3% vs 5% for axi-cel vs. liso-cel cohorts, respectively; $p = 0.58$), high-grade immune effector cell-associated neurotoxicity syndrome (ICANS) (18% [ASTCT] or 19% [CTCAE], 14% [ASTCT] or 12% [CTCAE] for axi-cel vs. liso-cel cohorts, respectively, $p = 0.055$). There were higher rates of any grade CRS with axi-cel, and duration of hospitalization was longer for axi-cel vs. liso-cel (10 vs 14 days, respectively). Best overall response rates (ORR) (93% vs. 84% axi-cel vs. liso-cel, respectively) and complete response (CR) rates (71% vs. 56% axi-cel vs liso-cel, respectively) did not statistically differ between the two groups. 12-month overall survival (OS) (76% vs. 81% axi-cel vs. liso-cel, respectively) and progression free survival (PFS) (61% vs. 45% of patients axi-cel vs. liso-cel, respectively) did not

statistically differ between the two groups ($p = 0.94$, $p = 0.51$ for OS and PFS, respectively).

Conclusions: Our study showed both products are similar in their high-grade toxicity profile as well as their efficacy. While axi-cel has more any grade CRS and ICANS, the lack of significantly higher high-grade toxicities likely reflects better and more aggressive toxicity mitigation strategies when patients present with low grade side effects. As a result, axi-cel in our study was found to be less toxic than previously seen in past clinical trials as well as real-world studies. Many factors go into selection of a CAR T-cell product, ranging from product performance attributes like safety and efficacy, to product manufacturing qualities like turnaround time and fidelity of manufacturing. With equivalency with regards to product performance, manufacturing qualities may then be most important in guiding product selection for LBCL patients.

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LIST OF ABBREVIATIONS

ALC.....	Absolute Lymphocyte Count
ASTCT	American Society for Transplantation and Cellular Therapy
Axi-cel.....	Axicabtagene Ciloleucel
B- ALL	B-cell Acute Lymphoblastic Leukemia
BCMA.....	B-cell Maturation Antigen
CAR T-cells	Chimeric Antigen Receptor T-cells
CIBMTR	Center for International Blood and Marrow Transplant Research
Cilta-cel.....	Ciltacaptagen Autoleucel
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CRP	C-Reactive Protein
CRS	Cytokine Release Syndrome
CTCASE	Common Terminology Criteria for Adverse Events
EFS.....	Event-Free Survival
Dex.....	Dexamethasone
DFCI	Dana-Farber Cancer Institute
DHL	Double Hit Lymphomas
DLBCL	Axicabtagene Ciloleucel
ECOG PS	Eastern Cooperative Oncology Group Performance Status
HGBL.....	High-Grade B-cell Lymphoma
ICANS.....	Immune Effector Cell-Associated Neurotoxicity Syndrome

ICU.....	Intensive Care Unit
Ide-cel	Idecabtagene vicleucel
IPI.....	International Prognostic Index
LBCL	Large B-cell Lymphoma
LDH	Lactate Dehydrogenase
Liso-cel	lisocabtagene maraleucel
MDR	Measurable Residual Disease
NHL	Non-Hodgkin lymphoma
ORR	Overall Response Rates
OS	Overall Survival
PD	Progressive Disease
PFS.....	Progression Free Survival
PMBL.....	Primary Mediastinal B-cell Lymphoma
PR.....	Partial Response
SD	Stable Disease
TCR.....	T-cell receptor
THL.....	Triple Hit Lymphomas
Tisa-cel.....	Tisagenlecleucel
Toci	tocilizumab
ULN	Upper Normal Limit

INTRODUCTION

History of CAR T-cell Therapy: From Phase 1 Studies to FDA Approval

Large B Cell Lymphoma (LBCL) is the most common Non-Hodgkin lymphoma (NHL) and includes diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBL), high-grade B-cell lymphoma (HGBL), and transformed lymphomas. The current treatment options used as first-line therapies include a combination of chemotherapies and immune therapy. If these lymphomas are refractory to treatment or relapse following treatment, appropriate patients may still achieve a cure with salvage chemotherapy and, in response to salvage therapy, consolidation autologous stem cell transplantation (Nagle 2013; Van Den Neste 2016; Seshardi 2008). However, for patients who either do not respond to salvage chemotherapy, who relapse following autologous stem cell transplantation, or patients who are not eligible for this approach in the first place, outcomes are poor, and survival is short. On the SCHOLAR-1 study, which represents a retrospective meta-analysis of both clinical trials and real-world databases of chemotherapy-refractory LBCL treated with available therapies in the 3rd line setting, these available 3rd line treatments resulted in remission in only 7% of patients, and only 20% of patients were alive after 2 years, with a median overall survival (OS) of approximately 6 months (Crump 2004). These are the patients who were treated on the pivotal phase 2 clinical trials with second-generation autologous anti-CD19 chimeric antigen receptor T-cells (CAR T-cells), which target and kill the malignant lymphocytes by a completely different mechanism from standard chemoimmunotherapy, which marked a transformative revolution in cancer-care for many patients with refractory B-

cell malignancies who had previously lacked any effective treatment options (Locke 2017).

A CD8 T-cell can bind to an MHC1 molecule via its T-cell receptor (TCR) and upon binding will initiate a cytotoxic effect on the MHC1-expressing cell. (Abbas 2013). CAR T-Cells were first developed exploiting the T-cell response by using viral vectors encoding a chimeric antigen receptor (CAR), which is part Fc variable fragment of an antibody molecule with tumor antigen specificity and part T-cell activating molecules, in order to equip the T-cell to directly recognize antigens independent of the MHC1 interaction. First-generation CAR T-cells were developed utilizing the known mechanism of T-cell cytotoxic activity in order to target HIV-infected cells and solid tumors (Braendstrup 2020). Early studies used a single part of the TCR: the intracellular and transcellular portion of a CD3 ζ , the stimulatory domain of the TCR, and an extracellular CD8 hinge region attached to a variable region of an antibody containing an antibody against human CD4 and human CD3 (Romeo 1991; Levine 1998). These first-generation CAR T-cells were shown to release interleukins indistinguishable from a TCR-MHC interaction and lysed target cells but failed to proliferate *in vivo*, and so the response was inadequate for clinical use (Sadelain 2009). Second-generation CAR T-cells were then developed on the basis of the two-signal hypothesis of T-cell activation and observations from studies showing B7 and CD80 interaction improved CAR T-cell function, expansion, and persistence (Brentje 2003; Baskar 1993). Second-generation autologous CAR T-cells join the Fc variable antibody fragment to both the signaling domains of the CD3 ζ molecule and a costimulatory molecule, often either CD28 or 4-1BB (Ying 2019).

The first-generation CARs developed were targeted against CD19, which is an ideal target because it is a cell surface molecule that is exclusively expressed by normal mature B cells, malignant B cells, B-cell precursors, and plasma cells, and a lack of antibody-producing B cells can be managed by repeated immunoglobulin infusions (Scheuermann 1995). The National Cancer Institute (NCI) first reported clinical proof of concept of second-generation CD19 CAR T-cells with a CD28 costimulatory domain in 2010 with the treatment of a patient with refractory follicular lymphoma (Kochenderfer 2010). Another second-generation anti-CD19 CAR T-Cell product with a 4-1BB costimulatory domain showed clinical proof of concept in B-cell chronic lymphocytic leukemia (B-CLL) in 2011 and then later in pediatric patients with B-cell acute lymphoblastic leukemia (B-ALL) in 2013 (Porter 2011; Grupp 2013). This latter CAR T-cell product, CTL-019, was licensed to Novartis and renamed tisagenlecleucel, and tested in a multicenter, global phase 2 study, the ELIANA study of relapsed/refractory pediatric and young-adult B-ALL (Figure 1). This study showed high rates of complete responses (CR) and measurable residual disease (MRD) negative responses, but more importantly, 12-month event-free survival (EFS) was 50%, and overall survival (OS) was 76%, indicating the curative potential of this therapy in a disease that had previously been nearly uniformly fatal (Maude 2018). This pivotal study led to the first FDA approval of an anti-CD19 CAR T-cell for pediatric patients with relapsed or refractory B-cell ALL. Tisagenlecleucel was then tested in the multicenter phase 2 JULIET study in relapsed/refractory LBCL, demonstrating a best overall response rate (ORR) was 52% and CR in 43% of patients with DLBCL and at a median follow-up of 28.6 months

progression-free survival was 43%, and OS was 48.2% (Schuster 2017) (Table 1). The aforementioned CD19 CAR T-cell with a CD28 costimulatory domain from the NCI was licensed to Kite Pharma and was renamed axicabtagene ciloleucel (axi-cel) (Figure 1) and was tested in a phase 2 multicenter clinical trial (ZUMA-1) in patients with refractory LBCL. ZUMA-1 showed a best OOR was 83%, and CR in 58% of patients and 12-month PFS was 44%, and overall survival (OS) was 59% (Neelapu 2017; Locke 2019) (Table 1). Contemporaneously, a third CD19-directed product with a 4-1BB costimulatory domain, JCAR019, was developed at the Fred Hutchinson Cancer Institute and subsequently licensed to Juno Therapeutics, which renamed it lisocabtagene maraleucel (liso-cel) (Figure 1). This product uses a precise ratio of CD4⁺ CAR T-cells and CD8⁺ CAR T-cells (1:1) (Ramsborg 2017). This product was tested in relapsed/refractory LBCL in the multicenter phase 2 TRANSCEND NHL-001 study that showed a best OOR was 83% and CR in 54% of patients, and 12-month PFS was 44.1% and overall survival (OS) was 57.9% (Abramson 2020) (Table 1). Based on these three phase 2 studies, axi-cel, tisagenlecleucel, and liso-cel were each approved by the FDA and other international authorities for the treatment of LBCL in the third line and beyond, with axi-cel's approval coming first (2017), followed shortly by tisagenlecleucel (2018) and finally most recently by liso-cel (2021).

