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CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the treatment of adult and pediatric patients with refractory or relapsed cHL, as monotherapy, who have failed ASCT, or who are not candidates for multi-agent salvage chemotherapy and ASCT

Sponsor: Merck Canada

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda should be reimbursed by public drug plans for the treatment of adult and pediatric patients with refractory or relapsed classical Hodgkin lymphoma (cHL) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be reimbursed to treat patients who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed as monotherapy and if the cost of pembrolizumab is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical study demonstrated that Keytruda delayed disease progression when compared with brentuximab vedotin.
- Keytruda may meet some of the needs that are important to patients by providing an outpatient treatment option with disease control benefits over currently available options and improved quality of life.
- Based on public list prices, Keytruda is not considered cost-effective relative to brentuximab vedotin at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population who are ASCT eligible. A price reduction is therefore required. The cost-effectiveness of Keytruda versus chemotherapy for ASCT-ineligible patients is unknown.
- Economic evidence suggests that a 13% to 29% price reduction is needed to ensure that Keytruda is cost-effective at a $50,000 per QALY threshold in an ASCT-eligible population. Further price reductions may be required in an ASCT-ineligible population.
- Based on public list prices, the 3-year budget impact is $5,410,737.

Additional Information

What Is Classical Hodgkin Lymphoma?

Hodgkin lymphoma is a type of blood cancer that originates from white blood cells called lymphocytes. cHL is a subtype of Hodgkin lymphoma that contains a particular type of abnormal lymphocytes called Reed-Sternberg cells. Most patients with cHL are diagnosed between the ages of 15 years and 39 years. In 2020, 1,000 Canadians were diagnosed with cHL and 100 died from the disease.

Unmet Needs in Classical Hodgkin Lymphoma

Current treatments are of limited effectiveness and may be associated with side effects. There is a need for treatments that could result in longer survival, longer remission, fewer side effects, and improved quality of life.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $8,800.00 in adults and $5,148.00 in children per 21-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab should be reimbursed, as monotherapy, for the treatment of refractory or relapsed classical Hodgkin lymphoma (cHL) in adult and pediatric patients who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (Keynote 204, N = 304) in adult patients with relapsed or refractory cHL demonstrated that treatment with pembrolizumab resulted in a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared with brentuximab vedotin (BV). Median PFS was 13.2 months (95% CI, 10.9 to 19.4) in the pembrolizumab arm compared with 8.3 months (95% CI, 5.7 to 8.8) in the BV arm (hazard ratio [HR] = 0.65; 95% CI, 0.48 to 0.88; P = 0.0027). Patients in the pembrolizumab arm showed higher response rates and longer duration of response, which support treatment benefit. Although evidence in pediatric patients was limited, pERC acknowledged that the response to pembrolizumab should be similar in adult and pediatric patients given the underlying disease biology.

Patients identified a need for individualized treatment options that could result in longer survival, longer remission, fewer side effects, and improved quality of life. pERC concluded that pembrolizumab provides an outpatient treatment option with PFS improvement and disease control benefit over currently available options and may improve quality of life. pERC noted that pembrolizumab is associated with significant but manageable side effects.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab in an adult population who are ASCT eligible is $733,624 to $2,071,825 per quality-adjusted life-year (QALY) compared with BV. This range reflects uncertainty concerning the potential cost savings associated with subsequent therapy use. Therefore, pembrolizumab is not cost-effective at a $50,000 per QALY willingness-to-pay threshold. A reduction in price of at least 13% to 29% is required for pembrolizumab to be considered cost-effective. Cost-effectiveness is unknown in an ASCT-ineligible population because of a lack of comparative evidence for pembrolizumab versus chemotherapy. Therefore, higher price reductions may be necessary to ensure cost-effectiveness in the ASCT-ineligible population. Under the assumption that efficacy in the pediatric population is similar to the adult population, pembrolizumab was dominant (less costly and more effective) in a pediatric population who are ASCT eligible.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Treatment with pembrolizumab should be initiated in adult and pediatric patients with relapsed or refractory classical Hodgkin lymphoma who either: 1.1. have failed to achieve a response or progressed after ASCT 1.2. are not eligible to receive ASCT due to chemotherapy-resistant disease, advanced age, or any significant coexisting medical condition that may have a negative impact on tolerability of ASCT.	Evidence from the Keynote 204 trial demonstrated that pembrolizumab resulted in significantly longer PFS and more durable antitumour responses in patients with relapsed or refractory cHL whose disease progressed after ASCT or who were ineligible for ASCT.
2. Patient must have good performance status upon treatment initiation with pembrolizumab.	There is no evidence to demonstrate a benefit of pembrolizumab in adult patients with ECOG PS > 1 at baseline because these patients were not enrolled in the Keynote 204 and Keynote 087 trials. There is no evidence to demonstrate a benefit of pembrolizumab in pediatric patients with a Lansky Play Scale < 50 or Karnofsky score < 50 because these patients were not enrolled in the Keynote 051 trial.
Renewal	
3. Treatment with pembrolizumab may be reimbursed for a maximum of 35 cycles (24 months).	In the Keynote 204 trial, a benefit of pembrolizumab was observed for up to 35 treatment cycles.
Discontinuation	
4. Treatment with pembrolizumab should be discontinued upon the occurrence of any of the following: 4.1. documented disease progression as per the International Working Group (IWG) response criteria 4.2. unacceptable toxicity.	In the Keynote 204 trial, treatment was continued up to 35 cycles unless disease progression or unacceptable toxicity occurred. This also aligns with the product monograph.
Prescribing	
5. Pembrolizumab should only be prescribed by clinicians who have been trained in oncology, and it should be administered under the supervision of a health professional experienced in the use of antineoplastic agents.	To ensure that pembrolizumab is prescribed only for appropriate patients and adverse effects are managed in a timely manner.
6. Pembrolizumab should be administered as monotherapy.	There is no evidence to suggest an additional benefit of pembrolizumab in combination with other treatments for relapsed or refractory cHL; pembrolizumab was administered as monotherapy in the Keynote 204, Keynote 087, and Keynote 051 trials.

