CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

brexucabtagene autoleucel (Tecartus)

(Gilead Sciences Canada Inc.)

Indication: Mantle cell lymphoma

January 22, 2021

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PG0219-000
Generic Drug Name (Brand Name)	**Brexucabtagene Autoleucel**
Indication	**For the treatment of adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) who have received treatment with a Bruton's tyrosine kinase inhibitor (BTKi).**
Name of the Clinician Group	**N/A**
Author of the Submission	**Dr. Neil Berinstein**
Contact information	Name: Dr. Neil Berinstein Title: Hematologist, Sunnybrook Health Sciences Centre [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Lymphoma Canada, a national non-for-profit organization for Canadian lymphoma and CLL patients, coordinated the group clinician response. For more information about Lymphoma Canada, please visit www.lymphoma.ca.

The following clinicians, leading experts in lymphoma across Canada, have provided feedback on this therapeutic for the submitted indication.

Dr. Neil Berinstein

Dr. John Kuruvilla

Dr. Nathalie Johnson

Dr. Mahmoud Elsawy

Dr. Mark Bosch

Dr. Mona Shafey

Dr. Isabelle Bence-Bruckler

2. Information Gathering

Please describe how you gathered the information included in the submission.

Clinicians provided responses to the questions in the submission based on research results, clinical experience, and understanding of patient needs and challenges.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Mantle cell lymphoma (MCL) is an often incurable subtype of non-Hodgkin's lymphoma, although there is some disease heterogeneity, with both more indolent or more aggressive presentations possible. Historically, the median survival for patients with MCL was approximately three years but this has improved substantially through treatments defined by randomized controlled trials including immunochemotherapy with rituximab-based regimens, the use of autologous stem cell transplantation (ASCT) in eligible patients, and rituximab maintenance as part of primary therapy. Unfortunately, despite the availability of certain biomarkers (SOX11, immunoglobulin gene mutational status, TP53 mutational or copy number status) that may help inform clinical behaviour, these are not routinely employed for prognosis or treatment selection in Canada. Clinicians are largely guided by symptoms along with age and comorbidity to guide treatment choices. The majority of MCLs behave more like the aggressive type of B lymphoma's and requires aggressive treatment with the possibility of cure. Observation may be considered in asymptomatic patients if they have no other indication for therapy such as cytopenia's related to lymphoma.

For younger patients often less than age 70 or with favourable comorbidity profiles, aggressive chemotherapy regimens including anthracycline-based chemotherapy combined with cytarabine-based chemotherapy is generally used for induction treatment and is followed by stem cell transplant. Maintenance therapy with rituximab is offered post treatment. For patients who are not eligible for a stem cell transplant or who are felt to have a more indolent variety of MCL, treatment with initial watchful waiting and less intense chemotherapy with Bendamustine and Rituximab (BR) would be offered as first line chemotherapy treatment upon development of symptomatic progressive disease. Rituximab maintenance is also offered to these patients. The median PFS for patients undergoing ASCT as part of primary therapy for MCL approaches 8-10 years while patients receiving R-chemo that are ineligible for transplant will have median PFS in the range of 3-5 years.

Second line therapies for patients with relapsed/refractory (RR) MCL are less defined. Novel drugs in MCL with proven single agent activity include the proteasome inhibitor bortezomib, lenalidomide and the mTOR inhibitor temsirolimus. None of these agents have been approved and funded in the Canadian environment. Median PFS in these trials ranged between 6-12 months. Clinicians have employed these agents in the context of clinical trials and when compassionate access may be available. Chemotherapy (or immunochemotherapy with rituximab) was typically of less benefit historically as typical patients would relapse early after primary therapy and derive less benefit from these traditional approaches. However, with more modern treatment, there remains a smaller subset of patients who may be treated with immunochemotherapy in the setting of late relapse (ie. beyond 5 years) and may be expected to have favourable outcomes with a regimen such as bendamustine-rituximab if they have not been exposed to this as part of primary therapy.