Table 1. Outcomes of Phase 2 Clinical Trials for Axi-cel, Tisagenlecleucel, and Liso-cel.

The best CR, 12 Month PFS, and 12 Month OS from ZUMA-1, JULIET, and TRANSCEND NHL-001 studies. NR= Not Reached. ‡12-month PFS for JULIET not reported, 43% used from median follow up at 28.6 months. (Schuster 2017; Neelapu 2017; Locke 2019)

Study	JULIET (N = 115)	ZUMA-1 (N = 101)	TRANSCEND (N = 256)
Product	Tisagenlecleucel	Axi-cel	Liso-cel
Best ORR	52%	83%	73%
Best CR	40%	58%	53%
Median OS	11.1 Months	NR	21.1 Months
OS at 12 Months	48.9%	59%	57.9%
Median PFS	NR	44 Months	6.8 Months
PFS at 12 Months	43%‡	44%	44.1%

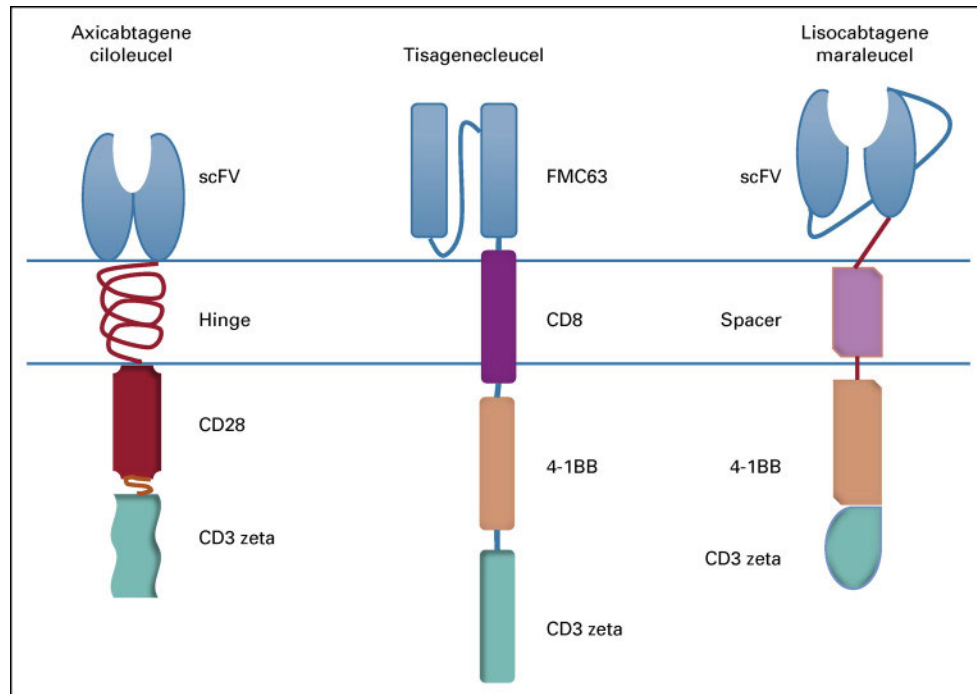


Figure 1. Representation of three different CAR T-cell products used to treat NHL. Each product has a CD3 ζ chain. Axi-cel has a CD28 costimulatory domain, while tisagenlecleucel and liso-cel have a 4-1BB costimulatory domain (Jacobson 2018).

CAR T-cell Toxicity

CAR T-cell toxicities differ from other anti-cancer therapies due to the mechanism of action of this cellular immunotherapy. The principal acute toxicities include cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS); other potential acute, and long-term side effects can include cytopenias and tumor lysis syndrome, and due to an on-target, off-tumor effect patients treated with CD19 CAR T-cell therapy develop, B-cell aplasia, and hypogammaglobulinemia (Schubert 2021). CRS and ICANs are particularly concerning due to acute and rapid onset that can escalate quickly and become life-threatening in

some patients and are among the reasons these therapies are offered only by highly specialized and trained centers equipped to manage these side effects. CRS is the result of the rapid expansion and activation of CAR T-cells following infusion and the subsequent release of cytokines and chemokines (Schubert 2021). Clinical manifestations of CRS include fever, fatigue, hypotension, hypoxia, tachycardia, and tachypnea, and in higher-grade cases can include arrhythmia, capillary leak coagulopathy, respiratory failure, shock, and end-organ dysfunction (Alvi 2019; Gupta 2020). CRS frequency, timing, and severity do vary with CAR T-cell tumor antigen target, the disease being treated, and the costimulatory domain of the CAR (Neelapu 2017; Abramson 2020; Porter 2011; Grupp 2013; Maude 2018) (Table 2). Among CD19 CAR T-cells, the 4-1BB CARs tend to expand later and more slowly and so CRS generally starts later and is lower-grade, whereas the CD28 CARs expand and activate quickly, leading to earlier CRS and higher rates of high-grade inflammation. Within diseases treated by CD19 CARs, patients with B-ALL have the highest rates of CRS, followed by LBCL and then indolent lymphomas (Maude 2018; Neelapu 2017; Schuster 2017). The use of the IL6 receptor antibody tocilizumab as a treatment of CRS was discovered surreptitiously during early phase studies, and when tocilizumab is insufficient, corticosteroids, most commonly dexamethasone, are added (Grupp 2013; Le 2018). ICANS, also referred to as neurotoxicity, also occurs commonly acutely after infusion. ICANS can occur simultaneously with CRS, after the resolution of CRS, or independently of CRS, but most often occurs after the onset of CRS (Lee 2014). Its pathophysiology is poorly understood but definitely involves some degree of transient inflammation of the brain, and as such,

can lead to impairment of attention, confusion, and expressive aphasia, and its most high-grade presentations can cause a depressed level of consciousness, coma, seizures, motor weakness and cerebral edema (Neelapu 2018; Lee 2014). Like CRS, risk of any grade and high-grade ICANS varies similarly with CAR T-cell target (greatest with CD19), CAR costimulatory domain (greatest with CD28), and the disease being treated (greatest with B-ALL) (Maude 2018; Neelapu 2017; Schuster 2017) (Table 2). Treatment of ICANS is limited to the use of corticosteroids since tocilizumab has poor blood brain-barrier penetration and has also been shown to be ineffective at treating ICANS (Nellan 2018; Santomaso 2018). Long term side effects such as B-cell aplasia and hypogammaglobulinemia, as well as cytopenias, do put patients at a higher risk of infection but can be managed with Ig replacement and granulocyte growth factor support (Neelapu 2018; Neelapu 2019).

Table 2. Toxicity of Phase 2 Clinical Trials for Axi-cel, Tisagenlecleucel, and Liso-cel. Toxicity of both CRS and ICANS reported by JULIET, ZUMA-1, and TRANSCEND. Both CRS and ICANS were graded from 1-5. High-grade CRS or ICAN is considered a grade ≥ 3 (Schuster 2017; Neelapu 2017; Locke 2019).			
Study	JULIET (N = 115)	ZUMA-1 (N = 101)	TRANSCEND (N = 256)
Product	Tisaglenlecleucel	Axi-cel	Liso-cel
Any Grade CRS	58%	93%	42%
High-grade CRS	22%	13%	2%
Any Grade ICANS	21%	64%	30%
High-grade ICANS	11%	28%	10%

CD19 CAR T-cells in LBCL: From FDA approval to Earlier and Expanded Indications

Following the success and approval of axi-cel, tisagenlecleucel and liso-cel in the 3rd line for relapsed/refractory LBCL, several retrospective real-world studies were done to investigate the activity of these therapies in non-clinical trial candidates, the majority of whom would not have been eligible for the pivotal clinical trials based on medical comorbidities and organ function. For tisagenlecleucel non-clinical trials, multiple studies demonstrate similar effectiveness to the JULIET trial, with the best ORR at 53%-60% (Bethge 2022; Iacoboni 2021); best CR rates 32% (Bethge 2022; Iacoboni 2021) (compared to best ORR and CR rates in 52% and 40%, respectively in JULIET). The toxicity of tisagenlecleucel in the non-clinical trial studies has been similar to improved compared with the JULIET trial, with grade 3 or higher CRS in these studies at 5-13% (Iacoboni 2021; Bethge 2022) and grade 3 or higher ICANS in 1-7% (Iacoboni 2021; Bethge 2022) (compared to grade 3 or higher CRS and ICANS rates of 22% and 11% respectively in JULIET) (Table 3). Axi-cel non-clinical trial studies have likewise demonstrated similar effectiveness to that seen on ZUMA-1, with the best ORR at 70%-82% (Jacobson 2020; Jacobson 2022; Nastoupil 2020); best CR rates 50%-64% (Jacobson 2020; Jacobson 2022; Nastoupil 2020) (compared to best ORR and CR rates in 83% and 58%, respectively in ZUMA-1). The toxicities of axi-cel in the non-clinical setting have also been similar to improved to that seen on ZUMA-1, with grade 3 or higher CRS in 7-16% (Nastoupil 2020; Jacobson 2020; Jacobson 2022), and grade 3 or higher neurotoxicity in 24-35% (Jacobson 2022; Nastoupil 2020; Jacobson 2020)

(compared to grade 3 or higher CRS and ICANS rates of 13% and 28% respectively in ZUMA-1) (Table 3).