Reimbursement condition	Reason
	Pricing
7. A reduction in price.	The ICER for pembrolizumab is $733,624 to $2,071,825 per QALY in the adult ASCT-eligible population. Pembrolizumab was less costly and more effective (dominant) when compared with BV in a pediatric ASCT-eligible population. CADTH undertook a price reduction analysis in an adult ASCT-eligible population. This analysis indicated that a 13% to 29% reduction in price is required to achieve an ICER of $50,000 per QALY. The range reflects uncertainty regarding subsequent therapy use. The cost-effectiveness of pembrolizumab is unknown in an ASCT-ineligible population meaning further price reductions may be required.

ASCT = autologous stem cell transplant; BV = brentuximab vedotin; cHL = classical Hodgkin lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; QALY = quality-adjusted life-year.

Implementation Guidance

Other Patient Characteristics for Eligibility

1. Patients who are otherwise eligible but decline to undergo transplant: pERC agreed with the clinical experts consulted by CADTH that transplant-eligible patients who refuse to receive ASCT would be eligible for treatment with pembrolizumab.
2. Patients with poor performance status: pERC discussed that the benefit for adult patients with an ECOG PS greater than 1 and pediatric patients with a Lansky Play Scale less than 50 (for children ≤ 16 years of age) or a Karnofsky score less than 50 (for children > 16 years of age) cannot be formally concluded from the reviewed Keynote trials because these patients were excluded. However, the clinical experts consulted by CADTH noted that these patients can experience treatment benefit. Based on pembrolizumab's manageable toxicity profile, pERC agreed that it would be reasonable to offer this treatment in situations in which the patient's poor performance status is caused by the underlying disease.
3. Patients who are currently receiving BV: pERC agreed with the clinical experts consulted by CADTH that these patients should continue receiving BV if they are responding well to the treatment and have not experienced disease progression.
4. Patients whose disease has progressed on a prior PD-1 or PD-L1 inhibitor: The clinical experts consulted did not support the use of pembrolizumab in these patients because the mechanism of action of checkpoint inhibitors is too similar. pERC also noted that patients who had received prior PD-1 or PD-L1 inhibitors were excluded from the Keynote 204 trial and that there are no data available to support the use of pembrolizumab in these patients.

Eligibility for Re-Treatment With Pembrolizumab

1. Patients who have completed the 35 cycles of treatment: pERC noted that the Keynote 204 trial did not allow for re-treatment with pembrolizumab. The clinical experts consulted by CADTH noted that there is evidence available from case reports and case series that supports re-treatment with pembrolizumab in patients who stopped treatment upon achieving a complete response after receiving 35 cycles, and patients who stopped achieving a good response after 35 cycles and discontinued treatment without signs of progression. pERC agreed with the clinical experts that these patients may be eligible for re-treatment with an additional 17 cycles of pembrolizumab upon experiencing disease progression.
2. Patients who proceed to transplant after responding to pembrolizumab and relapse after ASCT: The clinical experts indicated that there is currently insufficient evidence to support re-treatment in these patients. The Committee was not able to make an informed recommendation about re-treatment with pembrolizumab in these patients. However, pERC recognized that this a very small group of cHL patients with unmet need.
3. Patients who experience disease progression during a drug holiday: The clinical experts consulted by CADTH noted that there is currently no robust evidence to support resuming treatment after a progression event that may occur during a drug holiday. However, pERC felt it may be reasonable to restart treatment in these patients.

