CADTH OPTIMAL USE REPORT

Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma -Patient Input Submissions

Patient group input submissions were received from the following patient groups.
Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Leukemia and Lymphoma Society of Canada (LLSC) and Ontario Parents Advocating for Children with Cancer (OPACC)
Lymphoma Canada

CADTH received patient group input for this review on or before June 20, 2018

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Tisagenlecleucel-T (Kymriah) CTL019 CAR T-Cell Therapy (Novartis)**
Name of the Patient Group	**Childhood Acute Lymphoblastic Leukemia**
Author of the Submission	**Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Leukemia and Lymphoma Society of Canada (LLSC) and Ontario Parents Advocating for Children with Cancer (OPACC)**

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)
Ac2orn is committed to advocating for translational research and effective treatments to realize the goal of curing childhood, adolescent, and young adult cancers.
http://www.curesforourkids.com/

Leukemia and Lymphoma Society of Canada (LLSC)
The mission of The Leukemia & Lymphoma Society of Canada (LLSC) is: Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.
http://www.llscanada.org/

Ontario Parents Advocating for Children with Cancer (OPACC)
OPACC will be the leading voice and expert resource for families and organizations navigating the childhood cancer journey.
http://www.opacc.org/

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Information was gathered through one survey, provided in both English and French and jointly created by Ac2orn, LLSC and OPACC. The survey was created and made available to respondents in March 2018 and closed in June 2018. Four one-on-one interviews were also conducted.

An online survey was posted using Survey Monkey in both French and English and distributed by Ac2orn, LLSC, and OPACC through various social media channels and directly by email. The survey asked for input from patients and families who were treated for childhood leukemia, and who may or may not have had experience with CTL019.

There were 115 responses to the English survey, with 59 complete responses. There were 3 responses to the French survey. There were a total of 10 respondents with direct experience with CTL019.

The majority of respondents identified the location of their primary residence as Ontario (96 responses). Quebec (6 responses), Alberta (4 responses), and British Columbia (3 responses), Nova Scotia (2 responses) and Saskatchewan (2 responses) were also represented. There was one response from the United States and one response from an international respondent. Overall, the survey respondents were Ontario centric; however, there was representation from across Canada overall.

The majority of respondents were the parent of the patient (104 responses). 5 respondents were the actual patients, 2 respondents were an immediate family member of the patient, 1 respondent identified as the legal guardian of the patient and 4 stated other.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Pre-Diagnosis:

Children diagnosed with leukemia varied at their age of diagnosis. The following is the breakdown for the respondents by prevalence from most to least:

1. 2 years old
2. 3 years old
3. 10-14 years old
4. 4 years old
5. 5 years old

6. 8 years old
7. 15 years or older
8. 6 years old
9. Under 1 years of age
10. 9 years old
11. 1 year old
12. 7 years old

The main symptoms experienced prior to diagnosis included low energy level, pain, fevers, bruising, weight loss or gain, headaches, nausea and vomiting, skin changes, constipation, and other side-effects.

Indirect treatment side-effects and impact on quality of life included (in order from most prevalent to least prevalent):

1. Changes to physical activity
2. Eating challenges
3. Mental health and overall happiness
    - Withdrawn from normal activities and engagement with family and friends
4. Anxiety
5. Educational development
    - Not able to attend school
    - Scattered thinking and delayed cognitive development
6. Social development

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers. Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Experiences with Frontline Therapy:

Diagnosis:

Post initial diagnosis and during frontline therapy, the following treatments were experienced in the order of most common to least:

1. Chemotherapy
2. Maintenance Therapy
3. High Dose Chemotherapy
4. Radiation
5. Surgery

6. Steroid Treatment
7. Stem Cell Transplant
8. Immunotherapy

Direct treatment related side-effects and their impact (in order from most prevalent to least):

1. Neutropenia (low white blood cell counts)
2. Hair loss
3. Movement/ability to take part in physical activities
4. Fevers
5. Nausea
6. Pain
7. Vomiting
8. Constipation
9. Neuropathic pain
10. Organ damage
11. Impact to eye-sight

Respondents also commented on issues relating to steroid treatment with mood changes and anxiety, and mobility changes with paralysis and muscle stiffening.

Many respondents commented on both the negative and positive aspects of frontline treatments:

> "Negative: - major weight loss (20kg) – mouth sores - paralysis - reactions (rashes, inflamed hands) - weakness in extremities of hands and feet - weakness in legs (lost the ability to walk) - infections due to low neutrophil counts - nausea and reflux - back pain from lumbar punctures Positive: - gained an new perspective - became more appreciative."

> "I liked how **most of her treatment was done as a day patient** limiting how often she had to sleep in the hospital. She did have some planned an unplanned admissions, but for the most part, treatment was done in the day hospital or with oral medication at home."

> "**Very difficult**. Nausea, vomiting, severe weight loss, fatigue, falls, muscle pain, hair loss twice, bruising, general pain, stress/fear, loneliness, isolation, inability to run or do normal kid activities."