The mainstay of therapy for RR-MCL is the BTK inhibitor ibrutinib or more recently, the second-generation agent acalabrutinib (Health Canada approved but not currently publicly funded in all provinces). Ibrutinib was approved based on a single arm pivotal trial and a subsequent confirmatory phase III trial against temsirolimus demonstrating

significant benefit in (median 15 versus 6 months with 3 year follow-up). Given the use of BTK inhibitors in CLL, there is a great deal of comfort and experience with these agents in MCL. Unfortunately, additional novel agents in RR-MCL are typically unavailable if patients experience toxicity or progression. Medical comorbidity (AF, hypertension etc.) that may limit the use of ibrutinib in CLL is typically managed more aggressively in MCL given the lack of alternative agents.

There is no clear standard beyond immunochemotherapy, autologous transplantation and BTK inhibitors in MCL. As the disease is typically incurable, patients will likely require all of these therapies, and different available types of BTK inhibitors, through their lifetime if they maintain acceptable performance status and are medically fit for specific treatments. Clinicians may attempt to access unfunded targeted therapies or enrol patients in clinical trials. Allogeneic stem cell transplantation has been employed for younger patients that typically have disease progression following primary immunochemotherapy and BTK inhibitor therapy.

Third line with treatments for mantle cell lymphoma are quite heterogeneous. If patients haven't received a BTK inhibitor than the BTK inhibitor would be the treatment of choice. Other options include proteasome inhibitors such as Velcade or Carfilzomib, imids such as lenalidomide and the BCL2 inhibitor venetoclax. These treatments may offer 6 to 18 months duration of response. However, these options are not publicly re-imbursed and may not be a option for many patients.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

The most important goal of therapy for relapsed and refractory MCL is to produce clinical responses and remission that may prolong life. Relief of disease-related symptoms to improve health related quality of life is an important objective. Doing this in a fashion that is non-toxic would be preferable. Treatments that are finite and not continued indefinitely may be preferable to patients. Unfortunately, treatment in RR-MCL are frequently given indefinitely until progression, associated with significant costs and toxicity and ultimately are not curative in intent.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

At present there are a limited number of options for patients with relapsed and refractory MCL. In addition, these options benefit only a fraction of patients (35-75%) and typically do not offer durable responses (approximately 6-18 months). Many of these treatments must be administered indefinitely toxicities may adversely affect quality of life. For example lenalidomide may cause fatigue, gastrointestinal upset and cytopenia's that predispose to infections. Venetoclax also is associated with some toxicities including early tumour lysis syndrome. Unfortunately, the median survival in this population is quite short post-ibrutinib failure (median OS between 4-6 months, Martin Blood 2016). Further patients with p53 mutation have an average PFS of 4 months; 12 months in non-p53 mutated. The unmet need for patients post-BTK inhibitor failure is available, effective therapy. With CAR-T regimens, the duration of response is

better than expected for all other regimens. Intensive approaches such as allografting are only available to the minority that may have a donor and be of appropriate age and fitness.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient popu lation.

Would the drug under review address the unmet need in this patient population?

Response:

In patients with RR-MCL, there will be two patient populations – an older/frailer population that would not be eligible for more aggressive therapy and a patient population that will typically be younger, without comorbidity and with good performance status. Patients that would be candidates for CAR-T cell therapy will typically be younger (although age is not a specific criterion) and fitter. The population of MCL patients that are typically treated from an exclusively palliative approach will likely not change if CAR-T cell therapy is available. However, for patients that would be considered for experimental therapy or more intensive chemotherapy or allograft approaches, brexucabtagene would represent the preferred treatment option given the reported efficacy and toxicity outcomes.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

The drug under review is an example of an entirely novel patient-specific targeted therapy. Unlike most therapies for MCL that are aimed at direct killing of the MCL cells, BA augments the immune systems ability to control the cancer. This approach has been demonstrated to have significant efficacy in patients that have received typical standard chemotherapy and targeted agents. The current data support the role of this therapy as a single agent in multiply treated patients (similar to the approach in DLBCL). Patients are not further immunosuppressed and this mechanism of disease control may enhance the performance status and quality of life for the patient by controlling the underlying disease. This is a breakthrough first in class treatment for MCL. In the long term it is expected that other therapies or immune therapies could be combined to further enhance the activity of this immune therapy including BTK inhibitors. It is possible that BA could eventually complement or replace first line therapy with high-dose therapy and stem cell transplant for patients with MCL. As CAR-T therapy is an established therapy for NHL patients in Canada at certified centers, healthcare teams are well-versed in the management of short-lived toxicities and therefore the addition of this therapy for a very specific cohort of lymphoma patients should be well accommodated.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

