Hematology/Oncology and Stem Cell Therapy

Volume 15 | Issue 4 Article 1

Lisocabtagene maraleucel in relapsed or refractory diffuse large B cell lymphoma: What is the evidence?

Mohamed A. Kharfan-Dabaja
Division of Hematology–Oncology and Blood and Marrow Transplantation and Cellular Therapy Programs, Mayo Clinic, Jacksonville, FL, USA, KharfanDabaja.Mohamed@mayo.edu

Farah Yassine
Division of Hematology–Oncology and Blood and Marrow Transplantation and Cellular Therapy Programs, Mayo Clinic, Jacksonville, FL, USA

Muhamad Alhaj Moustafa
Division of Hematology–Oncology and Blood and Marrow Transplantation and Cellular Therapy Programs, Mayo Clinic, Jacksonville, FL, USA

Madiha Iqbal
Division of Hematology–Oncology and Blood and Marrow Transplantation and Cellular Therapy Programs, Mayo Clinic, Jacksonville, FL, USA

Hemant Murthy
Division of Hematology–Oncology and Blood and Marrow Transplantation and Cellular Therapy Programs, Mayo Clinic, Jacksonville, FL, USA

REVIEW ARTICLE

Lisocabtagene Maraleucel in Relapsed or Refractory Diffuse Large B Cell Lymphoma: What is the Evidence?

Mohamed A. Kharfan-Dabaja*, Farah Yassine, Muhamad Alhaj Moustafa, Madiha Iqbal, Hemant Murthy

Division of Hematology–Oncology and Blood and Marrow Transplantation and Cellular Therapy Programs, Mayo Clinic, Jacksonville, FL, USA

Abstract

Lisocabtagene maraleucel (liso-cel) is an autologous CD19-directed chimeric antigen receptor (CAR) T cell product, with a CD3ζ activatory domain connected to 4-1BB costimulatory domain. Liso-cel, unlike the other two approved products—axicabtagene ciloleucel and tisagenlecleucel—is manufactured separately from CD4 and CD8 T cells and then administered as a sequential infusion of the two components at equal target doses. The approval of liso-cel was based on the results of Transcend NHL 001, a single-arm, open-label, multicenter, seamless design trial that enrolled 344 patients, of whom 269 received conforming liso-cel. The most common histology was diffuse large B cell lymphoma, not otherwise specified (DLBCL NOS; $n = 137$, 51%) followed by DLBCL transformed from indolent lymphomas ($n = 78$, 29%). Encouraging results were reported, yielding an objective response rate across all dose levels of 73% [complete remission (CR) = 53%], with an estimated duration of response at 1 year of 55% for all patients and 65% for those achieving a CR. The estimated 12-month overall survival was 58% for all patients and 86% for those achieving a CR. Cytokine release syndrome and neurological adverse events were reported in 42% and 30%, respectively. This review summarizes the evidence on the safety and effectiveness of liso-cel, resulting in its addition to the current treatment armamentarium of relapsed or refractory large B cell lymphoma.

Keywords: CD19, Chimeric antigen receptor T cell, Diffuse large B cell non-Hodgkin lymphoma, Lisocabtagene maraleucel

1. Introduction

Chimeric antigen receptor T cell (CAR T) therapy represents a new addition to the treatment of relapsed or refractory (R/R) B cell lymphoid malignancies [1–5]. Historically, patients with R/R diffuse large B cell lymphoma (DLBCL) had low anticipated complete remission (CR) rates to subsequent chemoimmunotherapy combinations, particularly after failing two or more lines of therapy [6]. Crump et al. [6] in the retrospective non-Hodgkin lymphoma research study known as SCHOLAR-1 showed that the probability of attaining a CR in this population is less than 20% and the anticipated survival is generally poor. The role of high-dose therapy and autologous hematopoietic cell transplantation (auto-HCT) in DLBCL is limited to those who demonstrate an objective response rate (ORR), preferably a CR, to second-line therapy [7,8]. Unfortunately, auto-HCT has no role in patients with chemoresistant disease, a population that represents a therapeutic challenge.

