Cytotherapy 27 (2025) 1316–1325

Contents lists available at ScienceDirect

FULL-LENGTH ARTICLE

CYTOTHERAPY

journal homepage: www.isct-cytotherapy.org

International Society ISCT Cell & Gene Therapy®

Immunotherapy

Overcoming barriers to referral for CAR T-cell therapy in patients with non-Hodgkin aggressive B-cell lymphomas: A Delphi consensus

Stefano Luminari[1,2,*], Annalisa Chiappella[3,*], Alice Di Rocco[4,*], Luca Arcaini[5,6], Roberto Freilone[7], Marco Ladetto[8], Massimo Martino[9], Pellegrino Musto[10], Luigi Rigacci[11], Carlo Visco[12], Paolo Corradini[3,13,*], Pier Luigi Zinzani[14,15,*,]**

[1] Division of Hematology, Azienda Unità Sanitaria Locale–IRCCS, Reggio Emilia, Italy
[2] Chimomo Department, University of Modena and Reggio Emilia, Reggio Emilia, Italy
[3] Division of Hematology and Stem Cell Transplantation, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy
[4] Division of Hematology, Department of Translational and Precision Medicine, Sapienza University, Rome, Italy
[5] Department of Molecular Medicine, University of Pavia, Pavia, Italy
[6] Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[7] Division of Hematology and Stem Cell Transplantation Unit, University Hospital AOU "Città della Salute e della Scienza", Turin, Italy
[8] Department of Translational Medicine, Università del Piemonte Orientale and SCDU Ematologia AOU SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
[9] Department of Hemato-Oncology and Radiotherapy Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy
[10] Department of Precision and Regenerative Medicine and Ionian Area, "Aldo Moro" University School of Medicine, and Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy
[11] Research Unit of Hematology, Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Roma, Italy
[12] Department of Engineering for Innovation Medicine, Section of Hematology, University of Verona, Verona, Italy
[13] Department of Hematology, University of Milan, Milan, Italy
[14] IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy
[15] Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy
**Corresponding author: Pier Luigi Zinzani, MD, PhD and Professor, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Via Massarenti, 9 - 40138 Bologna, Italy. *E-mail address:* pierluigi.zinzani@unibo.it (P.L. Zinzani).
*These authors contributed equally to this work.

A B S T R A C T

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of aggressive B-cell non-Hodgkin lymphoma, particularly in relapsed/refractory large B-cell lymphoma and mantle cell lymphoma. Despite its transformative potential, significant challenges persist in optimizing patient identification and referral pathways to ensure timely and equitable access.

This expert consensus, developed through the Delphi methodology, analyzes key barriers to the referral process and proposes structured solutions to enhance collaboration between referring treatment centers (RTCs) and qualified treatment centers (QTCs). Our findings highlight the importance of early and timely identification of CAR T–eligible patients through standardized disease assessments and strategies to streamline patient access through structured collaboration between RTCs and QTCs that can help overcome patient-specific logistical challenges. Proposed solutions should be broadly applicable across different health care systems.

Addressing these clinical and logistical barriers in the referral process will be crucial for maximizing the benefits of CAR T-cell therapy and expanding its accessibility to a broader patient population.

Key Words: CAR T-cell, barriers to referral, non-Hodgkin aggressive B-cell lymphomas, consensus.

https://doi.org/10.1016/j.jcyt.2025.07.007

Introduction

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment armamentarium for aggressive B-cell non-Hodgkin lymphoma (NHL), demonstrating robust and durable responses even in heavily pretreated patients. For patients requiring a third-line approach or later, anti-CD19 CAR T cells have been approved since 2017, making this curative treatment available in refractory or relapsed (R/R) large B-cell lymphoma (LBCL) [1–3]. Subsequently, axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) demonstrated superiority compared with the previous standard of care (SoC) of high-dose chemotherapy and autologous stem cell transplantation (ASCT). As a consequence, both were approved for patients with primary refractory diffuse large B-cell lymphoma (DLBCL) or those with early disease relapse (≤12 months), thus becoming an established new SoC in second-line treatment [4,5]. CAR T cells have also received approval for R/R mantle cell lymphoma (MCL) [6].

In Europe, the current options for R/R disease after a covalent Bruton tyrosine kinase inhibitor (cBTKi) include brexucabtagene autoleucel (brexu-cel) and pirtobrutinib. Real-world data supported and confirmed trial results for both LBCL and MCL, with an improved safety profile due to the implementation of optimized adverse event (AE) management measures in everyday clinical practice [7,8].

CAR T-cell therapies can only be provided at qualified treatment centers (QTCs), where a CAR T multidisciplinary team (including hematologists, neurologists, nurses, intensivists, and transfusionists) and adequate facilities exist. However, a large number of patients eligible for CAR T are identified at referral treatment centers (RTCs), i.e., the site where the patient is diagnosed and/or treated but which is not qualified to administer CAR T-cell therapies. The patients' referral—in particular, the timing of referral—is critical to ensure that all patients with aggressive NHL who are eligible to receive CAR T can benefit from this potential curative option. Therefore, RTCs must refer their patients to QTCs and QTCs must take in charge referred patients, following pathways that are well defined in few cases [9]. Once a patient is identified as a potential candidate for CAR T-cell therapy by the treating hematologist, confirmation of treatment choice and eligibility ideally is sought directly from the QTC. Depending on the country, formal approval is also required by regional and/or national authorities [10]. A recent survey by the European Blood and Marrow Transplantation Society (EBMT) reflected significant international variation in the application of various cell therapy–based technologies, including CAR T-cell therapies. Treatment rates differed across European countries, particularly for CAR T, and QTC density per country varied more than 10-fold for the first top 25 countries. Not surprisingly, center density strongly correlated with CAR T treatment rates [11]. The analysis of the adoption of CAR T-cell therapies in R/R LBCL patients in 4 European countries (France, Germany, Italy, and Spain) has found that access to this therapeutic option remains limited, with between 29% and 71% of estimated eligible patients not receiving treatment [10]. Recent data show that misallocation to a treatment other than CAR T accounts for an estimated number of lives lost at 5 years of between 40 and 120 for a misallocation rate of 10% up to 30%, respectively. In addition, this misallocation is estimated to decrease life expectancy by over 8 months per eligible patient on average [12].

All these data support the concept that greater efforts are needed to optimize referral pathways to ensure that CAR T–eligible patients are systematically identified in a timely manner.

The present article aims to capture the challenges that might limit patient access to CAR T-cell therapies along the patient journey. In addition, we aim to state a consensus focused on practical instructions on the management of patients with LBCL and MCL, coming from results of the Delphi method [13–15]. Perspectives, opinion, and unmet needs of both QTCs and RTCs were taken into consideration as starting points for the rationale of the project.

Starting from a national consensus, our recommendations are intended to be broadly applicable across different health care systems as most of the identified issues have been reported from several countries worldwide [16,17].

Methods

Panel composition

The Expert Panel of 13 members included 2 scientific coordinators and an independent methodologist (without voting rights) with expertise in systematic reviews, meta-analysis, and the Delphi method. The panel was responsible for drafting the protocol, producing the surveys for QTCs and RTCs, and preparing the initial draft of the consensus statements based on clinical expertise and clinical and logistical practice considerations. The panel had a geographically balanced distribution of LBCL and MCL experts with cell and gene therapy experience, as demonstrated by their peer-reviewed publications, leadership in clinical trials, involvement in national and international lymphoma scientific committees, and international guidelines authorship.