> "Frontline treatment is **very hard**. Positive experience was all of the care team was great at explaining and offering different avenues of support for all of us as a family and not just for our child. Negative experiences is the process as a whole, the actual experience is hard. Being away from home I think was the most difficult part."

> "MRD negative after 4 weeks, 3 years 4 months of treatment, several admissions due to fever, almost no vomiting or discomfort. Moods changes due to steroids. Leg movement impacted and required physiotherapy. **Difficulty administering some home medications** due to age, frequency of meds, amount of and taste of meds. Increased lethargy throughout treatment."

"Frontline was very difficult. **Inpatient days during frontline totalled 232 days**. Exhaustion for both the patient and the caregiver. The negatives are as follows: - side effects of treatment, including but not limited to: blood clots, steroid induced diabetes, broken bones, neurotoxicity from IT MTX, seizures, vision issues, severe mucositis, weight loss, steroid induced rage, lumbar puncture headaches, severe anxiety around procedures. There was also some cognitive/mental regression as she was out of school for a full year. Social regression also. Mentally, physically and emotionally draining. Caregiver's inability to continue to work. Positives were minimal. She has managed to stay in remission thus far and for that we are grateful. Our experiences with the nursing staff at our hospital has been nothing but incredible. There has been little extra costs incurred by our family as a result of treatment."

"It was **very scary and heartbreaking** to watch your child get so sick from the chemo and not have any options."

"The worst side effects for my child was kidney function problems early in treatment that was resolved with albumin transfusion, and an extreme sensitivity to Vincristine that led to much smaller doses than called for on study but still caused neuropathy and foot drop that later needed double Achilles surgery and **still causes problems 5 years post treatment**. Best experiences were with staff and professionals at [hospital]."

Difficulties in Accessing Treatment:

For almost all of the respondents, accessing treatment was not an issue. Most respondents were able to receive care at a major centre; however, there were two comments from respondents about living in a rural area which required a long drive into the primary care hospital. Most respondents spoke very positively about their primary care hospital and the treatment that they received. One respondent noted: "Access to health care services and therapy we're more readily available. We unfortunately had move to the US after a year if treatment and health care services are not as readily available and not as good as Ontario!"

Respondents did comment on challenges for caregivers and their inability to continue working while their child was on treatment. The following comments were noteworthy:

"Mentally, physically and emotionally draining. Caregiver's **inability to continue to work**."

"Life was a big struggle, and we just did it. But I (the dad) had some weight gain, and some depression which linger to this day, as well as employment difficulties from being out of the job market at an advanced age (nearing 60 this year). **We are impoverished, and don't have good job prospects**; the mom and dad are separating, which stems partially from the relationship difficulties of constant stress in caring for our child."

"1 parent took an **unpaid leave of absence** to handle treatment and care. Hospital stays required 24 hour supervision by a parent making the maintenance of life and home very difficult, including parenting of other children."

"**Our family has a whole had a lower quality of life and struggled financially**, socially and our general health all together."

Difficulties in Receiving Treatment:

Some respondents mentioned issues with receiving treatment. For example, two respondents commented on the challenges with the formulation of medications:

> "It had it's ups and downs. We finally had to **change from oral suspension to pills as our son could not tolerate the suspensions and consistently vomited following having to consume the large dosages as required**. The steroids changed our son into being a very angry boy, very quickly and all the pokes and prods made for one very anxious and nervous and defiant child."

> "He was too young to take pills, **so we ground it up and he had to swallow it**. He avoided it lots, and was prone to heavy drama, especially when he was on steroids."

In general, one respondent noted "difficulty administering some home medications due to age, frequency of meds, amount of and taste of meds."

Experiences with Relapsed Therapies:

For relapsed leukemia, respondents noted that they have tried the following therapies (listed from most to least prevalent):

1. Chemotherapy
2. Radiation
3. Bone Marrow Transplant
4. Immunotherapy

The following were the most common patient reported side-effects experienced with treatments for relapse therapies:

1. Low platelets
2. Hair loss
3. Low white blood cell count
4. Fatigue
5. Nausea
6. Vomiting
7. Low red blood cell count
8. Infections
9. Diarrhea
10. Constipation
11. Allergic reactions
12. Mobility changes

13. Respiratory and breathing issues
14. High and low blood pressure

Respondents provided comments about their experiences with relapsed leukemia:

> "It was **3 1/2 years of torture**. Told the BEST kind of Leukemia to have was ALL B Cell. Constant challenges such as, how to pick him up without hurting him. Feeding tubes, diarrhea, fevers. Too many antibiotics as a regimen."

> "2nd relapse treatment **highly complicated** with viral and bacterial infections. High amounts and variety of antifungal, antibacterial, antibiotic meds used. There are too many challenges to list here, but include financial, organizational, emotional, and of course medical."