Table 3. Real World Comparative Studies for Axi-cel and Tisagenlecleucel. Comparison of the best ORR and CR along with toxicities including high-grade CR and ICANS from real world studies against JULIET and ZUMA-1 clinical trials (Schuster 2017; Neelapu 2017; Bethge 2022; Iacoboni 2021; Jacobson 2020; Nastoupil 2020; Jacobson 2022)				
Study	JULIET	Bethge et al. 2022		Iacoboni et al. 2021
	Tisa-cel	Tisa-cel		Tisa-cel
Best ORR	52%	53%		60%
Best CR	40%	32%		32%
High-grade CRS	22%	13%		5%
High-grade ICANS	11%	7%		1%
Study	ZUMA-1	Jacobson et al. 2020	Nastoupil et al. 2020	Jacobson et al. 2022
	Axi-cel	Axi-cel	Axi-cel	Axi-cel
Best ORR	83%	70%	82%	73%
Best CR	58%	50%	64%	56%
High-grade CRS	13%	16%	7%	8%
High-grade ICANS	28%	35%	31%	24%

These studies investigated only axi-cel and tisagenlecleucel given that the approvals for these products were considerably earlier than for liso-cel, and they largely recapitulated the results of the pivotal clinical trials in terms of response rates, duration of response, and overall survival, and also demonstrated improved toxicity profiles owing to the early and more aggressive management of CRS and ICANS. Additionally, each product was

tested against standard of care (SOC) (salvage chemotherapy and an autologous stem cell transplantation) for high-risk LBCL in the second line, defined as primary refractory or early relapsing disease to frontline chemoimmunotherapy (Locke 2020; Bishop 2020; Abramson 2021). Two of these studies, the ZUMA-7 study of axi-cel and the TRANSFORM study of liso-cel were positive studies in favor of the experimental CAR T-cell arm with respect to the primary endpoint (event-free survival; EFS) as well as complete and overall response rates and PFS with trends in improvement in OS despite the ability for the SOC arm to cross over to CAR T-cells given approval of CAR T-cells in the third-line setting (Locke 2020; Abramson 2021). The third study, the BELINDA study of tisagenlecleucel, was a negative study showing no advantage of tisagenlecleucel over SOC in this setting (Bishop 2020). Given these results, the use of tisagenlecleucel for relapsed/refractory LBCL has largely disappeared, and patients are either treated with axi-cel or liso-cel. Theoretical advantages of axi-cel are that the CAR T-cell manufacturing time is the shortest and most reliable, two very important factors to patients with resistant and progressing lymphoma who need treatment as quickly as they can get it. On the other hand, liso-cel has less high-grade CRS and ICANS and may be preferred for older patients with medical comorbidities. These biases toward product selection make it very difficult to make any cross-product comparison as different patients tend to be treated with the different products. However, following FDA approval of liso-cel in the US, the lymphoma group at the Dana-Farber Cancer Institute made the unanimous decision to treat all of the next CAR T-cell eligible patients with liso-cel in order to get an experience with this product, a practice which should have removed biases

surrounding patient selection, and provided an opportunity to compare outcomes for these patients treated with liso-cel against patients treated with axi-cel during a proximate timespan at the same institution. This thesis is an investigation of those comparisons. In order to better understand the hypotheses and findings of this investigation, it is important that the trial data regarding axi-cel and liso-cel efficacy and toxicity first be explored in further detail.

Axicabtagene ciloleucel

As introduced earlier, axicabtagene ciloleucel (axi-cel, Kite Pharma) is a second-generation autologous anti-CD19 CAR T-cell therapy that consists of an extracellular domain targeting CD19 with CD3 ζ and CD28 intracellular domains that trigger T-cell activation. ZUMA-1 was a critical phase 2 trial to show the efficacy and associated toxicity of axi-cel. On this clinical trial, the best overall response rates (ORR) and complete response (CR) rates in infused patients were 83% and 58%, respectively (Neelapu 2017). The 2-year data from the ZUMA-1 trial has shown a 39% durable remission at a median follow-up of 27.1 months; the median overall survival was not reached, and the median progression-free survival was 5.9 months, with a progression-free survival rate at 12 months of 44% (Locke 2019). Important CAR T-cell related toxicities of CRS and ICANS of any grade occurred in 93% and 64% of patients, respectively, and was grade 3 or higher in 13% and 28%, respectively (Neelapu 2017). The median time to onset of CRS was just 2 days. These results led to the FDA approval of axi-cel for relapsed/refractory LBCL in the 3rd line and beyond. Following this approval, multicenter retrospective studies of axi-cel in the standard of care setting, many

of which included up to 60% of patients who would not have been eligible for the ZUMA-1 clinical trial due to comorbidities or performance status, have shown axi-cel to be similarly effective with the best ORR and CR rates being 70% and 50%, respectively in Jacobson 2020 et al (2020). The clinical trial and non-clinical trials also had similar toxicity; Grade 3 or higher cytokine release syndrome occurred in 16% of patients and neurotoxicity occurred in 35% of patients in Jacobson et al. (compared to 13% and 28% respectively in ZUMA-1). Again, durable remission rates around 40-50% were seen, further supporting the curative potential for axi-cel in relapsed/refractory LBCL.

Previously referenced Nastoupil et al. (2020) included 43% of patients that would not have met ZUMA-1 eligibility showing axi-cel having a best ORR and CR being 82% and 64%, respectively; Grade 3 or higher cytokine release syndrome occurred in 7% of patients and neurotoxicity occurred in 31% of patients. Again, the success of axi-cel in heavily pre-treated LBCL patients supported the rationale for testing it, in a randomized fashion, in high-risk patients in the second-line against the standard of care – salvage chemoimmunotherapy followed by autologous stem cell transplantation in responsive patients (Locke 2022). The primary endpoint of this study was event-free survival (EFS) and axi-cel was superior to standard of care, with a median EFS of 8.3 months compared to 2.0 months, respectively (Locke 2022). Based on these results, axi-cel is now FDA approved for LBCL in the second-line for primary refractory or early relapsing patients as well.

Lisocabtagene maraleucel

As previously reviewed, lisocabtagene maraleucel (liso-cel) is a CD19-directed CAR T-cell product with a 4-1BB co-stimulatory domain approved by the FDA in 2021. This approval was based on the results of the phase 2 TRANSCEND NHL 001 that showed an ORR of 73% of patients and a CR rate of 53% in relapsed/refractory LBCL in the third-line and median PFS of 6.8 months, PFS rates at 12 months at 44.1%, and median OS of 27.3 months (Abramson 2020). CRS and ICANS of any grade occurred in 42% and 30% of patients, respectively, and was grade 3 or higher in 2% and 10% of patients, respectively (Abramson 2020). Due to the more recent approval, no major studies exist comparing clinical trials to non-clinical trial settings; however, we will likely see them soon. Again, similarly to the experience with axi-cel, these results supported testing liso-cel against standard of care (salvage chemoimmunotherapy and autologous stem cell transplantation) for high-risk early relapsing and/or primary refractory LBCL in the 2nd line setting in a randomized fashion in the TRANSFORM study (Abramson 2022). The primary endpoint EFS was superior for liso-cel over standard of care, with a median EFS of 10.1 months versus 2.3 months, respectively (Abramson 2022). Liso-cel was also tested in the 2nd line in all-comer LBCL patients who were not felt to be candidates for autologous stem-cell transplantation on the phase 2 PILOT study, which showed liso-cel to be safe and effective for this population (Seghal 2022). Based on the TRANSFORM and PILOT studies, liso-cel has been approved as a second line treatment for LBCL that is either early relapsing/primary refractory or occurring in a patient ineligible for autologous stem cell transplantation.

Our Study Rationale and Hypothesis

With the FDA approval of several CD19-directed CAR T-cell therapies for LBCL, clinicians must now choose between the different products to achieve the best outcomes for their patients, but no randomized data exists comparing the different products against each other. Comparing across the clinical trials is plagued with significant issues and challenges, but on their face, axi-cel and liso-cel appear to be quite similar with respect to efficacy, whereas liso-cel has a more favorable toxicity profile. However, due to differences in trial eligibility, patient management on trial, and manufacturing efficiency in terms of ability to manufacture a product as well as manufacturing turnaround time, the patients treated on each trial were likely quite different, making a comparison of the results likely meaningless. For example, axi-cel was able to be manufactured for 99% of patients enrolled on the ZUMA-1 trial and the average turnaround time was 17 days (Neelapu 2017). On the other hand, liso-cel could not be successfully manufactured for 8% of patients enrolled on the TRANSCEND-NHL 001 study, and the average turnaround time for manufacturing was 24 days (Abramson 2020). This could have resulted in patients with more aggressive lymphomas being treated with axi-cel compared with liso-cel because the faster turnaround time and more successful manufacturing would allow patients with more rapidly progressive lymphomas to remain well enough to receive their cells once they are successfully manufactured. The TRANSCEND NHL-001 study had broader eligibility criteria than the ZUMA-1 study and patients with some degree of comorbid cardiac and renal disease were allowed to be treated on study (Neelapu 2017; Abramson 2020). This coupled with the apparent

improved toxicity profile over axi-cel could favor sicker and frailer patients being treated with liso-cel.

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SPECIFIC AIMS

Clinical trials for the approval of two important CAR T-cell products, axi-cel and liso-cel, led to the approval by the FDA of both products as a 3rd line treatment to refractory or relapsed lymphoma after 2 or more lines of treatment. Further clinical trials against standard-of-care for 2nd line treatment of refractory or relapsed lymphoma led to the approval of both products as 2nd line treatments. In clinical trials and commercial usage trials have shown axi-cel having greater acute side effects of CRS and ICANS compared to similar trials of liso-cel usage. In clinical trials, response rates, OS, and PFS has also been shown to be similar in axi-cel as compared to liso-cel

In order to study the relative efficacy and safety of axi-cel and liso-cel in the clinic and to inform product selection choices for patients in the future, we conducted a retrospective analysis of all patients treated with standard of care liso-cel since FDA approval and the Dana-Farber Cancer Institute (DFCI), during which time the practice had been to treat as many patients as possible with this new product in order to gain familiarity and comfort with it. This cohort will be compared with a retroactive analysis of the side effect profile, response rates, OS, and PFS with axi-cel as standard of care during a similar timeframe at DFCI. In doing so, we will compare the two cohort's patient characteristics that are known or theorized to affect the acute toxicity and efficacy of CAR T-cell patients. This paper will also compare our data to the original ZUMA-1 and TRANSCEND clinical trials to show consistencies or differences as they relate to our commercial trial.

