CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

PEMBROLIZUMAB (Keytruda)

(Merck Canada)

Indication: Classical Hodgkin lymphoma

February 5, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0236-000
Generic Drug Name (Brand Name)	**Pembrolizumab (Keytruda)**
Indication	**Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.**
Name of the Clinician Group	**Lymphoma Canada Scientific Advisory Board**
Author of the Submission	**John Kuruvilla**
Contact information	[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. John Kuruvilla

Dr. Rebecca Deyell

Dr. Angela Punnett

Dr. Isabelle Bence-Bruckler

Dr. Joanne Hickey

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:

The treatment of relapsed/refractory classical Hodgkin's Lymphoma (RR-cHL) varies based on the patient population which includes patients that are either eligible for autologous stem cell transplantation (ASCT) or are ineligible for ASCT (either due to lack of treatment responsive disease, comorbidity or performance status) or have already experienced disease progression post-ASCT. Patients are typically treated in the first line setting with anthracycline-based therapy (ABVD and/or BEACOPP; potentially including radiation therapy) with regimen and duration based on disease risk and the fitness of the patient to tolerate multi-agent chemotherapy.

In the second-line curative setting, the role of ASCT is well defined based on two small randomized controlled trials (RCTs) that demonstrated progression free survival (PFS) advantage to patients with disease sensitive to salvage therapy. In patients eligible for ASCT, the typical second-line therapy is GDP (gemcitabine, dexamethasone, cisplatin), the Canadian standard which has similar efficacy to other regimens in the absence of any RCTs. Second line chemotherapy regimens in pediatrics have some variation across centres, but a gemictabine based regimen is also often utilized. Post-transplant consolidation with the anti-CD30 antibody drug conjugate brentuximab vedotin (BV) has been shown to be of significant PFS benefit in an RCT performed in high-risk patients undergoing transplantation (the AETHERA study) and is publicly funded in some provinces in Canada. Radiation therapy can be used as a component of this treatment approach, frequently as consolidation post stem celltransplant.

For patients ineligible for ASCT due to comorbidity or performance status, there is no clear gold standard and the treatment approach is palliative in nature. A variety of approaches may be employed including non-cross resistant chemotherapy, radiation or novel agents such as BV or anti-PD1 antibodies (pembrolizumab [pembro] or nivolumab [nivo]). Access to BV or anti-PD1 antibodies in this setting remains limited to due to lack of funding as trials have generally required patients to be post-ASCT (BV) or have been exposed to BV (anti-PD1 antibodies). Compassionate access in these settings remains challenging.

In patients that are ineligible for ASCT due to lack of adequate response to salvage therapy, a variety of approaches have been employed including non-cross resistant chemotherapy, radiation or novel agents (BV or anti-PD1 antibodies). Funded access to these agents remains inconsistent across provinces although there has been some compassionate access to BV and anti-PD1 antibodies. It is important to note the difference in treatment intent in this population as the goal remains cure.

For patients that have progressed post-ASCT, BV has a clear role as monotherapy and has been publicly funded across Canada. However, it is important to note that this patient population is slowly changing given the increasing usage of BV in the curative setting (as outlined above in the consolidation post-

ASCT setting and in select patients pre-ASCT and potentially in the frontline setting based on the ECHELON-1 study in adults and the pediatric AHOD1331 trial. Post BV, nivo and pembro have been established as standards in this patient population with public funding across the country.

Canadian patients have faced significant challenges to access novel agents should they be ineligible for an ASCT approach. RCT data in this patient population is sparse and access to agents such as BV and anti-PD1 antibodies is uncommon in Canada. International retrospective series have evaluated BV and experts in the field feel this a standard agent that can be employed at first relapse in non-ASCT eligible patients or increasingly as part of a salvage approach in transplant eligible patients (that may or may not have demonstrated lack of sensitive disease). Allogeneic SCT has also been considered in these patients but Canadian centres have generally not been supporters of these approaches (largely due to historic data emphasizing high non-relapse mortality and more recent data demonstrating more favourable safety but still concerns with relapse) and the usage of allo-SCT is not common in comparison to other countries.

