CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Classical Hodgkin Lymphoma

January 5, 2018

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pembrolizumab (Keytruda) for classical Hodgkin's Lymphoma (cHL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding pembrolizumab (Keytruda) for cHL conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pembrolizumab (Keytruda) for cHL, a summary of submitted Provincial Advisory Group Input on pembrolizumab (Keytruda) for cHL, and a summary of submitted Registered Clinician Input on pembrolizumab (Keytruda) for cHL are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of pembrolizumab (Keytruda) for the treatment of patients with cHL who (1) failed to achieve a response or progressed after autologous stem cell transplant (ASCT) and have relapsed after treatment with or failed to respond to brentuximab vedotin (BV) post ASCT; OR (2) did not receive an ASCT and have relapsed after treatment with or failed to respond to BV.

Pembrolizumab is a selective humanized monoclonal antibody that enhances immune system detection of tumours and facilitates tumour regression via the programmed cell death receptor 1 (PD-1) pathway. Pembrolizumab has a Health Canada indication that reflects the requested patient population for reimbursement. Pembrolizumab has been issued marketing authorization with conditions for the treatment of adults with refractory or relapsed cHL, who (1) have failed ASCT and BV OR (2) are not ASCT candidates and have failed BV. The recommended dose of KEYTRUDA® is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

[redacted] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two nonrandomized trials. The results of KEYNOTE-087 (KN-087, N = 210) and KEYNOTE -013 (KN-013, N=31) will be presented separately.

KEYNOTE-087

KN-087 was a phase II, single-arm trial that assessed the effect of pembrolizumab in three patient cohorts with relapsed or refractory (R/R) cHL (N= 210). The three cohorts consisted of patients who had (1) received ASCT and subsequent BV therapy (**cohort 1**); (2) received salvage chemotherapy and BV and were ineligible for ASCT due to chemoresistance (**cohort 2**); and (3) received ASCT and were BV-naïve (**cohort 3**).[1] This pCODR review will only present the efficacy results from cohorts 1 and 2 from KN-087 because cohort 3 was not approved in the Health Canada Notification of Compliance with Conditions, and is therefore, beyond the scope of this review.

Adult patients were included in the KN-087 trial if they met the following criteria: R/R cHL; measureable disease; an ECOG performance status of 0 or 1; and adequate organ function.[1] All the included patients in the trial received pembrolizumab at 200mg dose every 3 weeks for up to two years or until documented confirmed disease progression, intolerable toxicity or investigator decision. Treatment beyond first assessment of progressive disease was allowed for patients who were clinically stable.

Efficacy

The primary outcome in KN-087 was objective response rate (ORR) as assessed by a blinded review committee (BIRC) using the Revised Response Criteria for Malignant Lymphomas (RCC).[1] The cut-off date for the primary analysis occurred on 25-Sept-2016, which represents a median duration of follow up of 10.1 months (range: 1.0 to 15.0 months).[1] The authors reported that the ORR for cohort 1 was 73.9% (95% CI: 61.9% to 83.7%) and it was 64.2% (95% CI: 52.8% to 74.6%) for cohort 2.[1] Other secondary outcomes included: ORR as assessed by the study investigator, duration of response (DOR) as assessed by BICR and the study investigator, complete response rate (CRR) as assessed by BICR and the study investigator, progression free-survival (PFS), overall survival, safety and health-related quality of life (HRQoL).

Patient-reported outcomes (PROs) were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the (EQ-5D) scales. The majority of patients experienced maintenance or an improvement in disease-related symptoms, functioning and health states. There was also an improvement in global health status/QoL score and the EQ-5D visual analog scale.

Harms

Chen et al (2017) reported that the most common grade 1 or 2 treatment-related adverse events (TRAEs) that occurred in ≥ 5% of the safety population were hypothyroidism (12.4%) and pyrexia (10.5%).[1] Additionally, the most common grade 3 TRAEs were neutropenia (2.4%), diarrhea (1%) and dyspnea (1%).[1] No grade 4 adverse events during the trial and there were not treatment-related deaths.

Sixty patients experienced an immune-mediated adverse event (IMAE) or infusion related reaction.[1] The most common grade 1 or 2 IMAEs were hypothyroidism (13.3%) and infusion related reactions (4.8%). No grade 4 IMAEs occurred. The protocol stated that patients who had a grade ≥

2 IMAE were treated with steroids and 23% of patients (n = 14/60) received systemic steroids for the treatment of their IMAE.[3]

KEYNOTE-013

KN-013 trial was a single-arm, multi-cohort, open-label phase 1b trial that assessed the effect of pembrolizumab in patients with R/R cHL who had disease progression during or after treatment with BV (N = 31).[4] Patients were included in KN-013 if they had: confirmed diagnosis of R/R cHL; relapsed after, ineligible or refused ASCT; received treatment with BV; ECOG performance status of < 2; and adequate organ function.[4]

All patients in the trial received pembrolizumab at 10 mg/kg dose every 2 weeks for a maximum of 24 months or until confirmed disease progression or intolerable toxicity. Clinically stable patients with radiologic progressive disease at week 12 could remain on therapy if they were experiencing a clinical benefit or until disease progression was confirmed by a follow-up scan.[5]

Efficacy

The primary outcome in the trial was to assess complete remission rate (CRR) by BIRC using the International Harmonization Project (IHP) criteria. The primary analysis occurred on 3-June-2016.[6] The authors reported that CRR was 19.4% (90% CI: 8.8 to 34.7; p = 0.0834; N = 6/31).[7] A similar CRR was reported at the 27-Sept-2016 data cut-off (CRR: 19%, 95% CI: 8 to 38).[7] Other secondary outcomes included: safety, ORR, DOR, PFS and overall survival.

Harms

Using the later data cut-off of 27-Sept-2016, 68% (N=21) of patients reported having a TRAE.[8] The most common TRAEs that occurred in ≥10% of the safety population were: diarrhea (20%) followed by hypothyroidism (13%), pneumonitis (13%), nausea (13%), fatigue (10%) and dyspnea (10%).[8] Nineteen percent of patients had a grade 3/4 TRAE, which include: colitis (3%), axillary pain (3%), AST increased (3%), joint swelling (3%), nephrotic syndrome (3%) and back pain (3%).

No treatment-related deaths occurred during the trial.

Limitations

- KN-087 and KN-013 were non-comparative studies. The single-arm, nonrandomized design makes interpreting the efficacy and safety events attributable to pembrolizumab challenging, since all patients with R/R cHL received the same treatment.