Consensus methodology (Figure 1)

Twenty-seven QTCs and 42 RTCs were invited to fill in a survey formulated by the Expert Panel aimed at identifying the main referral barriers to CAR T therapy (Supplementary Material). Only one representative physician of each invited center had to answer.

Once the results of the surveys were available, the panel formulated preliminary consensus statements based on the referral barriers declared by the QTCs and RTCs in order to propose specific solutions to overcome them. The Delphi method was used to generate consensus statements addressing the role, timing, and sequence of CAR T-cell therapy pathways in patients with both LBCL and MCL.

The criteria of agreement and disagreement among experts have been previously described [18,19]. Consensus was defined as >80% of participant ratings within one 3-point region (1–3 = low level of agreement; 4–6 = borderline; 7–9 = high level of agreement). Disagreement was defined as being the only group reaching >80% by adding up the values of the other 2 groups (1–3 and 4–6 or 4–6 and 7–9). The systematic step-by-step approach used in this project is provided in Figure 1.

The consensus items covered 8 issues: risk assessment, timing of disease assessment (interim and at the end of treatment [EOT]), bridging therapy (BT), referral, follow-up, capacity both for a single QTC and at regional level, and communication between physician and patient (±caregiver).

The methodologist analyzed and summarized the results while keeping the individual ratings anonymous. Both rounds of the voting survey were sent to the same participants for rating the reformulated or newly added statements.

All surveys were administered online using specific dedicated software, and results were reviewed and collated independently by the methodological expert. In evaluating each statement, each voting participant had to refer both to one's own experience and clinical judgment and to the available scientific evidence.

The first voting round included 35 items for LBCL and 15 items for MCL. The results of the first round, along with the statements not reaching the consensus threshold (<80% of agreement), were presented during the virtual teleconference of the panel members. Consensus statements that met the predefined criteria for formal consensus were recommended for approval. Statements that failed to achieve predefined criteria for consensus were discussed during the virtual meeting and, based on the discussions, were dropped or modified (based also on comments received) for revoting in the second round.

Results

The referral barriers identified in the survey fall into the following domains: pathway from patient identification to referral; pathway

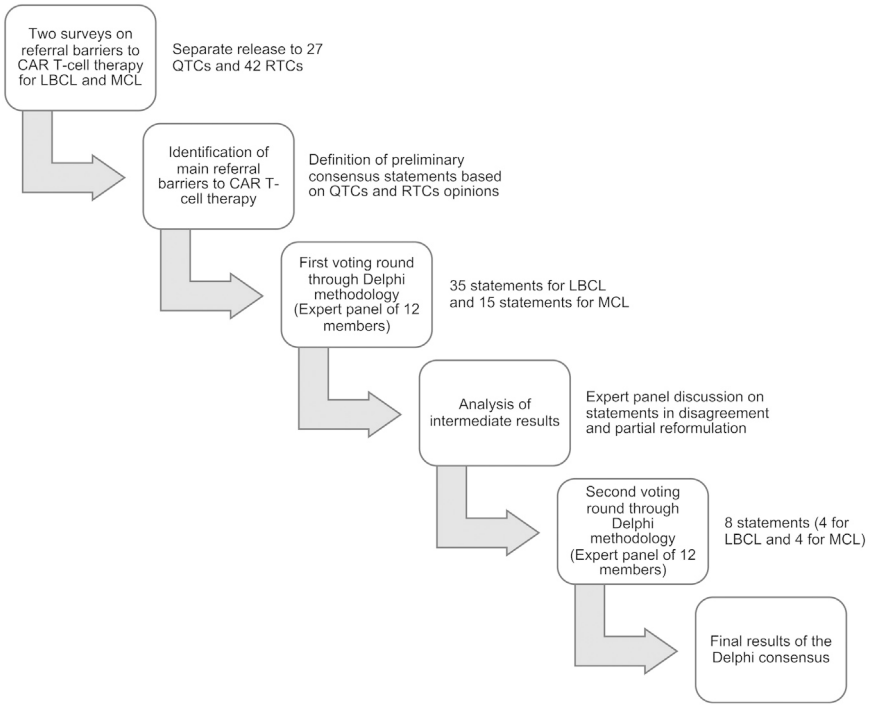

Fig. 1. Flowchart of consensus steps. CAR T-cell, chimeric antigen receptor T-cell therapy; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; QTC, qualified treatment centers; RTC, referring treatment centers.

from referral to CAR T-cell infusion and subsequent follow-up; QTCs and/or regional capacity; and patient's and/or caregiver's needs. QTC and RTC survey results constitute the actual and effective rationale that led to the subsequent consensus statements by the panel. Complete results of the survey are available in the Supplementary Tables 1 and 2.

Through the Delphi method at the end of the first round, 30 statements for LBCL and 11 for MCL received consensus for agreement, 4 LBCL and 4 MCL items obtained disagreement, and 1 (regarding LBCL) dispersed opinion. After discussion, a total of 9 statements (5 for LBCL and 4 for MCL) were proposed for the second round. Three out of 9 statements included in the second phase of voting (2 for LBCL and 1 for MCL) met the predefined criteria for consensus, whereas 6 (3 for LBCL and 3 for MCL) did not reach agreement.

Overall, we achieved 32/35 consensus for LBCL and 12/15 for MCL, respectively (Tables 1 to 3). However, since 9 items of LBCL (logistical issues) were applicable also for MCL, we reported them in a separate Table (Table 3). Thus, in the output of Table 1 for LBCL, the final results are 26 instead of 35.

LBCL

Full recommendations for LBCL are shown in Table 1. Many of the recommendations, particularly those related to disease assessment and treatment response, reflect existing recommendations from major international guidelines [20–26]. The intention of the consensus was to synthesize them within the overall patient journey and to give a practical perspective on the clear implications that such recommendations have for the referral process.

Recommendations at diagnosis

Risk stratification at diagnosis is crucial in LBCL to guide treatment decisions and predict patient outcomes. Patients with high-risk LBCL are more likely to have poor responses to first-line (1L) treatment. The panel questioned whether the QTC should be consulted before starting 1L treatment in the case in which high-risk patients are identified by RTCs. As the panel reported dispersion of opinions concerning this statement, the adoption of an integrated QTC–RTC care approach for high-risk patients at diagnosis remains an unaddressed issue.

Recommendations from first-line treatment to follow-up after end of treatment evaluation

Rapidly progressive disease was identified as one of the main issues in referral barriers through the CAR T-cell pathway. Ten consensuses were generated to ensure early identification of LBCL patients who are chemorefractory to 1L treatment. The panel agreed that response should be assessed after 3 to 4 cycles with a total-body computed tomography (CT) scan or fluorodeoxyglucose–positron emission tomography (FDG-PET) scan in all patients regardless of their risk profile [21,25]. This interim evaluation is crucial to enable early identification of chemorefractory patients defined by a reduction in lymph nodes (or other disease localizations) less than 50% on CT scan or by a persistence in FDG-PET uptake with a Deauville score (DS) of 4 to 5 [22]. Indeed, a patient who did not obtain at least a partial response (PR) at this time point should be promptly referred to the QTC to be addressed with CAR T-cell therapy [25]. Patients who have only partial chemosensitivity to 1L treatment obtaining a PR at the interim evaluation require close monitoring until EOT evaluation.