Historically, targeted approaches in RR-cHL have largely been ineffective but effective novel therapies have now been developed. CD30 is an antigen commonly expressed by the Hodgkin Reed-Sternberg cell and is the target of BV. BV is an antibody drug conjugate that allows delivery of a chemotherapy payload and minimizes systemic side effects of chemotherapy. Anti-PD1 antibodies target the immune checkpoint by blocking the interaction between PD1/PDL1. Genetic amplification of PD1 has been shown to be a biologic hallmark of cHL which contributes to unique immune milieu of the tumour and the high degree of activity for anti-PD1 antibodies in RR-cHL.

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:

As highlighted above, there are two distinct groups within the patient population enrolled in the Keynote-204 (KN204) clinical trial.

The larger group of patients are patients that have experienced disease progression post-ASCT and those who are ineligible for ASCT due to comorbidity or performance status. In this setting, treatment is largely palliative. As such the goals in this setting would be to improve overall survival (OS) or quality of life (QOL) and to prolong progression-free survival (PFS). Improvement in QOL would typically be associated with treatments that also minimize therapy-related adverse effects and the potential to allow patients to resume typical activities of living.

The other subgroup of patients includes those that may be eligible for ASCT but do not have sensitive disease. In such cases, if subsequent treatment leads to adequate treatment response, patients can proceed to ASCT and could potentially be cured by transplantation.

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:

As outline in section 3.1, there are significant access gaps to novel agents across the country due to lack of funding. “Standard” therapies such as non-cross resistant chemotherapy are typically more toxic and less effective than novel agents and are not associated with favourable PFS/OS. The vast majority of these patients will experience disease progression that will require retreatment and exposure to multiple therapies. Available therapies will come with increasing toxicities (myelosuppression, neuropathy etc.) and generally will not provide meaningful long-term disease control. As such, novel agents with favourable toxicities/QOL and longer PFS/OS are agents that would be favoured in this setting by clinicians and patients.

In those patients that are currently ineligible for ASCT due to lack of disease response, patients need an effective therapy that can act as a “bridge” to ASCT. Response rates to traditional therapy are not favourable in this setting and novel therapies with a favourable efficacy:toxicity ratio are clearly needed.

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:

The KN204 population contains the greatest unmet need populations in RR-cHL: older patients requiring treatment following failure of primary therapy as well as the subset of patients that have not responded to second-line therapy but could benefit from ASCT if their disease was responsive.

Clinical trials have tended to group older patients with younger patients that have experienced disease progression after multiple therapies and/or ASCT and as such tend to represent smaller proportions of this population. Data from an RCT including second-line therapy outcomes in older patients with RR-cHL is unprecedented.

The definition of “older” in HL is not strictly defined by numeric age although given the epidemiology of this lymphoma even relatively young age (45-50 years) has been identified as an adverse prognostic factor for outcome. Practically, age greater than 60 years has been used internationally to identify the “older population” and has been used as an enrolment criterion for clinical trials Survival in this population has been shown to be inferior to patients under the age of 60. Practically, the age of 70 may be a more in keeping with clinical practice as it is at this age (but more typically increasing comorbidity associated with

age) that influences treatment decisions around the safe administration of anthracycline-based chemotherapy and dose intensive ASCT procedures.

Although children and adolescents with RR-cHL <18y were not included in KN204, there is growing evidence of efficacy of anti-PDL1 antibody therapy in this group. There is active, ongoing clinical trial experience utilizing pembro in pediatric RR-cHL (KN051) and investigating the role of pembro in upfront therapy for children with slow early response to therapy (KN667). Additionally, adolescents (≥12y) with HL are increasingly being included in adult clinical trials due to overlapping biology and pharmacologic dose equivalence. Children and adolescents with RR-cHL following failure of ASCT are a rare sub-group, but who derive substantial benefit from access to anti-PDL1 therapy to achieve prolonged disease-free survival with excellent QOL.

In the refractory but potentially ASCT eligible population, the unmet need is even more concerning given the opportunity to deliver curative therapy if the disease may be sensitive to alternate therapy. Clinicians in Canada have struggles given funding restrictions around accessing BV and anti-PD1 antibodies, and this scenario ends up limiting curative therapy for this group of patients unless they are treated in a centre that may be able to access these treatments in clinical trials or on a case-by-case basis.

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:

Anti-PD1 antibodies have been established in the treatment of RR-cHL based on registrational single arm trials in patients that have received multiple therapies. Combination approaches (including frontline and second-line combinations pre-ASCT or studies in the non-ASCT population) have been performed or are currently being evaluated. In general, these studies show acceptable safety and favourable anti-lymphoma activity. There is mechanistic rationale to support combinations of anti-PD1 antibodies with chemotherapy or agents.