- Both KN-087 and KN-013 were single-arm, non-randomized, open-label trials. In open-label trials, the study investigator and the study participants are aware of their treatment status, which increases the risk of detection bias and performance bias. This has the potential to bias results and outcomes in favour of pembrolizumab if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. However, in order to mitigate the impact of this bias, the investigators used a blinded independent review committee to evaluate responses using standardized criteria for both trials. In addition, subjective outcomes (i.e. adverse outcomes and HRQoL) may be biased due to the open-label design.

- The adequacy of the ORR as a primary endpoint in KN-087 is unclear. Although ORR appears to be correlated with median overall survival, a statistical correlation does not necessarily equate to the prediction of a survival benefit from the response rate. Furthermore, the primary outcome in KN-013 was CRR as assessed by BIRC. The Clinical

Guidance Panel stated that ORR would have been a more clinically meaningful outcome to measure, since partial responses to therapy in advanced HL are common, may reflect residual inactive disease and may be associated with prolonged disease control.

- The robustness of the preliminary overall survival and PFS results are limited due to short follow-up of the study population and the lack of a randomized comparison treatment group in KN-087 and KN-013. The overall survival data should also be considered exploratory given the small sample sizes and no power calculation for PFS and OS.

- Although the results of these trials indicate that there is a clinical benefit, there are many examples of anti-cancer regimens where the findings from phase II were not replicated in phase III trials.[9] However, there is an ongoing randomized, international, open-label phase III trial, KN-204 trial. KN-204 will assess the efficacy and safety of pembrolizumab as compared to BV in patients with R/R cHL. The trial will include the following R/R cHL patient populations: 1) those who have relapsed (disease progression after most recent therapy) or are refractory (failure to achieve CR or have PR to most recent therapy) cHL; or 2) those who have previously been treated with and responded to (achieved a CR or PR) to BV or BV-containing regimens and then experienced disease progression.[2]

Table 1: Highlights of key outcomes in the KEYNOTE-087 and KEYNOTE-013 Trials

Treatment groups	KN-087			
	Cohort 1 (n = 69)	Cohort 2 (n = 81)	Cohort 3 (n = 60)	All patients (n = 210)
Primary Outcome				
ORR as assessed by BIRC[AB], (n [%, 95% CI])	51 (73.9, 61.9–83.7)	52 (64.2, 52.8-74.6)	42 (70.0, 56.8–81.2)	145 (69.0, 62.3-75.2)
Secondary and Exploratory Outcomes				
CRR as assessed by BIRC[AC], (n [%, 95% CI])	15 (21.7, 12.7-33.3)	20 (24.7, 15.8-35.5)	12 (20.0, 10.8-32.3)	47 (22.4, 16.9 - 28.6)
DOR as assessed by BIRC[AD], median (range)	NR	NR	NR	NR
PFS as assessed by BIRC[A], 6 month rate (n,%)[E] 9 month rate (n,%)[F]	 NR NR	 NR NR	 NR NR	 NA (72.4) NA (63.4)
OS, 6 month rate (n,%)[G] 9 month rate (n,%)[H]	 NR NR	 NR NR	 NR NR	 99.5% NA (97.4)

Abbreviations: **CI** – confidence interval; **NA** – not available; **NR** – not reported; **PFS** – progression-free survival; **OS** – overall survival; **BIRC** – Blinded Independent Review Committee; **CRR** – complete response rate; **DOR** – duration of response

Notes:
A: Progression was measured using the Revised Response Criteria for Malignant Lymphomas (RCC).
B: Proportion of patients who achieved complete response (CR) or partial response (PR) using at any time during the study and measured at the 25-Sept-2016 data cut-off. Best overall response was defined as best ORR during the period between the first dose and the first documented PD, death, or, in the absence of PD, last efficacy assessment before subsequent therapy.
C: Time between the first response and the date of the first documented PD, death, or, in the absence of PD, last disease assessment and measured at the 25-Sept-2016 data cut-off.
D: Time between first response to the date of first documented disease progression, death or last disease assessment (if disease progression did not occur) and measured at the 25-Sept-2016 data cut-off.

E: Time from first dose to first documented disease progression or death due to any cause, whichever occurred first and measured at the 25-Sept-2016 data cut-off.
F: Ad-hoc analysis measured at the 31-Dec-2016 data cut-off.
G: Time from first dose to date of death and measured at the 25-Sept-2016 data cut-off.
H: Ad-hoc analysis measured at the 31-Dec-2016 data cut-off.
Data Source: Chen et al (2017) JCO[1,10]

Treatment Groups	KN-013
	All patients (n = 31)
Primary outcome	
CRR as assessed by BIRC[AB], (n [%, 90% CI])	6 (19.4, 8.8 to 34.7)
Secondary and exploratory outcomes	
ORR as assessed by BIRC[AC], (n [%, 95% CI])	18 (58, 39-76)
DOR as assessed by BIRC[AD], median (range)	NR (0 – 26.1+)
PFS as assessed by BIRC[AE], 6 month rate (n,%) 9 month rate (n,%) Median PFS (95% CI), in months	 NR (66) NR (48) 11.4 (4.9 – 27.8)
OS [F], 6 month rate (n,%) 9 month rate (n,%) Median PFS (95% CI), in months	 NR (100) NR (87) NR

Abbreviations: **CI** – confidence interval; **NA** – not available; **NR** – not reported; **PFS** – progression-free survival; **OS** – overall survival; **BIRC** – Blinded Independent Review Committee; **CRR -** complete response rate**; DOR -** duration of response

Notes:
A: Progression was measured using the international harmonization (IHP) criteria.
B: Proportion of patients who have no evidence of disease, which was confirmed by patients being PET-negative and measured at the 3-June-2016 data cut-off.
C: Proportion of patients who achieved complete response (CR) or partial response (PR) and measured at the 27-Sept-2016 data cut-off. Best overall response as the best response during the period between the first dose and first efficacy assessment showing progressive disease, or in the absence of progressive disease, the last efficacy assessment before subsequent therapy.
D: Time between the first response to the date of first documented disease progression, or in the absence of disease progression, the last efficacy assessment before subsequent therapy and measured at the 27-Sept-2016 data cut-off.
E: Time from first dose to first documented disease progression or death due to any cause and measured at the 27-Sept-2016 data cut-off.
F: Time from first dose to date of death and measured at the 27-Sept-2016 data cut-off.
Data Sources: EPAR Report;[7] Armand et al.;[6] Armand et al.;[8] Health Canada Module 2.5[11]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient advocacy group, Lymphoma Canada provided input on pembrolizumab for the treatment of patients with classical Hodgkin Lymphoma (cHL).

