

CADTH REIMBURSEMENT REVIEW

Patient Input

PEMBROLIZUMAB (Keytruda) (Merck Canada)

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.

CADTH received patient input from:
Lymphoma Canada

February 5, 2021

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Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	Pembrolizumab (Keytruda) for 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 Patient Group	Lymphoma Canada
Author of the Submission	██████████
Name of the Primary Contact for This Submission	██████████
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1. About Your Patient Group

Lymphoma Canada is a national Canadian registered charity that empowers the lymphoma community through education, support, advocacy, and research. Based out of Toronto (ON), we collaborate with patients, caregivers, healthcare professionals, and other organizations and stakeholders, to promote early detecting, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma, and working together to find a cure. For more information about our organization, please visit us at www.lymphoma.ca

2. Information Gathering

Lymphoma Canada (LC) conducted 2 anonymous online surveys for Hodgkin Lymphoma (HL) patients. Both were conducted to understand patient's experience with their lymphoma and with pembrolizumab. The surveys were conducted and collected responses from June 5th -30th, 2017 and November 6th -January 13th, 2020. Links to the surveys were sent via e-mail to patients registered on the LC database. The links were also made available via LC Twitter and Facebook accounts, HL-specific forums and social media pages and groups, Canadian and American Cancer Society message boards, Facebook groups organized for lymphoma patients and survivors, and physicians at leading clinical trial sites across Canada. Telephone interviews were conducted with 3 HL patients in Canada who had direct experience with pembrolizumab. The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into surveys so respondents were asked questions only relevant to them. Open-ended responses to surveys that reflected the sentiment of a majority are included verbatim to provide a deeper understanding of patient perspectives.

Overall, 91 patients provided responses to the first survey (2017) and 37 patients provided responses to the second survey (2020-2021). There were no caregivers that provided their input. For patients who

provided their demographics (103/128), 55% live in Canada. Of those that provided their demographics (94/128), 46% are female and 78% are between the age of 20-59 years (Table 1 and 2).

Table 1: Country of survey respondents (128 respondents)							
Respondents	CAN	USA	UK	EU	Other	Skipped	Total
Patients <u>WITHOUT</u> Pembrolizumab experience	64	4	12	6	8	25	119
Patients <u>WITH</u> Pembrolizumab experience	7	2	-	-	-	-	9

Table 2: Gender and age of survey respondents								
Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	skipped	Female	Male	Skipped
Patients <u>WITHOUT</u> Pembrolizumab experience	3	38	29	15	43	60	25	43
Patients <u>WITH</u> Pembrolizumab experience	0	7	0	2	0	3	6	0

3. Disease Experience

The majority of patients (63%; 80/128) who completed the survey or participated in an interview were a teenager or young adult (13-39 years-old) when they were diagnosed with HL. Patients were asked about their experience receiving their diagnosis from their healthcare team: 11% of patients did not have all of their questions answered by their doctor, while 27% did not know what questions to ask their doctor and were not happy with the explanation their doctor provided (81 respondents).

Symptoms of HL that most commonly affected respondents' quality of life at diagnosis were fatigue or lack of energy (77%), enlarged lymph nodes (66%), drenching night sweats (44%), itching (40%), persistent cough (40%), and unexplained weight loss (35%) (97 respondents). Other symptoms affecting the quality of life for > 10% of respondents included unexplained weight loss, loss of appetite, trouble breathing, fever and chills and chest pain.

Respondents were asked which aspects of their life, including mental and emotional impacts associated with their disease and treatment, **NEGATIVELY** affected their quality of life at diagnosis. The majority of respondents had one or more symptom negatively impact their quality of life at diagnosis (Table 3).

Table 3: Impact of HL on patients' mental and emotional well-being (97 respondents)		
Symptom	# of respondents	% of respondents
Anxiety/worry	72	74%
Stress of diagnosis	62	64%
Difficulty sleeping	50	52%
Problems concentrating	43	44%
Loss of sexual desire	35	36%
Depression	27	28%
Memory loss	12	12%

Only a small portion of patients (n=35) provided information about which symptoms affect their current quality of life. The symptom profile between diagnosis and current is slightly different. Current symptoms patients experience includes fatigue/lack of energy (51%), no symptoms (43%), trouble breathing (17%), fever/chills (14%), loss of appetite (14%), and itching (14%). Current psychological and

social impacts for HL patients include anxiety/worry (53%), problems concentrating (42%), loss of sexual desire (33%), and memory loss (30%) (113 respondents).