PATIENTS AND METHODS

Study Design and Participants

All patients in this study were treated at DFCI in the cellular therapy program. DFCI's staff is trained to administer axi-cel and liso-cel products and are equipped to manage toxicities. All patients voluntarily signed the research consent form titled "Participation in the Center for International Blood and Marrow Transplant Research (CIBMTR) Research database for Patients Receiving Autologous Transplants or Cellular Therapies," and this research consent form has a protocol number of 03-022 at DFCI. All patients were treated between June 2021 and September 2022. Patient selection by clinicians for the treatment of any CAR T-Cell therapy followed DFCI guidelines, and selection between axi-cel and liso-cel to treat patients with LBCL was made at random. Data was extracted from patient chart notes and organized into a secure RedCaps database, then extracted for analysis.

To compare the two cohorts, their disease status, age, and prior treatments were considered. Clinicians assessed patients using Eastern Cooperative Oncology Group performance status (ECOG PS) at apheresis and International Prognostic Index (IPI) before lymphodepletion. Comparative characteristics that are proven or theorized to have an impact on the efficacy and toxicity of CAR T-cell therapy included the diagnosis of the type of LBCL, subtypes of double hit lymphomas (DHL) and triple hit lymphomas (THL), absolute lymphocyte count (ALC), tumor bulk, stage at the time of LBCL at diagnosis, lactate dehydrogenase (LDH) at apheresis, 5 days before infusion (day -5), and the day of infusion (day 0), prior autologous transplants and/or allogeneic transplants, the

use of bridging, and prior lines of therapy (Hay 2017; Nastoupil 2020; Neelapu 2017; Abramson 2020). Inflammatory markers such as C-reactive protein (CRP) and ferritin, recorded on day 0, were also compared due to their correlation with the severity of CRS (Teachey 2016).

Treatment and Clinical Assessment

Patients underwent leukapheresis to manufacture their respective products. Between leukapheresis and infusion of their manufactured cells, patients may or may not have undergone bridging therapy, and all patients underwent lymphodepletion 5 days before infusion. Bridging therapy was considered any lymphoma treatment after leukapheresis and before lymphodepletion and was up to the treating clinician's discretion. Lymphodepletion is administering cyclophosphamide and fludarabine conditioning daily for 3 days starting on day -5. Lymphodepletion is the standard of care prior to CAR T-cell therapy due to proven greater response rates (Klebanoff 2005). All patients receiving axi-cel and liso-cel were treated in a hospital and monitored regularly. CRS was graded from 1-5 using both the modified Lee et al. grading criteria and the American Society for Transplantation and Cellular Therapy (ASTCT) grading scale. Early studies used the Lee et al. grading criteria, but the system was inconsistent across studies, so the ASTCT scale was developed for standardizing CRS grading (Lee 2014; Lee 2019). Both scales were used since there is a current transition to use the ASTCT grading scale. ICANS was graded from 1-5 by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) as well as the ASTCT ICANS grading scale. For the same reasons as CRS, there has been a transition to a standardized

grading with ASTCT ICANS grading scale however, both were used for the purposes of this study (Lee 2019). Management of CRS and ICANS were treated with the current standard of care treatments. The incidence, timing, and severity of CRS and ICANS were analyzed. Severe CRS and ICANS were defined as grade 3 or higher. The outcome parameters analyzed included overall response (ORR) rate, complete response (CR) rate, overall survival (OS), and progression-free survival (PFS) rate.

Statistical Methods

Descriptive statistics use the mean, standard deviation, median, and range for continuous variables, and percentages for categorical variables. Differences between groups were assessed using Fisher's exact test to test two categorical variables and Wilcoxon rank-sum test to test differences in continuous variables. Response rates were determined with 95% exact binomial confidence intervals. Probabilities of OS and PFS were estimated using Kaplan-Meier plots and log-rank tests to identify differences between groups. OS was defined as the time from cellular therapy to death from any cause, and PFS was defined as the time from cellular therapy to relapse or disease progression or death from any cause (Xie 2014; Xie 2015; Xie 2022; R Core Team 2022)

RESULTS

Patient Characteristic

Over 16 months, 98 patients total were treated with either axi-cel or liso-cel, all at DFCL. 58 patients were treated with axi-cel, and 40 patients were treated with liso-cel. With the exception of age, ALC at apheresis, and LDH at apheresis, baseline characteristics between the two groups were comparable. All comparative characteristic data can be found on table 4. Age was significantly lower in the axi-cel group, with a median age of 62 years old, while the liso-cel group had a median age of 71 years old ($p < 0.001$). The median ALC at apheresis for axi-cel group was 530 cells/microliter, while the median ALC for the liso-cel group was 745 cells/microliter ($p = 0.035$). However, when corrected for ALC above and below the normal limits of 300 cells/microliter, it was found the two groups were comparable ($p = 0.52$). For the axi-cel group, LDH at apheresis was 221 units/liter, while the liso-cel group was 241 units/liter ($p = 0.034$). When LDH was adjusted to being above and below the upper limit of normal (ULN) of 256 units/liter, again the two groups were found to be comparable ($p = 0.14$). Of the 98 patients, 28% of patients had a performance status ECOG ≥ 2 . 67% of the total patients had de novo DLBCL, 16% had transformed follicular lymphoma (tFL), and 17% had other subtypes of LBCL, including high-grade B-cell lymphoma (HGBL), primary mediastinal B-cell lymphoma (PMBCL), transformed marginal zone lymphoma, and other various subtypes. Of the total patients, 82% of patients had an internal prognostic index (IPI) prior to lymphodepletion ≥ 3 , 19% had a prior autologous stem cell transplant, 2% had an allogeneic stem cell transplant, and 58% had bridging therapy before infusion.

These frequencies were similar between the two groups. Most patients had ≥ 2 prior lines of therapy prior to infusion, and of the axi-cel cohort, only 5% of patients had only 1 prior line of therapy. There were no patients treated with liso-cel in the second-line, given that it was not approved for this indication in the timeframe when this study was conducted.

Table 4. Patient characteristics. Data collected from each patient on various biomarkers, clinical assessments, and treatment history to compare the axi-cel cohort vs. liso-cel cohort. Units if applicable are listed next to the defined variable in parenthesis. Day 0 = day of infusion, Day -5 = 5 days before infusion. Apheresis is the date of T-cell collection. ULN = Upper Limit of Normal

		Product		
	Total n = 98 (%)	Axi-cel n = 58 (59)	Liso-cel n = 40 (41)	p-value
Age at treatment (years old)				
Median (range)	66 (34 - 84)	62 (34 - 81)	71 (54 - 84)	< 0.001 [†]
ECOG pre-apheresis				
0	23 (23)	15 (26)	8 (20)	0.21 [‡]
1	48 (49)	31 (53)	17 (42)	
2	26 (27)	12 (21)	14 (35)	
3	1 (1)	-	1 (2)	
Diagnosis (scale 1-5)				
De novo DLBCL	66 (67)	34 (59)	32 (80)	0.20 [‡]
HGBL	8 (8)	5 (9)	3 (8)	
Other	5 (5)	4 (7)	1 (2)	
PMBCL	1 (1)	1 (2)	-	
tFL	16 (16)	13 (22)	3 (8)	
tMZL	2 (2)	1 (2)	1 (2)	
IPI Before Lymphodepletion (scale 1-5)				
0-2	18 (18)	13 (22)	5 (12)	0.29 [‡]
3-5	80 (82)	45 (78)	35 (88)	
Prior Autologous Transplantation				
No	79 (81)	44 (76)	35 (88)	0.20 [‡]
Yes	19 (19)	14 (24)	5 (12)	
Prior Allogenic Transplantation				
No	96 (98)	57 (98)	39 (98)	> 0.99 [‡]
Yes	2 (2)	1 (2)	1 (2)	

Bridging Therapy					
No	41 (42)		27 (47)	14 (35)	$0.30^{\ddagger}$
Yes	57 (58)		31 (53)	26 (65)	
Tumor Bulk (length of longest axis of tumor in cm)					
>5	54 (55)		30 (52)	24 (60)	$> 0.99^{\ddagger}$
5-10	18 (18)		10 (17)	8 (20)	
>10	10 (10)		6 (10)	4 (10)	
<i>Unknown</i>	<i>16 (16)</i>		<i>12 (21)</i>	<i>4 (10)</i>	
Day 0 CRP (milligrams/liter)					
Median (range)	16.1 (0.8 - 203.6)		16.8 (2.0 - 174.5)	15.4 (0.8 - 203.6)	$0.54^{\ddagger}$
ALC at Apheresis (cells/microliter)					
Median (range)	605 (130 - 2240)		530 (130 - 2240)	745 (210 - 1840)	$0.035^{\ddagger}$
< 300	10 (10)		7 (12)	3 (8)	$0.52^{\ddagger}$
≥ 300	88 (90)		51 (88)	37 (92)	
Stage at Time of Diagnosis (scale 1-4)					
1	2 (2)		1 (2)	1 (2)	$0.41^{\ddagger}$
2	5 (5)		2 (3)	3 (8)	
3	19 (19)		9 (16)	10 (25)	
4	72 (73)		46 (79)	26 (65)	
LDH at Apheresis (units/liter)					
Median (range)	218 (127 - 2196)		210 (127 - 2196)	224 (171 - 1253)	$0.34^{\ddagger}$
LDH at day -5 (units/liter)					
Median (range)	219 (138 - 1652)		203 (138 - 1652)	232 (139 - 1351)	$0.22^{\ddagger}$
LDH at day 0 (units/liter)					
Median (range)	235 (126 - 1867)		221 (126 - 1627)	242 (166 - 1867)	$0.034^{\ddagger}$
$\leq$ ULN	59 (60)		39 (67)	20 (50)	$0.14^{\ddagger}$
>ULN	38 (39)		19 (33)	19 (48)	
Ferritin at day 0 (micrograms/liter)					
Median (range)	450 (131 - 10286)		462 (203 - 10286)	404 (131 - 6633)	$0.12^{\ddagger}$
Pre-Infusion lines of therapy					
1	5 (5)		5 (9)	-	$0.27^{\ddagger}$