This therapy is active in a significant percentage of patients with r/r MCL and has not been evaluated against standard frontline approaches or in a large cohort of BTK-inhibitor naïve patients. Thus, CAR-T cell approaches should be reserved for patients who have received a standard chemoimmunotherapy and BTK inhibitor approach unless these are contraindicated. Trials to determine its efficacy and toxicity when administered earlier in the disease course are required to support earlier integration in the disease course.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Based on the available data, patients will have received typical standard therapies prior to CAR-T cell therapy. Patients who relapse after BA could be considered for retreatment if they're functional status is acceptable and if they've had a good duration of response to their first course of treatment. However, such retreatment may require data from clinical trials to support its rational. Re-treatment with CAR-T cells has been described in DLBCL with moderate activity. It would not be expected that any/many of these patients would be re-treated but it would be possible if additional product was available and the tumour still expressed the target CD19 antigen.

Post-relapse, patients would be eligible for other standard palliative measures as well as novel agents that could be available on clinical trials or compassionately. This would not be a specific departure from current practice as these agents are not approved or in trials. Options can include those mentioned in section 3.1 such as proteasome inhibitors, imids such as lenalidomide and the BCL2 antisense inhibitor. However, it is important to note that Velcade and imids are not publicly re-imbursed options and therefore may not be available to patients requiring treatment. There is no reason to believe that their efficacy would be diminished post BA therapy

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients who have disease progression post- chemo immunotherapy and BTK inhibitor therapy would all be good candidates for this treatment because this treatment is working through an entirely different and novel mechanism of action. Because of the initial toxicities with treatment, patients need to have a good functional status. Age alone should not be an exclusion to treatment with this treatment. At present there are no clinical or biologic biomarkers that can identify patients who are most likely to respond. Of course, patients would need to express CD19 but this is almost universal in MCL and standard immunohistochemical assays are not sensitive enough to exclude lower levels of expression of target antigen which could be sufficient for efficacy. Patients must have adequate numbers of circulating T

lymphocytes to allow generation of CAR-T cell product and these may be reduced by multiple previous lines of chemotherapy

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Patients who would be candidates for this therapy would be identified by the treating haematologist or oncologist. It is very clear when patients are becoming refractory to their second line therapy such as BTKs and progression can usually be documented by standard clinical testing (imaging, laboratory findings). Initiation of treatment for asymptomatic progression would be optimal. Such patients should be referred to treatment centres earlier rather than later so that the chimera antigen receptor T cells can be prepared before patients become excessively symptomatic or run into organ dysfunction.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients with comorbid illnesses that may increase their risk of sepsis, cytokine release related complications or neurologic complications immediately after the T cell reinfusion may be less suitable for this treatment. Such comorbidities could include patients with her difficult to manage diabetes or diabetic complications, chronic renal failure with impairments of creatinine clearance or on dialysis or patient with significant symptomatic cardiomyopathies. Patient with obvious uncontrolled infections would not be acceptable candidates. Patients with active CNS lymphoma may not be good candidates unless the CNS disease is controlled and stable.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Currently no biomarkers to identify these patients.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Standard clinical parameters would be used to document clinical response including CT scans and possibly PET scans. Bloodwork and assessments of organ function and the haematologic profile would also be important.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Clinically meaningful results to therapy include stabilization of disease or objective response to therapy. These responses would usually be associated with improvement in constitutional or organ related symptoms. Success with this treatment should ensure improve quality of life and independence in the activities of daily living. Durable responses would be important given the logistical difficulties and expense of treatment.

6.10. How often should treatment response be assessed?

Response:

Response to treatment should be assessed radiologically post treatment and several months again post treatment. Ongoing imaging may be dependent upon symptoms and the results of the previous testing, clinical findings as well as laboratory results.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Clearly, progression of disease or a recurrence of symptomatology would indicate treatment failure. Consideration of initiating a new treatment at that time would be appropriate. As a single infusion therapy, the main question around discontinuation would be for patients that have disease control issues prior to T cell infusion.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

This treatment should be administered in a tertiary referral cancer centre that has experience and infrastructure for cell therapies, or that is an autologous stem cell transplant center. Currently, this would be centres with CAR-T cell experience in DLBCL/ALL which typically would be regional academic transplant programs.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:
Not relevant