Optimal Sequencing With Other Treatment Options

1. pERC was unable to make an informed recommendation on the sequencing options after pembrolizumab because the Committee did not review evidence to inform optimal sequencing of treatments after disease progression with pembrolizumab.
2. pERC discussed the optimal sequencing of pembrolizumab and BV in patients with relapsed or refractory cHL who are transplant-ineligible and noted that it did not review sufficient evidence to inform the clinical scenario in which BV is used in patients who experience disease progression after pembrolizumab. pERC acknowledged that, in general, there is potential benefit in the sequencing of drugs that have different mechanisms of action. However, the Committee was unable to make an informed conclusion regarding the sequence of these treatments for the indication under review.

Discussion Points

- Patient and clinician input to pERC recognized that, if funded, pembrolizumab would address the unmet need for therapies for patients who have failed ASCT or ASCT-ineligible patients who have had no publicly funded access to novel therapies. pERC noted that reimbursement of BV for patients who are not candidates for ASCT because of age, comorbidities, or refractoriness to salvage therapy is not uniform across Canada and agreed that this has resulted in a significant treatment gap for this subgroup of patients in most provinces.
- pERC discussed the efficacy results from the Keynote 204 comparative randomized phase III trial that showed a clinically meaningful and statistically significant improvement in PFS (by blinded independent central review assessment) in patients who received pembrolizumab monotherapy versus those who received BV (HR = 0.65; 95% CI = 0.48 to

0.88; P = 0.0027). Objective response rate (ORR) was 66% in the pembrolizumab group versus 54% in the BV group; the median response durations were 20.7 months and 13.8 months in the pembrolizumab and BV groups, respectively.

- pERC discussed the benefit of pembrolizumab for pediatric patients and acknowledged that the studies identified in this review do not provide a sufficient evidence base for a standalone reimbursement recommendation for the pediatric population. The clinical experts consulted by CADTH noted that clinical characteristics and treatment approaches are similar for adult and pediatric patients with cHL, regardless of patient age. As such, although the median age of adult patients from the Keynote 87 and Keynote 204 trials ranged from 32 years to 40 years, the clinical experts believed these results would also be applicable to cHL patients younger than 18 years of age. pERC agreed that it is biologically plausible to extrapolate the adult trial results to pediatric patients and assume pembrolizumab may also benefit pediatric patients.
- pERC deliberated on the toxicity profile of pembrolizumab in the patient population of interest and acknowledged that patients who received pembrolizumab in the Keynote 204 trial were more likely to experience immune-related adverse events (AEs) and serious immune-mediated AEs compared with the BV-treated patients. However, pERC considered pembrolizumab to have an overall manageable toxicity profile.
- pERC discussed that pembrolizumab provides an outpatient treatment option that offers PFS improvement and disease control benefit over currently available options and it may improve quality of life.
- pERC discussed the uncertainty in estimating the ICER for pembrolizumab in adult ASCT-eligible patients, noting that the ICER was highly dependent on the subsequent therapies that patients received. The Committee felt both reanalyses, which used different assumptions regarding subsequent therapy use, were relevant to reflect the underlying uncertainty around cost-effectiveness and the associated price reductions.

Background

Pembrolizumab has a Health Canada indication as a treatment for adult and pediatric patients with refractory or relapsed cHL, as monotherapy, who have failed ASCT, or who are not candidates for multi-agent salvage chemotherapy and ASCT. Pembrolizumab is an IgG4 monoclonal anti–PD-1 antibody. It is available as a 100 mg/4 mL solution for infusion in a single-use vial, and the Health Canada–approved dose for cHL is 200 mg (for adult patients) or 2 mg/kg (for pediatrics; up to a maximum of 200 mg) administered as an IV infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 phase III, open-label, randomized controlled trial (Keynote 204) and 1 phase I/II, single-arm trial (Keynote 87) in adult patients with relapsed or refractory cHL, and 1 non-randomized, single-arm trial in pediatric patients with relapsed or refractory cHL