2	40 (41)	21 (36)	19 (48)		
3	35 (36)	22 (38)	13 (32)		
4	10 (10)	5 (9)	5 (12)		
5	3 (3)	1 (2)	2 (5)		
6	5 (5)	4 (7)	1 (2)		
*Wilcoxon rank-sum test, †Fisher's exact test					

Toxicity

CRS

The incidence of any grade CRS was statistically significantly different between the two groups. Note that the Lee et al. grading system and the ASTCT correlated to be the same grade for all patients. CRS of any grade was 72% across all patients. In the axi-cel cohort, 83% of patients had any grade CRS compared to 57% of patients in the liso-cel group ($p = 0.011$). For all patients, only 4% of patients had a high-grade CRS ($\geq$ grade 3), and there was not a significant difference in high-grade CRS between the two groups 3% for axi-cel and 5% for liso-cel, ($p = 0.58$). Both the time to any grade CRS and max grade CRS did not differ between the two cohorts (3 days vs. 2 days for CRS onset for axi-cel vs. liso-cel, respectively; 5 days vs. 4 days for onset of highest-grade CRS for axi-cel and liso-cel, respectively). The duration of CRS did differ between the two groups, with a median duration of 5 days vs. 4 days for the axi-cel and liso-cel cohorts, respectively ($p = 0.0087$). The tocilizumab (toci) and dexamethasone (dex) administered for CRS also differed between the two groups, with more of both treatments being given to patients in the axi-cel cohort compared with the liso-cel cohort (71% vs. 30% of patients receiving toci for CRS in axi-cel vs. liso-cel $p = 0.0072$, respectively;

62% vs. 22% of patients receiving dex for CRS in axi-cel and liso-cel $p = 0.031$, respectively). This data can be found on table 5 and figure 2.

ICANS

Any grade ICANS was observed in 45% of patients in the axi-cel cohort compared with a frequency of 25% in the liso-cel cohort ($p = 0.056$). Among all the patients, using both the CTCAE scale and the ASTCT ICANS grading scale 16% of patients had grade 3 or higher ICANS. High-grade (grade $3 \geq$) ICANS occurred in 18% (ASTCT) or 19% (CTCAE) of patients treated with axi-cel compared with 14% (ASTCT) or 12% (CTCAE) of patients treated with liso-cel. These differences in severe ICANS between both groups using both scales were not statistically significant (ASTCT $p = 0.60$, CTCAE $p = 0.055$). The median time to any grade ICANS was 7 days in the axi-cel cohort compared with 6 days in the liso-cel cohort ($p = 0.031$) (Table 5) (Figure 2).

Other Safety Endpoints

Cardiac events (9% vs 2%; axi-cel vs liso-cel), intensive care unit (ICU) admissions (5% vs 8%; axi-cel vs liso-cel), total days in the ICU (51 days vs 5 days; axi-cel vs liso-cel), and readmittance within 30 days of infusion (7% vs 8%; axi-cel vs liso-cel) did not differ between the two cohorts ($p > 0.99$, $p = 0.69$, $p > 0.99$, $p = 0.52$, respectively). The length of initial hospitalization was longer for the axi-cel compared with the liso-cel cohort at 14 versus 10 days, respectively ($p = 0.0047$) (Table 5).

Table 5. Selected Safety Outcomes of Axi-cel and Liso-cel. Rates, duration, and lengths of CRS and ICANS in axi-cel vs liso-cel. Other safety data including treatments for CRS and ICANS, Cardiac events, ICU admission and length of stay, and readmission within 30 days of infusion.

		Product		
	Total n = 98 (%)	Axi-cel n = 58 (59)	Liso-cel n = 40 (41)	p-value
CRS				
No	27 (28)	10 (17)	17 (42)	0.011 [‡]
Yes	71 (72)	48 (83)	23 (57)	
Max Lee grade (scale 1-5)				
1	30 (31)	17 (29)	13 (32)	0.044 [‡]
2	35 (36)	29 (50)	6 (15)	
3	2 (2)	1 (2)	1 (2)	
4	2 (2)	1 (2)	1 (2)	
Max Lee grade 3+				
No	65 (66)	46 (79)	19 (48)	0.58 [‡]
Yes	4 (4)	2 (3)	2 (5)	
Time to CRS any grade (days)				
Median (range)	3 (0 - 8)	3 (0 - 8)	2 (1 - 7)	0.44 [‡]
Time to CRS grade 2+ (days)				
Median (range)	5 (0 - 10)	5 (1 - 10)	4 (0 - 7)	0.68 [†]
Time to CRS max grade (days)				
Median (range)	5 (0 - 11)	5 (0 - 10)	4 (1 - 11)	0.17 [†]
Duration of CRS, days				
Median (range)	4 (1 - 20)	5 (1 - 20)	4 (1 - 9)	0.0087 [†]
Tocilizumab given for CRS				
No	18 (18)	7 (12)	11 (28)	0.0072 [‡]
Yes	53 (54)	41 (71)	12 (30)	
Number of toci doses for CRS				
Median (range)	2 (1 - 4)	2 (1 - 4)	1 (1 - 3)	0.33 [‡]

Time of toci initiation (days)					
Median (range)	4 (1 - 8)		4 (1 - 8)	3 (1 - 7)	0.85 [‡]
Dexamethasone given for CRS					
No	25 (26)		11 (19)	14 (35)	0.0031 [‡]
Yes	46 (47)		37 (64)	9 (22)	
Number of dex doses for CRS					
Median (range)	2 (1 - 6)		2 (1 - 6)	2 (1 - 6)	0.98 [‡]
Time of dex initiation (days)					
Median (range)	7 (0 - 13)		7 (4 - 13)	7 (0 - 10)	0.51 [‡]
ICANS					
No	62 (63)		32 (55)	30 (75)	0.056 [‡]
Yes	36 (37)		26 (45)	10 (25)	
Max grade ICANS (ASTCT) (scale 1-5)					
1	12 (12)		9 (16)	3 (8)	0.60 [‡]
2	7 (7)		6 (10)	1 (2)	
3A	14 (14)		9 (16)	5 (12)	
3B	1 (1)		-	1 (2)	
4	1 (1)		1 (2)	-	
Max grade ICANS (CTCAE) (scale 1-5)					
1	13 (13)		11 (19)	2 (5)	0.55 [‡]
2	7 (7)		4 (7)	3 (8)	
3	15 (15)		10 (17)	5 (12)	
4	1 (1)		1 (2)	-	
Time to ICANS any grade (days)					
Median (range)	6 (1 - 13)		7 (3 - 13)	6 (1 - 7)	0.031 [†]
Duration of ICANS (days)					
Median (range)	5 (1 - 60)		5 (1 - 60)	5 (1 - 30)	0.75 [†]
Dexamethasone given for ICANS					
No	44 (45)		24 (41)	20 (50)	0.14 [‡]
Yes	26 (27)		19 (33)	7 (18)	
Solumedrol given for ICANS					

No	34 (35)		23 (40)	11 (28)		> 0.99 [‡]
Yes	1 (1)		1 (2)	-		
Cardiac events						
No	92 (94)		53 (91)	39 (98)		0.40 [‡]
Yes	6 (6)		5 (9)	1 (2)		
Length of hospital stay (days)						
Median (range)	13 (6 - 163)		14 (8 - 163)	10 (6 - 48)		0.0047 [†]
ICU admission						
No	92 (94)		55 (95)	37 (92)		0.69 [‡]
Yes	6 (6)		3 (5)	3 (8)		
Total ICU days						
Median (range)	6 (1 - 100)		15 (1 - 100)	5 (4 - 6)		> 0.99 [‡]
Readmitted within 30 days of infusion						
No	88 (90)		51 (88)	37 (92)		0.52 [‡]
Yes	10 (10)		7 (12)	3 (8)		

[‡]Fisher's exact test, [†]Wilcoxon rank-sum test

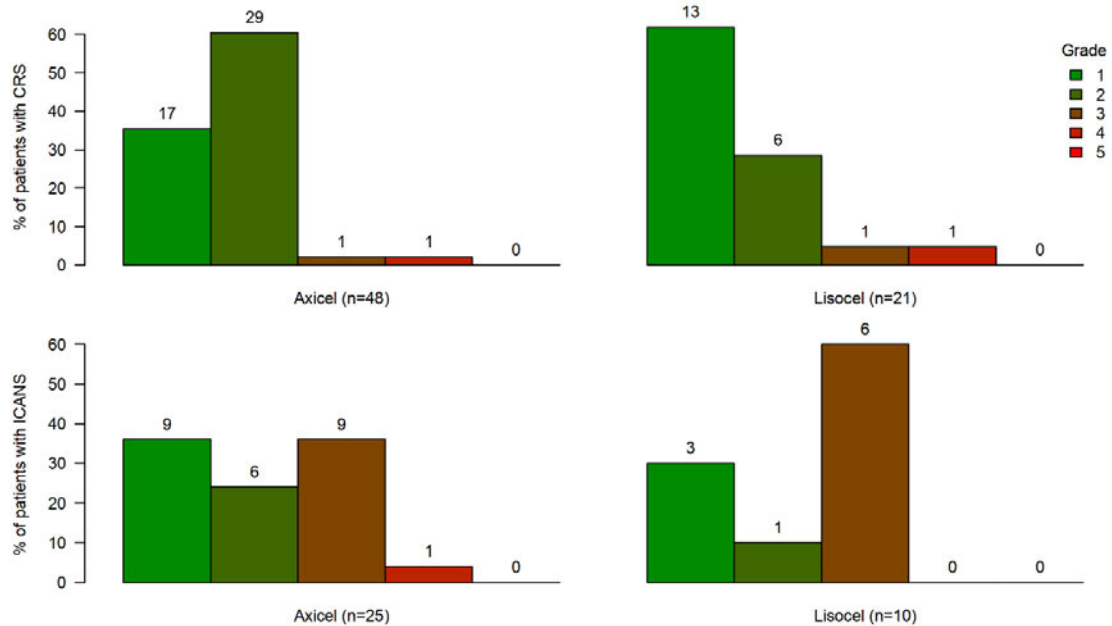


Figure 2. Rates of max CRS and max ICANS. The percentage of each is based off the number of patients effected by max CRS or max ICANS over total number of patients infused respective product. Grading scale is using the ASTCT grading scale from 1-5 for both CRS and ICANS. The number above the bars is the number of patients affected.