> "There really was **no set treatment plan**. No one knew what to do once the first round of chemo was ineffective & the cancer actually grew, we did a trial treatment that they found....we felt lost, helpless and completely let down by the medical world."

> "The first relapse gave us the ability to get into remission with use of intense chemo and radiation. It is **scary how much poison has been tossed into his body under the guise of chemo**. Radiation of his skull is obviously another large concern. He was unable to walk due to infections and needed a wheel chair and walker for months for mobility. He is behind in reading and writing. His joints have limited range."

> "Spent **longer time in hospital** and as such child developed some behaviour issues that were difficult to manage at times."

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Respondents provided a great deal of insight into the challenges faced when in frontline treatment for leukemia. The most common theme in the majority of the comments provided was the challenge of isolation due to the risk of their child getting an infection because of low white blood cell counts. Respondents commented on the changes to their daily life, being separated from family, not being able to engage in public events, their child not attending school regularly, changes in relationships with family and friends, and being away from home. The following are some comments provided by respondents which illustrate these points:

> "The treatment requires a lot of time spent at hospital and away from normal childhood activities. My son had many extreme side effects so **missed lots of school hence was isolated from friends** for most of the first two years of treatment. He also reacted physically and mentally to the drugs, including medication induced psychosis. Once he returned to attending more school he routinely missed a week at a time due to fever and other symptoms if he caught a cold."

> "Being a teenager at school having cancer **became difficult to fit in**. Loss of extracurricular sports due to low platelets. Hospitalized many times due to side effects of treatment. Isolation."

> "We were in the hospital so much and apart from my husband and our other son. We felt isolated from the rest of the world. **We would finally get to go home and then didn't know how to be at home**. Just when we were getting used to home life, we'd be admitted again."

> "It's difficult to identify whether our son experiences some of the more common side effects as he is unable to verbalize what is happening. As a parent, this life is devastating for reasons that don't need explanation. **Time spent admitted to hospital is extremely depressing**. Time spent as an outpatient makes you feel like an outsider knocking on the window wanting attention."

> "My quality of life has deteriorated to the level of needing my parents to push me in a wheel chair, my mom helps me with my personal hygiene. **I have had to give up going to College**."

When making decisions about a new cancer treatment, the most important factors that respondents consider are (from most to least prevalent):

1. Quality of life
2. Physician recommendation
3. Possible impact on the disease
4. Out-patient treatment
5. Closeness to home
6. Family recommendation
7. Religious considerations

The survey asked "if you did not have CTL019 treatment, but would consider it – why would you be willing to tolerate the side effects? If you did have CTL019 treatment, why were you willing to tolerate the side-effects from CTL019 treatment?

> "If treatment has better chance at saving life (or same) and it means there is weeks or months of treatment rather than years of treatment that causes severe physical and mental disabilities we would be **willing to try**."

> "If relapse happened, and CTL19 was the best option, we would be willing to try it. **As bad as the side effects are, the outcome would be worth it**."

> "Yes I **would be willing to help my daughter tolerate the side effects** if it would significantly increase remission and survival."

> "**All treatment comes with side effects**. If the first protocol didn't do the trick we would find it difficult to go through it again rather than try something else."

> "We would have **done anything we could."**

> "Would **depend on success rate** on cure whether to tolerate side effects."

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families. How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

In choosing the CTL019 therapy, respondents noted that there weren't many options available to them when they were facing a second or greater relapse. CTL019 offered a last hope, and respondents felt that it offered significantly lower risk than going forward with a bone marrow transplant.

> "It is an easy choice when you don't have a lot of options. Early signs of this treatment were very strong. The only other remote option was a Bone Marrow Transplant by a third party donor. The **complications associated with BMT are extreme**, severe and he had been through a lot at that point. The fact that he relapsed twice in the cerebral spinal fluid did not guarantee that BMT would work."

> "Wanted **anything other than a bone marrow transplant**. It has been exciting to be a part of a clinical trial with so much amazing potential. Even though his T cells haven't persisted, he has been healthy and in remission for 6 months."

Access to CTL019 for ALL:
10 patients received the treatment through a clinical trial (all patients were from Ontario except one from Saskatchewan). An additional respondent stated that "access was denied by OHIP. We proceeded with cell collection but my daughter's sample was not enough to qualify for CAR T." The majority of respondents (8) stated that it was either normal, not difficult or not difficult at all to access the CTL019 treatment. Three respondents stated that it was difficult or extremely difficult to access the CTL019 treatment. The following are comments from respondents:

> "We were VERY VERY lucky. The clinical trial at Ste-Justine had just opened. **It was and continues to be a miracle**."

> "The main obstacle was getting provincial funding for the treatment since it was out of province. This was mostly impacting our doctors, not us. **There was significant anxiety about whether approval would be granted**."

> "The challenge was in getting my son's body in a state that it could generate enough t cells to qualify and also, rid his body of numerous infections, complications that resulted from the relapse: bacterial blood infections, flesh infections."

> "We had to make sure she qualified to have it done, so that was **stressful with the not knowing**, but thankfully she qualified."