Patients indicated how their mental health, emotions, and disease and treatment, have had a NEGATIVE impact on different aspects of their life. Notably, 64% and 59% indicated that their HL negatively impacted their ability to work and their personal image, respectively. Responses are summarized in Table 4.

Table 4: Effect of HL on day-to-day life of patients (109 respondents)		
Aspect of life NEGATIVELY impacted by HL	# of respondents	% of respondents
Ability to work	70	64%
Personal image	64	59%
Family	59	54%
Friendships	49	45%
Intimate relations	52	48%
Ability to attend school	19	17%

As described by 3 patients:

"In remission since 2019 but dealing with long-term effects like "chemo brain", some PTSD and anxiety about recurrence. Plus, because of COVID and increased risk of complications if I catch it, I'm more nervous than most about gathering (when permitted) with even small groups of people."

"I immediately lost my job, as I worked in an environment not safe for someone with a compromised immune system. I had to give up my study at university, and both devastated me. I was very fit, but now if I try to exercise at the same level I become exhausted very easily. It's very hard."

"I experience more fatigue than I used to and although I'm able to work, I'm exhausted at the end of the day. Exercise is difficult to do on a weekday."

4. Experiences with Currently Available Treatments

All patient respondents who provided information had previously received treatment or were currently undergoing treatment. Of the 85 patients who provided responses regarding their treatments, 94% had been treated with at least one line of conventional chemotherapy and 24% of respondents had received ≥ 3 lines of therapy. The most common conventional chemotherapy regimen received was ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) (85%), followed by GDP (gemcitabine, dexamethasone, cisplatin) (11%), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) (7%), and Brentuximab Vedotin (6%). Other types of treatment individuals received included radiation therapy (49%), autologous stem cell transplant (20%), and surgery (25%) (83 respondents). Of the 101 respondents who indicated their treatment phase, 85% are in remission following their most recent line of therapy, of which 32% have been in remission for longer than 5 years.

Side effects of current treatments: Of great concern to many respondents was the toxicity and side effects associated with their previous treatments. The most common side effects respondents experienced during their HL treatments are listed in Table 5.

Table 5: Side effects of HL Treatments (90 Respondents)			
Side effect (n)	% of respondents	Side effect (n)	% of respondents
Fatigue (86)	96%	Diarrhea (38)	42%
Hair loss (83)	92%	Cough or Breathing difficulties (44)	49%
Nausea/vomiting (80)	89%	Back/joint pain (34)	38%
Mouth sores (56)	62%	Skin rashes/severe itching (32)	36%
Peripheral neuropathy (52)	58%	Loss of menstrual periods (27)	30%
Anemia and/or neutropenia (59)	66%	Infections (25)	28%
Low platelets (39)	43%		

When asked which side effects they found most difficult to tolerate, respondents most commonly reported nausea/vomiting (43%), fatigue (41%), hair loss (13%), mouth sores (10%), and bowel obstruction (4%) (68 respondents). Long-lasting side effects of treatments, reported lasting longer than 2 years or appearing 2 years or later after treatment, included fatigue (66%), “chemo-brain” (60%), peripheral neuropathy (41%), loss of menstrual periods (18%) and sterility (18%), chest pain or infection (15%), and thyroid problems (20%) (80 respondents).

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

Table 6: Impact of treatment on quality of life (90 respondents)		
Treatment aspect	Weighted average	Number of responses
Fatigue	4.2	90
# of clinic visits	3.2	89
Infusion time	3.0	90
Infusion reaction	3.3	88
# of infections	2.1	90

Treatment also had a very significant impact on many respondents’ ability to work, travel and intimate relationships (Table 7).