Outcomes: Responses, Progression-free Survival, and Overall Survival

For all patients, the best ORR was 90% (95% CI, 82%-95%) (Table 6). For the axi-cel cohort, the best ORR was 93% and for the liso-cel cohort, it was 84%; however, there was no statistically significant difference between the two groups. For all patients the rate of best CR response was 65% (95% CI, 55%-74%); for the axi-cel cohort it was 71% (95% CI, 57%-82%) and the liso-cel was 56% (95% CI, 40%-72%) (Table 7).

The median follow-up for all 98 patients was 6.1 months. The median follow-up for both axi-cel (n= 58; 59%) and liso-cel (n = 40; 41%) patients was 6.1 months. For all

patients, the median overall survival (OS) was not reached; median progression-free survival (PFS) was 12.4 (range: 0.0 - 18.2) months (Table 8; Figure 3). Ten total patients had OS events defined as death from any cause. PFS events were progressive disease (n = 29) or death from any cause (without progression) (n = 3).

The median PFS and OS for the axi-cel cohort was not reached, with a projection of 76% of patients alive at 12 months (95% CI, 60%-97%) (Table 9) and 61% of patients alive and free of relapse (progression free survival, PFS) at 12 months (95% CI, 46%-81%) (Table 10). For the liso-cel cohort, median OS was not reached and median PFS was 10.5 months with a projection of 81% of patients alive at 12 months (95% CI, 63%-100%) (Table 9) and 45% of patients alive and free of relapse at 12 months (95% CI, 27%-73%) (Table 10). There was not a statistically significant difference between the two groups ($p = 0.94$, $p = 0.51$ for OS and PFS, respectively) (Figure 4).

Table 6. Patient Response at 1, 6, and 12 months and Best Overall for All Patients. Type of response/number of patients, %, (95% CI). Overall response rate was defined as partial response (PR) or better. Not Entered = NE, Progressive Disease = PD, Stable Disease= SD, Partial Response = PR, Complete Response = CR.

	Evaluation					Outcome	
	NE	PD	SD	PR	CR	PR or better	SD or better
Time point response							
Response at month 1	0/93, 0% (0 - 4%)	11/93, 12% (6 - 20%)	2/93, 2% (0 - 8%)	28/93, 30% (21 - 40%)	52/93, 56% (45 - 66%)	80/93, 86% (77 - 92%)	82/93, 88% (80 - 94%)
Response at month 3	0/43, 0% (0 - 8%)	9/43, 21% (10 - 36%)	1/43, 2% (0 - 12%)	9/43, 21% (10 - 36%)	24/43, 56% (40 - 71%)	33/43, 77% (61 - 88%)	34/43, 79% (64 - 90%)
Response at month 6	0/35, 0% (0 - 10%)	7/35, 20% (8 - 37%)	1/35, 3% (0 - 15%)	6/35, 17% (7 - 34%)	21/35, 60% (42 - 76%)	27/35, 77% (60 - 90%)	28/35, 80% (63 - 92%)
Response at month 12	0/18, 0% (0 - 19%)	3/18, 17% (4 - 41%)	1/18, 6% (0 - 27%)	2/18, 11% (1 - 35%)	12/18, 67% (41 - 87%)	14/18, 78% (52 - 94%)	15/18, 83% (59 - 96%)
Best overall response							
Best response up to month 3	0/97, 0% (0 - 4%)	10/97, 10% (5 - 18%)	1/97, 1% (0 - 6%)	25/97, 26% (17 - 36%)	61/97, 63% (52 - 72%)	86/97, 89% (81 - 94%)	87/97, 90% (82 - 95%)
Best response up to month 6	0/97, 0% (0 - 4%)	9/97, 9% (4 - 17%)	1/97, 1% (0 - 6%)	25/97, 26% (17 - 36%)	62/97, 64% (54 - 73%)	87/97, 90% (82 - 95%)	88/97, 91% (83 - 96%)
Best response up to month 12	0/97, 0% (0 - 4%)	8/97, 8% (4 - 16%)	2/97, 2% (0 - 7%)	24/97, 25% (17 - 35%)	63/97, 65% (55 - 74%)	87/97, 90% (82 - 95%)	89/97, 92% (84 - 96%)

Table 7. Patient Response at 1, 6, and 12 months and Best Overall for Axi-cel vs. Liso-cel. Type of response/number of patients, %, (95% CI). Overall response rate was defined as partial response (PR) or better. Not Entered = NE, Progressive Disease = PD, Partial Response = PR, Complete Response = CR.

		Product	
	Total n = 98 (%)	Axi-cel n = 58 (59)	Liso-cel n = 40 (41)
Response at month 1			
CR	52/93, 56 (45 - 66)	35/56, 62 (49 - 75)	17/37, 46 (29 - 63)
PR	28/93, 30 (21 - 40)	16/56, 29 (17 - 42)	12/37, 32 (18 - 50)
SD	2/93, 2 (0 - 8)	0/56, 0 (0 - 6)	2/37, 5 (1 - 18)
PD	11/93, 12 (6 - 20)	5/56, 9 (3 - 20)	6/37, 16 (6 - 32)
NE	0/93, 0 (0 - 4)	0/56, 0 (0 - 6)	0/37, 0 (0 - 9)
Response at month 3			
CR	24/43, 56 (40 - 71)	18/24, 75 (53 - 90)	6/19, 32 (13 - 57)
PR	9/43, 21 (10 - 36)	3/24, 12 (3 - 32)	6/19, 32 (13 - 57)
SD	1/43, 2 (0 - 12)	0/24, 0 (0 - 14)	1/19, 5 (0 - 26)
PD	9/43, 21 (10 - 36)	3/24, 12 (3 - 32)	6/19, 32 (13 - 57)
NE	0/43, 0 (0 - 8)	0/24, 0 (0 - 14)	0/19, 0 (0 - 18)
Response at month 6			
CR	21/35, 60 (42 - 76)	16/23, 70 (47 - 87)	5/12, 42 (15 - 72)
PR	6/35, 17 (7 - 34)	2/23, 9 (1 - 28)	4/12, 33 (10 - 65)
SD	1/35, 3 (0 - 15)	0/23, 0 (0 - 15)	1/12, 8 (0 - 38)
PD	7/35, 20 (8 - 37)	5/23, 22 (7 - 44)	2/12, 17 (2 - 48)
NE	0/35, 0 (0 - 10)	0/23, 0 (0 - 15)	0/12, 0 (0 - 26)
Response at month 12			
CR	12/18, 67 (41 - 87)	9/14, 64 (35 - 87)	3/4, 75 (19 - 99)
PR	2/18, 11 (1 - 35)	2/14, 14 (2 - 43)	0/4, 0 (0 - 60)
SD	1/18, 6 (0 - 27)	1/14, 7 (0 - 34)	0/4, 0 (0 - 60)
PD	3/18, 17 (4 - 41)	2/14, 14 (2 - 43)	1/4, 25 (1 - 81)
NE	0/18, 0 (0 - 19)	0/14, 0 (0 - 23)	0/4, 0 (0 - 60)

Best response up to month 3			
CR	61/97, 63 (52 - 72)	40/58, 69 (55 - 80)	21/39, 54 (37 - 70)
PR	25/97, 26 (17 - 36)	13/58, 22 (13 - 35)	12/39, 31 (17 - 48)
SD	1/97, 1 (0 - 6)	0/58, 0 (0 - 6)	1/39, 3 (0 - 13)
PD	10/97, 10 (5 - 18)	5/58, 9 (3 - 19)	5/39, 13 (4 - 27)
NE	0/97, 0 (0 - 4)	0/58, 0 (0 - 6)	0/39, 0 (0 - 9)
Best response up to month 6			
CR	62/97, 64 (54 - 73)	41/58, 71 (57 - 82)	21/39, 54 (37 - 70)
PR	25/97, 26 (17 - 36)	13/58, 22 (13 - 35)	12/39, 31 (17 - 48)
SD	1/97, 1 (0 - 6)	0/58, 0 (0 - 6)	1/39, 3 (0 - 13)
PD	9/97, 9 (4 - 17)	4/58, 7 (2 - 17)	5/39, 13 (4 - 27)
NE	0/97, 0 (0 - 4)	0/58, 0 (0 - 6)	0/39, 0 (0 - 9)
Best response up to month 12			
CR	63/97, 65 (55 - 74)	41/58, 71 (57 - 82)	22/39, 56 (40 - 72)
PR	24/97, 25 (17 - 35)	13/58, 22 (13 - 35)	11/39, 28 (15 - 45)
SD	2/97, 2 (0 - 7)	1/58, 2 (0 - 9)	1/39, 3 (0 - 13)
PD	8/97, 8 (4 - 16)	3/58, 5 (1 - 14)	5/39, 13 (4 - 27)
NE	0/97, 0 (0 - 4)	0/58, 0 (0 - 6)	0/39, 0 (0 - 9)