> "Traveling to Toronto from Saskatchewan for collection of T cells. Time and expense. Also since the treatment was offered in Philadelphia there is **time away from work, kids miss school, no family or friends, cost is a lot**."

Six respondents had to travel a long distance by airplane and to another county to receive treatment, with five respondents traveling from Ontario to the USA and one respondent traveling from Saskatchewan to the USA. Three respondents had to travel long distances by car within their home province. One respondent had to travel by airplane within their home country and one respondent was able to access the treatment at their home hospital.

In terms of access, one respondent eloquently noted: “This is the future of treatment for relapsed or refractory ALL. If I had to pay out of pocket and CAR T was twice the cost of a bone marrow transplant, I would choose CAR T every time.”

Experience with CTL019:

“Today is day 40 post CAR-T, so it hasn't been that long since she received her T cells. The first hard part was the waiting at the beginning to see if she qualified, because she couldn't be given any chemo until we found out. The second hard part was waiting for the cells to come back so she could receive them. She had to wait 2.5 months, so not bad compared to other cases. During that time she pretty much lived in the hospital because she became sick so often, and she required so many blood transfusions. She had a maintenance schedule of chemo while waiting for her cells. Things became so much better after she received her T cells. She handled everything so well. She did receive one fever after the first week, but it was for only about 24 hours on and off. As of the time of me completing this form, she has not experienced any of the severe reactions that may happen. On day 30 post CAR-T, my daughter had a bone marrow biopsy which has shown that she is in remission. I feel that it is still a bit too early to answer question 20 as it has only been 40 days, but so far CTL19 has eliminated her disease with no relapse. She no longer needs hemoglobin or platelet transfusions on a regular basis and she looks and feels great.”

Benefits Compared to Other Treatments:

Respondents made the following comments about the benefits of the CTL019 therapy:

> “My son had only a very mild reaction and spent only 1 night as inpatient due to fever. We needed a reinfusion at 7 months due to returning B cells. To sum it up, my son asked why we couldn’t have just done this in the first place (instead of the original treatment). **So far his quality of Life is much improved and his physical condition is nearly normal again after almost 8 years**.”
>
> “Excellent. It's remarkable to see the **CAR T therapy transform my son's health**. In one month he went from being very ill to his old self....just a skinnier version. The medical team was kind, caring and had a great deal of experience. Felt like we were in very good hands.”
>
> “**Compared to front line treatment, CAR T-Cell therapy is a much more pleasant experience**. Although there is still a significant investment in time, much of the inconvenience that we experienced centered around being away from home more than the actual therapy itself. There were no serious complications.”
>
> “Amazing! Finally **Hope given to the hopeless**. We are the patients really with no hope and Car T Cell has given us incredible hope when essentially there was none. His complications were very limited. He spent one night in hospital with a fever. He was a bit dizzy and a bit absent for a bit but we could not be happier with these results. HOPEFULLY this can someday become front line treatment and children (and adults) won't need to be tortured endlessly in the future!”
>
> “**Amazing**. We were well taken care of and everyone was wonderful.”

Disadvantages:

For those respondents who had the CTL019 therapy, many stated that a significant amount of expenses were covered by the pharmaceutical company; however, other respondents noted many costs associated with the CTL019 treatment. These included:

1. Automobile expenses (e.g., parking, gas, mileage, car rental)
2. Food (e.g., for parents and child when out of the hospital)
3. Accommodations (e.g., Ronald McDonald House, apartment rental, hotel)
4. Travel (e.g., airfares)
5. Medications
6. Other (e.g., professional accountant to do taxes to claim as many costs as possible)

"We've spent a total of 13 weeks in Philadelphia since the end of September 2017. Loss of wages and time away from home."

Only one respondent noted their child becoming very sick: "Pretty good although they should tell you, you WILL be so sick that you will end up in intensive care. They tell you that you might.... you WILL!"

Impact of Advantages and Disadvantages:

Respondents noted the positive impact CTL019 has had on their child's disease:

> "**1.5 years cancer free** - the longest timeframe cancer free since he was 3 - he is now 11."
>
> "Eliminated the disease for **9+ months and counting**."
>
> "**Eliminated disease** but CAR T cells have lost persistence requiring two additional infusions."
>
> "After 6 months **Still MRD negative** but b-cells returned."

Respondents who received CTL019 treatment were overwhelmingly positive about the therapy and its advantages (100%) and expressed how it has changed their lives for the better:

> "Too early to tell. We have been told that we will be trained to give our daughter an immunoglobulin injection, so that will be different. But we have already had to learn so much during the past 5.5 years of her cancer experiences that this will just be one more thing. **We would learn how to do anything to keep her healthy**."
>
> "This treatment has **exceeded my expectations**. If successful or available at a first line treatment, I would highly encourage it to others."
>
> "**Life changing**!! My son is healthy right now even though the future is uncertain. It's truly and medical miracle."
>
> "We were able to **regain a higher degree of normalcy** than we would have had we stayed on the normal course of chemo treatment. Being part of the trial and having to be away from our home city for an extended period was a challenge, but overall the general level of anxiety around the leukemia challenge has gone down significantly."
>
> "POSITIVE!! This is the **best breakthrough in medicine since penicillin**. Please do not deprive those people that really have no other options. My child is enjoying being a child - imagine that!"