Canadian practice typically includes anthracycline-based therapy in the primary treatment setting, platinum-containing salvage therapy in ASCT eligible patients and palliative chemotherapy/radiation in non-ASCT eligible patients. As such, the KN204 data would support the use of pembro for patients with RR-CHL after primary therapy if they are ineligible for ASCT due to comorbidity/performance status and in other patients that have received at least two prior lines of therapy and/or relapsed post-ASCT.

In Canada, these data would be expected to change practice. KN204 provides RCT data demonstrating the superiority of pembro for the unmet need population (patients with RR-cHL after one prior therapy that are typically older and non-ASCT eligible due to comorbidity/performance status) and establishes pembro as the preferred choice in the post ASCT population (where previously BV was approved and funded based on a single arm registrational trial) and in patients that are also ASCT eligible but non-

responsive to other treatments (currently now expected to have received two prior lines of chemotherapy).

This aligns with the Canadian treatment paradigm which previously had limited access to funded novel agents (BV or pembro/nivo) and largely reserved anti-PD1 antibodies to the setting post-BV failure. KN204 demonstrates superior PFS and favourable QOL in patients in comparison to BV which is a Canadian standard in the setting where it is funded and an international standard in the broader KN204 population that was evaluated in this RCT.

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:

KN204 is a trial in the second-line or beyond setting so patients will require primary therapy (which would typically be anthracycline based ie. ABVD/BEACOPP) before consideration of pembrolizumab. In Canada, it would be expected that patients that are potentially ASCT eligible would proceed to second-line salvage chemotherapy (typically GDP or similar). In patients where the response to this treatment was inadequate or in patients that subsequently relapse, pembrolizumab would be considered. Further trials would be required to determine the superiority of novel approaches over conventional chemotherapy in the second-line transplant eligible setting although an increasing body of single arm prospective data supports this hypothesis.

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:

It would be expected that pembrolizumab would replace BV as monotherapy for RR-cHL in the patient population studied in this RCT. Given the adoption of BV earlier in the disease course in the curative setting (although with variable funding across the country) as part of primary therapy (AVD+BV based on the ECHELON-1 study, BV maintenance based on the AETHERA trial, the use of BV uncommonly in the non-ASCT eligible RR-cHL population based on small single arm prospective or retrospective trials), the adoption of pembro in this setting is rational and would avoid the potential consideration of re-treatment with BV for which there is limited data and no provincial funding.

If pembro were available earlier in the disease course as defined by KNK204, BV would then be used post pembro failure in patients that have not had BV exposure. This would reverse the current sequencing where prior data established pembro/nivo as the preferred approach in BV failure.

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:

The patient population has been clearly outlined in the section above with explanations around specific subpopulations based on treatment practice in Canada.

The study generally described favourable PFS outcomes when hazard ratios were evaluated in disease subpopulations of interest although the sample size limits interpretation and care must be taken with retrospective subset analyses. It is important to note that outcomes for pembro appeared favourable in high risk/unmet populations including primary refractory HL, patients ineligible for ASCT and in patients that were BV naïve.

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:

Hodgkin's lymphoma is a relatively common diagnosis and patients with relapsed/refractory are frequently assessed at expert centres around the potential of SCT or novel therapy. However, patients are typically managed well at their primary hematology/oncology centre as the diagnostic algorithms for this disease have been well described and are part of the routine laboratory workup of lymphoma. With the advent of standard of care BV previously, it has been possible to return care of these patients back to their local centres for further workup and management. Pediatric and adolescent patients with HL are managed at one of 16 national pediatric oncology tertiary care centres and follow established treatment and response evaluation algorithms.

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

Response:

The vast majority of patients with RR-cHL would be suitable for this therapy. As an immune checkpoint directed antibody, important considerations would include a pre-existing history of autoimmune disease or prior significant allergic/anaphylactic reactions to antibodies. These patients may have been excluded from clinical trials, but outcome data exist for these populations in other cancers where anti-PD1 antibodies have benefit which speak to the general safety and efficacy in some populations that have

been excluded from trials due to potential safety concerns. This should involve a careful discussion of risk:benefit ratio with the patient.

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:

Robust clinical biomarkers to predict outcome of patients to anti-PD1 antibodies in RR-cHL that would be available in routine clinical practice are not available.