From a patient's perspective, there are a number of symptoms associated with HL that impact quality of life, which include fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough and mental/ emotional problems such as anxiety and difficulties with concentrating. Respondents also reported on aspects of their life negatively impacted by HL, including ability to work, personal image, family obligations, intimate relations, friendships and ability to attend school. Most respondents indicated that current treatment options (e.g. ABVD, GDP, BEACOPP and MOPP/COPP, radiation, stem cell transplant, BV and surgery) work well in managing their HL symptoms. LC noted that toxicity associated with their previous treatments were of great concern to many respondents; specifically, fatigue, "chemo-brain", peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility and lung damage were the most commonly reported. LC also indicated that respondents also experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). In the current sample LC noted that 93% of respondents had been treated with at least one line of conventional and 16% of respondents had received ≥ 3 lines of therapy. Respondents' expectations about the new drug under review were most importantly "effectiveness" followed by "minimal side effects" or "less side effects than current treatments". Respondents who have experience with pembrolizumab reported few side effects, and that they were tolerable. Some of the side effects reported with pembrolizumab included fatigue, cough, shortness of breath, nausea, itching, rash and joint pain. Reasons for beginning treatment with pembrolizumab included: no other treatment options available, progressed after stem cell transplant and fearing risk of toxicity associated with stem cell transplant and not responding to 3 previous lines of chemotherapy. The majority responded that pembrolizumab had positively impacted their health and well-being, notably no negative impacts on work/school, family obligations, friendships, intimate relations, activities or travel had been experienced.

Provincial Advisory Group (PAG) Input

Input was obtained from five of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation pembrolizumab for cHL:

Clinical factors:

- New treatment option for relapsed or refractory classical Hodgkin Lymphoma (cHL)
- Clarity on eligible patients

Economic factors:

- New treatment option
- Chair time

Registered Clinician Input

Two clinician inputs were provided: One joint submission from four clinicians submitted on behalf of the Hematology Drug Advisory Committee at Cancer Care Ontario and one group input from six oncologists across five provinces: British Columbia, Manitoba, Newfoundland, Ontario and Quebec.

Overall the oncologists providing input agreed that this indication and funding will only affect a very small number of patients and that there is currently no standard of care in relapsed/refractory patients with Hodgkin Lymphoma (cHL). Two of the key benefits identified by both clinician groups was the encouraging response rate and good safety profile of pembrolizumab. An unmet need was identified by both groups. Pembrolizumab would be used in patients with refractory/relapsed HL past autologous stem cell transplant (auto-SCT) and brentuximab vedotin (BV) and patients who are ineligible for transplant and have no access to BV. In patients who are eligible for allogeneic stem cell transplant (allo-SCT), pembrolizumab may replace conventional chemotherapy to provide a bridge to transplant. In patients who have

chemo-refractory HL, but who are BV-naïve, PD1 inhibitors may replace BV in patients who would not be able to tolerate BV (e.g. baseline neutropenia or neuropathy). The clinicians also noted that PDL1 testing would not be required.

Summary of Supplemental Questions

Summary of the manufacturer-submitted indirect treatment comparison (ITC) of the relative efficacy and safety of pembrolizumab versus active therapies in R/R cHL patients.

See section 7.1 for more information.

The Manufacturer submitted a naive ITC that compared pembrolizumab to gemcitabine in patients who progressed after ASCT and BV.

The Manufacturer noted that that they were unable to construct a NMA due to the lack of clinical trial data for this patient population, and therefore, conducted a naïve treatment comparison. The naïve ITC was performed using an outcome regression analysis. The regression model utilizes the outcome data from the intervention of interest and expresses the index intervention as a function of the relevant patient-reported factors. This index intervention was used to as a common link to incorporate the effect estimates from the nonrandomized trials into the network.

A systematic review identified two trials (KEYNOTE-087 [1] and Cheah et al.[12]) for conducting an ITC comparing pembrolizumab to gemcitabine (as proxy for chemotherapy) in patients refractory to BV treatment. The results of the naïve ITC indicate that treatment with gemcitabine was associated with a detrimental effect on PFS (HR: 5.16, 95% CI, 3.61 to 7.38) as compared to pembrolizumab. Likewise, ORR was higher in patients treated with pembrolizumab as compared to gemcitabine. However, grade ≥ 3 AEs could not be assessed because the results were not reported in Cheah et al (2016).[7] On the other hand, the effect estimates of overall survival were not assessed in the ITC because the results from KN-087 were immature.

Although the ITC suggests that pembrolizumab associated with improved efficacy and safety as compared to gemcitabine, these results should be interpreted with caution. Cheah et al (2016) was a retrospective cohort study and the PFS and OS rates were hand calculated using time to event data from electronic records.[7] Thus the reliability and robustness of these estimates are uncertain. In addition, the overall conclusions of the ITC are very limited because of substantial heterogeneity in the studies and patient characteristics among the included studies. Finally, the Manufacturer performed a naïve ITC and there was no attempt to adjust for any differences among the trials included in the analysis. Thus the treatment effect estimates from the ITC may be overestimated because other aspects of the included studies (i.e. patient populations, interventions or outcomes) may have biased the reported effect.[13] Given these limitations, the comparative efficacy of pembrolizumab versus gemcitabine is uncertain.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review."

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for pembrolizumab

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance Status</td><td><u>KN-087</u>
Patients were included in the trial if they had ECOG status of 0 or 1
<table>
<tr><th>ECOG</th><th>Cohort 1</th><th>Cohort 2</th><th>Cohort 3</th></tr>
<tr><td>0</td><td>29 (42)</td><td>44 (54.3)</td><td>29 (48.3)</td></tr>
<tr><td>1</td><td>39 (56.5)</td><td>37 (45.7)</td><td>31 (51.7)</td></tr>
<tr><td>2</td><td>1 (1.4)</td><td>0 (0)</td><td>0 (0)</td></tr>
</table>
No ECOG subgroup analysis was performed.