EOT assessment should be done within 1 month after the administration of the last cycle of chemoimmunotherapy. In the event that 1L treatment contains 2 additional doses of rituximab, EOT evaluation should be performed before this maintenance phase. At this time point, all patients achieving PR, stable disease (SD), or progressive disease (PD) are defined as *chemorefractory* and should be referred for CAR T-cell therapy [26]. On the other hand, patients obtaining a complete metabolic response (CMR) at EOT are recommended to be

Table 1
Large B-cell lymphoma final results.

Parameter	1–3 %	4–6 %	7–9 %	4–9 %	1–6 %	Final result
LBCL—Risk evaluation at diagnosis						
For patients with high-risk LBCL, the QTC should be consulted before initiating first-line therapy.	**25.0%**	**33.3%**	**41.7%**	**75%**	**58.3%**	**Dispersed opinions**
First line—Interim evaluation						
Response should be evaluated after 3-4 cycles of first-line therapy in all patients, regardless of risk profile.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Response to first-line therapy should be evaluated after 3-4 cycles with total body CT scan with contrast or FDG-PET (interim PET).	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
At the interim evaluation after 3-4 cycles of first-line therapy, a patient is to be defined as chemorerefractory if: the reduction in lymphadenopathies or other localizations of disease on CT scan is less than 50% or there is a persistence of uptake on PET (DS 4-5).	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
A patient with LBCL, regardless of risk class, with a clinically unresponsive disease (not obtaining at least a partial response) upon re-evaluation after 3-4 cycles of first-line therapy, should be referred to the QTC.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
First line—End of therapy						
At the end of first-line therapy, a patient is to be defined as chemorefractory if there is a DS of 4 or 5 on FDG-PET.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Histologic confirmation should be performed, where possible, in patients with LBCL who have an incomplete metabolic response (DS 4-5) at the end of first-line therapy.	**0.0%**	**33.3%**	**66.7%**	**100.0%**	**33.3%**	**Disagreement**
CAR T therapy should be considered for patients with PD, SD, or PR at the end of first-line therapy, and the patient should be reported as soon as possible.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
First line—Follow-up						
After obtaining a complete metabolic response (DS 1-3) at the end of first-line therapy, CT scan with contrast is the recommended method for monitoring the patient with LBCL. The use of PET should be reserved for cases of doubtful evaluation on the CT scan.	**0.0%**	**16.7%**	**83.3%**	**100.0%**	**16.7%**	**Agreement**
In the monitoring of the first year after the end of first-line therapy, all patients should have a CT scan with contrast at about 6 months and within 12 months after the end of therapy.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
It is necessary to monitor more closely with CT scan with contrast patients who at the end of therapy have a complete metabolic response but persistence of lymph node lesions >3 cm.	**8.3%**	**41.7%**	**50.0%**	**91.7%**	**50.0%**	**Disagreement**
It is worth considering CAR T therapy for R/R patients within 12 months after the end of the first-line approach.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
In the event of any suspicion of recurrence during follow-up, it is recommended to proceed with histologic confirmation of the event by biopsy and, in the meantime, to immediately contact the QTC.	**0.0%**	**16.7%**	**83.3%**	**100.0%**	**16.7%**	**Agreement**
LBCL—Referral						
In patients with LBCL refractory to the first line of therapy or in first relapse within 1 year, the RTC should contact the QTC as quickly as possible in order to confirm the actual eligibility for CAR T therapy and organize lymphocytoapheresis.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
The assessment of eligibility for CAR T therapy, even in the presence of minimal deviations, is shared between the RTC and QTC, but the final decision is the responsibility of the QT.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
The QTC must undertake to perform the first assessment visit of a referred patient as soon as possible according to priority criteria (disease status, prognostic risk, etc.).	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Once a patient eligible for CAR T therapy has been identified, the QTC must agree with the RTC on the scheduling of diagnostic investigations for lymphocytoapheresis (viral serologies, brain MRI, echocardiography, etc.) and the remaining therapeutic program, at each stage of the CAR T pathway.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Holding therapy (cytoreductive therapy between the indication for CAR T therapy and lymphocytoapheresis) should not be initiated without first contacting the QTC in order not to affect the collection of lymphocytes.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
LBCL—Bridging therapy						
BT, which is therapy administered after leukapheresis and prior to CAR T infusion, should be agreed upon with the QTC.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
BT after lymphocytoapheresis is recommended in LBCL patients who are candidates for CAR T therapy in the case of progressing disease and high tumor burden.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
In patients progressing with high tumor burden after BT, CAR T infusion should be evaluated on a case-by-case basis and should not be excluded *a priori*.	**8.3%**	**0.0%**	**91.7%**	**91.7%**	**8.3%**	**Agreement**
CAR T infusion should also be performed in patients in complete remission at the end of BT.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
The choice of a short BT with an optimal toxicity/efficacy ratio is recommended.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Critical mass radiotherapy may be considered in patients with diffuse disease.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Myeloablative chemotherapy with autologous stem cell transplantation is contraindicated as BT in patients with active disease owing to its high infectious and hematologic toxicity.	**8.3%**	**0.0%**	**91.7%**	**91.7%**	**8.3%**	**Agreement**
The use of polatuzumab-vedotin in patients with LBCL can be considered a valid BT and seems to be associated with better outcomes, albeit on a limited series of patients.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**

BT, bridging therapy; CAR T, chimeric antigen receptor T-cell therapies; CT, computed tomography; DS, Deauville Score; FDG-PET, fluorodeoxyglucose–positron emission tomography; LBCL, large B-cell lymphoma; PD, progression of disease; PR, partial response; QTC, qualified treating centers; RTC, referring treatment centers; R/R, relapse/refractory; SD, stable disease.

followed with a CT scan whereas FDG-PET should be reserved in cases of doubtful CT scan evaluation [23]. The timing of disease monitoring for patients achieving CMR should be at 6 months and within 12 months after EOT [21]: indeed, CAR T-cell therapies are indicated for patients experiencing relapse within 12 months after the completion of 1L chemoimmunotherapy. These patients should be referred for CAR T-cell therapy. In addition, it is recommended to immediately contact the QTC to agree on the need to confirm the suspicion of disease recurrence through histologic confirmation.

The panel disagreed on 2 items: the need to perform a histologic confirmation for patients with incomplete metabolic response at EOT [20] and the need to plan closer monitoring with a CT scan in patients

Table 2
Mantle cell lymphoma final results.