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:

Serial imaging is typically employed in patients with RR-CHL in both the ASCT eligible and ineligible/failure population. The frequency of this imaging is less common in clinical practice and FDG PET scanning is less likely to be routinely employed (particularly at multiple timepoints).

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 response could include one or more of: improvement in disease related symptoms, tumour response and disease control measured by PFS or OS. The data provided in KN204 show clinically meaningful benefits for patients receiving therapy.

6.10. How often should treatment response be assessed?

Response:

In routine practice this has been variable in practice across the country. In patients that may be candidates for ASCT, FDG PET imaging should be performed as it as an important predictor of outcome post-ASCT and traditionally serial imaging has been performed at routine time points post ASCT (ie. 3 months and 1 year). In the non-ASCT setting, response could be documented at 3 months and then subsequently imaging could be directed based on patient symptoms/findings and less frequently than in the trial (ie. 1 year and end of treatment). Consideration to costs of imaging versus drug costs to detect asymptomatic progression would be a consideration.

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:

As is typical for most anti-cancer therapy, disease progression and significant toxicities would be appropriate reasons to discontinue treatment. The adverse events with pembro were typically grade 1-2 but uncommon Grade 3-4 events (particularly immune related adverse events such as pneumonitis) may necessitate discontinuation of the treatment.

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

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

Response:

There is extensive experience with anti-PD1 antibodies in a variety of malignancies with treatment being given in the community setting as well as tertiary cancer centres or hospitals.

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:

N/A

7. Additional information

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

Response:

It is important to highlight the importance of this therapy in the Canadian landscape. There was substantial enrolment from Canadian centres onto this clinical trial as both the control arm (BV – largely unfunded in this setting) and the pembro arm helped to address significant unmet patient need due to lack of funded novel therapy in many areas of the country. Given the paucity of RCTs in RR-cHL, reviewers should appreciate the value of these data for the Canadian patient population. It is also important to emphasize that Canadian children and adolescents with RR-cHL have a similar unmet need for which there is an important role for access to anti-PDL1 directed therapy.

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.

Lymphoma Canada helped to coordinate the group of clinicians for this submission, however they were not involved in analyzing or adding feedback to any of the responses in this submission.

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	*John Kuruvilla*
Position	*Hematologist, Princess Margaret Cancer Centre.* *Chair, Scientific Advisory Board of Lymphoma Canada*
Date	*29-01-2021*
☒	**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**
Seattle Genetics	☐	☐	☒	☐
Merck	☐	☐	☒	☐

Declaration for Clinician 2

Clinician Information	
Name	*Rebecca J Deyell*

Position	*Pediatric hematologist oncologist, BCCH; Clinical Associate Professor, UBC*
Date	*30-01-2021*
☒	**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**
N/a	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Angela Susanne Punnett*
Position	*Staff Oncologist, SickKids*
Date	*02-02-2021*
☒	**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**
n/a	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Isabelle Bence-Bruckler*
Position	*Hematologist, Associate Professor of Medicine*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**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	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Seagen	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Joanne Hickey*
Position	*Hematologist, Medical Director Newfoundland and Labrador Cell Therapy and Transplant Program Eastern Health, St. John's Newfoundland*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**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**
n/a	☐	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0236-000**
Generic Drug Name (Brand Name)	**Pembrolizumab (Keytruda); Manufacturer: Merck Canada**
Indication	Indications: Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT. Manufacturer Requested Reimbursement Criteria1: Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.
Name of the Clinician Group	Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee
Author of the Submission	Dr. Tom Kouroukis, Dr. Anca Prica, Dr. Janet MacEachern, Dr. Jordan Herst, Dr. Lee Mozessohn, Dr. Pierre Villeneuve
Contact information	[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. Note: the pivotal trial was only available in abstracts and presentation slides at the time of discussion.

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:

Patients who failed autologous stem cell transplantation (ASCT), they will go on to receive brentuximab vedotin (BV).

Patients who are not eligible for ASCT, they may try to get some of the drugs compassionately, or be treated with combination chemotherapy, radiation or clinical trials.

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, delay disease progression, improve QoL, ability to return to employment (as some of the patients are quite young).

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:

In patients who failed ASCT, BV did not demonstrate improvement in overall survival (OS), improvement in response duration

In patients ineligible for ASCT, we don't have drugs that meaningfully improve OS and progression free survival (PFS), and allow patients to return to employment. There are limited treatment options if patients are ineligible for ASCT.