CAR T therapy has emerged as an effective treatment of R/R DLBCL, even after failing two or more lines of therapy. Thus far, the United States Food and Drug Administration (FDA) has approved

Received 14 September 2021; revised 28 September 2021; accepted 30 September 2021.
Available online 23 December 2022

* Corresponding author at: Blood and Marrow Transplantation and Cellular Therapies, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA.
E-mail address: KharfanDabaja.Mohamed@mayo.edu (M.A. Kharfan-Dabaja).

https://doi.org/10.1016/j.hemonc.2021.09.004

three CAR T products for commercial use [2–4]. One of those products is lisocabtagene maraleucel (liso-cel), which is an autologous CD19-directed CAR T product with a CD3ζ activatory domain connected to 4-1BB costimulatory domain [4]. Different from the other two approved products, namely axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, liso-cel is manufactured separately from CD4 and CD8 T cells, and then administered as a sequential infusion of the two components at equal target doses. A recently published, large multicenter, seamless design, Transcend NHL 001 study (TRANSCEND) treated 269 patients (median age, 63 years), who were heavily pretreated, with a median of three prior therapies and 67% having refractory disease [4]. The ORR and CR rates were 73% and 53%, respectively [4]. Liso-cel is approved for R/R large B cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified (NOS), DLBCL arising from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal large B cell lymphoma (PMBCL), and follicular lymphoma (FL) grade 3B.

Here, we provide a comprehensive review of liso-cel in DLBCL and highlight available data of ongoing studies in other histologies.

2. Liso-cel in large B cell lymphoma

2.1. Efficacy

Transcend NHL 001 was a single-arm, open-label, multicenter, seamless design trial that led to the approval of liso-cel for commercial use [4]. The included histologies comprised DLBCL, high-grade B cell lymphoma with rearrangements of *MYC* and either *BCL2*, *BCL6*, or both, DLBCL transformed from any indolent lymphoma, PMBCL, and FL grade 3B [4]. Patients must have received two or more prior lines of systemic treatment and they could have received a previous auto-HCT or allogeneic HCT [4]. Lymphodepleting chemotherapy consisting of fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 was administered intravenously daily for 3 days [4]. After 2–7 days from completion of lymphodepleting chemotherapy, liso-cel was administered as two sequential infusions of CD8 and CD4 CAR T cells, at one of three target dose levels: (a) 50×10^6 CAR + T cells (dose level 1), (b) 100×10^6 CAR T cells (dose level 2), and (c) 150×10^6 CAR T cells (dose level 3) [4]. Although 344 patients were enrolled, only 294 received the intended CAR T cell infusion; however, 25 of those patients received a nonconforming product. In the end, 269 patients received conforming liso-cel and the majority were male ($n = 174$, 65%) [4]. The most common histology was DLBCL NOS ($n = 137$, 51%) followed by DLBCL transformed from indolent lymphomas ($n = 78$, 29%). A total of 139 (52%) participants had failed ≥ 3 lines of therapy [4]. The study allowed for bridging therapy to be administered at the investigator's discretion, as was the case in 159 (59%) patients [4]. The authors did not identify a maximum tolerated dose (MTD).[4] The median time to first CR or partial response (PR) was 1 month [4]. The ORR across all dose levels was 73% (CR = 53%) [4]. The ORR for dose levels 1, 2, and 3 were 67.5%, 74%, and 73.2%, respectively [4]. The median duration of response (DOR) was not reached at the time results were reported. The estimated DOR at 1 year was 55% for all patients and 65% among those who achieved a CR [4]. The 1-year progression-free survival (PFS) was 44% for all patients and 65% among those who attained a CR [4]. The median overall survival (OS) was 21.1 months [4]. The estimated 12-month OS was reported as 58% for all patients and 86% for those who achieved a CR [4]. This certainly represents a significant improvement in OS compared to therapies that preceded CAR T cell availability [4].

Pertaining to other histologies, DOR and PFS in PMBCL and DLBCL transformed from FL were longer than for other subtypes. Moreover, the median OS was not reached for patients with high-grade B cell lymphoma, transformed FL, FL grade 3B, or PMBCL [4].