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

This is a transformational therapy that may life-extending for patients with recurrent refractor MCL-condition which is currently an unmet medical need and in dire need of better and innovative therapies.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   No

2. Did you receive help from outside your clinician group to collect or analyze any information 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. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Neil Berinstein*
Position	*Hematologist, Sunnybrook Health Sciences*
Date	*04-12-2020*

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

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca Gilead Servier Sapvax	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. John Kuruvilla*
Position	*Hematologist, Princess Margaret*
Date	*Please add the date form was completed (01-10-2021)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Mahmoud Elsawy*
Position	*Assistant Professor of Hematology and SCT, Dalhousie University*
Date	*07-01-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Kite/Gilead	☒	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Mark Bosch*
Position	*Transplant Hematologist*
Date	*11-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
BMS/Celgene	☐	☒	☐	☐
Novartis	☒	☐	☐	☐
Gilead	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐
Jansen	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Mona Shafey*
Position	*Hematologist*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Kite/Gilead Sciences	☒	☐	☐	☐
Bristol-Myers Squib	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Dr. Nathalie Johnson*
Position	*Hematologist*
Date	*12-01-2020*

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

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck	☐	☒	☐	☐
Bristol-Myers Squib	☒	☐	☐	☐
Roche	☐	☒	☐	☐
Lundbeck	☒	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Dr. Isabelle Bence-Bruckler*
Position	*Hematologist*
Date	*12-01-2020*

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

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Kite/Gilead	☒	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PG0219-000
Generic Drug Name (Brand Name)	**Brexucabtagene autoleucel (Brand: TBC); Manufacturer: Gilead Sciences Canada Inc.**
Indication	**Indications:** For the treatment of adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) who have received treatment with a Bruton's tyrosine kinase inhibitor (BTKi). **Manufacturer Requested Reimbursement Criteria[1]:** For the treatment of adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) who have received treatment with a Bruton's tyrosine kinase inhibitor (BTKi).
Name of the Clinician Group	Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee
Author of the Submission	Dr. Tom Kouroukis, Dr. Janet MacEachern, Dr. Jordan Herst, Dr. Pierre Villeneuve, Dr. Lee Mozessohn
Contact information	Name: Dr. Tom Kouroukis Title: Provincial Head – Complex Malignant Hematology (OH-CCO) [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Discussed jointly at a DAC meeting.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

For patients who had received multiple lines of treatment – current treatments for MCL include: palliative chemo, clinical trials, or in young fit patients, consideration for allogeneic stem cell transplantation (allo SCT).

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Prolong life, disease control, disease response

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Current treatments are mainly palliative in this line of therapy or allo SCT for young fit patients

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

All patients who failed BTKi

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Brexucabtagene autoleucel would replace palliative chemotherapy, or allo SCT in young fit patients

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

No.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

As noted above, brexucabtagene autoleucel would replace palliative chemotherapy, or allo SCT in young fit patients

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients who are eligible for CAR T-cell therapy – based on comorbidities, performance status, fitness assessment

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Per standard measures for disease relapse; patients who progressed after a BTKi and eligible for CAR T-cell therapy

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

If unable to control patient's disease short term to allow the patient to proceed to CAR T-cell therapy

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

No.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Remission after CAR T-cell therapy

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Disease remission

6.10. How often should treatment response be assessed?

Response:

PET CT after 1st month, and then at 3 months

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Not applicable. Usually single infusion.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

CAR T-cell treatment centres (inpatient and outpatient)

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

NA

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

Tocilizumab may be required to manage cytokine release syndrome in some patients.

Some patients may require bridging therapy (e.g., chemo) to keep disease under control before proceeding with brexucabtagene autoleucel.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   OH-CCO provided secretariat support to the DAC in completing this input.

2. Did you receive help from outside your clinician group to collect or analyze any information 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. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Tom Kouroukis*
Position	Provincial Head – Complex Malignant Hematology (OH-CCO)
Date	*21-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Janet MacEachern*
Position	*Hematologist/oncologist*
Date	*21-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Jordan Herst*
Position	*Hematologist/oncologist*
Date	*21-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Pierre Villeneuve*
Position	*Hematologist/oncologist*
Date	*21-Jan-2021*

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

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Lee Mozessohn*
Position	*Hematologist/oncologist*
Date	*21-Jan-2021*

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

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