Parameter	1–3 %	4–6 %	7–9 %	4–9 %	1–6 %	Final result
MCL—Risk assessment						
Blastoid or pleomorphic histotype identifies the patient with MCL at high risk of recurrence or progression.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Elevated MIPI identifies the patient with MCL at high risk of recurrence or progression.	**16.7%**	**25.0%**	**58.3%**	**83.3%**	**41.7%**	**Disagreement**
The presence of *TP53* deletion/mutation and/or elevated Ki67 identifies the patient with MCL at high risk of recurrence or progression.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
In the patient with MCL with *TP53* deletion/mutation negative at diagnosis, it is necessary to assess the presence of the *TP53* deletion/mutation at each episode of relapse/progression.	**0.0%**	8.3%	91.7%	100.0%	100.0%	**Agreement**
It is important to consider the time to relapse after standard first-line treatment (POD24) in order to identify patients with MCL at high risk of further relapse or progression.	**0.0%**	**0.0%**	100.0%	100.0%	100.0%	**Agreement**
The patient with high-risk MCL at diagnosis remains at high risk even at the time of the first relapse and subsequent events.	**0.0%**	16.7%	83.3%	100.0%	100.0%	**Agreement**
Timing of disease assessment during BTKi therapy						
The patient with MCL on second-line BTKi therapy should be monitored with instrumental examination (ultrasound or CT) every 3 months in the first year of treatment.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
In the case of MCL with high biological risk (*TP53* mutation, high Ki67 kinetics, blastoid morphology, POD24), it is necessary to re-evaluate the disease within a short time period (monthly blood chemistry tests) during the first 12 months of second-line therapy.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
MCL—Referral						
For patients with MCL who are potential candidates for CAR T, it is recommended to alert the QTC before starting second-line therapy.	**16.7%**	**16.7%**	**66.7%**	**83.3%**	**33.3%**	**Disagreement**
In patients with MCL who are potential candidates for CAR T, the use of a treatment regimen containing bendamustine should be carefully considered in view of the lymphocytotoxicity of this drug.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Patients with MCL who are persistent or who have lost response to BTKi treatment should be referred to the QTC prior to starting a new line of therapy in order to perform lymphocytoapheresis as early as possible.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
MCL—Bridging therapy						
In patients with MCL, BT should be agreed upon between the RTC and QTC.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
In patients with MCL who are candidates for CAR T therapy, BTKi therapy may be continued even after lymphocytoapheresis if progression is slow.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
In patients with MCL who are candidates for CAR T therapy, the use of Bcl2 inhibitors as BT may be considered.	**0.0%**	**25.0%**	**75.0%**	**100.0%**	**25.0%**	**Disagreement**
In patients with MCL who are candidates for CAR T therapy, the use of non-covalent BTK inhibitors may be advisable as BT.	**0.0%**	**16.7%**	**83.3%**	**100.0%**	**16.7%**	**Agreement**

BT, bridging therapy; BTKi, Bruton tyrosine kinase inhibitor; CAR T, chimeric antigen receptor T-cell therapies; CT, computed tomography; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; POD24, progression of disease within 24 months; QTC, qualified treating center; RTC, referring treatment center.

who have a CMR at EOT but persistent lesions greater than 3 cm [21]. The false-positive rate with PET scans is low and does not justify systematic biopsies, but rather requires timely patient referral to CAR T therapy [21]. Although it could be stated that patients in CMR at EOT but with a persistence of lesions greater than 3 cm could have a greater risk of recurrence, available data do not recommend closer monitoring [21].

LBCL—recommendations for referral

The time between the identification of patient candidates for CAR T therapy and lymphocytoapheresis is critical, as emerged from the survey results (Supplementary Tables 1 and 2). The adoption of an integrated QTC–RTC care approach is mandatory to optimize the CAR T journey. Five consensuses were generated for the referral pathway. As soon as RTCs identify a patient who is potentially eligible for CAR T therapy, the RTC should contact the QTC as quickly as possible to confirm the actual eligibility for CAR T therapy and, thus, to organize lymphocytoapheresis. The RTC and QTC share the responsibility for the eligibility assessment of patients for CAR T, but the QTC has the responsibility for the final decision. If patients are deemed eligible, the QTC must perform the "first" visit as soon as possible, prioritizing according to patient's clinical status (e.g., disease kinetics, prognostic risk). Moreover, the RTC and QTC must agree on the therapeutic program scheduling. In agreement with the recent British Society of Haematology guidelines [24], in the exceptional case when a holding therapy might be needed before lymphocytoapheresis due to an aggressive disease dynamic, the RTC and QTC must closely discuss and agree upon both the treatment strategy and timelines in order to not affect the apheresis product while preserving fitness and performance status [17,27]. Where possible, the use of bendamustine in holding therapy should be avoided owing to its association with increased risk of manufacturing failure [24].

Recommendations for BT

As highlighted in the survey, BT plays a critical role in the management of patients with R/R LBCL who are candidates for CAR T therapy. The main goal of BT is to control disease progression during the time required for manufacturing while preserving CAR T eligibility. In addition, effective BT may mitigate CAR T-cell toxicity by reducing the tumor burden [24]. The Expert Panel generated eight consensus statements on BT. BT should be recommended in LBCL patients in the case of progressing disease and high tumor burden and should be agreed upon between the RTC and QTC [24,27]. If progressing disease with high tumor burden persists after BT, CAR T therapy should not be excluded *a priori* since chemosensitivity is not mandatory [24,28]. On the other hand, CAR T infusion should be performed even in patients with CR after BT, since this population is expected to achieve the best outcomes [29]. Concerning the different types of BT, the

Table 3
Logistical requirements and patient perspective recommendations.

Parameter	1–3 %	4–6 %	7–9 %	4–9 %	1–6 %	Final result
QTC capacity						
The application of standardized protocols on the prevention and treatment of complications from CAR T therapies can be useful for a better clinical outcome and to promote a shorter discharge time.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
In light of current real-world safety reports, it is not essential to reserve an ICU bed, but it is important that the ICU is informed of the scheduling of a CAR T treatment.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
Regional capacity						
It is recommended to establish a reference network between the QTC and RTC in order to ensure sharing best practices in terms of early access for patients who are candidates for CAR T therapies.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
The QTC should be available to refer patients to other QTCs if timely management cannot be guaranteed.	**8.3%**	**0.0%**	**91.7%**	**91.7%**	**8.3%**	**Agreement**
Communication between physician and patients and their caregivers						
Once the patient candidate for CAR T therapy has been identified, the RTC must have an interview with the patient in order to agree on the management with the QTC.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
The specialists of the RTC must explain to the patient and caregiver that the transfer to the QTC is essential for the execution of the best available therapeutic option, for curative intent.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
It is important to convey to the patient and caregiver the concept that CAR T therapy requires a limited time commitment away from home.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**
Patient needs, such as the need for caregivers and/or transport/accommodation logistics near the treatment center, should be shared as early as possible with the QTC in order to find solutions to ensure the safe feasibility of CAR T therapy.	**0.0%**	**8.3%**	**91.7%**	**100.0%**	**8.3%**	**Agreement**
The description of the risks and benefits of CAR T treatment should be discussed appropriately between the patient and the QTC.	**0.0%**	**0.0%**	**100.0%**	**100.0%**	**0.0%**	**Agreement**

CAR T, chimeric antigen receptor T-cell therapies; ICU, intensive care unit; QTC, qualified treating center; RTC, referring treatment center.

choice of a short treatment with an optimal toxicity/efficacy ratio is recommended. Radiotherapy may be considered as well in the case of a critical mass, when feasible. BT based on the use of polatuzumab vedotin can also be considered as a valid option; recent evidence suggests better outcomes compared with alternatives [29]. Myeloablative therapy with ASCT is contraindicated in patients with active disease owing to the high risk of both hematologic toxicities and infections [28]. The CAR T journey of the LBCL patient is reported in Figure 2.