<u>KN-013</u>
ECOG status was not reported.</td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Results can be generalized to the population of patients with ECOG performance status of 0-3, as the treatment is fairly non-toxic, and patients often experience rapid improvement of symptoms (B symptoms, asthenia, pruritic, fatigue) within 1-2 cycles</td></tr>
<tr><td>Biomarkers</td><td><u>KN-087</u>
PD-L1 expression was reported using the following scores: intensity score (0 to 3), membrane staining score (percentage of tumor cells with membrane staining; 0%, >0 to < 50%, ≥ 50 to < 100%, or 100%), and histiocyte score (1 to 3; semiquantitative assessment of histiocytes/macrophages staining positive).

<u>KN-013</u>
PD-L1 was considered positive if at least 1% of HL cells (including HRS cells and variants) demonstrated at least partial membrane staining with moderate or strong intensity.</td><td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td><td>PDL-1 is highly expressed on Reed-Sternberg cells that characterize Classical HL (subtypes nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted); PDL-1 is expressed less frequently in nodular lymphocyte predominant HL. In addition, data on relative effectiveness in patient according to degree or intensity of PDL-1 expression are exploratory; assessment of PDL-1 expression, gene copy number, polysomy etc. with regard to response to PD-1 antibodies still requires validation (but may not be important).</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Intervention	Line of therapy	**KN-087** Three patient cohorts with R/R cHL who had (1) received ASCT and subsequent BV; (2) received salvage chemotherapy and BV and were ineligible for ASCT due to chemoresistance; and (3) received ASCT and are BV-naïve. **KN-013** Patients with R/R cHL who had disease progression on or after the treatment with BV.	Are the results of the trial generalizable to other lines of therapy	Based on the results from cohort 3, the response rate seen in cohorts 1 and 2 could be generalized to those who have BV as part of salvage therapy or who received it as part of primary therapy (currently in Canada as part of a randomized trial KEYNOTE 204), who would not receive BV post-ASCT; or those who have not been exposed to BV at all, whether or not they have undergone ASCT.
Comparator	Standard of Care	**KN-087** Single-arm, nonrandomized trial **KN-013** Single-arm, nonrandomized trial	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	KN-87 and KN-013 are single arm studies and do not have any comparators. In the Canadian context either single agent or combination therapy may be used following progression after ASCT and BV (including involved field or extended field radiation).The results from these two non-comparative phase IB and II studies compare favorable to currently available therapies, such as single agent vinca alkaloids or gemcitabine.
	Dose and Schedule	**KN-087** 200mg dose of pembrolizumab every three weeks	If the dose and/or schedule is not standard, are the results	Results are relevant to Canada; flat dose every 3 weeks is

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		KN-013 10kg/m^2 mg dose of pembrolizumab every two weeks	of the trial relevant in the Canadian setting?	widely used in solid tumors; either would be acceptable to patients and physicians
Outcomes	Appropriateness of Primary and Secondary Outcomes	**KN-087** Primary: ORR by BIRC Secondary: ORR by SI; DOR by BIRC; DOR by SI; CRR by BIRC; CRR by SI; PFS; OS; Safety; HRQoL **KN-013** Primary: CRR by BIRC Secondary: Safety; ORR by BIRC; DOR by BIRC; PFS by BIRC; OS		Response rate—especially CR rate—has been associated with disease control measures (PFS) in studies of advanced lymphomas, including HL. The results easily satisfied the estimates of ORR outline in the statistical analysis section of the KEYNOTE87 publication.
Setting	Location of the participating centers	**KN-087** 84% of the participating sites were located in academic centers and 16% were located in community hospitals [checkpoint]. **KN-013** All of the participating sites were located in academic centers [checkpoint].	If the trial was conducted only in academic centers are the results applicable in the community setting?	Results of this therapy can be generalized to community practice settings with expertise in diagnosis and management of immune mediated complications.
	Supportive medications, procedures, or care	Are the supportive medications, procedures, or care used with the intervention in the trial the same as those used in Canadian clinical practice?	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Supportive care as described in the trials is available in most Canadian centers, and would be very similar to that provided in the study (as there are published guidelines for management of IMAEs, etc)

1.2.4 Interpretation

Burden of Illness and Need

Even after treatment with salvage chemotherapy followed by autologous stem cell transplantation (ASCT), only approximately half of patients aged less than 65-70 years (the upper age limit in most transplant centres) will have been cured with that second line therapy. For those with cHL resistant to chemotherapy and who, therefore, do not undergo ASCT, or who have comorbidities that preclude ASCT or who are age >70, treatment for relapsed/refractory cHL is palliative. Most

relapses following ASCT occur within the first year, and prognosis is particularly poor for those with recurrence within 6 months of transplant (median survival 15mos vs 36 mos for those relapsing after 6 months).[14] Median survival of 122 patients who experienced relapse following ASCT at Princess Margaret Hospital prior to 2008 (40% within 6 months of transplant) was 27 months.[15] After failure of ASCT at least 85% of patients will receive some form of chemotherapy; prior to the availability of BV this would have been platinum-based in many centres[16] or single agent treatments. In patients with cHL relapsed after ASCT, and with extensive prior therapy (median number of prior regimens 3.5, range 1-11), the response rate to BV administered at 1.8 mg/kg every 3 weeks was 75% and complete response rate was 34%; the median progression-free survival was 6 months.[17] Response rates to conventional chemotherapy following progression after BV are <50%, and progression free survival is only 3-4 months.[12]

Further the CGP agreed with PAG and the clinicians providing input for this submission that pembrolizumab would address an unmet need in patients who are ineligible for ASCT and have not received BV. Funding for BV for those who are not candidates for ASCT because of age, comorbidities or refractoriness to salvage therapy is not uniform across Canada and results in a significant treatment gap for this subgroup of patients in most provinces. The CGP acknowledged that Health Canada has issued an indication for cHL excluding BV naïve patients; in the Keynote 87 trial, the response rate in this patient subgroup (n=35) was similar to the whole study population (71%). The CGP commented on PAG and clinician inputs, which stated that pembrolizumab may fulfill an unmet need by facilitating a bridge to allogeneic stem cell transplant in patients who failed ASCT and are eligible for transplant.

Overall these data illustrate the pressing need for more effective treatments for relapsed cHL following relapse after ASCT, and for those with disease that is resistant to salvage chemotherapy or who are otherwise not candidates for ASCT.

