HEMATOLOGY

## CARE™ GUIDANCE

# INTEGRATION OF CAR T IN DLBCL

**VERSION 1.0**

CONTENT AS OF JUNE 2021

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## CARE™ GUIDANCE

# INTEGRATION OF CAR T IN DLBCL

**VERSION 1.0 -** CONTENT AS OF JUNE 2021

The aim of this guidance is to provide education on(chimeric antigen receptor T-cell therapy (CAR T) options and considerations for effective integration of these therapies in Canadian practice, with emphasis on where CAR T fits in current paradigms, candidates for CAR T referral and post treatment monitoring and adverse event management.

**This is the 1st iteration (V.1) of the CARE™ CAR T in DLBCL Guidance for 2021.**


**Faculty involved**

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## BACKGROUND

On February 19th, 2021 a needs assessment was initiated with Canadian Hematologists to gather current perceptions and practice patterns with CAR T in lymphoma.

Response gathered from the assessment identified several needs with Canadian centric education on CAR T use and patient management being top priorities.

Please refer to Appendix B for the response data collected.

## CONTENT IN THIS REPORT PROVIDES UPDATES ON:

# First… A Quick Primer on CAR T

### What is CAR T-cell therapy?

T- cells play significant role as immune effectors. Modification of a patient's own T cells facilitates their identification of cancer cells with subsequent activation of the T cell effector mechanism and proliferation. The result is targeted killing of cancer cells.

The starting material for the manufacture of the CAR-T product comes from the patient whose viable T cells are then genetically modified. Currently, only autologous CAR-T cell products are available for clinical use outside of clinical trials, however work is underway with the potential of having allogeneic cell products in the future.

### What is Approved in Canada Currently?

There are 2 CAR T agents currently Approved for use in Canada:

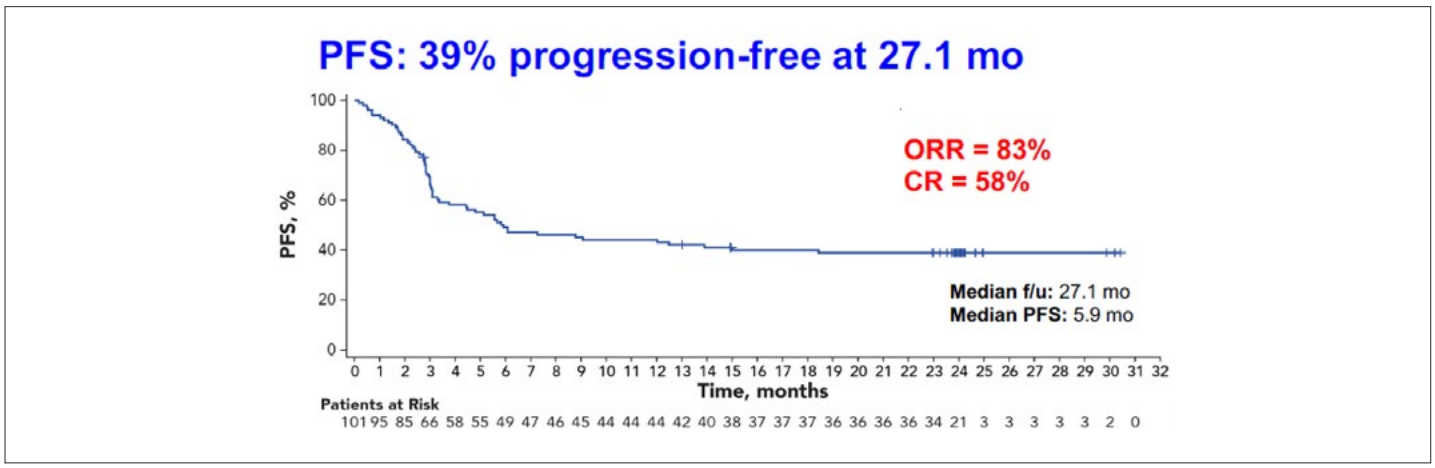
- Axicabtagene ciloleucel (Yescarta; Axi-Cel)- CD19/CD3z/CD28
- Tisagenlecleucel (Kymriah; Tisa-Cel)- CD19/CD3z/4-1BB