"It worked, life is rather normal again and **back to being a kid**!!"

"It has **improved our quality of life significantly**. Only issue is living with the anxiety that he could relapse."

Side-Effects of CTL019:

Cytokine Release Syndrome:
Most respondents did not experience this side-effect or classified it as a manageable or minor side-effect. One respondent classified it as a very serious side-effect.

Low White Blood Cell Count, Low or High Blood Pressure, Fever, Nausea/Vomiting, Pain:
One or two respondents classified the above side-effects as very serious or serious. The majority of respondents classified the above side-effects as manageable, minor, or did not experience.

"Appetite and weight loss, neutropenia and low counts that were slow to recover. After second infusion same but neutropenia lead to fever due to ParaInfluenza 3 and PJP pneumonia with long hospital stay."

"Severe drop in blood pressure during CRS nearly killed my son. We were very VERY lucky."

Dizziness, Confusion, Headache, Low Platelet Count, Low Red Blood Cell Count, Count, and Sleepiness:
Manageable side-effects but most did not experience those listed above.

"Poor appetite was hardest. Needed to keep him hydrated and eating. He also truly felt like crap. Not much made him feel better but his symptoms weren't severe."

"Some sleepiness and fever but nothing we hadn't done before. We experienced no Unexpected issues."

Comparison to Previous Therapies:

50% of respondents who received CTL109 states that they strongly agreed that CTL019 improved their quality of life. The other 50% of respondents stated that they were "neutral" about this statement.

"It has **saved my son's life**: no question about it."

"**Physical recovery has been steady**. Energy level much higher. Personal demeanor much more positive."

"You may take for granted your child laughing, running, playing. Those of us that have suffered endlessly with our children take great joy in so many things that many take for normal and don't appreciate. **This treatment has given my son a "normal" life for the first time in 6.5 years**. He is enjoying life without endless medications and doctor's appointments. This treatment means that a child can just be a child. Imagine that! The treatment may stop working tomorrow and I would be grateful for the gift of the past 1.5 of a 'normal' child."

"CAR-T has been, so far and almost 2 years post infusion, successful and **less disruptive than the previous treatments** which included chemotherapy and radiation both inpatient and outpatient."

> "Traditional treatment for ALL is an incredibly long grind (3.5 years for boys) with an incredible amount of scary poisons pumped into a young body that will have lifelong effects. Car-T cell **Immunotherapy holds hope not only for those without any options** for to the future children with the hope that some day, this will be the first line of attach for ALL cancer diagnosis. The amount of suffering it will save children, parents, family and friends - there is HOPE!!!"

Most respondents who received CTL019 felt that the treatment was significantly less challenging than what they have otherwise experienced for ALL. One respondent felt "neutral" on this question and one respondent felt that it was "more challenging" than other ALL treatments.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

Not Applicable.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

For patients and families who have received CAR T-Cell therapy, specifically CTL019, this treatment has given them improved quality of life, more time to live, and an opportunity to achieve remission. For the respondents to the survey who have experienced CTL019 therapy, this treatment has also provided hope and an opportunity for their child to be a kid again.

> "I didn't know much about treatment of childhood cancers prior to our son's diagnosis but am **pleased to live in a country where access to treatment was readily available**. The fact that I had medical benefits to cover the cost of most drugs helped tremendously. Even the cost of anti nausea drugs can be prohibitive for some. I had to "fight" for sick benefits for myself in this time of family crisis."

> "The treatments for ALL are 40 or 50 years old with horrible impacts during treatment, for years of recovery and then the life-long impacts. **We can do better with new treatments and children deserve better**. Please help kids access the newer, better treatments with less effects."

“I hope that through genetic coding, researchers will figure out who will relapse anyway with chemo and bone marrow transplant (my son had BMT before CAR-T) so that they can spare patients the agony of relapse and the adverse effects of chemo, radiation and BMT and go straight to CAR-T. **CAR-T is a miracle**.”

“It is far too harsh on their little bodies. Our son already has kidney and liver issues. This doesn't leave much confidence for the future. Our 2 year old has been tortured and will continue to be for 3 years. **There's got to be a better way**.”