There are approximately 900 patients found to have classical Hodgkin Lymphoma each year in Canada. Approximately 25% (n=225) are not cured with primary treatment and approximately 80% (n=180) of such patients then receive 2nd line treatment including ASCT, which cures approximately 50% (n=90)[18]. Those 90 patients who relapse after ASCT are then candidates for BV but at least 90% (n=80) of them relapse again and will, therefore, be candidates for pembrolizumab (~80/year)[19,20] To those 80 it would be reasonable to add another 20-30 eligible for pembrolizumab after BV but who did not undergo ASCT. Therefore, net annual number of candidates for this use of pembrolizumab in Canada should not exceed 100-110 and will probably be at least 10% to 20% lower because of contraindications to the use of a checkpoint inhibitor. The CGP agreed with the clinicians providing input for this submission that pembrolizumab fulfills a need in a considerably young patient population who can potentially return to work and contribute to the Canadian economy.

Effectiveness

The large phase II KEYNOTE-87 trial evaluated pembrolizumab in patients with relapsed or refractory Hodgkin lymphoma who were age >18 years, had good performance status (ECOG 0,1) and were HIV negative, without autoimmune conditions requiring treatment in the preceding 2 years. Three cohorts were evaluated according to history of prior therapy: 1) relapse after ASCT, and progression following subsequent BV; 2) refractory to salvage chemotherapy, and therefore not eligible for ASCT, and progression after BV; 3) progression after ASCT and no post-transplant BV (35/60 patients in this group were BV-naïve). Pembrolizumab was given at a dose of 200mg IV every 3 weeks without premedication until disease progression or for up to 24 months. Treatment beyond the first signs of disease progression was allowed if the patient was felt by the investigator to be benefitting from therapy (pseudoprogression).

The primary endpoints were overall response rate (ORR) according to a blinded independent central radiology review, and safety. Secondary endpoints included investigator assessed ORR and CR rate. With 60 patients enrolled in each cohort, the study had a power of 0.93 to detect an improvement in ORR from 15% to >35% in cohort 1 and from 5% to >20% in cohort 2 (one-sided alpha 0.025).

At the time of reporting, the median duration of treatment was 8.3 months and median follow-up 10 months (maximum 15 months); median number of cycles delivered was 13 (maximum 21). Among 210 patients, 120 patients remained on treatment. The overall response rate was 69% (62.3-75.2) and complete response rate 22.4% (16.9-28.6). Response rates according to treatment cohort by independent review were: cohort 1: 73.9% (61.9-83.7) and cohort 2: 64.2% (52.8-74.6). The response rate observed among those who were refractory to primary therapy was 79.5% (68.4 - 88.0) and for patients who were judged to be refractory to all lines of prior therapy was 56.5% (34.5 - 76.8; n=23). Progression-free survival for the entire cohort was 63.4% at 9 months. Improvement in quality of life as measured by the EORTC QLQ-core 30 global health status/quality of life score and EQ-5D also improved, although no comparator group is available to provide a reference point for these changes. The CGP considered that the improvement in quality of life observed in the trial was in line with patient group inputs for this submission, indicating that a majority of patients felt that pembrolizumab was able to manage all their disease symptoms as well as dramatically improve their health and well-being similar to their pre-disease state.

KEYNOTE013 included patients with cHL who had relapsed after ASCT, patients who refused ASCT or patients who were ineligible for ASCT. All patients had disease progression during or after treatment with BV. Patients received pembrolizumab 10mg/kg every 2 weeks for 2 years or until progression or toxicity. The overall response rate among 31 patients was 58% (39-76)% and CR rate 19.4% (8.8-34.7). After a median follow-up of 11.4 months, PFS was 66% at 24 weeks and 48% at 52 weeks.

Different dosing schedules were used in KN-013 and KN-087. Patients in KN-013 received a 10mg/kg dose of pembrolizumab Q2W for up to two years while those in KN-087 received a 200 mg dose of pembrolizumab Q3W for up to two years. The CGP confirmed that while flat dose every 3 weeks is widely used in solid tumours, either schedule would be acceptable to patients and physicians. Further, the CGP discussed that a weight based dose of 2mg/kg Q3W would be equally relevant in the Canadian setting. This was stated in reference to input from PAG which noted that there are trials to suggest that a weight based dose of 2mg/kg and a 200 fixed dose have similar efficacy. In their feedback to the initial recommendation the submitter commented that there is currently no clinical evidence to support the usage of pembrolizumab cHL with a 2mg/kg dose in the cHL population and that Health Canada has approved pembrolizumab based on the 200mg fixed dose every three weeks. In response to the submitter's feedback, the CGP acknowledged that while a weight-based dose of 2 mg/kg every three weeks has been approved for other indications, there is currently no evidence for the 2 mg/kg dose for the current indication in the cHL population.

The CGP agree that while PFS is the most important initial endpoint in the evaluation of therapies for the palliation of advanced, multiply relapsed cHL, disease response is a meaningful endpoint for patients because it results in improvement in performance status and resolution of constitutional symptoms. The response rates observed in the cohorts are high, consistent, and associated with symptomatic improvement in the majority of cases. It is too early to evaluate the true duration of PFS or OS, but these results—though from non-comparative phase IB and II studies—compare favourably to currently available therapies, such as single agent vinca alkaloids or gemcitabine, and to the published pivotal trial of BV reported by Younes et al[17]. Chemotherapy in this advanced disease setting is associated with significant myelosuppression, occasionally resulting in infectious complications requiring inpatient and outpatient supportive care, which is

largely avoided when pembrolizumab is used. The CGP also acknowledges that the aggregate data reported by Chen et al[1] includes that obtained from cohort 3, which is not part of this submission, and included patients who had no post-ASCT BV because of receipt of this agent with salvage therapy, and with no prior BV exposure: the response rate reported in this latter group is the same as the other 2, and these data would support the use of pembrolizumab in such patients. As mentioned above HC has currently issued an indication for cHL excluding BV naïve patients. The ongoing phase III trial (KEYNOTE-204) may provide additional data on PFS outcomes and toxicities in BV naïve patients.

Safety

Overall, pembrolizumab in both the doses and schedules used in these two trials was well tolerated, with a low rate of immune-mediated and other toxicities. In the KEYNOTE087 trial, only 9 of 210 patients (4.3%) discontinued therapy because of treatment-emergent adverse events, and 12% required treatment delay for management of toxicities. The most common immune-mediated adverse events (IMAEs) was hypothyroidism (29 patients, 13.8%); infusion reactions (grade 1 or 2) were observed in 10 patients (4.8%) and cytokine release syndrome in 6 patients (2.9%; one grade 3). Only five cases of grade 3 IMAEs were reported: single instances of hypothyroidism, cytokine release syndrome, colitis, myositis and dermatitis.