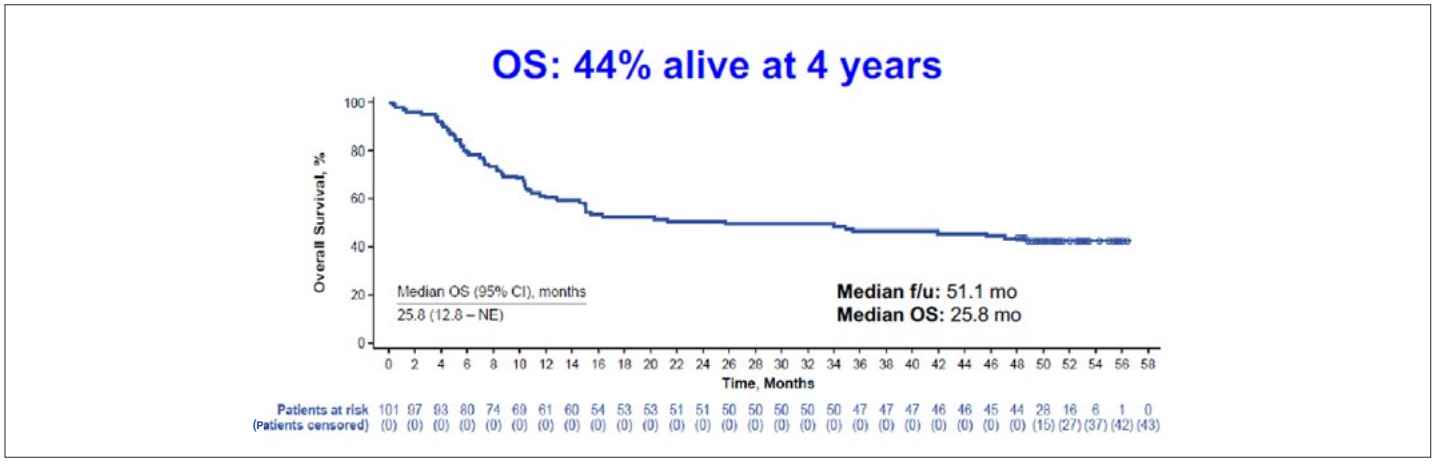
*Lisocabtagene maraleucel, another CD19-directed CAR T therapy, is currently under review with Health Canada and expected to gain approval for Relapsed or Refractory LBCL before the end of this year.*

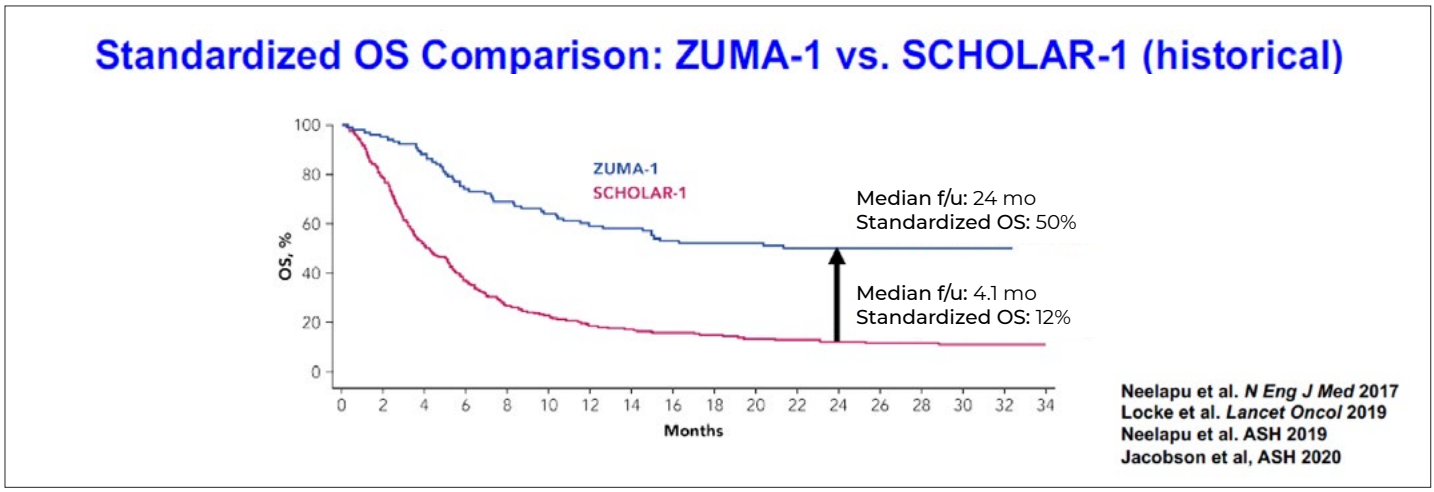
### Relevant Clinical Trial Highlights:

**Axi-Cel:**

ZUMA-1. Safety and Efficacy of KTE-C19 in Adults with Refractory Aggressive Non-Hodgkin Lymphoma