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:

Greatest unmet need - In Ontario, transplant ineligible patients currently do not have access to BV and will be treated on clinical trial or palliation.

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:

Younger population who failed 1L treatment (e.g., ABVD, BEACOPP) will likely get GDP salvage and if the patient does not respond, then the patient is deemed ineligible for ASCT and then can be treated with pembrolizumab.

Older populations who failed frontline therapy and are not candidates for ASCT due to age/comorbidities can be treated with pembrolizumab instead of salvage chemo.

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:

Pembrolizumab is a better option compared to currently available treatment options.

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:

If a patient receives and fails pembrolizumab post ASCT, is the patient able to get BV after? (e.g., potentially as a bridge to allogeneic stem cell transplantation)

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:

As per the trial population

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 with relapsed disease – patients who failed ASCT or patients who are not candidates for salvage treatment and ASCT

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

Response:

Patients with poor performance status, or who are not candidates for immunotherapy

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 specific disease factors for this population

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:

Determined by standard response criteria including imaging

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:

Alleviation of symptoms, clinical stability, no progression.

6.10. How often should treatment response be assessed?

Response:

Clinical monitoring every 3 months; imaging as needed per clinical judgement

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: Clinical evidence of progressive disease and toxicities.
6.12. What settings are appropriate for treatment with the drug under review?
Examples: Community setting, hospital (outpatient clinic), specialty clinic ***Response:*** Outpatient clinic
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: None.

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 <u>each clinician</u> 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. Anca Prica*
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.

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

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.

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

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.

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

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				
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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 6

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.

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CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0236-000**
Generic Drug Name (Brand Name)	**Pembrolizumab (Keytruda)**
Indication	Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.
Name of the Clinician Group	**Pediatric Oncology Group of Ontario (POGO)**
Author of the Submission	**Dr. Paul Gibson**
Contact information	[redacted]

1. About Your Clinician Group

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

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

POGO is a collaboration of Ontario's 5 specialized childhood cancer centres and the official advisor to the Ministry of Health and Long-Term Care on pediatric cancer care and control. This submission represents a collaboration of pediatric cancer clinicians from across the province with membership informed by POGO's Therapeutic and Technology Advisory Committee (TAC). For more information on POGO, please visit www.pogo.ca

2. Information Gathering

This submission was prepared in a consultative manner. Dr. Gibson discussed the indication with members of the submission panel and also sought input from the POGO TAC. Dr. Gibson subsequently drafted the initial response and all others contributing to the submission reviewed and edited the draft that has led to this final submission.

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:

Pediatric Hodgkin Lymphoma is a common pediatric malignancy with generally excellent prognosis. (https://www.pogo.ca/research-data/data-reports/2020-pogo-surveillance-report/). In Ontario, children and adolescents are treated in a risk adapted manner with chemotherapy and in a significant portion of patients, radiation therapy. The most common upfront protocols utilized are the Children's Oncology Group (COG) based ABVE-PC and the Euronet Group's OEPA-COPDAC. The small portion of patients that fail to respond to upfront therapy (refractory) or who relapse are treated with salvage cytotoxic chemotherapy and most will proceed to autologous stem cell transplant.

Brentuximab vedotin (Bv) is funded in Ontario for patients that relapse following autologous transplant and for patients deemed high risk of relapse following autologous transplant. In select cases, Bv may be used in non-funded circumstances, including primary refractory disease and high risk first relapses. The goal of therapy in the vast majority of cases remains cure.

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:

The goal of Hodgkin Lymphoma therapy, even in the relapse setting remains cure. Pembrolizumab may offer a curative option even for unfortunate patients with multiple relapses or refractory disease.

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:

When patients have been treated with aggressive cytotoxic therapy (including autologous transplant) and Bv, there are no clear options for further therapy. The patients need a life sustaining, and ideally curative therapeutic option. Pembrolizumab provides a promising therapeutic option with a mechanism of action completely different than previous lines of therapy.

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:

Patients with relapsed and/or refractory Hodgkin Lymphoma that have had previous exposure to Bv represent the greatest unmet need. These patients will have been exposed to both multi-agent cytotoxic therapy and CD30 targeted therapy with Bv. They require an alternative mechanism of action to achieve a response.

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:

Pembrolizumab extends the options for curative therapy in patients with very difficult to treat disease. We suggest that current data supports it being the next line of therapy in relapsed and refractory patients with past exposure to Bv.