The most common treatment related adverse events (TRAEs) of any grade were fever (10%), fatigue (9%), diarrhea (7%), rash (8%), cough (6%) and headache (6%). The spectrum of toxicities in KN-013 was similar to the larger phase II study. The CGP acknowledged that IMAEs represent a new spectrum of toxicities associated with PD-1 antibodies that may arise late in the course of treatment and their incidence in relapsed HL may not be fully captured in the short treatment durations reported in the KN-87 trial; nonetheless the incidence of these events is very low and they are easily managed with prednisone.

Despite the clear limitations of naïve comparisons between non-randomized studies, the CGP agreed that pembrolizumab has a favourable toxicity profile compared to chemotherapy. Chemotherapy in this advanced disease setting is associated with significant myelosuppression, with grade3/4 neutropenia often over 50%,[21] occasionally resulting in infectious complications requiring inpatient and outpatient supportive care, which is largely avoided when pembrolizumab is used. Further the CGP acknowledged patient advocacy group input stating that the majority of patients with pembrolizumab exposure reported that pembrolizumab had a positive impact on their health and well-being, with very few adverse events that were all tolerable.

1.3 Conclusions

The Clinical Guidance Panel concluded that there ***is*** a net clinical benefit to pembrolizumab, compared with chemotherapy, in the treatment of patients with relapsed Hodgkin lymphoma with disease progression after both ASCT and BV, or who are not eligible for ASCT and disease progression after BV. This is based on the non-comparative KEYNOTE 013 and 87 studies which showed a high response rate (58-70%) and encouraging early PFS, with a toxicity profile that is better than that experienced with chemotherapy, a low rate of immune-mediated toxicities, and evidence of improvement in quality of life during the course of study KEYNOTE 087. Responses in this patient population are important because of accompanying improvement in distressing symptoms (pruritis, fever, night sweats) and improvement in performance status.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Brentuximab vedotin is currently standard therapy in Canada for patients who have relapsed after ASCT, but is not available in many provinces to those who have not received ASCT; the CGP considers that the data from cohort 3 of the KN-087 study are relevant to the latter patient population who have few treatment options because of the lack of availability of post-transplant BV.
- BV is not currently funded in Canada for consolidation therapy post-ASCT for patients at a high risk of relapse, but may be in the future; this would decrease the number of patients who would receive pembrolizumab after BV for relapse following ASCT.
- The data supporting this conclusion are from non-randomized studies. Hence there is no reliable estimate of the comparative efficacy or effectiveness of pembrolizumab to chemotherapy. Results from a phase III randomized comparison of BV to pembrolizumab in BV-naïve patients (or those with a previous documented response to BV or BV-containing regimens as part of salvage therapy or primary therapy) will provide important information on relative PFS and toxicities with these agents as well as comparative data on quality of life.
- The follow-up of both trials considered is short and additional data on longer-term toxicities PFS outcomes and toxicities are awaited.
- In their feedback to the initial recommendation, PAG agreed with the recommendation to reimburse pembrolizumab in patients with cHL who have failed transplant and failed BV. However, PAG noted that the recommendation to reimburse pembrolizumab in patients who are ineligible for transplant and failed BV is not applicable due to the previous pERC recommendation to reimburse BV for patients with HL who have failed transplant but not for those who were transplant ineligible. In provinces that have funded BV in HL, reimbursement is only for patients who have failed a transplant and not for patients who are ineligible for transplant. In response to PAG's feeback the CGP acknowledged that previously pERC did not recommend funding BV in patients with HL who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent chemotherapies. The CGP noted, however, that despite pERC's negative recommendation, there currently is a population of non-transplant patients with twice relapsed HL who have subsequently received BV in Canada. The CGP referred to British Columbia as an example, were BV is currently funded for: (1) relapsed HL after high dose chemotherapy and autologous stem cell transplant, or (2) relapsed HL after standard ABVD or equivalent treatment in transplant ineligible patients. Further the CGP identified a high need for treatment options in this small patient population. The CGP noted that although many will have a very useful response to BV, almost all of them will relapse again. They should then be given a checkpoint inhibitor such as pembrolizumab because it is effective and well-tolerated and can induce quite durable responses.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Classical Hodgkin lymphoma (cHL) is an uncommon but distinct lymphoma subtype that typically presents in young adults, but is seen in both children and adolescents, and those over the age of 60 years.[18] cHL accounts for approximately 8-10% of all diagnoses of lymphoma. cHL is characterized by rare malignant Reed-Sternberg cells, which positive for CD30 and negative for the B cell antigens CD20 and CD79a; this includes nodular sclerosis, mixed cellularity and CHL not otherwise specified subtypes. PDL-1 is strongly expressed by cHL R-S cells and by infiltrating cells of the microenvironment, but is less strongly expressed on the malignant cell population of nodular lymphocyte predominant HL (NLPHL);[22] this latter subgroup comprises only about 5% of all patients with HL. The median age at diagnosis in most reported series is 35-40 years and approximately 15% are older than 60 years. There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease.[18]

2.2 Accepted Clinical Practice

Approximately two thirds of patients with HL will present with localized disease (stage I and II according to the Ann Arbor classification), and are generally treated with combination chemotherapy and involved field radiation (IFRT).[23] Those who present with advanced stage disease (stage III and IV) and some with stage I and II who present with constitutional ("B") symptoms or for whom radiation is felt to carry significant risk of late toxicities (second cancers, cardiovascular disease) are usually managed with combination chemotherapy alone.[23] In Canada, the standard regimen is ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for stage I-II disease (2-4 cycles prior to IFRT depending on risk factors) and for advanced stage disease (6 or 8 cycles). Increasingly, FDG-PET scanning is being used to direct treatment decisions in those with early and advanced HL, with the goal of limiting toxicities in those with favourable response following 2 cycles of therapy, and improving outcome through treatment intensification for those with less that complete response.[24] Despite the excellent complete remission rates with current doxorubicin, vinblastine, bleomycin, dacarbazine (ABVD) chemotherapy (>95% for localized and >80% for advanced stage disease), relapse is experienced by up to 10-15% of patients with early and 30% of those with advanced disease.[25,26]