- Patients' perspectives gathered by 1 patient group: Lymphoma Canada
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Three clinical specialists with expertise in diagnosing and treating patients with cHL
- Input from 3 clinician groups: Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO DAC), Lymphoma Canada, and the Pediatric Oncology Group of Ontario (POGO)
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient advocacy group, Lymphoma Canada, provided input based on the results of 2 online surveys which yielded 128 responses. The patient group input indicated that patients often experience fatigue, trouble breathing, fever and/or chills, loss of appetite, itching, anxiety, problems concentrating, loss of sexual desire, and memory loss. The majority of survey participants reported they had to quit working or school due to their diagnosis. Patients identified a need for individualized treatment options that could result in longer survival, longer remission, fewer side effects, and improve quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts highlighted that patients with cHL who relapse after ASCT or who are not candidates for multi-agent chemotherapy and ASCT have limited treatment options. The available treatments can be associated with significant side effects and are seldom curative. Both the pediatric and adult cHL experts expected pembrolizumab to be effective earlier in the treatment paradigm but agreed that it was also appropriate for use in patients who have failed or are ineligible for ASCT. However, patients who have recently been on therapy for autoimmune disease, patients with poor performance status, patients with organ failure, and those at high risk of autoimmune side effects may not be suited for pembrolizumab. According to the clinical experts consulted by CADTH, a response to therapy would be marked by resolution of disease symptoms, radiologic evidence of disease improvement, improved ability to perform activities of daily living, reduction in size of lymph nodes and other disease sites, and in some patients, becoming eligible for an allogeneic or ASCT. Clinical experts noted that patients receiving pembrolizumab are typically assessed clinically every 3 weeks and radiologically every 3 to 4 cycles. Treatment should be discontinued if any of the following occurs: disease progression, severe immune-related AEs, or severe infusion or hypersensitivity reactions.

Clinician Group Input

Twelve clinicians representing the following 3 clinician groups provided input for this review: Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO DAC), Lymphoma Canada, and the Pediatric Oncology Group of Ontario (POGO) The input provided by the clinician groups was consistent with the advice provided from the clinical experts consulted by CADTH.

Drug Program Input

Input was obtained from all the provinces participating in CADTH Drug Reimbursement Reviews. The following were identified as factors that could impact the implementation:

- clarity on eligible patients
- eligibility for re-treatment with pembrolizumab
- optimal sequencing with other treatment options.

Clinical Evidence

Description of Studies

Keynote 51

The Keynote 51 trial was a non-randomized, open-label, single-arm trial of pembrolizumab 2 mg/kg administered intravenously every 3 weeks in 7 pediatric patients aged 3 years to 18 years with relapsed or refractory cHL. A 28-day screening period was performed before patient enrolment to collect necessary laboratory, diagnostic, and demographic information and assess study eligibility. The Keynote 51 trial evaluated safety and efficacy, including ORR, duration of response (DOR), PFS, and overall survival (OS) for 35 cycles of treatment or until discontinuation due to disease progression or unacceptable AEs. Post-treatment follow-up assessments occurred every 12 weeks. The study was funded by the sponsor and had a data cut-off date of January 2020.

Keynote 87

The Keynote 87 trial was a non-randomized, single-arm study of pembrolizumab 200 mg administered intravenously every 3 weeks in adult patients with cHL. A 28-day screening period was performed before patient enrolment to collect necessary laboratory, diagnostic, and demographic information and to assess study eligibility. The study evaluated ORR, PFS, DOR, health-related quality of life (HRQoL), and OS, with a treatment duration up to 2 years or until discontinuation of treatment due to disease progression or occurrence of unacceptable AEs. Post-treatment follow-up assessments occurred every 12 weeks. The study was funded by the sponsor with a data cut-off date of March 2019. The study consisted of 3 cohorts:

- Cohort 1: Patients who failed to respond to or progressed after ASCT and also relapsed after or failed to respond to treatment with BV post-ASCT (N = 69)
- Cohort 2: Patients who were ineligible for ASCT and relapsed after or failed to respond to BV (N = 81)
- Cohort 3: Patients who failed to respond to or progressed after ASCT and had not yet received BV (N = 60).

Keynote 204

The Keynote 204 trial was a phase III, randomized (1:1 ratio), active-controlled, open-label clinical trial comparing pembrolizumab 200 mg administered intravenously every 3 weeks (N = 151) with BV 1.8 mg/kg (maximum dose of 180 mg) administered intravenously every 3 weeks (N = 153) in adult patients with relapsed or refractory cHL. A 28-day screening period occurred before patient enrolment to collect necessary laboratory, diagnostic, and

demographic information and to assess study eligibility. The study evaluated PFS, OS, ORR, DOR, time to response, HRQoL, and safety for 35 cycles of treatment or until early discontinuation due to disease progression, unacceptable AEs, or other reasons to withdraw therapy. Post-treatment follow-up assessments occurred every 12 weeks. The study was funded by the sponsor with a data cut-off date of February 2020.