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Childhood Cancer Canada provided Ac2orn with the use of their Survey Monkey account to administer the English survey. They only provided access to Survey Monkey and Ac2orn did all of the English survey set-up and analysis.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Antonia Palmer, Novartis CAR T-Cell Consultation Meeting, Info gathering for patient materials, February 2018	x			
Nadine Prevost (LLSC), Novartis CAR T-Cell Consultation Meeting, Info gathering for patient materials, February 2018. Partnerships for patients programs			x	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Antonia Palmer
Position: Co-Founder
Patient Group: Ac2orn
Date: June 11, 2018

Name: Nadine Prevost
Position: Senior Manager, Community Engagement
Patient Group: Leukemia & Lymphoma Society of Canada

Date: June 16, 2018

Name: Sarai Porretta
Position: Administrative Coordinator
Patient Group: OPACC
Date: June 11, 2018

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Tisagenlecleucel for relapsed or refractory diffuse large B cell lymphoma (DLBCL)**
Name of the Patient Group	**Lymphoma Canada**

9. About Your Patient Group

www.lymphoma.ca

10. Information Gathering

Lymphoma Canada (LC) conducted 2 anonymous online surveys of diffuse large B cell lymphoma (DLBCL) patients from April 18th – June 15th, 2018. Links to the surveys were sent via e-mail to patients registered on the LC database. The links were also made available via LC Twitter and Facebook accounts, Canadian and American Cancer Society message boards, Facebook groups organized for lymphoma patients and survivors, and international lymphoma organizations' own contacts. The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into surveys so respondents were asked questions only relevant to them. Open-ended responses to surveys that reflected the sentiment of a majority are included verbatim to provide a deeper understanding of patient perspectives.

Overall, 107 patients provided input. Of patients who provided their demographic information (see Tables 1 and 2), 90% live in Canada, 62% are female, 53% are ≥ 60 years-old, 33% are 40-59 years-old and 14% are < 40 years-old.

Table 1: Country of survey respondents (107 respondents)

Respondents	CAN	USA	Other	Skipped	Total
Patients WITH tisagenlecleucel experience	2	3	0	4	**9**
Patients WITHOUT tisagenlecleucel exp.	85	5	2	6	**98**

Table 2: Gender and age of survey respondents

Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	skipped	Female	Male	Skipped
Patients WITH tisagenlecleucel exp.	0	1	1	3	4	3	2	4
Patients WITHOUT tisagenlecleucel exp.	2	11	31	48	6	57	35	6

11. Disease Experience

Symptoms of DLBCL that most commonly affected respondents' quality of life at diagnosis (98 respondents) were fatigue or lack of energy (72%), enlarged lymph nodes (49%), drenching night sweats (37%), unexplained weight loss (28%), loss of appetite (25%), flu-like symptoms (18%), and persistent cough (18%). Other symptoms affecting quality of life for ≥ 10% of respondents included itching, chest pain and trouble breathing.

Respondents were asked which aspects of their life have been NEGATIVELY impacted by DLBCL. Notably, 56% and 42% indicated that DLBCL had a negative impact on their ability to work or attend to family obligations, respectively. Additional responses are summarized in Table 3.

Table 3: Effect of DLBCL on day-to-day life of patients (95 respondents)		
Aspect of life NEGATIVELY impacted by DLBCL	**# of respondents**	**% of respondents**
Ability to work	53	56%
Family obligations	40	42%
Personal image	36	39%
Intimate relations	27	28%
None of these	23	24%
Friendships	21	22%
Ability to attend school	2	2%

The majority of respondents (85%) also reported that their quality of life has been negatively affected by mental and emotional problems associated with their disease or treatments (Table 4).

Table 4: Impact of DLBCL on patients' mental and emotional well-being (98 respondents)		
Symptom	**# of respondents**	**% of respondents**
Fear of disease recurrence	66	67%
Memory loss	41	41%
Anxiety/worry	38	38%
Problems concentrating	37	38%
Difficulty sleeping	28	29%
Loss of sexual desire	25	26%
Stress of diagnosis	18	18%
Depression	17	20%
None of these	15	15%

As described by 4 patients:

" [Fear of disease recurrence] is very high and consumes a lot of my thought process almost every day. Even after two years since my Chemo treatments finished and I had a complete response."

"I retired early due to memory loss, lack of concentration and ongoing depression."

"It affected our personal lives my husband had to stay home from work to help me. We had no income. Very stressful. Our community did a couple benefits which helped us pay our bills. Big life changer for sure."

"I was an avid exerciser and have difficulty walking right now. The cancer is in my pelvis, its a sizeable tumour and limits my movements. In the last year I have sold my businesses and am now retired. I could not manage business, family , daily activities. There were times I had brain fog or chemo brain, not good for decision making. I try to do daily activities, laundry, cooking etc. The trial I am on right now has given me more fatigue, so I rest more than ever."

12. Experiences With Currently Available Treatments

Ninety-six (96) respondents provided information about their experience with DLBCL treatments. All respondents had received at least one line of treatment or were undergoing first-line treatment for DLBCL, 46% had received more than one line of treatment, and 5% had received 3 or more lines of treatment. The most commonly reported first-line treatment (84% of respondents) was the chemoimmunotherapy regimen R-CHOP. Of those who received more than one line of treatment (44 respondents), 25% had undergone an autologous stem cell transplant and 5% had undergone an allogeneic stem cell transplant.