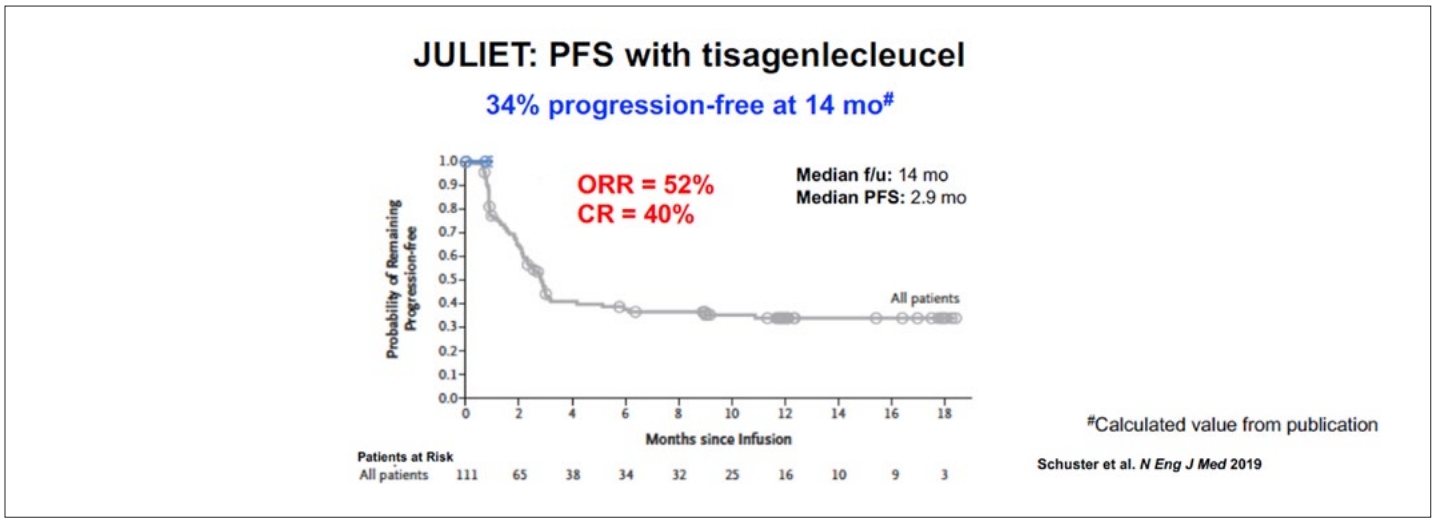


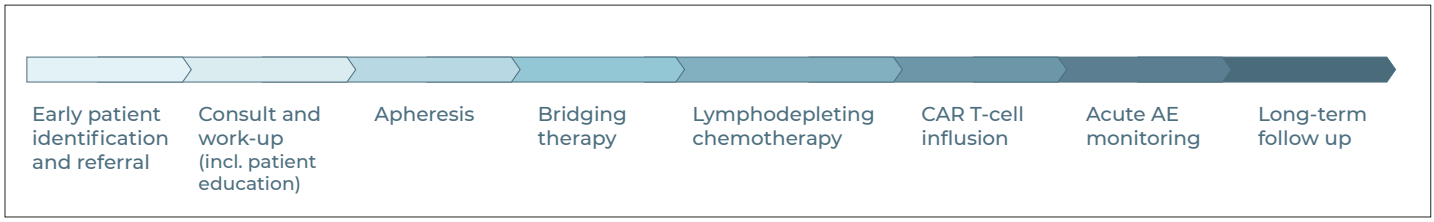



**Tisa-Cel:**

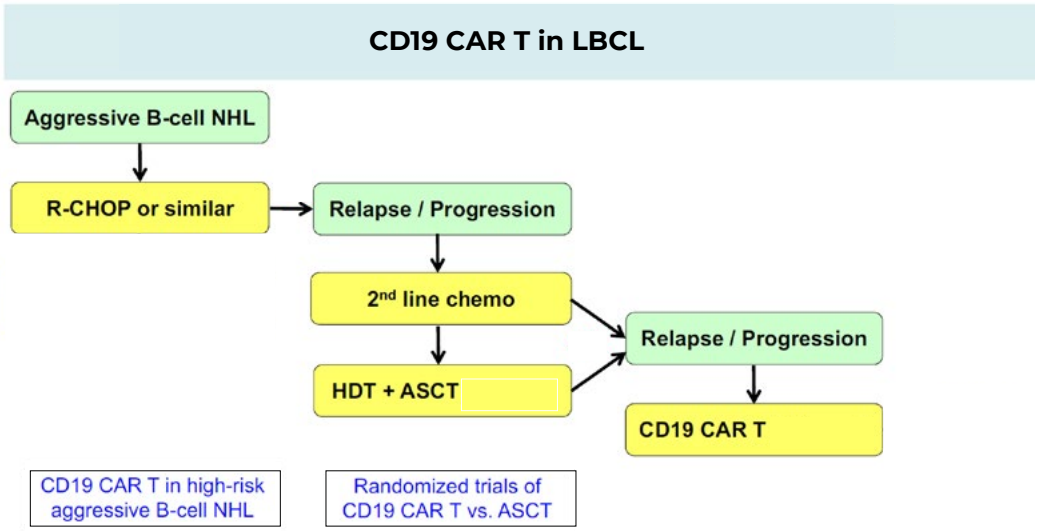
JULIET. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma




## Stages of CAR T-Cell Therapy



# Considerations for Integrating CAR T in Current DLBCL Practice




*Adapted from S. Neelapu, WHU 2021 Presentation.*
*Access on Demand here: https://careeducation.ca/dr-sattva-neelapu-cell-therapy-whu-2021/*

### Which Patients are candidates for CAR T?

Referral for CAR T therapy should be considered in patients who have relapsed DLBCL after 2 therapies. Specific indications include DLBCL not otherwise specified, high grade B-cell lymphoma, high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double hit by FISH), DLBCL arising from follicular lymphoma, as well as Primary mediastinal large B-cell lymphoma (PMBCL).