The recommended target dose for liso-cel is 100×10^6 CAR T cells (50×10^6 CD8 and 50×10^6 CD4 CAR T cells).

2.2. Toxicities

In TRANSCEND NHL 001, 139 patients were evaluable for dose limiting toxicities (DLTs). Only 9 (6%) had DLTs with one reported death from diffuse alveolar hemorrhage at the lowest tested dose. As such, no MTD or a relationship between dose levels and toxicity was identified [4].

Two hundred and sixty-seven (99%) patients had treatment-emergent adverse events (TEAEs) with the most common being neutropenia ($n = 169$, 63%) followed by anemia ($n = 129$, 48%), fatigue ($n = 119$, 44%), and cytokine release syndrome (CRS) ($n = 113$, 42%) [4]. A total of 213 patients (79%) experienced grade 3 or greater TEAE with the most common being neutropenia ($n = 161$, 60%) followed by anemia ($n = 101$, 37%) and thrombocytopenia ($n = 72$, 27%). Only six (2%) patients experienced grade 3 or greater CRS [4].

Specifically for CRS of all grades (graded per Lee et al. criteria [9]), the median time to both onset and

resolution was reported at 5 days each, with the most common symptoms being fever (95%) followed by hypotension (49%). No patient died because of CRS. The authors reported that 20% of patients received either tocilizumab alone, corticosteroids alone, or a combination of tocilizumab and corticosteroids to treat CRS. For patients who received tocilizumab, the median number of doses was 1 (range, 1–4) with median time from onset of CRS to administration of tocilizumab being 1.5 (range, 0–8) days. Only one person was treated with siltuximab and anakinra for grade 4 CRS [4].

Neurological events (NEs) were graded by the investigators using National Cancer Institute common terminology criteria for adverse events version 4.03. Eighty (30%) patients experienced neurological adverse events (NAEs) of all grades [4]. Twenty-seven (10%) experienced grade 3 or greater NAE; two of these patients had evidence of secondary central nervous system (CNS) lymphoma at enrollment. Median time to onset and resolution were 9 and 11 days, respectively, for NAE of any grade [4]. Fifty-eight (73%) patients experienced both CRS and NAE. The most common NAE of any grade was encephalopathy (71%) followed by tremors (33%), aphasia (33%), and delirium (20%) [4]. The most common grade 3 or greater NAE was encephalopathy (7%) [4]. No patient died because of NAE, and 4% were admitted to the intensive care unit (ICU) for management of CRS, NAE, or both. A higher incidence of CRS, NAE, or both was observed in patients who had a high tumor burden prior to liso-cel infusion [4].

For patients who received liso-cel in the outpatient setting, 18 (72%) were hospitalized because of AEs at a median of 5 days [4]. Additional TEAE that have been associated previously with CAR T cell therapy such as prolonged cytopenias at Day 29, hypogammaglobinemia, and grade 3 or higher infections were reported in 37%, 14%, and 12% patients, respectively [4]. It is important to note that most patients had resolution of cytopenias by Day 180 post-infusion [4].

3. Comparing liso-cel to other commercially approved CAR T cell products

3.1. Efficacy

The primary end point of the TRANSCEND NHL 001 study was the ORR of patients who received the DL 2 at the confirmational study phase; ORR was 74% and CR was 54%. In the intention-to-treat set of 344 patients who underwent leukapheresis, ORR and CR rates were 61% and 44%, respectively. The median time to response was 1 (range, 0.7–8.9) month, and the median PFS was 6.8 months. For patients who achieved a CR, median PFS was not reached. The estimated 1-year OS was 58% for the entire population and 86% for patients who achieved a CR [4].