Baseline Characteristics

Patients in the Keynote 51 trial had a median age of 15 years, whereas the median age in the Keynote 87 and Keynote 204 trials ranged from 32 years to 40 years. The proportion of female patients ranged from 41.2% among BV-treated patients in the Keynote 204 trial to 47.8% in cohort 1 of the Keynote 87 trial. The proportion of patients with an ECOG score of zero ranged from 42.0% in cohort 1 of the Keynote 87 trial to 65.4% among BV-treated patients in the Keynote 204 trial. The proportion of patients with an ECOG score of zero was 54.3% and 48.3% in cohorts 2 and 3, respectively, in the Keynote 87 trial, and was 57.0% in the pembrolizumab arm of the Keynote 204 trial. Cohorts 1 and 3 of the Keynote 87 trial had higher rates of prior radiation use (46.4% and 40.0%, respectively) relative to either arm in the Keynote 204 trial (pembrolizumab: 38.4%; BV: 39.9%), whereas those in cohort 2 had lower rates (25.9%). Patients in either arm of the Keynote 204 trial had more bulky disease (pembrolizumab: 23.2%; BV: 16.3%) relative to any cohort in the Keynote 87 trial (cohort 1: 2.9%; cohort 2: 6.2%; cohort 3: 1.7%). Baseline B symptoms were present in 30.4%, 33.3%, and 31.7% of patients in cohort 1, cohort 2, and cohort 3, respectively, in the Keynote 87 trial. Baseline B symptoms were also present in 28.5% and 23.5% of patients who received pembrolizumab and BV, respectively, in the Keynote 204 trial. The 2 arms within the Keynote 204 trial seem relatively balanced, except that patients who were in the pembrolizumab arm had higher rates of bulky disease compared to patients in the BV arm(23.2% versus 16.3%). Patients in the Keynote 204 trial could be treated with a subsequent anticancer medication after pembrolizumab or BV was discontinued.

Efficacy Results

Progression-Free Survival

In the Keynote 51 trial, 3 patients (42.9%) experienced an event (disease progression or death). In the Keynote 87 trial, there were 43 (62.3%), 54 (66.7%), and 36 (60.0%) events in cohorts 1, 2, and 3, respectively. In the Keynote 204 trial, the proportion of patients experiencing an event was similar between the pembrolizumab (53.6%) and BV (57.5%) arms. In the Keynote 51 trial, the median PFS was reported to be 11.1 months (95% CI, 2.6 to not reported). In the Keynote 87 trial, the median PFS was reported to be 16.4 months (95% CI, 11.3 to 27.6), 11.1 months (95% CI, 7.3 to 13.5), and 19.4 months (95% CI, 8.4 to 22.1) in cohorts 1, 2, and 3, respectively. In the Keynote 204 trial, the median PFS was higher in the pembrolizumab arm (median = 13.2 months; 95% CI, 10.9 to 19.4) than the BV arm (median = 8.3 months; 95% CI, 5.7 to 8.8). In the Keynote 51 trial, the PFS rate at 12 months was 27.8% (95% CI not reported). In the Keynote 87 trial, the PFS rate at 12 months was 61.3%, 43.0%, and 53.9% in cohorts 1, 2, and 3, respectively (95% CI not reported). In the Keynote 204 trial, the 12-month PFS rate was higher in the pembrolizumab arm (53.9%; 95% CI, 45.0% to 61.9%) than the BV arm (35.6%; 95% CI, 26.9% to 44.4%). In the Keynote 87 trial, the 24-month PFS rate was 41.6%, 21.9%, and 34.0% in cohorts 1, 2, and 3, respectively (95% CI not reported). In the Keynote 204 trial, the 24-month PFS rate was 35.4% (95% CI, 26.2% to 44.6%) in the pembrolizumab arm and 25.4% (95% CI, 17.1% to 34.5%) in the BV arm. The hazard ratio

for time to progression was 0.65 (95% CI, 0.48 to 0.88), which was statistically significant (P = 0.0027).