Side effects of current treatments: The most common side effects respondents experienced during their DLBCL treatments are listed in Table 5.

Table 5: Side effects from treatment (96 respondents)

Side effect	% of resp.	Side effect	% of resp.	Side effect	% of resp.
Hair loss	92%	Mouth sores	47%	Trouble breathing	23%
Fatigue	86%	Thrombocytopenia	35%	Cough	22%
Memory problems	73%	Infections	35%	Other	22%
Neutropenia	67%	Anemia	32%	Loss of menstruation	19%
Nausea	61%	Diarrhea	27%	Irregular heartbeat	16%
Constipation	50%	Pain	27%	Viral reactivation	7%
Peripheral neuropathy	50%	Skin rashes/severe itching	23%	Bowel obstruction	7%

When asked which side effects they found most difficult to tolerate, respondents most often reported fatigue (32/80; 40%), nausea/vomiting (15/80; 19%), chemo-brain (13/80; 16%), and hair loss (8/80; 10%). Eighty (80) respondents provided responses to this question.

Impact of treatments on quality of life: When asked about the impact of various aspects of treatment on daily living (on a scale of 1 – 5, where 1= No impact and 5 = significant negative impact), respondents noted that treatment-related fatigue and other side effects had the most significant impact on their quality of life (Table 6).

Table 6: Impact of treatment on quality of life (96 respondents)

Treatment aspect	Weighted average	Significant negative	Number of

		impact (rating = 4-5)	responses
Fatigue	3.8	63%	95
Side-effects	3.6	57%	93
# of clinic visits	2.4	22%	93
Infusion time	2.4	21%	92
# of infections	2.4	24%	91
Infusion reaction	2.4	21%	92
Frequency of infections	2.2	21%	92

Treatment also had a very significant impact on many respondents' ability to work, travel and participate in daily activities (Table 7).

Table 7: Impact of treatment on daily living (95 respondents)

Activity	Weighted average	Significant negative impact (rating = 4-5)	Number of responses
Work	4.0	61%	94
Travel	3.9	64%	94
Activities	3.9	69%	94
Intimate relations	3.3	45%	92
Family	2.9	36%	91
Friendships	2.5	23%	93
School	2.1	6%	85

As reported by 3 respondents:

"I needed to make extra visits to emergency or to the clinic between treatments as a result of fever. Eventually I was given neupogen injections after treatments to keep my white blood cells at a better level (these were daily in my home for several days - impact, had to be home)"

"Learning to not to push myself with physical activity ie yard work, house reno etc.
Not taking on extra duties at work, and possibly retiring early in age"

"There is always some stress getting time off work to attend check-ups with oncologist. I am tired after work so I do very little during the work week to make sure I will have enough energy for my job."

When asked about the financial implications of treatment, almost half of respondents from Canada (40/85; 47%) reported that their absence from work or school impacted them financially.

As reported by 2 respondents:

"Had to give up a new career and job to have treatment"

"I was unable to continue working so I had to retire early, and therefore I lost my salary and health benefits"

Additional financial costs for respondents living in Canada are reported in Table 8.

Table 8: Financial implications of treatment for DLBCL patients in Canada (85 Canadian resp.)		
Financial impact	**% of respondents**	**Number of respondents**
Absence from work or school	47%	40
Cost of medications	33%	28
None	24%	20
Travel	13%	11
Other	13%	11
Accommodation	8%	7
Drug administration supplies	4%	3
Clinical trial charges	0%	0

13. Improved Outcomes

Patient preferences: Respondents were asked to rate, on a scale of 1 -5 (1 = not important; 5 = extremely important), the importance of various factors regarding a new drug or therapy for DLBCL. "Longer survival" and "longer remission" than current therapies were rated as the most important outcomes for a new therapy (Table 9). "Fewer side effects" was rated as the least important outcome, overall.

Table 9: Treatment preferences (94 respondents)			
Treatment outcome or factor	**Rating = 5 (Extremely important)**	**Weighted average**	**Number of responses**
Longer survival	90%	4.9	94
Longer remission	87%	4.8	94
Better quality of life	77%	4.6	94
Fewer side effects	55%	4.1	94

Respondents were also asked if they would choose a treatment with known side effects, potentially serious, if their doctor recommended it was the best option for them. Of the 94 respondents who answered this question, 49% selected "Yes", while only 3% selected "No". The remaining 49% of respondents selected "I'm not sure". Furthermore, 42% or respondents would be willing to tolerate potential side effects if the benefits were short term, while only 7% were not.