The other two commercially approved CD19 CAR T cell products for treatment of R/R B cell lymphomas are axi-cel, evaluated in the ZUMA-1 [2], and tisagenlecleucel in the JULIET trial [3]. Among the 101 patients who received axi-cel, the ORR was 82% (CR = 54%). The median time to response was also 1 month, and the median PFS was 5.8 months. The estimated 1-year OS was 59% [2]. Among the 93 patients who received tisagenlecleucel, ORR was 52% with CR in 40%. The median PFS has not been reached for patients who had a CR. The estimated OS at 1 year was 49% among all patients and 90% for those in CR [3].

A recently published matching-adjusted indirect comparison (MAIC) of liso-cel versus axi-cel demonstrated a comparable MAIC-weighted efficacy outcomes between these two products for ORR, CR, OS, and PFS [10]. However, MAIC-weighted safety outcomes favored liso-cel by showing lower odds of all-grade and $\geq$ grade 3 CRS and study-specific NEs [10].

These three products have minor differences in their FDA-approved indications based on histologies included in their respective studies. The ORRs and CRs of various histologies per each product are summarized in Table 1.

3.2. Toxicities

Safety analysis in the TRANSCEND NHL 001 trial included 269 patients, among whom 127 (47%) developed CRS, NAE, or both, leading to 19 (7%) admissions to the ICU [4]. The CRS of any grade occurred in 113 (42%) patients within a median onset of 5 days after infusion, including six (2%) patients reporting grade $\geq$ 3 CRS. The most common CRS symptoms included fever (95%) and hypotension (49%) [4]. CRS was managed with tocilizumab (10%), corticosteroids (2%), or both (8%) [4]. NEs of any grade were reported in 80 (30%) patients within a median onset of 9 days, including 27 (10%) grade $\geq$ 3 events [4]. NAEs were mostly manifested as encephalopathy (71%), tremor and aphasia (33%), and delirium (20%). Notably, no patients died from either CRS or NE. Other treatment-related adverse events included headache (30%), dizziness (22%), prolonged cytopenias at Day 29 (37%), hypogammaglobulinemia (14%), and grade $\geq$ 3 infections (12%) [4].

Table 1. Efficacy of CAR T Products in TRANSCEND NHL 001, ZUMA-1, and JULIET studies.

CAR-T product [ref]		All histologies	R/R DLBCL-NOS	R/R high-grade B cell lymphoma	R/R primary mediastinal large B cell lymphoma	R/R DLBCL arising from follicular lymphoma	R/R DLBCL arising from indolent lymphoma (apart from follicular lymphoma)	R/R Follicular lymphoma grade 3B
Lisocabtagene maraleucel[4]	**Included**		Yes	Yes	Yes	Yes	Yes	Yes[a]
	ORR, *n* (%)	186 (73)	89 (67.9)	25 (75.8)	11 (78.6)	48 (84.2)	11 (61.1)	2 (100)
	CR, *n* (%)	136 (53)	64 (48.9)	20 (60.6)	7 (50)	36 (63.2)	7 (38.9)	2 (100)
Axicabtagene ciloleucel[2]	**Included**		Yes	Yes	Yes	Yes	No	No
	ORR, *n* (%)	83 (82)	63 (82)[b]	4 (100)[c]	6 (75)	14 (87.5)	Not included	Not included
	CR, *n* (%)	55 (54)	38 (49)[b]	3 (75)[c]	6 (75)	12 (75)	–	–
Tisagenlecleucel[3]	**Included**		Yes	Yes	No	Yes	No	No
	ORR, *n* (%)	48 (52)	Not reported[d]	Not reported[d]	Not included	Not reported[d]	Not included	Not included
	CR, *n* (%)	37 (40)	–	–	–	–	–	–

Note. CAR = chimeric antigen receptor; CR = complete remission; DLBCL = diffuse large B cell lymphoma; HGBCL = high-grade B cell lymphoma; NOS = not otherwise specified; ORR = objective response rate; R/R = relapsed or refractory.
[a] Only two patients included in analysis.
[b] Included all patient with large B cell lymphoma.
[c] Only four patients (double hit or triple hit HGBCL).
[d] Per phase 2 JULIET study authors; the response was comparable between all histological groups included in the study.