Table 8. Time-to-event for All Patients. Duration of response was defined by patients having a PR or better. Progression-free survival was defined as a sustained CR and the patient still living. Median follow-up was 6.1 months. Not Reach = NR

Months	No. at risk	No. event	Percent (95% CI)	Median
Overall survival				
0	98	0	100 (100, 100)	NR (range: 0.0 - 18.2)
4	58	5	94 (88, 99)	
8	27	3	87 (78, 97)	
12	12	2	78 (66, 94)	
16	1	0	78 (66, 94)	
Progression-free survival				
0	98	0	100 (100, 100)	12.4 (range: 0.0 - 18.2)
4	50	21	75 (66, 85)	
8	23	5	66 (56, 78)	
12	10	4	53 (40, 70)	
16	1	1	47 (33, 68)	
Duration of response				
0	87	0	100 (100, 100)	NR (range: 0.0 - 17.2)
4	44	10	84 (75, 94)	
8	16	6	68 (55, 84)	
12	8	2	57 (41, 79)	
16	1	0	57 (41, 79)	

Table 9. Overall survival by product. Overall survival is defined as patients living, with or without disease. Median follow-up was 6.1 months. Not Reach = NR				
Months	No. at risk	No. event	Percent (95% CI)	Median
Axi-cel				
0	58	0	100 (100, 100)	NR (range: 0.9 - 18.2)
4	34	2	95 (89, 100)	
8	14	3	83 (70, 99)	
12	9	1	76 (60, 97)	
16	1	0	76 (60, 97)	
Liso-cel				
0	40	0	100 (100, 100)	NR (range: 0.0 - 15.2)
4	24	3	92 (83, 100)	
8	13	0	92 (83, 100)	
12	3	1	81 (63, 100)	

Table 10. Progression-free survival by product. Progression-free survival was defined as a sustained CR and the patient still living. Median follow-up was 6.1 months. Not Reach = NR				
Months	No. at risk	No. event	Percent (95% CI)	Median
Axi-cel				
0	58	0	100 (100, 100)	NR (range: 0.6 - 18.2)
4	28	11	77 (66, 90)	
8	11	3	68 (55, 84)	
12	7	1	61 (46, 82)	
16	1	1	51 (32, 81)	
Liso-cel				
0	40	0	100 (100, 100)	10.5 (range: 0.0 - 15.2)
4	22	10	72 (59, 89)	
8	12	2	64 (50, 83)	
12	3	3	45 (27, 73)	

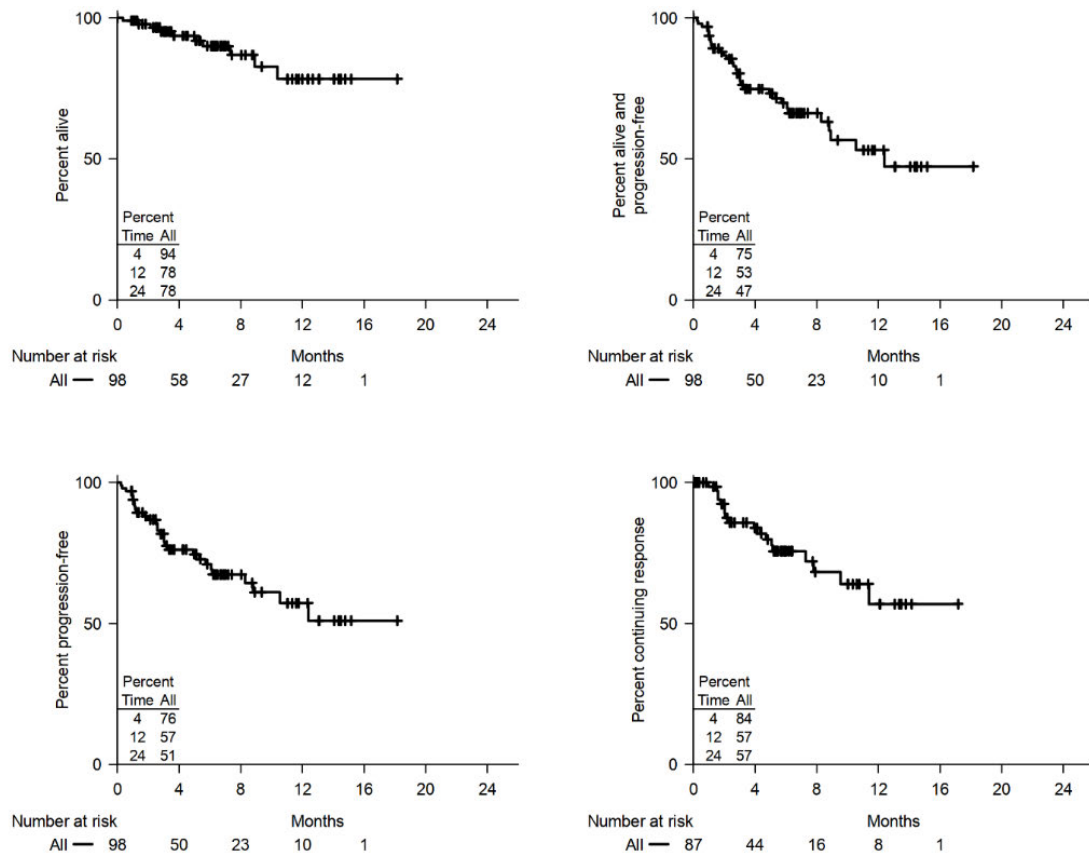


Figure 3. Kaplan-Meier Estimator for All Patients. Following from right to left, top to bottom: percentage of patients alive (overall survival), alive and progression-free (progressive free survival), progression free (excludes patients dying from other cause), and a continued response (duration of response).

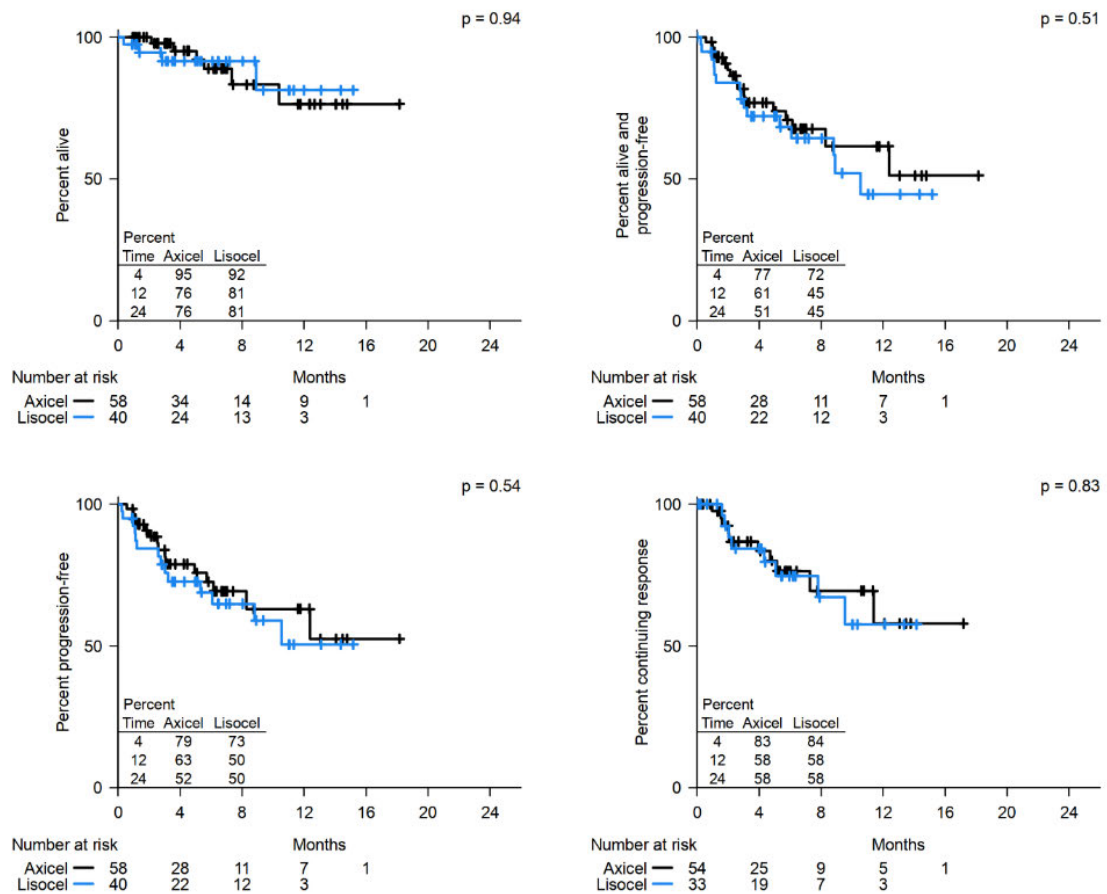


Figure 4. Kaplan-Meier Estimator for Axi-cel vs. Liso-cel. Following from right to left, top to bottom: percentage of patients alive (overall survival), alive and progression-free (progressive free survival), progression free (excludes patients dying from other cause), and a continued response (duration of response).