Table 7: Impact of treatment on daily living (90 respondents)		
Activity	Weighted average	Number of responses
Work	3.6	90
Travel	3.5	89
Intimate relations	3.5	90
Family	3.3	90
Friendships	3.3	90
School	1.2	87

As reported by 3 respondents on their experience with HL treatments and side effects:

"Treatments were very difficult, and it took everything in me to complete my 6-month protocol. In fact, the last 2 [months] I almost begged not to have [treatment]. I have a lot of fear of recurrence because I feel I could not go through that experience again especially now that my body has changed so drastically since my initial experience with chemo. I felt young and fit prior to treatment and 3 years later I feel physically like an old woman which I was not mentally prepared for."

"The chemotherapy I received before and with my bone marrow transplant put me into premature menopause (i'm in my 20s) and that has negatively affected my intimate relations."

"I was unable to finish the first semester of nursing school at the time. I was unable to help coach basketball because of low self esteem from hair loss and fatigue. Did not really want to go places and visit friends because of hair loss."

Access to treatment: 75/90 (83%) of individuals were able to access treatment in their own community. For those who could not access treatment in their own community (15), reasons included living in a community without a cancer centre (73%), or the treatment was not available at their local cancer centre (26%). The most commonly reported financial impact of treatment was absence from work or school (72%). Other financial burdens included parking (45%), cost of medications (31%), and travel to and from appointments (22%). Additional financial costs are reported in Table 8.

Table 8: Financial implications of treatment for HL patients (86 respondents)		
Financial impact	% of respondents	Number of respondents
Absence from work or school	72%	62
Parking	45%	39
Cost of medications	31%	27
Travel	22%	19
None	14%	12
Accommodation	7%	6
Drug disposal issues	3%	3

5. Improved Outcomes

Patient preferences: From a patient perspective, patients seek individualized treatment options that will offer disease control and remission, ideally with fewer side effects than current treatments. Respondents were asked to rate, on a scale of 1 -5 (1 = not important; 5 = extremely important), the importance of various factors regarding a new drug or therapy for HL. Only a small portion of respondents (n=24) were able to provide an answer, stating "longer survival" and "longer remission" as the most important outcomes for a new therapy (Table 9).

Table 9: Treatment preferences (24 respondents)		
Treatment outcome or factor	Rating = 5 (Extremely important)	Weighted average
Longer survival	96%	4.96
Better quality of life	92%	4.92
Longer remission	96%	4.88
Fewer side effects	67%	4.46

Respondents were asked if they would be willing to tolerate the side effects of a new treatment if they were short term. Of the 89 respondents, 55% would be willing to tolerate potential short term side effects, while 31% were not; the remaining were unsure (14%). Respondents were also asked if they would choose a treatment with known side effects, potentially serious, if their doctor recommended it was the best option for them. Of the 100 patients who answered this question, 53% selected “Yes”, while only 3% selected “No”; the remaining 44% were unsure.

When asked how important it is for patients and their physicians to have a choice of which therapy to take, (1 = not important; 10 = very important), 79/100 (79%) rated the importance as 7, 8, 9 or 10, with a weighted average of 8.2. When asked about which HL symptoms would be most important for new treatments to control, patients rated on a scale of 1 (least important) to 10 (most important). Of the 100 respondents, patients rated the most important symptoms for new treatments to control include difficulty breathing (8.1), drenching night sweats (7.2), chest pain (7.6), fatigue/lack of energy (7.4), and enlarged spleen/abdominal discomfort (7.0).

6. Experience with Drug Under Review

Nine (9) patient respondents had experience with pembrolizumab; 3 of these patients were also interviewed for this submission. Details for HL patient experience are found in Table 10.

Patient	Gender	Age	Location	Date of dx	Access to drug	Date started pembro
1	Male	20-39	USA	2011	Clinical trial	Not reported
2	Male	31	Canada	2014	Clinical trial	2016
3	Male	24	Canada	2016	Clinical trial	2017
4	Female	20-39	USA	2014	Private insurance	Not reported
5	Female	27	Canada	2010	Clinical trial	2015
6	Female	60-69	Canada	n/a	n/a	2018
7	Male	31-39	Canada	2012	Clinical trial	2017
8	Male	70-79	Canada	2014	Clinical trial	2017
9	Male	20-25	Canada	2017	n/a	2020

All 9 patients had received at least 2 prior lines of conventional chemotherapy and 3 patients had received 6 or more lines of therapy. Previous chemotherapy regimes included ABVD (8), GDP (6), GVD (2), COPP (1), DHAP (1), Bendamustine (1), Revlimid (1), and unknown (1). Seven patients had undergone an autologous stem cell transplant, one had undergone an allogeneic stem cell transplant and four had received treatment with brentuximab vedotin prior to beginning treatment with pembrolizumab.