In the ZUMA-1 study, CRS and NE occurred in 93% and 64% of patients who received axi-cel, respectively [2]. Grade $\geq$ 3 CRS and grade $\geq$ 3 NE were reported in 13% and 28% of patients, respectively [11]. As for the JULIET study, tisagenlecleucel was associated with CRS and NE in 58% and 21% of patients, respectively, including grade $\geq$ 3 CRS and grade $\geq$ 3 NE in 22% and 12% of patients, respectively [3]. Table 2 compares toxicities associated with each of the three available CAR T cell products.

Notwithstanding the limitations of non-randomized comparisons, liso-cel appears to have a lower incidence of CRS and NAE relative to axi-cel or tisagenlecleucel. The higher rates of grade $\geq$ 3 CRS reported in the JULIET study could be attributed to the use of a different set of grading criteria [12], compared to the Lee et al. [9] criteria used in TRANSCEND NHL 001 and ZUMA-1. Notably as well, broader eligibility criteria were followed in the TRANSCEND NHL 001 trial, allowing for more generalizability of the safety and efficacy results, which could be closely replicated in the real-world setting [4].

4. Liso-cel in other B cell histologies

Various commercially available autologous CD19 CAR T products have demonstrated efficacy in B cell malignancies apart from DLBCL. KTE-X19 is approved for mantle cell lymphoma (MCL) after demonstrating impressive ORR and CR rates in a highly pretreated population [5]. Also, axi-cel received approval for R/R FL, without evidence of transformation into DLBCL, after demonstrating ORR and CR rates of 92% and 76%, respectively, despite a large number of patients (64%) having failed three or more prior lines of treatment [13]. Below, we summarize the results of studies evaluating liso-cel in these histologies. Some of these results may represent interim analyses or preliminary results.

Table 2. Treatment-Related Toxicity in TRANSCEND, ZUMA-1, and JULIET Studies.

Study [ref]	CAR T-cell product	Treated patients (*n*)	Safety -evaluable patients (*n*)	Any grade CRS *n* (%)	CRS grade $\geq$ 3*n* (%)	Any grade NE *n* (%)	NE grade $\geq$ 3*n* (%)	Infections grade $\geq$ 3*n* (%)	Cytopenia *n* (%)	TLS *n* (%)
TRANSCEND NHL 001 [4]	Liso-cel	294	269	113 (42)	6 (2)	80 (30)	27 (10)	33 (12)	100 (37)	2 (1)
ZUMA-1 [2]	Axi-cel	101	101	94 (93)	13 (13)	65 (64)	28 (28)	NA	NA	NA
JULIET [3]	Tisagen -lecleucel	111	111	64 (58)	24 (22)	23 (21)	13 (12)	22 (20)	49 (44)	1 (1)

Note. CAR = chimeric antigen receptor; CRS = cytokine release syndrome; NE = neurological event; NA = not available; TLS = tumor lysis syndrome.

4.1. Liso-cel in MCL

MCL is a rare aggressive subtype of non-Hodgkin lymphoma with an annual incidence of 0.8 per 100,000 population in the United States [14]. The median survival of MCL is reported to be 3 to 5 years, although in younger patients treated with intensified cytarabine-based induction regimens and auto-HCT it can be as high as 10 years [15]. Prognosis for R/R refractory MCL is considerably worse. The efficacy of ibrutinib in this setting has been remarkable with a median PFS of 13.9 months, but in patients who progress on ibrutinib, the median OS was only 8.4 months [16]. Given the success of CD19 CAR T therapy with KTE-X19 in R/R MCL with progression on Bruton tyrosine kinase (BTK) inhibitor [5], it certainly supports investigating the efficacy of liso-cel in R/R MCL.