DISCUSSION

With now three major CAR T-cell products for relapsed or refractory LBCL, providers will need to make complex evidence-based decisions on which product to use for a patient based on the efficacy and safety profile. They must also make this decision based on potential patient characteristic correlates that may exacerbate toxicity or decrease efficacy. This study was limited to comparing the safety and outcomes of two of these products, liso-cel and axi-cel, which are both now approved as second-line options for patients with relapsed or refractory LBCL based on randomized clinical trials; with the negative results of the randomized trial of tisagenlecleucel, this product is nearly universally not being used in LBCL, and so we chose to omit it from our study.

When comparing the two cohorts to assess any clinically meaningful differences between the two groups, median LDH at day 0, ALC at apheresis, and age of the patients did differ significantly between the two groups. However, the median LDH and ALC for both the axi-cel and liso-cel arms were actually within the normal ranges, and so when instead comparing by percent of patients with abnormally high LDH or low ALC in each group, these differences disappeared. The median age of patients, however, did differ by 9 years. This is likely due to selection bias of providers choosing liso-cel for older patients over axi-cel, despite expressed efforts not to do this, due to the impression that liso-cel is less toxic than axi-cel and thus safer for older patients. In univariate analysis, older age has been shown to not have an association with an increased risk of severe CRS or ICANS (Nastoupil 2020; Neelapu 2020). In fact, older age has been shown to have

higher CR rates and improved PFS (Jacobson 2020). Based on this information, we can reasonably assume that the two cohorts are relatively similar and can be compared.

When the ZUMA-1 and TRANSCEND NHL-001 study are compared, it is often believed that axi-cel is more toxic with greater rates of high-grade CRS ($\geq$ grade 3) when compared to liso-cel (13% and 2% respectively) (Neelapu 2017; Abramson 2020).

However, grading of CRS has become standardized with the ASTCT grading scale, CRS management is standardized, and our study lacked any eligibility criteria that may have a confounding effect on toxicity (Lee 2019; Schubert 2021). Our studies did show that any grade CRS was higher in the axi-cel patients (83%) when compared to the liso-cel patients (57%). This is close to the ZUMA-1 (93%) and the TRANSCEND NHL-001 (42%) rates of any grade CRS (Neelapu 2017; Abramson 2020). Perhaps surprisingly, however, in our study, the rates of high-grade CRS were statistically similar in both groups: 3% for the axi-cel patients and 5% in the liso-cel patients. The ZUMA-1 trial showed 13% of patients having high grade CRS and the TRANSCEND NHL-001 study showed high-grade CRS in 2% of patients (Neelapu 2017; Abramson 2020). The lower high-grade CRS that we found in the axi-cel cohort may be due to better management of CRS, as early intervention for CRS has been shown to reduce the frequency of severe CRS (Gardner 2019; Berg 2022); indeed, more patients in the axi-cel cohort received toxicity mitigating therapies such as tocilizumab and corticosteroids, supporting this hypothesis. High-grade CRS is life threatening so the fact that our study has shown a lower rate of high-grade CRS in axi-cel patients has clinical implications on a provider's choice for a product. Since tocilizumab and corticosteroids such as dexamethasone is

used for patients starting at grade 2 CRS, it is unsurprising that these treatments were used more often in the axi-cel group as 29% of patients had grade 2 CRS compared to 6% in the liso-cel group (Lee 2014). Previous studies have also noted that axi-cel had a median onset of any grade CRS 2 days after infusion while liso-cel had a median onset of 5 days after infusion (Neelapu 2017; Abramson 2020). Interestingly, our study showed a comparable median time to any grade CRS (3 days in the axi-cel group vs. 2 days in the liso-cel group). Time to median max grade CRS for axi-cel and liso-cel was found to be 5 and 4 days, respectively. It was also found the duration of any grade CRS after onset in the axi-cel group to be 5 days which statistically differed from 4 days in the liso-cel group, but by 1 day. The ZUMA-1 trial had an 8-day duration of any grade CRS for axi-cel patients while the TRANSCEND NHL-001 study had a 5-day duration of any grade CRS for liso-cel patients (Neelapu 2017; Abramson 2020). The gap between the two products may not be as large as previously seen as our study showed a 1-day difference between the two. The onset of any grade CRS being so soon in liso-cel compared to the TRANSCEND NHL-001 and the reduction in rates of high-grade CRS and duration of CRS in axi-cel for the treatment of CRS may indicate a hypervigilance the DFCI staff had regarding monitoring CRS. This hypothesis could be supported if we could compare data from the ZUMA-1 and TRANSCEND NHL-001 of when tocilizumab and corticosteroids were administered or time to grade 2 CRS when intervention is recommended. We found that 50% of axi-cel patients had a CRS max grade of 2 as compared to 15% in the liso-cel group. The sharp drop in high-grade CRS in axi-cel in our cohort (2%) compared to ZUMA-1 (13%) further supports this idea that early

intervention at grade 2 reduces rates of high-grade CRS (Neelapu 2017). With low rates of grade 2 CRS in liso-cel patients (15%) it makes sense that high-grade CRS in our cohort (5%) is comparable to the TRANSCEND NHL-001 study (2%) (Abramson 2020). To cut down on the costs, outpatient infusion and monitoring are being considered, so a delayed time to any grade CRS and a shorter duration of CRS become important factors in determining the feasibility of outpatient therapy.

Rates of ICANS followed a similar pattern to rates of CRS in the ZUMA-1 and TRANSCEND NHL-001 studies. On ZUMA-1, rates of any grade ICANS were 64%, and high-grade ICANS ($\geq$ grade 3) were 28% (Neelapu 2017) following axi-cel. On TRANSCEND NHL-001, rates of any grade ICANS were 30%, and severe ICANS ($\geq$ grade 3) were 10% (Abramson 2020) following liso-cel. Our study showed lower rates of any and high-grade ICANS following axi-cel compared with ZUMA-1 (45% and 18% [ASTCT] or 19% [CTCAE], respectively), while rates of any and high-grade ICANS following liso-cel was similar to that seen on TRANSCEND-NHL-001 (25% and 14% [ASTCT] or 12% [CTCAE], respectively). In our study, there was no statistically significant difference between the two products with regards to rates of high-grade toxicities and duration of these toxicities, an opposite finding than what had been expected. The noticeable reduction in severe ICANS for the axi-cel group compared to ZUMA-1 and previous non-clinical trial settings (35% (Jacobson 2020), 31% (Nastoupil 2020), and 24% (Jacobson 2022)). This observation is possibly due to the same hypothesis for CRS; earlier intervention by clinicians to treat. High-grade ICANS is also associated with high-grade CRS (Teachy 2016). If high-grade CRS is prevented due to

early intervention, either early intervention of ICANS or the prevention of high-grade CRS by early intervention of CRS, might also prevent high-grade ICANS, and our data supports this. The slightly higher rates of high-grade ICANS in liso-cel cohort (5%) compared to the TRANSCEND NHL-001 (2%) is possibly due to the small sample size rather than anything meaningful.

The only other safety measure that we measured and found to be different was the length of hospital stay to be 14 days for the axi-cel patients and 10 days for the liso-cel patients, while ICU admission, ICU length of stay, and cardiac evidence were not found to be different. This difference may be meaningful in terms of morbidity and healthcare costs as it represents a 40% extension of hospitalization following axi-cel and may reflect an aspect of these toxicities that is not appreciated from our qualitative analysis. Too much data is missing regarding B-cell aplasia and hypogammaglobulinemia to analyze any meaningful differences between the two cohorts.

Efficacy outcomes in our axi-cel cohort were comparable to those seen on ZUMA-1, with a best ORR of 93% vs. 83%, respectively, and a best CR rate of 65% vs. 58%, respectively. With relatively short follow-up (median 6.1 months), median PFS and OS were not reached for the axi-cel cohort, but 12 months PFS was comparable to ZUMA-1 (61% vs. 44%, respectively). Similarly, efficacy outcomes in our liso-cel cohort were also comparable to those seen on TRANSCEND NHL-001, with an ORR of 84% vs. 73% and CR rate of 65% vs. 53%, respectively. Again, with a median of 6.1 months follow-up, median OS was not reached and median PFS was 10.5 months; median OS and PFS on TRANSCEND NHL-001 were 6.8 months and 27.3 months, respectively. In

addition to not being markedly different from the pivotal trials, these outcome measures did not differ significantly between our two cohorts, axi-cel versus liso-cel. In terms of the effect that differences in baseline characteristics could have played on these outcomes, the younger median age of the axi-cel would be expected to contribute to a lower CR rate and PFS (Jacobson 2020) if anything.

Summarizing our results, we have relatively similar cohorts, similar toxicity profiles, and similar outcomes between axi-cel and liso-cel. Past studies have shown axi-cel to be more toxic as compared to liso-cel with similar efficacy outcomes. Our study shows axi-cel to be less toxic than hypothesized, possibly due to the product being less distinct than previously thought but more likely due to more aggressive management of CRS and ICANS. Due to the power and potential cure for certain malignancies CAR T-cell development has continued to grow beyond the second-generation CAR T-cell products we have studied. Third-generation CAR T-cells are undergoing current clinical trials and contain both the 4-1BB costimulatory domain as well as the CD28 costimulatory domain (Carpenito 2009). CARs that target more than one tumor antigen are in clinical trials in an effort to decrease the risk of antigen escape. Combination strategies of CARs with checkpoint inhibitors or other immunomodulatory drugs, as well as engineering strategies to knock-out genes involved in T-cell exhaustion are being explored to improve the functionality and durability of the CAR T-cell response. Lastly, alternative sources of immune cells, including T and NK cells, derived from healthy donors or immune cells developed from pluripotent stem cells are under investigation.

The hope is that these strategies will not only improve outcomes for B-cell malignancies but expand the indications for cell therapies into the more common, and more immune protected, solid tumors. If and when that happens, we will have even more products and product profiles to choose from and comparative data like this, in the absence of any expected prospective randomized studies, will become even more important.

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CURRICULUM VITAE