Mantle Cell Lymphoma Full recommendations for MCL are shown in Table 2.

Recommendations for risk assessment

Five areas of consensus were established, while 1 point of disagreement remained regarding the prognostic risk assessment of MCL.

Firstly, high-risk patients at diagnosis are consistently classified as high risk even at the time of first and subsequent disease recurrences [30]. Low-risk patients must be re-evaluated for risk assessment at any subsequent disease recurrence [30].

Blastoid or pleomorphic phenotypes are indicators of patients at high risk for disease recurrence or progression, as is the presence of

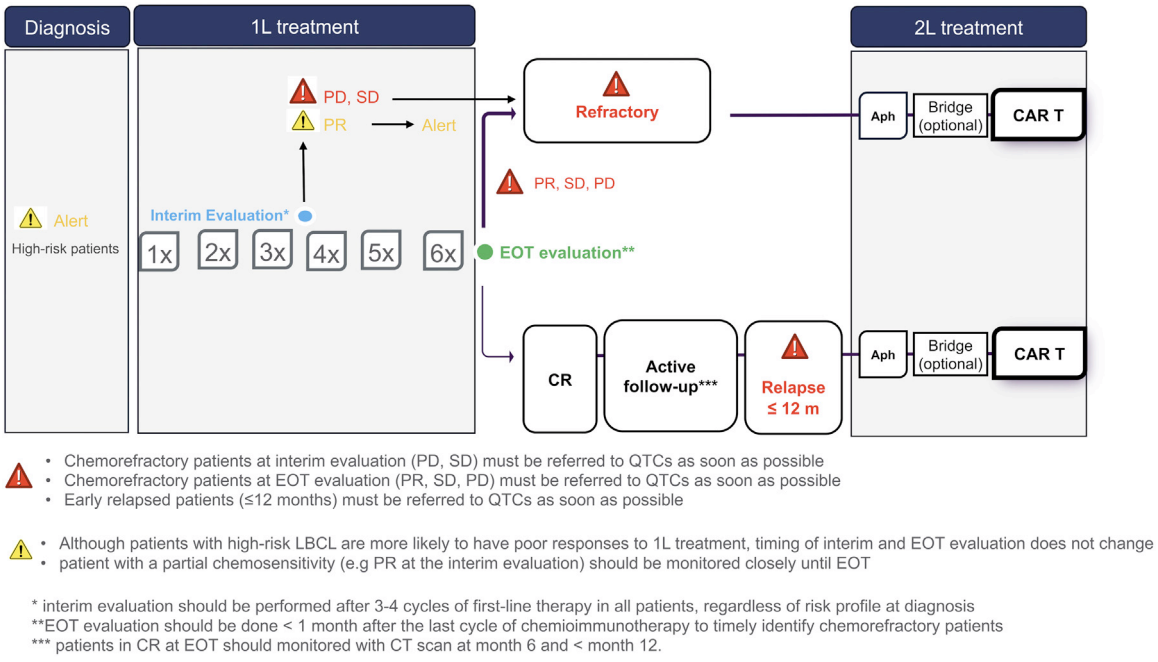

Fig. 2. Large B-cell lymphoma patient journey to CAR T-cell therapy. Aph, apheresis; CAR T, chimeric antigen receptor T-cell therapy; CR, complete response; CT, computed tomography; EOT, end of treatment; LBCL, large B-cell lymphoma; m, months; PD, progression of disease; PR, partial response; QTC, qualified treatment centers; SD, stable disease; 1L, first-line treatment; 2L, second-line treatment.

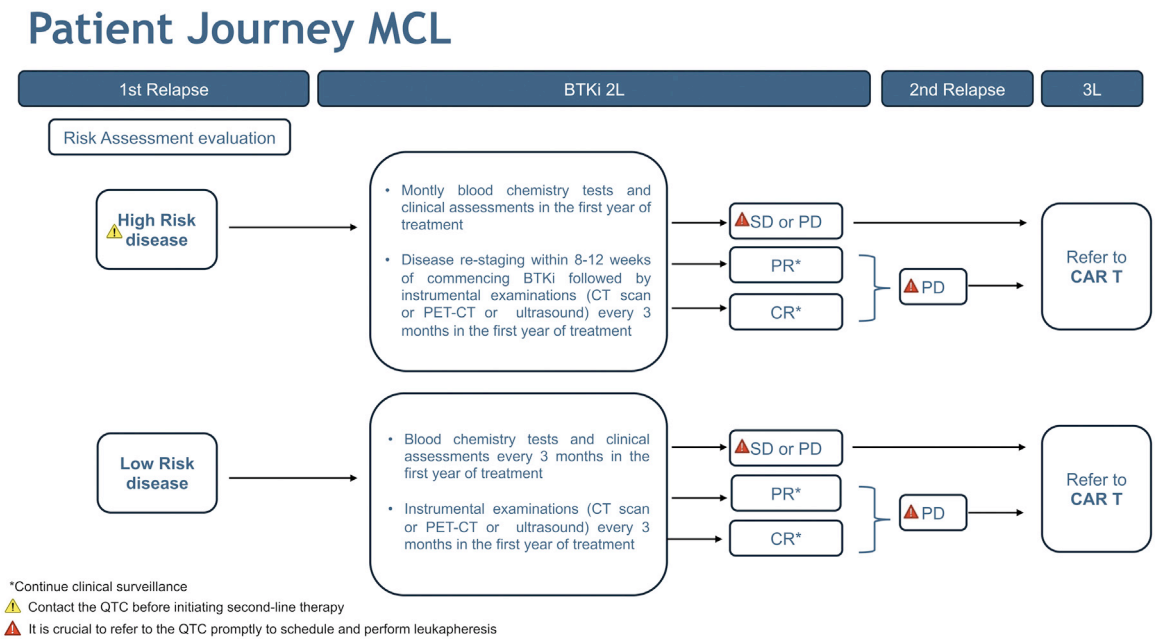

Fig. 3. Mantle cell lymphoma patient journey to CAR T-cell therapy. CAR T, chimeric antigen receptor T-cell therapy; CR, complete response; CT, computed tomography; MCL, mantle cell lymphoma; PD, progression of disease; PET, positron emission tomography; PR, partial response; QTC, qualified treatment center; SD, stable disease; 2L, second-line treatment; 3L, third-line treatment.

TP53 deletions or mutations and/or elevated Ki67 levels [30,31]. Notably, patients who tested negative for *TP53* deletions or mutations at diagnosis should be reassessed at each recurrence or progression of the disease.

In recent years, the concept of POD24 (progression within 24 months after 1L treatment) has emerged as a prognostic factor, identifying patients at high risk of disease relapse or progression [32].

Regarding the Mantle Cell Lymphoma International Prognostic Index (MIPI), the panel disagreed on its usefulness as a factor for identifying high-risk patients in terms of disease recurrence or progression [30,31]. For patients deemed at high risk of recurrence or progression, it is recommended to contact the QTC before initiating 2L therapy [33].