4.1.1. Efficacy and toxicity of liso-cel in MCL

As part of the TRANSCEND-NHL-001 clinical trial (ClinicalTrials.gov Identifier: NCT03484702), a cohort of MCL with R/R disease after one or more prior lines of therapy were included. Findings from the phase 1 dose escalation portion were recently presented at the American Society of Hematology meeting in 2020 [17]. A total of 41 patients underwent leukapheresis but only 32 received liso-cel (six at DL1 of 50×10^6 CAR T cells and 26 at DL2 of 100×10^6 CAR T cells) [17]. MCL patients were heavily pretreated with a median of 3 (1–7) prior systemic therapies, and 87.5% had received a BTK inhibitor. More than half (53%) received bridging therapy prior to liso-cel. The resulting ORR and CR rates were 84% and 59%, respectively [17]. Dose expansion at DL2 is currently accruing.

Toxicities were generally manageable. CRS (all grades) was reported in 50% of patients, although only one patient in the DL2 had CRS grade 3 or higher. Interestingly, CRS onset was reported at a median of 6 (2–10) days, which is later than what was reported with KTE-X19 [5,17]. NAEs were reported in 28% of patients, with a one-third being grade 3 [17]. These preliminary results are definitely promising. Final results are awaited to confirm these findings.

4.2. Liso-cel in chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) represents the most prevalent leukemia in the Western Hemisphere [18]. Despite therapeutic advances with incorporation of BTK, BCL2 inhibitors, and others, the disease remains incurable unless patients are offered an allogeneic HCT (allo-HCT). Unfortunately, allo-HCT could be contraindicated in this population because of advanced age, suboptimal performance status, and/or existing comorbidities. Moreover, despite the availability of better tolerated reduced intensity preparative regimens, the anticipated nonrelapse mortality still exceeds 20% [19].

4.2.1. Efficacy and toxicity of liso-cel in CLL

Much of the rationale for investigating liso-cel (JCAR017) for CLL stems from experience with its predecessor CD19 CAR T known as JCAR014. In fact, JCAR017 differs slightly from JCAR014. Although both JCAR014 and JCAR017 target CD19, have set defined composition of CD4/CD8 CAR T cells, and have the same 4-1BB costimulatory signaling, the two products differ in that JCAR014 contains CD28 transmembrane domain whereas JCAR017 possesses immunoglobulin 4 (IgG4) transmembrane domain.

JCAR014 has demonstrated efficacy and ability to achieve some durable responses in patients refractory to or having relapsed after ibrutinib therapy. It was also reported that higher ORR and deeper remissions were attained when ibrutinib was administered concurrently with JCAR014 [20]. Given these findings, the efficacy of CD19 CAR T therapy in CLL/small lymphocytic lymphoma (SLL) with or without a concurrent BTK inhibitor is being investigated in the ongoing TRANSCEND-CLL 004 study (ClinicalTrials.gov Identifier: NCT03331198).

Most recent findings presented from phase 1 dose escalation trial in patients with R/R CLL were reported at the American Society of Clinical Oncology Annual Meeting in 2019 [21]. In this study, patients had received two or more prior lines of therapy, including BTK inhibitors, unless medically contraindicated, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$ 1. Consistent with liso-cel studies in other histologies, 16 patients received either a DL1 of 50×10^6 ($n = 6$) or a DL2 of 100×10^6 ($n = 10$) CAR T cells [21]. In 75%, high-risk features were present: a *TP53* mutation, a complex karyotype, or del17p; and 100% and 50% had prior ibrutinib or venetoclax, respectively. The reported ORR in 15 patients at 6 months with minimal residual disease (MRD) negative state was 67%.

Pertaining to toxicities, only one patient developing grade 3 CRS and three patients grade 3 NAE were reported thus far. TRANSCEND-CLL 004 is currently accruing in a dose expansion phase in patients with CLL/SLL with prior exposure to BTK and BCL-2 inhibitors, with additional cohorts investigating the role of treatment with a ibrutinib

or venetoclax administered concurrently with liso-cel.

At the American Society of Hematology meeting in December 2020, results from 19 patients on the TRANSCEND-CLL 004 who received ibrutinib with liso-cel were reported [22]. With more than 1 month follow-up, the ORR was 95% with 47% CR, including 17 (89%) achieved undetectable MRD in blood by flow cytometry and 15 (79%) in BM by next-generation sequencing. The combination was safe with no DLT, only one patient with grade 3 or higher CRS and three patients with grade 3 or higher NAE were reported. Ibrutinib-related adverse events were observed in 13 patients, with more than half experiencing diarrhea, and only one developing atrial fibrillation.