1. Experience With Drug Under Review

Nine respondents from Canada and the United States reported that they had been treated with CAR-T therapy for diffuse large B cell lymphoma. Most patients received CHOP +/- R as their first line of treatment. All but one of the respondents were diagnosed from 2014-16 and treated with CAR-T therapy between 2015 and 2018 (the lone exception was diagnosed in 2011 and treated in 2012). Two patients received CTL019 (Kymriah), one received KTE-C19 (Yescarta), two received JCAR017 and four did not specify what type of CAR-T therapy they had received. All of the respondents received CAR-T therapy through a clinical trial. Four patients are currently in remission, one remains in treatment with CAR-T therapy and four patients did not indicate their current status. Patients who provided demographic information are profiled below:

- A male patient from Ontario (50-59 years old) was interviewed. He was diagnosed in 2014 and treated with CHOP +/- R, followed by CHEOP +/- R, GCVP +/- R, DHAP +/- R and radiation therapy. The patient indicated that he had exhausted the available lines of treatment prior to his enrollment in the clinical trial. He began CAR-T therapy (CTL019) in July 2016 and has been in remission for 1-2 years. He commented that: "*I did not experience any significant adverse effects from the treatment.*"

- A female patient from the United States (70-79 years old) was diagnosed in 2016. She was treated with CHOP +/- R, followed by GemOx +/- R, cisplatin, ibrutinib + buparlisib and high-dose methotrexate. She was treated with CAR-T therapy (JCAR017) beginning in March 2018 and is newly in remission. She was admitted to hospital four days prior to the infusion and remained for five weeks, due in part to a C. difficile infection.

- A male patient from the United States (60-69 years old) was diagnosed in 2015. He was treated with CHOP +/- R, followed by lenalidomide +/- rituximab and HDT + auto-SCT. He was treated with CAR-T therapy (JCAR017) beginning in May 2017 and has been in remission for six months to one year. He suffered from skin issues related to his therapy that lasted for more than two months. He remarked that "*I was supposed to be dead last April. I couldn't walk 5 feet. After CAR-T therapy, I am now in remission and I just golfed 18 holes. Life is good.*"

- A female patient from Canada (20-29 years old) was diagnosed in 2015. She was previously treated with CHOP +/- R and began CAR-T therapy (CTL019) in June 2017. She is currently in remission.

- A female patient from the United States (60-69 years old) was diagnosed in 2011. She began CAR-T therapy (KTE-C19) in 2018 and remains in treatment.

Side Effects: Neutropenia was the most commonly reported side effect of CAR-T therapy followed by decreased appetite, cytokine release syndrome and febrile neutropenia. Only one patient required hospitalization to manage side effects due in part to a C. difficile infection and one patient reported side effects that lasted longer than two months (skin issues).

Quality of Life: Five respondents answered a question asking them to rate the impact of different aspects of their CAR-T therapy on a scale of 1 (no negative impact on my life) to 5 (significant negative impact on my life). None of the weighted averages for these responses was higher than 3 and only 1 of 5 respondents gave a rating > 3 for any aspect of CAR-T therapy, suggesting that CAR-T had a reasonably benign effect of their quality-of-life.

Table 10: Impact of CAR-T therapy on patients' lives (5 respondents)	
Aspect of CAR-T therapy	**Weighted average**
Number of clinic visits	2.8
Travel to treatment centre	2.8
CAR-T cells infusion	2.6
Short-term side effects of treatment	2.5
Activity level	2.5
Treatment-related fatigue	2.5
Lasting side effects of treatment	2.0
Leukapheresis	1.8

As reported by 1 patient:

"For all intents and purposes, despite having reviewed and discussed all of the potential side effects with respect to the CAR-T cell therapy program, the experience was fairly uneventful. I did not experience any significant adverse effects from the treatment." (Male, 50-59, Ontario)

Recommend CAR-T Therapy: When asked to describe the positive and negative effects of CAR-T therapy, patients provided these two responses:

"Nothing negative but the cost for travel. It was so much easier than the auto stem cell transplant." (Male, 60-69, United States)

"Positive, in that it removed the cancer. But it was a very difficult treatment." (Female, 70-79, United States)

When asked if they would recommend CAR-T therapy to other DLBCL patients based on their own experience, patients answered:

"After 25 days I am cancer free, so that was worth it, since nothing else worked." (Female, 70-79, United States)

"I would recommend it to any patient with relapsed DLBCL." (Male, 60-69, United States)

14. Companion Diagnostic Test

CD19 CAR-T cell therapy requires expression of CD19 on the tumour cells. Hematologists and oncologists with knowledge of CAR-T therapy and experience treating DLBCL indicated that this is a routine test that can be performed on archival biopsy tissue using readily available laboratory testing and would not need to be performed on new tissue prior to the initiation of CAR-T therapy.

15. Anything Else?

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

4. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, helped promote the patient surveys, analyzed the survey data for patients with CAR-T therapy experience and wrote the "Experience with Drug Under Review" section of the submission.

5. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, helped promote the patient surveys, analyzed the survey data for patients with CAR-T experience and wrote the "Experience With Drug Under Review" section of the submission.

6. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novartis			X	
Gilead			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Elizabeth Lye
Position: Scientific Advisor
Patient Group: Lymphoma Canada
Date: June 20, 2018