Recommendations for timing of disease reassessment during BTKi

Two consensuses were established. For high-risk patients, as defined in the previous section, disease restaging is recommended within a short time frame using monthly blood chemistry tests and clinical assessments during the first 12 months of 2L treatment [21,34]. These patients should undergo imaging restaging (CT or PET-CT, or ultrasound) within 8 to 12 weeks, sooner if there are concerns, followed by further imaging restaging every 3 months during the first year [43,44]. Low-risk patients receiving 2L treatment with a BTKi should undergo imaging (CT scan or PET-CT, or ultrasound), blood chemistry tests, and clinical assessments every 3 months during the first year [35,36]. These guidelines are consistent with the recent recommendations from the British Society for Haematology on the diagnosis and management of MCL [33]. In the case in which there is no early response and the disease remains stable or progresses on BTKi, an urgent referral to a QTC is recommended. If there is an ongoing PR or CR, the patient should continue on clinical surveillance [33].

Recommendations for referral

Regardless of risk stratification, patients considered potential candidates for CAR T-cell therapy are patients with MCL who develop resistance or experience a loss of response to BTKi. It is crucial to refer these patients to the QTC promptly to schedule and perform leukapheresis [21,34]. Careful consideration should be given to the use of bendamustine-containing regimens before leukapheresis owing to their known lymphotoxic effects.

Recommendations for BT

As previously stated for patients with LBCL, the decision to implement BT should be made collaboratively between the RTC and QTC. BTKi therapy may be continued after leukapheresis if the patient is in SD or if PD is considered slow. Another potential BT option to consider is the use of non-covalent BTKi [37,38]. In contrast, the use of anti-Bcl2 as a BT is not recommended due to a lack of robust data and evidence in the literature, particularly in real-world settings, as well as due to the aggressive nature of the lymphoma. The CAR T journey of the patient with MCL is reported in Figure 3.

Logistical Requirements and Patient Perspective

Full recommendations for logistical requirements and patient perspectives are presented in Table 3.

Recommendations for QTC and regional capacity and communication between physician and patient

Consensus for QTC and regional capacity and for communication between physician and patient (and their caregiver) was reached on 9 statements valid both for patients with LBCL and patients with MCL.

Regarding the QTC capacity issues, the adoption and application of standardized protocols in preventing CAR T complications can be useful for better clinical outcomes and shorter discharge time [29,39–41]. Nevertheless, it is not essential to reserve an intensive care unit (ICU) bed: the ICU could simply be advised about the scheduled infusion and alerted in the case of severe or serious complications. Finally, if a QTC cannot guarantee timely management, the QTC should be available to refer patients to another QTC, ensuring the best pathway for patients' timely access to CAR T-cell therapy.

From a clinical practice perspective, particularly in the context of CAR T-cell therapy, communication with the patient is a core element of clinical decision-making. It directly influences treatment acceptance, adherence, and informed consent—as such, it has an integral role in patient-centered care. Once a patient is identified as a candidate for CAR T therapy, the RTC specialist must explain to the patient (and caregivers) that transferring to the QTC is essential to access the best available treatment option. The RTC specialist should also convey that CAR T therapy requires a logistical commitment, such as being away from home, but only for a limited period of time. To simplify the treatment pathway and ensure the feasibility of the therapy, patient and caregiver specific needs should be communicated to the QTC as early as possible. The QTC is responsible for providing a comprehensive explanation of the risks and benefits of CAR T-cell therapy and may also be able to offer tailored solutions to address logistical challenges, ensuring a smooth transition between centers.

Discussion

CAR T-cell therapy has significantly shifted the treatment paradigm for aggressive B-cell NHL, particularly in R/R LBCL and MCL, now substantiated by consistent efficacy data from long-term clinical trial results and the real-world setting, supporting unprecedented therapeutic value. However, despite these advancements, challenges remain in standardizing patient pathways from RTCs to QTCs. Addressing these gaps requires well-structured referral frameworks to ensure streamlined patient access and optimized treatment timelines.

Our article highlights that receipt of CAR T therapy at an institution different from the primary hematology hospital could be complex and, above all, a multistep process for physicians, patients, and their caregivers. The absence of clear and well-defined referral pathways may limit the likelihood and timeliness of referral of an eligible patient to a QTC. In addition, treating hematologists might be hesitant to refer eligible patients owing to the perceived complexity and duration of the CAR T-cell therapy pathway, potentially not even considering or delaying patient access to this therapy. The distance between RTCs and QTCs can also be considerable and may even require patients to travel outside of their own region. As patients with LBCL or MCL endure a reduced health status, they often require assistance. Thus, family members are also likely to be required to travel with them [18]. This Delphi consensus may serve as a useful guide to plan improvements in the referral process within different health system environments.

Timely referral to a QTC is a critical determinant of CAR T-cell therapy outcomes. Regarding patients with LBCL, our consensus recommendations identify critical time points throughout the 1L treatment that enable early identification of patients who must be addressed with CAR T treatment in 2L. The consensus emphasizes the importance of early identification of patients with LBCL who are chemorefractory, ideally at the first interim evaluation or, at the latest, at EOT. Additionally, post-treatment monitoring strategies for patients achieving CR are pivotal to ensure clear identification of early relapsed patients (within 12 months), who should receive expeditious evaluation for CAR T-cell therapy. Timely referral to a QTC is even more crucial in MCL. Patients who are high risk for MCL should be discussed with a QTC at first relapse. Independently from risk assessment, each patient with MCL should be monitored closely while receiving 2L with a BTKi, integrating clinical and instrumental assessments. A prompt early referral at the first signs of BTKi failure might mitigate the drop-out risk and improve CAR T-cell accessibility. Once CAR T−eligible patients have been identified, the adoption of an integrated QTC−RTC care approach is mandatory to drive the patient to product infusion.

The interventions mentioned above could help reduce the so-called "vein-to-vein time," associated with more favorable efficacy outcomes compared with longer times [41]. Additionally, other factors should be considered for optimal timing. The time between patient referral and infusion (often referred to as "decision-to-vein" or "brain-to-vein" time) is not currently well defined, as it is neither reported in clinical trials nor studied in real-world settings [42].

The Expert Panel identified key areas for improvement in referral logistics, emphasizing the need for structured collaboration between RTCs and QTCs. Established formal hub-and-spoke partnerships aim to address existing barriers, such as delays in eligibility assessments, logistical challenges in patient transfer, and inconsistencies in pre-treatment evaluation requirements. These models could be used as examples of good practice for creating common standards in CAR T clinical networks and referral systems. They can help set up ways to share information between networks and regions, breaking down barriers and making referral processes more efficient [43]. Guidelines on referral pathways could also require that capacity and wait times of QTCs should be visible to RTCs to facilitate informed choice of the referral destination.

A few limitations should be acknowledged, such as the fact that the expert opinion is based on input from a limited panel. Nevertheless, it was based on large surveys that involved 69 hematologic centers. In addition, the panel has broad expertise in CAR T-cell therapy and is representative of both RTCs and QTCs. Regarding the potential lack of prospective validation, we note that some projects have already started with promising results [43].