4.3. Liso-cel beyond MCL and CLL

Other studies investigating liso-cell in various B cell malignancies are actively accruing. The TRANSCENDWORLD trial (ClinicalTrials.gov Identifier: NCT03484702) is investigating liso-cel in a variety of B-cell malignancies. It is a single-arm, multi-cohort, multi-center, phase 2 study aimed at determining the safety and efficacy of liso-cel in adults with aggressive B-cell NHL including double hit high-grade B cell lymphomas, primary CNS lymphoma, and grade 3b FL. This study is accruing in Europe and Japan. Also, TRANCEND FL (ClinicalTrials.gov Identifier: NCT04245839) is investigating liso-cel in relapsed or refractory FL (Grade 1, 2, or 3a) and marginal zone lymphoma (MZL) in those who had received two to three lines of prior therapy. These studies are anticipated to report results by the end of 2021.

5. Discussion

CAR T cell therapy has revolutionized the treatment of R/R DLBCL and other B cell lymphoid malignancies and has improved the therapeutic outlook of these diseases. Liso-cel and other CD19 CAR T cell products are demonstrating encouraging response rates in the setting of a very resistant disease. Although limited by the absence of randomized controlled trials (RCTs), published data appear to show a lower incidence of CRS with liso-cel, using the same grading Lee et al. [9] criteria, when compared to axi-cel. A lower incidence and severity of NAE with liso-cel versus axi-cel also appears to be the case. Comparing the toxicity profile of liso-cel versus tisagenlecleucel is more challenging because the JULIET study used a different set of grading criteria to assess severity of CRS, known as the Penn grading system [12]. Notably, the Penn grading system appears to result in higher rates of severe CRS when compared to the Lee et al. [9] criteria used in both TRANSCEND NHL 001 and ZUMA-1 [12].

To our knowledge, there are no RCTs that compare these three products head-to-head and, presently, choice of a particular product is based on physician familiarity with the product and/or center preference. In our opinion, important criteria to also consider when selecting one product over another are related to anticipated toxicity(ies) and timeliness and manufacturing success.

6. Future direction

The results of ongoing trials exploring the efficacy and safety of liso-cel in other B cell histologies are highly awaited. Given the high efficacy and favorable toxicity profile of liso-cel in large B cell lymphoma, it is expected that the results of these trials will lend FDA approval for liso-cel in other B cell histologies.

Currently liso-cel is approved for patients who have received two or more prior lines of systemic treatment. TRASCEND PILOT (NCT03483103) is currently registered and investigates liso-cel in aggressive B cell lymphoma after failure of only one line of systemic therapy. JCAR017 is also being investigated in the TRANSFORM (NCT03575351) trial against the current standard of care (SOC) of salvage chemoimmunotherapy followed by high-dose chemotherapy and auto-HCT in patients with R/R aggressive B cell lymphoma. Pending the results of these clinical trials, we may see a shift in the current second-line SOC for patients with R/R aggressive B cell lymphomas. This is of significance as with the current SOC of salvage chemo-immunotherapy followed by auto-HCT, long-term remissions are seen in only about 50% of patients [23].

The low rates of high-grade toxicity observed with liso-cel in TRANSCEND-001 are encouraging for continued expansion of outpatient administration of CAR T cell products. TRANSCEND-OUTREACH-007 (NCT03744676) is currently exploring the safety and efficacy of liso-cel in the outpatient setting. A recent study reported efficacy and safety data for 53 patients who received liso-cel as an outpatient [24]. Twenty-three patients were 65 years or older with 16 having tumor burden. CRS and NAEs of any grade were reported in 34% and 26% patients, respectively [24]. High-grade CRS or NAEs were reported in only two patients and were reversible. The median time to onset of CRS and NAE was 5 (2–9) and 8.5

(3–22) days, respectively. Tocilizumab and/or corticosteroids for treatment of CRS and/or NAE was required in 15% of patients. Thirty (57%) patients required hospitalization at a median of 5.5 (range, 2–22) days after infusion. Only two were admitted to the ICU. Efficacy and safety data were consistent with patients who received liso-cel in the inpatient setting [24].