- Includes relapse after autologous stem cell transplant (ASCT)
- Includes patients with chemo-refractory disease who are not eligible for ASCT
- Patients who may not have been candidates for ASCT due to age, fitness or co-morbidities may potentially still be candidates for CAR T therapy
- Diagnoses not specifically included in the Health Canada approved product monographs are not eligible for consideration.

*Additional Notes:*
Relapsed disease: indicates a partial or complete response to the last line of therapy and subsequent progression before enrolment.
Refractory disease: indicates progressive or stable disease as the best response to the last therapy before enrolment or response status unknown.

| Factor | Comments/Questions |
|---|---|
| **Indications** | • Does the patient have relapsed/refractory B-cell lymphoma after > 2 lines of systemic therapy?<br>• Does the patient meet the criteria for a clinical trial? |
| **Kinetics of disease progression** | • Would the patient be able to go through leukapheresis (without immediate use of steroids/ chemotherapy) and remain stable until the T-cell infusion (3-4 wks)?<br>• Does the patient need alternative therapy prior to CAR T-cell therapy consideration? |
| **Immediate prior therapy** | • How would this affectthe ability to successfully manufacture CAR T-cells (i.e., obtain sufficient numbers of T-cells and expand)? |
| **Performance Status** | • ECOG 0-2 |
| **Concomitant immunosuppressive therapy** | • Can this be safely stopped prior to collection? |
| **Active infection** | • Higher risk of complications if patient experiences Cytokine Release Syndrome (CRS) |
| **Non-disease related comorbidities** | • i.e. severe cardiac dysfunction, active symptomatic neurologic symptoms<br>• Patients with primary central nervous systems (CNS) lymphoma are not candidates. However, CNS involvement can be treated and eradicated and then the patient may safely move forward |

### *"Early referral/discussion with transplant centre is important"*

Early referral and timely treatment with CAR T cell therapy may improve outcomes by:

- Planning appropriate and timely bridging therapy if required to lower tumor burden
- Lessening the likelihood of having aggressive and refractory disease (relapsed rather than chemo-refractory)
- Reducing number of prior lines of therapy and increasing likelihood of having more fit T cells for CAR T manufacturing

**Additional Considerations for Referring Care Team**

Patient education should include:

- That they may need transfusion of red cells or platelets to meet criteria to get on the apheresis machine and that a minimum absolute lymphocyte count of 100 is also preferred for successful collection
- The potential for placement of a temporary central venous catheter, as well as the risks for hypotension, dizziness, and paresthesia due to hypocalcemia
- Manufacturing of the CAR T product may take 2.5-4 weeks in some instances and that each product must undergo strict quality control before it can be released for infusion (not all products pass the release criteria).

Providers, nurses, and other aHCPs should:

- Review the patient's medications to determine if a meeting is needed with a PharmD. Certain medications, such as anticoagulants or multiple antihypertensives, may need to be placed on hold.
- Have a complete medical history and physical performed- It is important to consider the original and most recent diagnostic scans, biopsies, health history, and medication list.
    - It's also recommended for patients to be screened for infectious diseases such as hepatitis A, B, and C and HIV, as well as other comorbidities using Echo, MUGA, or PFTs as required, so that a plan can be developed to address any infections or risk factors.
- Monitor patients closely for symptoms and pain management needs, as well as for potential side effects, if they receive bridging therapy. Patients with aggressive disease can decline to a point where it is no longer safe to administer the cells.

## Posttreatment Monitoring and AE Management

Inpatient and outpatient post-treatment monitoring includes adverse event assessments, count recovery (Infection), response to therapy, potential long-term adverse events.

Acute toxicities associated with anti-CD19 CAR T cell therapy:

- CRS: characterized by fever at the onset; symptoms can be progressive and, in addition to fever, may include capillary leak/ hypoxia, end organ dysfunction, and hypotension
- ICANS: toxic encephalopathy with symptoms of mild headaches, confusion, and delirium; expressive aphasia; occasional seizures; and rarely, cerebral edema; can occur in the presence or absence of systemic CRS

Table. CRS and NT Rates in ZUMA-1 and JULIET

| Study | N | CRS All Grades | CRS Grade ≥3 | NT All Grades | NT Grade ≥3 | Toci usage | Steroid usage | Ref |
|---|---|---|---|---|---|---|---|---|
| **ZUMA1** | 108 | 92% | 11% | 67% | 32% | 45% | 29% | Neelapu et al, NEJM 2017 |
| **JULIET** | 111 | 58% | 22% | 21% | 12% | 15% | 11% | Schuster et al, NEJM 2019 |

- Lee criteria used for CRS grading on ZUMA1
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading

Strategies with earlier steroid intervention has the potential to reduce the rate of severe CRS and neurologic events (based on the updated results from a separate ZUMA-1 safety management study- Cohort 4). In this cohort analysis there was numerically lower rates of grade ≥3 CRS (2%) and neurologic events (17%) than reported in the registrational cohorts of ZUMA-1 (13% CRS, 31% neurologic events).