Patients who experience treatment failure (disease progression on or relapse after primary therapy) are usually candidates for second-line (sometimes called salvage) chemotherapy followed by high-dose chemotherapy supported by autologous stem cell transplantation (ASCT).[20,27] The outcomes of this second treatment are most favourable in those with first remission duration longer than one year, lower disease burden at relapse and a complete response to second line chemotherapy assessed by either CT scan or FDG-PET scanning. Approximately 50% of those undergoing ASCT will be alive and relapse-free five years after treatment and are generally considered cured. ASCT is not considered appropriate treatment for older patients (those older than 70 years), especially those with significant medical comorbidities. The results of ASCT are poor in patients with HL that is refractory to initial therapy (progression during or within 3 months of completion of treatment), those with less than a complete response to salvage therapy or those who require more than one second-line regimen prior to ASCT.[20] For those who experience disease progression following ASCT, the prospects of long term remission with additional therapy are very limited, and the duration of disease control (as measured by progression free survival) is very short with currently available therapies. The median survival following relapse after ASCT is

approximately 2-3 years, and is shorter for patients who relapse within 6 months of transplant and for those transplanted with disease that was refractory to primary therapy.[14]

Treatment of patients with relapse after ASCT has generally been for relief of symptoms and employs single agent chemotherapy. The most common drugs used are vinblastine, gemcitabine or vinorelbine, which are given every other week (vinblastine) or weekly intravenously for 3 weeks out of 4 each month, unless hematologic toxicity mandates a shorter cycle of 2 doses every 3 weeks (vinorelbine, gemcitabine).[28-30] Reported response rates range from 20-40% and progression-free survival from 6-8 months. Combination regimens, such as, gemcitabine, vinorelbine and liposomal doxorubicin (GVD) may achieve response rates that appear higher than with the single agents above, but progression-free survival is similar and hematologic toxicity of this combination therapy is significant.[21] Due to restrictions on reimbursement in many provinces, this regimen is not generally available in Canada, and other combination regimens such as COPP (cyclophosphamide, vincristine, procarbazine, prednisone) are used if patients have good performance status and bone marrow reserve. Involved field radiation is beneficial for those with localized relapse outside of a previous radiation field, but there are few long-term survivors.

In some centres, for young patients who have relapsed after ASCT with a long disease-free interval (more than one year), and a good response to additional salvage therapy, reduced intensity allogeneic stem cell transplantation from an HLA-matched sibling donor or unrelated matched donor, or haploidentical donor, may be considered. The CGP agreed with comments made by PAG and the clinician inputs regarding pembrolizumab fulfilling an unmet need by facilitating a bridge to allogeneic SCT. However, the CGP discussed that while some centres have reported good short-term outcomes with this strategy, results have not always been reproducible, and many centres consider that allogeneic transplantation post-ASCT is still investigational. The CGP also noted that HC has included in the 'warning and precaution' section of the product monograph that cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients undergoing allogeneic HSCT after previous exposure to pembrolizumab. Overall, allogeneic transplantation may be considered appropriate therapy for approximately 10-15% of patients who relapse after ASCT.[31-34] Otherwise, treatment following relapse after ASCT is generally symptomatic and considered palliative.

The anti-CD30 chemoimmunoconjugate brentuximab vedotin (BV) is approved for the treatment of patients with HL after failure of ASCT or at least two prior multi-agent chemotherapy regimens.[35] In a large phase II trial in heavily pretreated patients (median number of prior regimens 3.5, range 1-11), the response rate to BV at a dose of 1.8 mg/kg every 3 weeks was 75% and complete response rate 34%; median progression-free survival was 6 months and median duration of complete response 20.5 months.[17,36] In most provinces, BV has become the treatment of choice as initial therapy for relapse after ASCT because of its favourable toxicity profile (grade 3 neutropenia: 14%, grade 4: 6%; other grade 3-4 events, < 2%). Direct comparison to other agents has not been carried out, but in a correlated survival analysis of a subgroup of patients who had received systemic therapy for relapse following ASCT and before treatment with BV, PFS was significantly longer with BV compared to the prior systemic treatment (7.8 vs 4.1 months, $p<.001$).[17] Funding for BV for those who are not candidates for ASCT because of age, comorbidities or refractoriness to salvage therapy is not uniform across Canada and results in a significant treatment gap for this subgroup of patients in most provinces.

In a trial reported by Moskowitz et al, 329 patients with cHL refractory to primary therapy, relapse within one year of completion of therapy or extranodal involvement at relapse (ie, high risk for treatment failure) were randomized following ASCT to BV (1.8mg/kg IV every 3 weeks for 16 doses) or placebo infusion as maintenance treatment.[37] These risk factors for treatment failure are present in approximately 50% of patients who undergo ASCT in Canada, although the exact proportion may vary according to the referral practice of the transplant centre. This study showed

a significant improvement in median progression-free survival with BV compared to placebo (43 vs 24 months, HR 0.57 [0.40-0.81]), regardless of the number of risk factors present at the time of initiation of salvage chemotherapy. No difference in overall survival has been reported to date. This trial has led to the approval of BV as maintenance therapy post-ASCT in the US and many countries in Europe, and currently this treatment is available in British Columbia as a treatment standard. It may be anticipated that an increasing number of patients who relapse after ASCT in Canada will have had BV as part of their second attempt at cure, creating an need for new therapies in this population. In addition, current trials are evaluating the impact of the addition of BV to primary therapy in patients with advanced stage cHL, and as a component of induction therapy prior to transplant, either in combination or in the setting of poor response to standard platinum-based salvage treatment. Thus, the number of patients with relapsed and refractory cHL who require additional therapy and who do not have access to BV, or who would not be expected to benefit from re-treatment with BV because of toxicity or short remission, is expected to increase, and new therapies for this population are clearly needed.

2.3 Evidence-Based Considerations for a Funding Population

There are a variety of mechanisms by with the malignant Hodgkin-Reid Sternberg (RS) cells in HL evade the immune system and persist despite therapy, including secretion of cytokines that attract regulatory T cells and inhibit cytotoxic T cells; overexpression of FAS ligand leading to apoptosis of CTLs, and increased expression of the programmed death receptor (PD1) ligands PDL-1 and PDL-2.[38] RS cells demonstrate copy number gain or amplification of chromosome 9p24.1, the region that includes genes for PD-L1, PD-L2 and for JAK2, resulting in constitutive activation of the JAK-STAT pathway, which also leads to PDL overexpression.[39] PD-L1 expression on the surface of Hodgkin Reid Sternberg cells has been shown to be correlated with these genetic alterations, leading to engagement of the PD-1 receptor on T cells and induce PD-1 signaling and T-cell exhaustion by reversible inhibition of T-cell activation and proliferation.