Recently, to improve on the current development of CAR T cell therapy, including liso-cel, the Nex-T platform was developed. Nex-T utilized machine learning to optimize patient selection and process improvements with the goal of increasing turnaround time, and reducing costs while maintaining or improving on liso-cel efficacy. The Nex-T CD19 CAR T or CC-97540 (NCT04231747) was recently opened and is currently enrolling in a phase 1 dose escalation study.

Authors' contributions

All authors have contributed significantly to this review by writing, revising and approving the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439–48.
[2] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell Lymphoma. N Engl J Med 2017;377:2531–44.
[3] Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019; 380:45–56.
[4] Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839–52.
[5] Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2020;382: 1331–42.
[6] Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800–8.
[7] Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540–5.
[8] Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol 2012;30:4462–9.
[9] Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124: 188–95.
[10] Maloney DG, Kuruvilla J, Liu FF, Kostic A, Kim Y, Bonner A, et al. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. J Hematol Oncol 2021;14:140.
[11] Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol 2019;20:31–42.
[12] Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. J Hematol Oncol 2018;11:35.
[13] Jacobson C, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Primary analysis of Zuma-5: a phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/ refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). Blood 2020;136:40–1.
[14] Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016; 66:443–59.
[15] Cheah CY, Seymour JF, Wang ML. Mantle cell lymphoma. J Clin Oncol 2016;34:1256–69.
[16] Cheah CY, Chihara D, Romaguera JE, Fowler NH, Seymour JF, Hagemeister FB, et al. Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. Ann Oncol 2015;26:1175–9.
[17] Palomba ML, Gordon LI, Siddiqi T, Abramson JS, Kamdar M, Lunning MA, et al. Safety and preliminary efficacy in patients with relapsed/refractory mantle cell lymphoma receiving lisocabtagene maraleucel in Transcend NHL 001. Blood 2020;136:10–1.
[18] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
[19] Kharfan-Dabaja MA, Moukalled N, Reljic T, El-Asmar J, Kumar A. Reduced intensity is preferred over myeloablative conditioning allogeneic HCT in chronic lymphocytic leukemia whenever indicated: a systematic review/meta-analysis. Hematol Oncol Stem Cell Ther 2018;11:53–64.
[20] Gauthier J, Hirayama AV, Purushe J, Hay KA, Lymp J, Li DH, et al. Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. Blood 2020;135:1650–60.
[21] Siddiqi T, Dorritie KA, Soumerai JD, Stephens DM, Dubovsky JA, Gillenwater HH, et al. TRANSCEND CLL 004: Minimal residual disease (MRD) negative responses after lisocabtagene maraleucel (Liso-Cel; JCAR017), a CD19-directed CAR T cell product, in patients (pts) with relapsed/ refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL). J Clin Oncol 2019;37(15_suppl):7501.
[22] Wierda WG, Dorritie KA, Munoz J, Stephens DM, Solomon SR, Gillenwater HH, et al. Transcend CLL 004: phase 1 cohort of lisocabtagene maraleucel (liso-cel) in combination with ibrutinib for patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Blood 2020;136:39–40.
[23] Hamadani M, Hari PN, Zhang Y, Carreras J, Akpek G, Aljurf MD, et al. Early failure of frontline rituximab-containing chemo-immunotherapy in diffuse large B cell lymphoma does not predict futility of autologous hematopoietic

cell transplantation. Biol Blood Marrow Transplant 2014;20: 1729–36.
[24] Bachier CR, Godwin JE, Andreadis C, Palomba ML, Abramson JS, Sehgal AR, et al. Outpatient treatment with lisocabtagene maraleucel (liso-cel) across a variety of clinical sites from three ongoing clinical studies in relapsed/refractory (R/R) large B-cell lymphoma (LBCL). J Clin Oncol 2020;38:8037.