These occur in most circumstances while patient is admitted and observed after CAR T-cell infusion BUT may be delayed and occur after patient discharged (referral centres may become involved). Most toxicities resolve by 3-4 weeks following CAR T cells infusion.

***"However, different products have different timelines with acute toxicities"***

Table. Time Course of Toxicities with Approved CAR T Therapies

| Number of Days (Range) | CRS | | Neurologic AEs | |
|---|---|---|---|---|
| | Median Time to Onset | Median Duration | Median Time to Onset | Median Duration* |
| Axicabtagene ciloleucel | 2 (1-12) | 7 (2-58) | 4 (1-43) | 17 |
| Tisagenlecleucel | 3 (1-51) | 8 (1-36) | 6 (1-359) | 14 |

**With tisagenlecleucel, encephalopathy has been observed to last up to 50 days.*

***"It is critical to maintain open dialogue with the transplant site in the early discharge period"***

Late Toxicities after CD19 CAR T:

- Late neurotoxicity events including transient aphasia and seizures have occurred up to 2 months after CAR T therapy. Patients are advised not to drive or operate machinery for 8 weeks post CAR T cell therapy.
- Prolonged ≥ grade 3 cytopenias beyond day 30 observed in ~30% of patients
- B-cell aplasia occurs in almost all patients and can persist >1 year although durable remissions can be seen in patients who recover B cells
- Infections (delayed) occurred in up to 55% of patients in pivotal trials often after discharge from hospital

# Appendix A. Additional Resources

## CARE™ Resources

**WHU 2021 On Demand Videos and Presentation Slides**
Incl. presentation on CAR T Therapy in Lymphoma from international expert Dr. Sattva Neelapu

https://careeducation.ca/reports/whu-2021-videos-on-demand/

**CARE™ Education Program at ASH 2020 On Demand Videos, Presentation Slides, and Conference Reporting**

https://careeducation.ca/events/join-the-conference-care-at-ash-2020/

**CARE™ Community Allied Health CAR-T Primer Video**

https://www.youtube.com/watch?v=Dt-tWxaKhmw

## Other resources/ reference materials

**Cancer Care Ontario- CAR T-cell Therapy Enrolment Process and Forms**

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/hematologic/car-t-cell-therapy-enrolment

**CADTH- Optimal Use Report Axicabtagene Ciloleucel for Large B-Cell Lymphoma**

https://www.cadth.ca/sites/default/files/pdf/car-t/ct0002-ipe-report.pdf

**CADTH- Optimal Use Report Tisagenlecleucel for ALL and DLBCL**

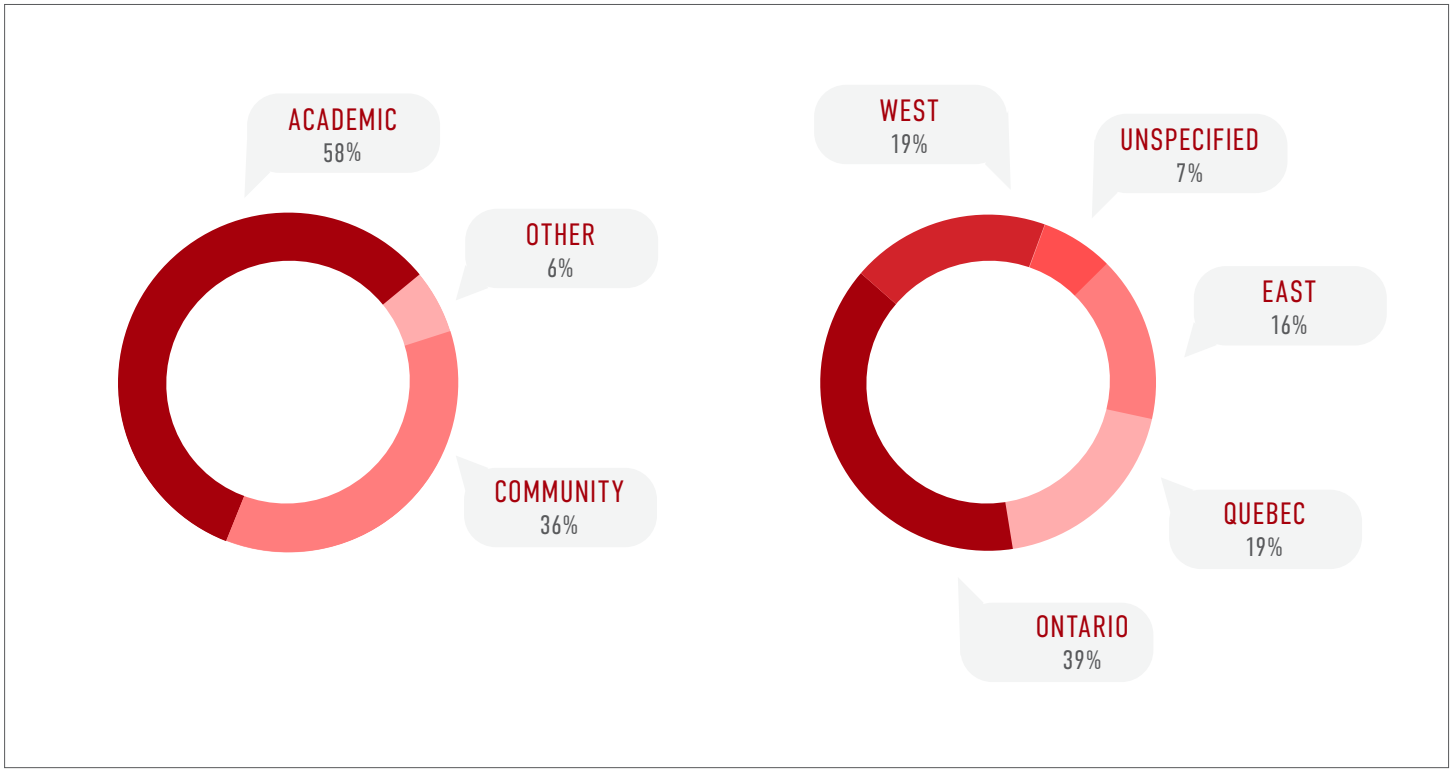
https://cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-ethics-and-implementation-jan2019.pdf