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:

As outlined above, we believe patients eligible for autologous transplant should receive that therapy and also Bv therapy prior to a trial of pembrolizumab. For patients with that fail to respond adequately or experience unacceptable Bv toxicity (i.e. pulmonary toxicity) pembrolizumab is an appropriate substitution.

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:

We do not suggest that pembrolizumab will alter current sequencing, but rather serve as an additional line of 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 progressive or relapsed disease after Bv therapy or patients unable to tolerate Bv are most in need of pembrolizumab therapy. These patients should have acceptable performance status (ECOG 0 or 1, Lansky >60) to allow tolerance of any potential adverse events.

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:

Relapsed and refractory Hodgkin Lymphoma is not generally a challenging diagnosis in our opinion. The diagnosis can usually be made with the combination of cross-sectional imaging and PET scan. In cases

where the diagnosis is not clear from imaging, an open or image guided biopsy may add clarity. These are routine processes in our centres.

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

Response:

Patients with poor performance status at the time of presentation of relapsed or refractory disease may be less able to tolerate pembrolizumab toxicity.

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:

There are not clear clinical predictors at present to estimate those most likely to respond to treatment.

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:

Hodgkin Lymphoma response is assessed by cross sectional imaging and PET scanning. This is true both in clinical trials and clinical practice.

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:

Meaningful responses include reduction in disease measurements by cross sectional imaging and decreased PET avidity. Patients may also report decrease in subjective symptoms including itching and respiratory distress. Importantly, treating physicians should be mindful of the potential of 'pseudo-progression' and consider treating beyond initial potential progression if clinically feasible.

6.10. How often should treatment response be assessed?

Response:

We suggest disease status should be assessed at minimum every 12 weeks.

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:

Patients with progressive disease should discontinue therapy. In patients experiencing significant high-grade toxicities from therapy, thoughtful discussion should be held with the patient and family, including the potential risks and benefits of continuing further treatment.

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

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

Response:

We suggest this therapy should be delivered to pediatric cancer patients in specialized pediatric cancer programs only.

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:

N/A

7. Additional information

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

Response:

We recognize that KEYNOTE-087 included patients only 18 years or older. We feel strongly, however, that Hodgkin Lymphoma shares common biology along the age spectrum. Given that KEYNOTE-051 showed safety in pediatric patients (and activity in 60% of 15 refractory Hodgkin Lymphoma patients) we believe the results of KEYNOTE-087 can be safely applied to younger patients. Furthermore, as cooperative groups such as the Children's Oncology Group (COG) are moving to joining adult oncology groups for clinical trials in Hodgkin Lymphoma, it is unlikely that a pediatric only study for pembrolizumab in this rare, multiply relapsed or refractory population will be feasible.

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. All work was completed by collaboration of the listed contributors.

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. All work was completed by collaboration of the listed contributors.

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 <u>each clinician</u> 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. Paul Gibson*
Position	*Associate Medical Director, POGO, Pediatric Oncologist, McMaster Children's Hospital*
Date	*01-02-2021*
☒	**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	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Angela Punnett*
Position	*Pediatric Oncologist, SickKids Hospital*
Date	*01-02-2021*
☒	**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				
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Add company name	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Vicky Breakey*
Position	*Pediatric Oncologist, McMaster Children's Hospital*
Date	*01-02-2021*
☒	**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				
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Add company name	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Sumit Gupta*
Position	*Pediatric Oncologist, SickKids Hospital*
Date	*01-02-2021*
☒	**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.

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Add company name	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Jennifer Seelisch*
Position	*Pediatric Oncologist, Children's Hospital London Health Sciences Centre*
Date	*02-02-2021*
☒	**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.

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Brianna Empringham*
Position	*Pediatric Oncologist, Children's Hospital of Eastern Ontario*
Date	*February 4, 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.

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Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Ms. Alicia Koo*
Position	*Pediatric Oncology Pharmacist, SickKids Hospital*
Date	*02-02-2021*
☒	**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

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Dr. David Hodgson*
Position	*Radiation Oncologist, Princess Margaret Hospital, Medical Director, POGO*
Date	*February 4, 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			
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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	Dr. Laura Wheaton
Position	Pediatric Oncologist, Kingston Health Sciences Centre
Date	04-02-2021
☒	**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**			
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Add or remove rows as required	☐	☐	☐	☐