Overall Survival

In the Keynote 51 trial, minimal information regarding OS was provided. In the Keynote 87 trial, 15.9%, 16.0%, and 15.0% of patients in cohorts 1, 2, and 3, respectively died. [redacted]. Median survival was not reported in the Keynote 51 trial and not reached in the Keynote 87 trial [redacted]. In the Keynote 51 trial, 100% of patients were alive at 12 months. In the Keynote 87 trial, OS at 12 months was 95.7%, 96.2%, and 96.6% in cohorts 1, 2, and 3, respectively (95% CI not reported). [redacted] At 24 months in the Keynote 87 trial, 92.6%, 91.0%, and 89.4% of patients were alive in cohorts 1, 2, and 3, respectively (95% CI not reported). [redacted]

Objective Response Rate

In the Keynote 51 trial, 42.9% (95% CI, 9.9% to 81.6%) of patients experienced a partial or complete response. In the Keynote 87 trial, 78.3% (95% CI, 66.7% to 87.3%), 64.2% (95% CI, 52.8% to 74.6%), and 71.7% (95% CI, 58.6% to 82.5%) of patients experienced a partial or complete response in cohorts 1, 2, and 3, respectively. In the Keynote 204 trial, more partial or complete responses were observed in the pembrolizumab arm (65.6%; 95% CI, 57.4% to 73.1%) relative to the BV arm (54.2%; 95% CI, 46.0% to 62.3%), which was associated with a statistically insignificant 11.3% (95% CI, 0.2% to 22.1%) difference in favour of pembrolizumab.

Complete Response Rate

In the Keynote 51 trial, 28.6% of patients (95% CI, 3.7% to 71.0%) experienced a complete response. In the Keynote 87 trial, 26.1% (95% CI, 16.3% to 38.1%), 25.9 (95% CI, 16.8% to 36.9%), and 31.7% (95% CI, 20.3% to 45.0%) of patients in cohorts 1, 2, and 3, respectively, experienced a complete response. In the Keynote 204 trial, the complete response rate was comparable between the pembrolizumab (24.5%, 95% CI, 17.9% to 32.2%) and BV (24.2%, 95% CI, 17.6% to 31.8%) arms.

Duration of Response

In the Keynote 51 trial, median DOR was not reached. In the Keynote 87 trial, the median DOR in cohorts 1, 2, and 3 were 25.0 months (range = 0 to 36.1), 11.1 months (range = 0 to 35.9), and 16.8 months (range = 0 to 39.1), respectively. In the Keynote 204 trial, the median DOR was higher among patients in the pembrolizumab arm (median = 20.7 months; range; =: 0 to 33.2) than in patients in the BV arm (median = 13.8 months; range = 0 to 33.9).

Time to Response

Median time to response in the Keynote 51 trial was 2.6 months (range = 2.1 to 2.8). The median time to response in cohort 1, cohort 2, and cohort 3 of the Keynote 87 trial was 2.7 months (range = 2.1 to 12.9), 2.8 months (range = 2.2 to 11.0), and 2.8 months (range = 2.6 to 16.5), respectively. Finally, the median time to response in the pembrolizumab arm of the Keynote 204 trial was 2.8 months (range = 1.0 to 31.2) and 2.8 months (range = 1.3 to 7.3) in the BV arm.

Health-Related Quality of Life

HRQoL data were only measured in the Keynote 87 and Keynote 204 trials. In the Keynote 87 trial, the least squares mean (LSM) change in EORTC QLQ-C30 global health status between baseline and week 24 was 11.8, 13.9, and 6.6 in cohorts 1, 2, and 3, respectively. No confidence intervals were reported for the Keynote 87 trial. In the Keynote 204 trial, the LSM change in EORTC QLQ-C30 global health status between baseline and week 24 was 8.60 points (95% CI, 3.89 to 13.31) higher in the pembrolizumab arm versus the BV arm. Consistent results were reported for the EORTC QLQ-C30 physical functioning scale (LSM change = 6.24; 95% CI, 1.87 to 10.62), EQ-5D-3L utility score (LSM change = 0.09; 95% CI, 0.04 to 0.14) and EQ-5D-3L visual analogue scale (LSM change = 6.12; 95% CI, 1.91 to 10.34).

Harms Results

In the Keynote 51 trial, 85.7% of patients experienced at least 1 AE. In the Keynote 87 trial, 98.6%, 98.8%, and 95.0% of patients experienced at least 1 AE in cohort 1, cohort 2, and cohort 3, respectively. In the Keynote 204 trial, 98.0% of patients in the pembrolizumab arm and 94.1% in the BV arm experienced an AE. The most common AEs were pyrexia, vomiting, headache, abdominal pain, anemia, cough, fatigue, diarrhea, and upper respiratory tract infections. In the Keynote 204 trial, patients who received pembrolizumab were more likely than those who received BV to experience endocrine disorders (20.3% versus 3.9%); infections (66.2% versus 45.4%); musculoskeletal and connective tissue disorders (37.8% versus 31.6%); neoplasms (7.4% versus 1.3%); renal or urinary disorders (14.9% versus 4.6%); respiratory, thoracic, or mediastinal disorders (45.3% versus 26.3%); and skin and subcutaneous tissue disorders (43.9% versus 36.8%). However, they were less likely to experience blood or lymphatic system disorders (18.2% versus 25.7%), gastrointestinal disorders (43.9% versus 52.0%), and nervous system disorders (26.4% versus 50.7%).