**CAR T-Cell Therapy: How Does It Work- Video from Dana-Farber Cancer Institute**

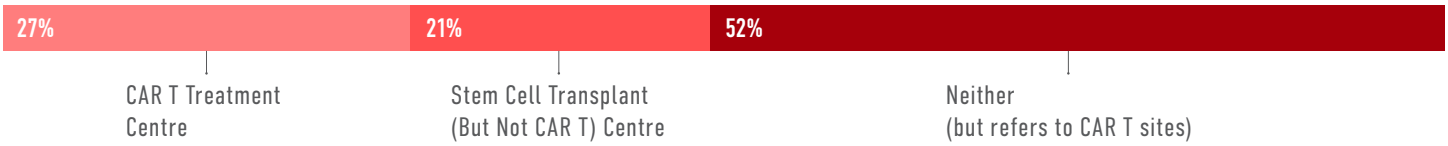
https://www.youtube.com/watch?v=OadAW99s4Ik

# Appendix A. Additional Resources

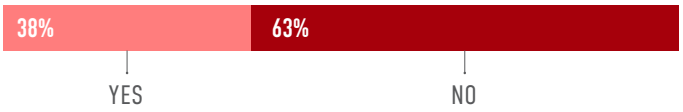
## Responder Demographics




**Is the Centre a:**



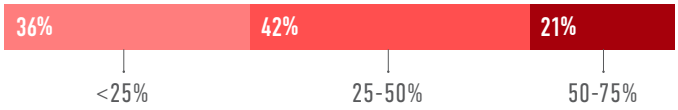

**If you work in a CAR T treatment centre (n=24), do you personally treat patients with CAR T therapy?**




**On average, how many relapsed/refractory (R/R) DLBCL patients do you manage per year?**


**On average, how many newly diagnosed DLBCL patients do you manage per year?**


**Approximately what portion of these patients relapsed after Autologous stem cell transplant?**



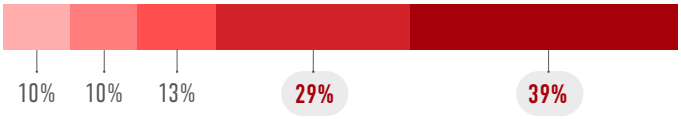
# SURVEY DATA ANALYSIS

1 Strongly Disagree
2 Disagree
3 Neutral
4 Agree
5 Strongly Agree

**[1] To what extent do you agree with the following statements:**

**[A]** I am aware of clinical trial data on efficacy and safety of HC approved CAR T agents:

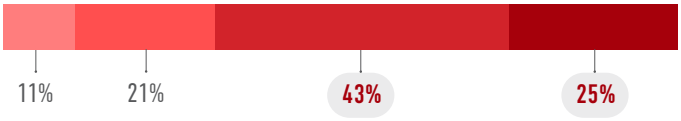
Axicabtagene ciloleucel




Tisagenlecleucel

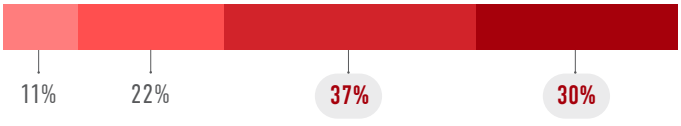

**[B]** I view CAR T as a potentially curative therapy option


**[C]** I am confident identifying patients who are candidates for referral for CAR T treatment

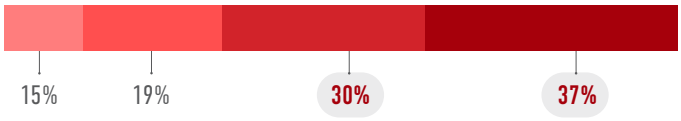



**[D]** I know how to navigate the process to enroll/refer patients for CAR T treatment in my region

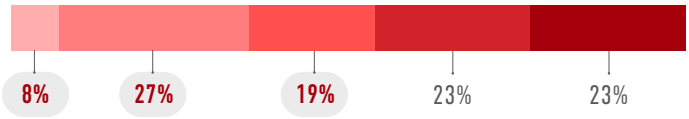