Reasons for beginning treatment with pembrolizumab included: no other treatment options available (2), progressed after autologous transplant and did not want to risk the potential toxicity of an allogeneic transplant (4), hoping for remission in order to proceed to allogeneic transplant (1), did not respond to 3 previous lines of chemotherapy and did not want to undergo an autologous transplant (2).

Respondents were asked which of their HL symptoms were managed by pembrolizumab. Seven of nine patients (77%) reported that pembrolizumab was able to manage all their disease symptoms, including fatigue, enlarged lymph nodes, frequent infections, weight loss, night sweats, shortness of breath, and pain. Two patients reported that their fatigue was not resolved by pembrolizumab.

Side effects of pembrolizumab: Pembrolizumab was well-tolerated by 8 patients, however one patient had to stop pembrolizumab because of toxicity/side effects related to treatment. These difficult to tolerate side effects included peripheral neuropathy and inflammatory arthritis for which medication was taken. Side effects reported by patients can be found in Table 11.

Table 11: Side effects experienced with pembrolizumab (9 respondents)			
Side effect	Number of responses (%)	Side effect	Number of responses (%)
Fatigue	3 (33%)	Peripheral Neuropathy	1 (11%)
Cough	2 (22%)	Joint pain	4 (44%)
Shortness of breath	4 (44%)	Diarrhea	3 (33%)
Nausea	2 (22%)	None of these	1 (11%)
Itching/rash	3 (33%)	Other (fever)	2 (22%)

Participants were asked if they would take this drug again if their doctor thought it was the best choice, knowing the potential side effects. All 9 individuals responded “yes”; even the patient that had to end treatment due to toxicity reported that the *“PFS was worth the side effects.”*

When asked how pembrolizumab compared to previous therapies, with respect to side effects, three individuals provided the following comments:

“It's night and day, compared to chemo. It should be the first treatment offered to patients - it is so much better than chemo, no awful side effects, only a 30-minute infusion.”

“No side effects at all! This is the best drug ever given to me!”

“Due to this drug, I'm able to go back to work as a nurse part-time. I don't have to take any other meds to manage side effects, which cost a lot when I was taking chemotherapy.”

Impact on day-to-day life and quality of life: Seven of nine individuals reported that pembrolizumab had no negative impact on work/school, family obligations, friendships, intimate relations, activities or travel. Two individuals reported that they were able to begin working (1 full-time; 1 part-time) for the first time since they began treatments for HL. One individual reported experiencing lasting fatigue (thought to have been due to the drug) and that it somewhat limited aspects of their life. The other individual with lasting side effects of peripheral neuropathy and inflammatory arthritis had this negatively impact areas of their life including family and personal image.

Overall Experience and Recommendation Pembrolizumab Therapy: When asked to describe their experience with Pembrolizumab, all nine patients responded they had a good to excellent experience with this therapy, and all patients mentioned they would take this treatment option again if available to them.

When asked if they would recommend Pembrolizumab therapy to other HL patients based on their own experience, all nine respondents answered that they would recommend it. Three patients provided the following responses on how pembrolizumab changed their overall health and well-being:

“I felt like I was back to normal for the first time since I was diagnosed. I was able to do everything again and not think about my cancer. I could work again and have a normal social life.”

"I finally feel well enough to start looking forward in life. I still can't work because of side effects from previous treatments, but I'm able to enjoy life again."

"Everybody should be able to take this drug instead of going through chemo. It has been so much better for me."

7. Companion Diagnostic Test

There is no companion diagnostic testing for Pembrolizumab.

8. Anything Else? n/a

Appendix: Patient Group Conflict of Interest Declaration

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

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.
No
2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.
No
3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

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

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

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Date: January 18, 2021