Furthermore, our findings highlight the significance of addressing patient-specific barriers, such as the presence of a caregiver and patient hesitancy owing to the travel required to reach QTCs. To overcome this challenge, caregiver support resources should be made available, and most patients may qualify for patient support programs that provide professional caregivers as well as assistance with travel, logistical needs, and supportive services such as physiotherapy or nutritional care [44]. These programs can be facilitated by QTCs, which, if properly informed about patient-specific needs, can help alleviate patient hesitancy. Moreover, an essential yet often underemphasized component of the referral and treatment pathway is the quality of communication between clinicians and patients or caregivers. Clear, timely, and empathetic communication is critical not only to convey the potentially curative intent of CAR T-cell therapy but also to appropriately set expectations regarding efficacy and risks. Such communication supports shared decision-making and may ultimately influence patient adherence, satisfaction, and clinical outcomes.

In conclusion, our Expert Consensus reinforces the expanding role of CAR T-cell therapy in the treatment of aggressive NHL. While real-world data confirm the clinical efficacy of CAR T-cell therapy, optimizing referral processes is crucial for maximizing patient outcomes. Establishing structured referral frameworks, fostering collaboration between RTCs and QTCs, and addressing unresolved clinical uncertainties will be essential to ensure equitable access to these life-saving therapies.

Funding

Medical writing support was provided by Delphi International SRL, funded by Gilead Kite.

Author Contributions

PC, PLZ, SL, AC, and ADR conceived the idea and wrote the manuscript. LA, RF, ML, MM, PM, LR, and CV provided advice and helped with the writing of the manuscript. All authors revised and approved the final manuscript.

Declaration of Competing Interest

MM declared honoraria from Abbvie, Roche, Gilead-Sciences, Incyte, and Janssen-Cilag; consulting from Gilead-Sciences, Novartis,

Jansenn-Cilag, Vertex, and BMS; and travel from Gilead-Sciences, Janssenn-Cilag, and Roche. LA declared consulting from Roche, Janssen-Cilag, Verastem, Incyte, and EUSA Pharam; speakers' bureau from EUSA Pharma, Novartis, Kite, and Beigene; and travel from Roche. ADR declared consulting from Roche, Kite, Abbvie, Incyte, J&J, and Novartis; speakers' bureau from Roche, Kite, Abbvie, Incyte, J&J, Eli-Lilly, Recordati, and Novartis. PM declared honoraria from Abbvie, Gilead, Sanofi, J&J, GSK, Takeda, and Novartis. PLZ declared honoraria from BMS, Gilead, Roche, Kyowa Kyrin, Sobi, Incyte, and Novartis; consulting from BMS, Gilead, Roche, Kyowa Kyrin, Sobi, Incyte, and Novartis; speakers' bureau from BMS, Gilead, Roche, Kyowa Kyrin, Sobi, Incyte, and Novartis. PC declared honoraria from AbbVie, Amgen, BeiGene, BMS, Daiichi Sankyo, and Eli-Lilly; consulting from AbbVie, Amgen, BeiGene, BMS, Daiichi Sankyo, and Eli-Lilly, and travel from AbbVie, Amgen, BMS, Kite/Gilead, Janssen, Novartis, and Roche. SL declared consulting from Roche, Kite, BMS, Novartis, Abbvie, and Incyte; speakers' bureau from Roche, Kite, and BeiGene; and travel from Roche and BeiGene; AC declared consulting from Abbvie and Gilead-Sciences and a lecture fee from Eli-Lilly. CV declared honoraria from Abbvie, BMS, Astra Zeneca, Servier, Incyte, Roche, and Pfizer; and consulting from Astra Zeneca and Roche. LR declared speakers' bureau from Kite/Gilead, Abbvie, Takeda, Novartis, and J&J; and travel from Sobi and J&J. RF declared honoraria from Kite and Incyte; and consulting from Incyte, Sobi, and Novartis. ML declared consulting from Abbvie, Amgen, ADC Therapeutics, SOBI, Beigene, and BMS; and speakers' bureau from Abbvie, Amgen, ADC Therapeutics, SOBI, Beigene, and BMS.

Acknowledgments

We would like to thank all referring treatment centers and qualified treatment centers that adhered to and completed the initial surveys to identify main issues in referral barriers through the CAR T-cell pathway. We also thank Doctor Alessandro Urbani, the independent methodologist, for his active effort in this project.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2025.07.007.

Article History:

Received 22 April 2025
Accepted 22 July 2025

References

[1] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Timmerman JM, Stiff PJ, Friedberg JW, Flinn IW, Goy A, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma. N Engl J Med 2017;377(26):2531–44.
[2] 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(10254):839–52.
[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(1):45–56.
[4] Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, et al. Survival with axicabtagene ciloleucel in large B-cell lymphoma. N Engl J Med 2023;389(2):148–57.
[5] Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood 2023;141(14):1675–84.
[6] National Cancer Institute. CAR T-Cell Therapy Approved by FDA for Mantle Cell Lymphoma. https://www.cancer.gov/news-events/cancer-currents-blog/2020/fda-brexucabtagene-mantle-cell-lymphoma#:~:text=The%20new%20treatment%2C%20a%20CAR%20T-cell%20therapy%20called,B%20cells%2C%20a. (2020). [accessed 01.02.2025].
[7] Lee DC, Kambhampati S, Silvina Odstrcil Bobillo M, Adedokun B, Shadman M, Olson AL, et al. Real-world early outcomes of second-line axicabtagene ciloleucel (axi-cel) therapy in patients (pts) with relapsed or refractory (r/r) large B-cell lymphoma (LBCL). Blood 2024;144(Supplement 1):526.
[8] Wang J, Bhaskar S, Adedokun B, Oluwole OO, Metheny L, Moskop A, et al. Real-world trends of cytokine release syndrome and neurologic events, and pattern of their management among patients receiving axicabtagene ciloleucel for relapsed or refractory (r/r) large B-cell lymphoma (LBCL) in the US: A CIBMTR Report. Blood 2024;144(Supplement 1):527.
[9] Jommi C, Bramanti S, Pani M, Ghirardini A, Santoro A. CAR T-cell therapies in Italy: patient access barriers and recommendations for health system solutions. Front Pharmacol 2022;13:915342.
[10] Canales Albendea MÁ, Canonico PL, Cartron G, Deiters B, Jommi C, Marks R, et al. Comparative analysis of CAR T-cell therapy access for DLBCL patients: associated challenges and solutions in the four largest EU countries. Front Med (Lausanne) 2023;10:1128295.
[11] Passweg JR, Baldomero H, Atlija M, Kleovoulou I, Witaszek A, Alexander T, et al. The 2023 EBMT report on hematopoietic cell transplantation and cellular therapies. Increased use of allogeneic HCT for myeloid malignancies and of CAR-T at the expense of autologous HCT. Bone Marrow Transplant 2025;60(4):519–28.
[12] Buecklein VL, Ayuk FA, Holderried TAW, Mai C, Kievit B, Blisset R, et al. Estimating the impact on survival of not receiving CAR T therapy despite being eligible in relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) patients in Germany. Blood 2024;144(Supplement 1):5037.
[13] Dalkey NC, Helmer O. An experimental application of the Delphi method to the use of experts. Management Science 1963;9:458–67.
[14] Linstone HA, Turoff M. The Delphi Method, Techniques and Applications. Boston: Addison Wesley; 1975.
[15] Ayyub BM. A Practical Guide on Conducting Expert-Opinion Elicitation of Probabilities and Consequences for Corps Facilities. IWR Report 01-R-01, Alexandria, VA, 2001.
[16] Hu B, Vaidya R, Ahmed F, Ehsan H, Moyo TK, Jacobs RW, et al. Real-World analysis of barriers to timely administration of chimeric antigen receptor T cell (CAR T) therapy in diffuse large B-cell lymphoma. Transplant Cell Ther 2024;30(11). 1082.e1-1082.e10.
[17] Hoffmann MS, Hunter BD, Cobb PW, Varela JC, Munoz J. Overcoming barriers to referral for chimeric antigen receptor T cell therapy in patients with relapsed/refractory diffuse large B cell lymphoma. Transplant Cell Ther 2023;29(7):440–8.
[18] Kahan JP, Bernstein SJ, Leape LL, Hilborne LH, Park RE, Parker L, et al. Measuring the necessity of medical procedures. Med Care 1994;32(4):357–65.
[19] Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND Corporation; 2001 https://www.rand.org/pubs/monograph_reports/MR1269.html [accessed 01.02.2025].
[20] Moskowitz CH, Schöder H, Teruya-Feldstein J, Sima C, Iasonos A, Portlock CS, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced-stage diffuse large B-cell lymphoma. J Clin Oncol 2010;28(11):1896–903.
[21] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059–68.
[22] Dührsen U, Müller S, Hertenstein B, Thomssen H, Kotzerke J, Mesters R, et al. Positron emission tomography-guided therapy of aggressive non-Hodgkin lymphomas (PETAL): a multicenter, randomized phase III trial. J Clin Oncol 2018;36(20):2024–34. Epub 2018 May 11. PMID: 29750632.
[23] Kostakoglu L, Martelli M, Sehn LH, Belada D, Carella AM, Chua N, et al. End-of-treatment PET/CT predicts PFS and OS in DLBCL after first-line treatment: results from GOYA. Blood Adv 2021;5(5):1283–90.
[24] Chaganti S, Fox CP, Maybury BD, Burton C, Barrington SF, Illidge T, et al. Management of relapsed or refractory large B-cell lymphoma: A British Society for Haematology Guideline. Br J Haematol 2025;206(6):1593–603.
[25] Eertink JJ, Burggraaff CN, Heymans MW, Dührsen U, Hüttmann A, Schmitz C, et al. Optimal timing and criteria of interim PET in DLBCL: a comparative study of 1692 patients. Blood Adv 2021;5(9):2375–84.
[26] Bock AM, Mwangi R, Wang Y, Khurana A, Maurer MJ, Ayers A, et al. Defining primary refractory large B-cell lymphoma. Blood Adv 2024;8(13):3402–15.
[27] Bücklein V, Perez A, Rejeski K, Iacoboni G, Jurinovic V, Holtick U, et al. Inferior outcomes of EU versus US patients treated with CD19 CAR-T for relapsed/refractory large B-cell lymphoma: association with differences in tumor burden, systemic inflammation, bridging therapy utilization, and CAR-T product use. Hemasphere 2023;7(8):e907.. Erratum in: Hemasphere. 2023 Oct 31;7(11):e982.
[28] Società Italiana di Ematologia. Linee Guida SIE. https://www.siematologia.it/linee-guida-sie.html (2023). [accessed 01.02.2025].
[29] Stella F, Chiappella A, Casadei B, Bramanti S, Ljevar S, Chiusolo P, et al. A multicenter real-life prospective study of axicabtagene ciloleucel versus tisagenlecleucel toxicity and outcomes in large B-cell lymphomas. Blood Cancer Discov 2024;5(5):318–30.
[30] Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. Am J Hematol 2017;92(8):806–13.
[31] Dreyling M, Klapper W, Rule S. Blastoid and pleomorphic mantle cell lymphoma: still a diagnostic and therapeutic challenge!. Blood 2018;132(26):2722–9.
[32] Armitage JO, Longo DL. Mantle-cell lymphoma. N Engl J Med 2022;386(26):2495–506.
[33] Eyre TA, Bishton MJ, McCulloch R, O'Reilly M, Sanderson R, Menon G, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. Br J Haematol 2024;204(1):108–26.

[34] Rule S, Dreyling M, Goy A, Hess G, Auer R, Kahl B, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis. Haematologica 2019;104(5):e211–4.
[35] McCulloch R, Lewis D, Crosbie N, Eyre TA, Bolam S, Arasaretnam A, et al. Ibrutinib for mantle cell lymphoma at first relapse: a United Kingdom real-world analysis of outcomes in 211 patients. Br J Haematol 2021;193(2):290–8.
[36] Villa D, Jiang A, Visco C, Crosbie N, McCulloch R, Buege MJ, et al. Time to progression of disease and outcomes with second-line BTK inhibitors in relapsed/refractory mantle cell lymphoma. Blood Adv 2023;7(16):4576–85.
[37] Stella F, Chiappella A, Magni M, Bonifazi F, De Philippis C, Musso M, et al. Brexucabtagene autoleucel in-vivo expansion and BTKi refractoriness have a negative influence on progression-free survival in mantle cell lymphoma: results from CART-SIE study. Br J Haematol 2025;206(2):644–51.
[38] Davis DD, Ohana Z, Pham HM. Pirtobrutinib: A novel non-covalent BTK inhibitor for the treatment of adults with relapsed/refractory mantle cell lymphoma. J Oncol Pharm Pract 2024;30(1):182–8.
[39] Topp MS, van Meerten T, Houot R, Minnema MC, Bouabdallah K, Lugtenburg PJ, et al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol 2021;195(3):388–98.
[40] Oluwole OO, Bouabdallah K, Muñoz J, De Guibert S, Vose JM, Bartlett NL, et al. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol 2021;194(4):690–700.
[41] Leslie L, et al. ZUMA-24 preliminary analysis: a phase 2 study of axicabtagene ciloleucel in the outpatient setting with prophylactic corticosteroids in patients with relapsed/refractory large B-cell lymphoma. In: Poster Presentation: P1159 EHA; 2024.
[42] Locke FL, Siddiqi T, Jacobson CA, Nikiforow S, Ahmed S, Miklos DB, et al. Impact of vein-to-vein time in patients with R/R LBCL treated with axicabtagene ciloleucel. Blood Adv 2025;9(11):2663–76.
[43] Di Rocco A, Galli E, Sorà F, et al. The CARCHAT project and the Regione Lazio Lymphoma Network "RELLI" hub-and-spoke model for managing CAR-T patients journey. In: 51st Congress of the Italian Society of Hematology, Milan, Italy; 2024.
[44] Bramanti S, Chiappella A, Di Rocco A, Sorà F, Ateri E, Balzano RL, et al. CARe-Together: the first Italian Patient Support Program for CAR T patients. In: Poster ID number 6675676 presented at 7th EHA-EBMT European CAR T-cell Meeting; 2025. [accessed 01.03.2025].