**[E]** I understand the steps and timeline of CAR T delivery



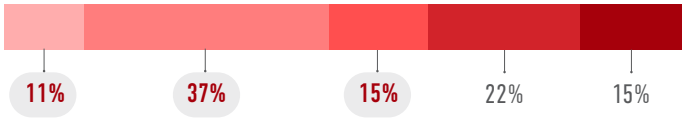

**[F]** I understand which steps of CAR T therapy are delivered at my centre vs. the referral centre



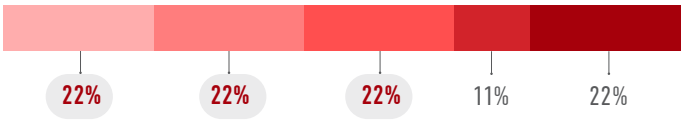

**[G]** All members of my treatment team understand the steps and timeline of CAR T delivery



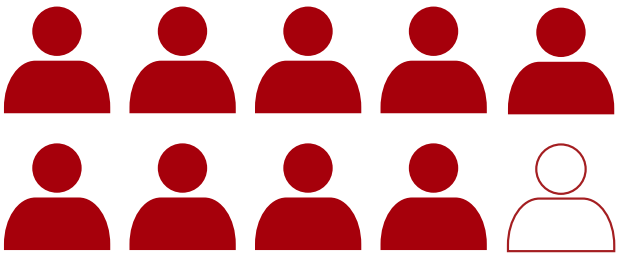

**[H]** All members of my treatment teams are comfortable discussing all facets of CAR T treatment with patients and caregivers




**[I]** My treatment team/clinic is prepared/set-up to provide post-CAR T treatment care



**[2] Do you have standard algorithms for the treatment of front-line DLBCL?**



**9 IN 10** RESPONDERS **HAVE STANDARD ALGORITHMS FOR TREATMENT**

**Specific Regimen Listed in Response Included:**

**[97%] R-CHOP**

[24%] Dose Adjusted (DA) EPOCH- R

[3%] R hyped VAP (post R CHOP)

[3%] R-DHAC, R-ICE, Auto

[3%] Salvage GDPR-R + auto transplant following R-CHOP first line

[3%] R-CHEOP

**[3] Do you have standard treatment algorithm for first relapse DLBCL?**


**Specific Regimen Listed in Response Included:**

**[64%] R-GDP ± ASCT**

**[24%] GDP ± ASCT**

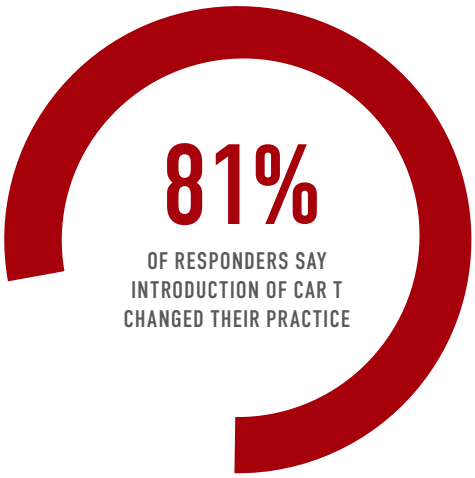
[8%] Palliation

[4%] DICEP + ASCT

[4%] R-CHOP

[4%] For unfit patients, we make a compassionate request for Pola-Benda, but often the access is too long, and the patient ends up in palliative care before having access