In the Keynote 51 trial, 28.6% of patients experienced at least 1 serious AE. In the Keynote 87 trial, 21.7%, 22.2%, and 25.0% of patients experienced a serious AE in cohort 1, cohort 2, and cohort 3, respectively. In the Keynote 204 trial, 29.7% of patients in the pembrolizumab arm and 21.1% of patients in the BV arm experienced a serious AE. The most common serious AEs in the Keynote 51 trial were diaphragmatic hernia and pneumonia. The most common serious AEs in cohort 1 of the Keynote 87 trial were pneumonia and pericarditis. The most common serious AE in cohort 2 of the Keynote 87 trial was herpes zoster and the most common serious AEs in cohort 3 of the Keynote 87 trial were pyrexia and pneumonitis. There were no notable differences in frequency of serious AEs between the pembrolizumab and BV arms in Keynote 204. The most common serious AEs in the pembrolizumab arm of the Keynote 204 trial were infections or infestations; respiratory, thoracic, or mediastinal disorders; neoplasms; general disorders or administration site conditions; and hepatobiliary disorders. The most common serious AEs in the BV arm of the Keynote 204 trial were infections or infestations; respiratory, thoracic, or mediastinal disorders; nervous system disorders; gastrointestinal disorders; and general disorders or administration site conditions.

No patients in the Keynote 51 trial discontinued treatment due to an AE, whereas 11.6%, 6.2%, and 8.3% of patients in cohort 1, cohort 2, and cohort 3, respectively, of the Keynote 87 trial discontinued treatment due to an AE. In the Keynote 204 trial, 13.5% and 17.8% of patients receiving pembrolizumab and BV, respectively, discontinued treatment due to an AE.

In the Keynote 51 trial, 28.6% of patients experienced at least 1 immune-mediated AE. In cohort 1, 2, and 3 of the Keynote 87 trial, 31.9%, 32.1%, and 38.3% of patients, respectively,

experienced at least 1 immune-mediated AE. In the Keynote 204 trial, more patients in the pembrolizumab arm (35.8%) than the BV arm (13.8%) experienced an immune-mediated AE. No patients in the Keynote 51 trial experienced a serious immune-mediated AE. In the Keynote 87 trial, 4.3%, 2.5%, and 5.0% of patients in cohort 1, cohort 2, and cohort 3 experienced a serious immune-mediated AE. In the Keynote 204 trial, more patients treated with pembrolizumab than BV-treated patients experienced a serious immune-mediated AE (8.8% versus 3.3%).

Limitations of the Included Studies

The Keynote 51 and Keynote 87 trials were single-arm, open-label trials, whereas Keynote 204 was an open-label randomized controlled trial. The single-arm trials are unable to provide definitive evidence of a medication's superiority over the standard of care, whereas the open-label design of all trials puts them at risk of bias in either direction. However, some bias from the open-label design would be attenuated by the fact that tumour progression was assessed by an independent and blinded assessor in all 3 trials. Further, the randomized nature of the Keynote 204 trial will balance prognostic factors at the beginning of the study. The Keynote 204 trial permitted patients to be treated with a subsequent anticancer medication following discontinuation of the trial medication (pembrolizumab or BV). This could introduce a potential bias to the efficacy analyses, particularly the OS estimates in the intention-to-treat population. The Keynote 51 trial did not originally aim to specifically recruit patients with relapsed or refractory cHL patients. Following a protocol amendment, 7 pediatric participants with refractory or relapsed cHL were identified among the study participants; the sample size is insufficient to be representative of the true treatment effect in children with this condition. The clinical experts consulted by CADTH believed that it might be biologically plausible to extrapolate the results of the Keynote 87 and Keynote 204 trials to pediatric patients and assume pembrolizumab may also benefit pediatric patients. However, evidence from studies with rigorous methodological quality are needed to confirm pembrolizumab's benefits in the pediatric population. Further, it is uncertain if the pembrolizumab dosing regimen used in the Keynote 87 and Keynote 204 trials could be extrapolated to pediatric patients for whom the pharmacokinetic profile of pembrolizumab may differ.