**[4] Has the Introduction of CAR T in Canada changed your practice?**

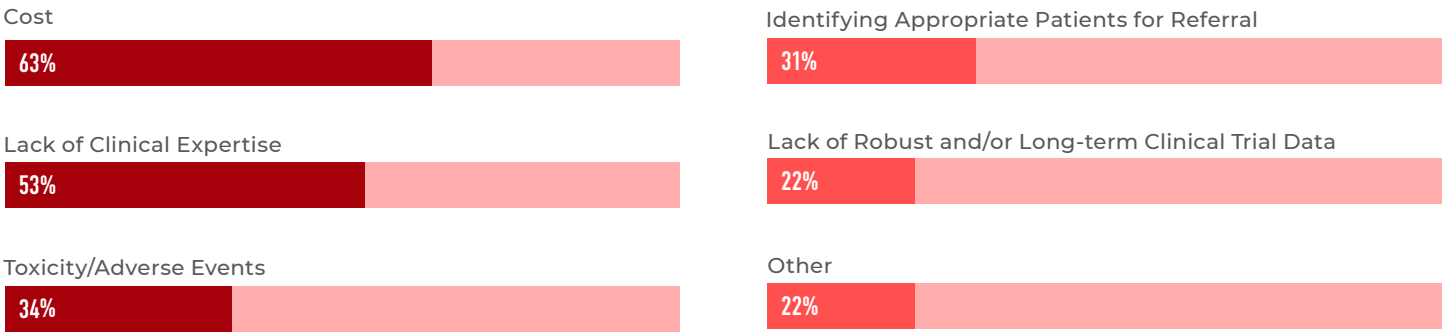



**Specific Regimen Listed in Response Included:**

- New option for relapsed patients post-ASCT or those that are not candidates for transplant [55%]
- Shifted relapsed post transplants patients from palliative care to CAR T
- More patients willing to go do it given no international travel
- These patients previously went into clinical trials or were treated palliativelyR-CHOP

**[5] What do you perceive as the biggest challenges/concern for integrating CAR T strategies in routine practice?**

(Note: Responders were asked to choose all answers that apply so response data adds to greater than 100%)

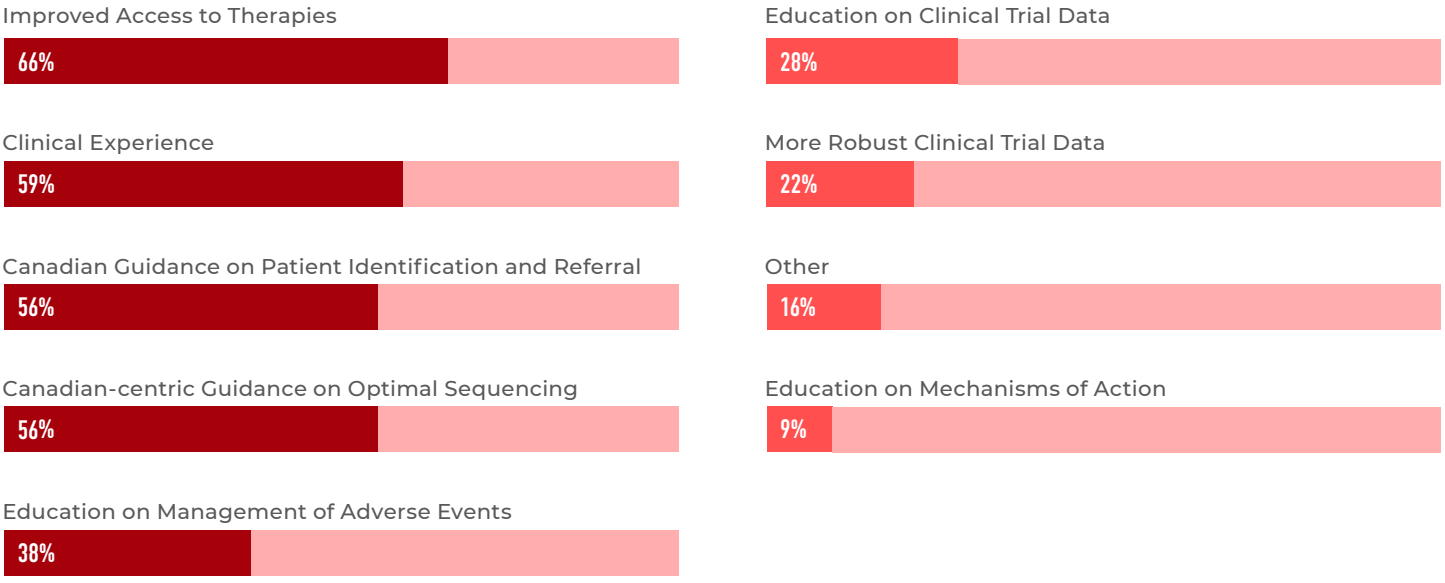



**'Other' responses:**

- Access to CAR T centre and wait time for manufacturing
- Access
- None
- Disease control ahead of/during CAR T manufacturing
- Some centers can administer it, but with COVID (and even before the pandemic) they are overwhelmed, and transfers are not always fast. (This is not a criticism of these centers, but an observation that resources are limited).

**[6] Which of the following do you feel are most needed to improve adoption of CAR T therapy?** (Please select all that apply)

(Note: Responders were asked to choose all answers that apply so response data adds to greater than 100%)




**'Other' responses:**

- Resources to provide the clinical care
- Streamlining referral process
- Reduction of cost

# CARE™ HEMATOLOGY FACULTY

The CARE™ (Community. Academic. Research. Education) Faculty is a Pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

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