Economic Evidence

Table 2: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partition survival model
Target populations	• Adult patients with refractory or relapsed classical Hodgkin lymphoma who relapsed post-ASCT or were ineligible for ASCT • Pediatric patients with refractory or relapsed classical Hodgkin lymphoma who relapsed post-ASCT or were ineligible for ASCT
Treatment	Pembrolizumab
Submitted price	Pembrolizumab 100 mg: $4,400.00

Component	Description
Treatment cost	The cost for pembrolizumab is $4,400 per 100 mg vial, equating to a cost per 21-day cycle of $8,800.00 in adults and $5,148.00 in a pediatric population (assuming no wastage)
Comparator	Brentuximab vedotin (BV)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	35 years
Key data source	• KEYNOTE-204 trial to inform PFS • Published literature to inform overall survival
Submitted results	• Adult population: Pembrolizumab is dominant (incremental cost savings $24,231; incremental QALYs gained 0.840) • Pediatric population: Pembrolizumab is dominant (incremental cost savings $47,937; incremental QALYs gained 0.843)
Key limitations	• The sponsor, in their base case, evaluated pembrolizumab against BV in a mixed population consisting of individuals who were either ASCT eligible (and relapsed) or ineligible. Across Canada, BV has limited utilization in an ASCT-ineligible subpopulation, and it was not recommended by the CADTH pan-Canadian Oncology Drug Review in this patient population. • Chemotherapy is primarily used in the treatment of patients who are ASCT ineligible. Given a lack of direct or indirect comparative evidence, the cost-effectiveness of pembrolizumab vs. chemotherapy, and therefore the cost-effectiveness in an ASCT-ineligible population, could not be determined. • Treatment-specific utility values were used by the sponsor in their model, which overestimated long-term QALY gains associated with pembrolizumab. The utility benefit for pembrolizumab during the trial was applied across a 35-year time horizon, thus assuming that even post-treatment, pembrolizumab provides an indefinite utility benefit. • The sponsor assumed the observed PFS benefits for pembrolizumab in the trial continued past the trial duration. Clinical experts consulted by CADTH for this review anticipated that any benefit from pembrolizumab over existing therapies would likely be negligible after 10 years; therefore, treatment waning needed to be incorporated in long-term extrapolations of PFS. • The sponsor's base case used data which did not censor individuals who received an SCT after primary treatment initiation, thus capturing the benefit of an SCT in PFS estimates. This approach was deemed inappropriate given insignificant but differential SCT rates between treatments, and that its inclusion artificially inflates PFS extrapolation across the model time horizon. • Subsequent therapy use did not align with what was seen in the trial. • Drug wastage was not incorporated in the sponsor's base case, however the product monograph for pembrolizumab states it is supplied as a single-use vial, and weight-based dosing is used in the pediatric population. • The sponsor's model was unnecessarily complex and lacked transparency, preventing CADTH from fully validating the model and its findings. CADTH identified some errors in the model coding.

Component	Description
CADTH reanalysis results	• In the CADTH reanalysis only patients who are ASCT eligible were evaluated, as the cost-effectiveness of pembrolizumab in patients who are ASCT ineligible could not be determined given a lack of comparative evidence on pembrolizumab vs. chemotherapy. • Changes to derive a CADTH base case included: only evaluating an ASCT eligible population; adding health state specific utility values; incorporating treatment waning; using PFS data that censors SCT events; including drug wastage; and using Canadian gemcitabine costs. • Based on the CADTH reanalysis in patients who are ASCT eligible, pembrolizumab compared with BV is: ◦ Dominant (less costly and more effective) in a pediatric population ◦ Associated with an ICER of $733,624 per QALY gained in an adult population • A price reduction of 13% is required for pembrolizumab to be considered cost-effective at a WTP threshold of $50,000 per QALY in an adult ASCT-eligible population. • Using an alternative breakdown of subsequent therapy use from the trial, the ICER for pembrolizumab compared with BV increased to $532,115 in pediatrics and $2,071,825 in adults. A 29% price reduction is needed to ensure cost-effectiveness at a $50,000 per QALY threshold in the adult population. • The cost-effectiveness of pembrolizumab compared with chemotherapy in patients who are ASCT ineligible is unknown.

ASCT = autologous stem cell transplant; BV = brentuximab vedotin; ICER = incremental cost-effectiveness ratio; LY = life-year; PFS = progression-free survival; QALY = quality-adjusted life-year; SCT = stem cell transplant; WTP = willingness to pay.

Budget Impact

CADTH's reanalysis removed clinical trials' market share and redistributed it among existing treatments, increased the first-year uptake rate of pembrolizumab, included drug wastage, and revised the price of gemcitabine to the Canadian list price. Based on the CADTH base case, the expected budget impact for funding pembrolizumab is $305,213 in year 1, $2,070,116 in year 2, and $3,035,408 in year 3, for a total 3-year budget impact of $5,410,737.

CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: July 15, 2021

Regrets: None

Conflicts of interest: None