The novel PD-1 antibodies nivolumab and pembrolizumab have been tested in patients with relapsed cHL, producing high response rates and resulting in relatively little toxicity. Among 80 patients with refractory HL treated with nivolumab 3mg/kg IV every 2 weeks, the overall response rate was 66% (CR rate 9%) and 6 month PFS was 76%; all patients had progressed after both ASCT and BV administered for post-ASCT relapse treatment.[40] Treatment with pembrolizumab 200 mg IV every 3 weeks resulted in an overall response rate of 74% (CR 22%) in patients progressing after ASCT and then BV;[1] response rates in patients who progressed on salvage therapy and on BV, without prior transplant (RR 64%, CR 25%) and who progressed after ASCT and who had not received prior BV (RR 70%, CR 20%), were similar. Progression-free survival at 6 months for all patients was 72.4%. Given the important role of PDL-1 overexpression as part of the underlying pathophysiology of HL, PD-1 antibodies will play an increasingly important role in treatment and offer important benefit to patients whose HL has recurred after transplant and for those for whom transplant is not indicated.

Patients with relapsed or refractory Hodgkin lymphoma		
Line of Therapy	ASCT eligible	Not eligible for transplant (age >70)
1st-Line	Salvage therapy + ASCT (responding patients)	Salvage, non-cross-resistant chemotherapy or radiation (note brentuximab vedotin not funded for this population)
Maintenance	Brentuximab vedotin currently not funded in most provinces	Not applicable
2nd-Line	Brentuximab vedotin	No funded or effective alternative

2.4 Other Patient Populations in Whom the Drug May Be Used

Current trials are evaluating the impact of the addition of BV to primary therapy in patients with advanced stage cHL, and as a component of induction therapy prior to transplant, either in combination or in the setting of poor response to standard platinum-based salvage treatment. These patients would be appropriate candidates for a PD1 antibody at the time of progression after transplant. Similarly, a funding and therapy gap exists for patients who are not eligible for ASCT because of age or comorbidities, or because salvage therapy has not produced sufficient response; these patients are not currently eligible in many provinces for BV treatment. Given the excellent toxicity profile reported in phase II trials of PD1 antibodies, and the similarity in response rate and time to progression across subgroups reported for pembrolizumab, treatment with a PD1 antibody would be of benefit in this population which has an unmet medical need for additional, more effective and less toxic treatment alternatives. The CGP acknowledged that Health Canada has issued an indication for cHL excluding BV naïve patients.

PROVINCIAL FUNDING SUMMARY
Brentuximab vedotin (Adcetris) for Hodgkin Lymphoma

PROVINCE	STATUS	DECISION DATE	FUNDING CRITERIA
BC	Funded	Jun 1, 2014	Relapsed after high dose chemotherapy and autologous stem cell transplant or Relapsed after standard ABVC or equivalent treatment in transplant ineligible patients; Disease no longer controlled by involved field radiation, vinblastine, lomustine, gemcitabine and bendamustine
AB	Funded	May 1, 2014	For patients with Hodgkin's lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status of 0 or 1.
SK	Funded	Feb 4, 2014	In patients with Hodgkin lymphoma who have relapsed disease following autologous stem cell transplant (SCT)
MB	Funded	Mar 1, 2014	For the treatment of patients with: • Hodgkin lymphoma AND - Confirmed CD 30 antigent positive disease AND • An Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less AND • Relapsed disease following autologous stem cell transplant
ON	Funded	Feb 19, 2014	Brentuximab will be used in patients with Hodgkin's lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status of 0 or 1. Funded Dose: Brentuximab 1.8 mg/kg IV every 3 weeks until disease progression or unacceptable

PROVINCE	STATUS	DECISION DATE	FUNDING CRITERIA
			toxicity Notes: a. A clinic note confirming relapse post autologous stem cell transplantation and a pathology report confirming CD30+ve Hodgkin's lymphoma must be submitted to CCO prior to the start of treatment. b. Treatments beyond 16 cycles require documentation showing continued evidence of benefit (i.e., a clinic note and CT scan confirming that there is no evidence of disease progression). The documentation can be submitted with the treatment claims. c. Patients who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent chemotherapies are not eligible for brentuximab funding. d. Use of brentuximab prior to ASCT or as maintenance after ASCT will not be funded. e. As per the manufacturer's product monograph, the maximum dose that can be administered is based on a weight of 100kg.
NS	Funded	Jan 1, 2015	As a single agent in patients with Hodgkin's Lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status (PS) of 0 or 1.
NB	Funded	Oct 1, 2014	For use in patients with CD30 antigen positive Hodgkin Lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status of 0 or 1.
NL	Not funded		
PEI	Under provincial consideration*		

**Under provincial consideration* means that the province is reviewing pCODR's recommendation. This may include the province working with the drug manufacturer to reach an agreement for a drug product that both parties can accept, in particular in cases where the pCODR Expert Review Committee has recommended that the drug be funded only on the condition of cost-effectiveness being improved to an acceptable level. This may occur before or after the pan-Canadian Pricing Alliance negotiations. Please contact the specific provincial drug program and/or cancer agency in your province for information about the status of a given drug product.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lymphoma Canada provided input on pembrolizumab for the treatment of patients with classical Hodgkin Lymphoma (cHL).

Lymphoma Canada (LC) conducted two anonymous online surveys (for patients and caregivers), which were directed via e-mail to patients registered on the LC database. The links were also made available via LC Twitter and Facebook accounts, as well as through HL patient forums, other HL-dedicated social media pages and groups, and international lymphoma organizations own contacts. Responses were collected from June 5th to 30th, 2017.

LC also conducted telephone interviews with three (3) cHL patients in Canada who had direct experience with pembrolizumab.

A total of 91 patients and 15 caregivers provided input to LC. Please see the table below listing participants by country and those with/without pembrolizumab experience who participated in the telephone interviews and surveys.

Table 1: Respondents by Country

Respondents	Canada	USA	UK	EU	Other	Skipped	Total
Patients WITH pembrolizumab experience	3	2	-	-	-	-	5
Patients WITHOUT pembrolizumab experience	36	7	11	6	8	20	86
Caregivers	5	2	4	1	-	3	15

For patients who provided their demographic information (73/91), 53% live in Canada, 68% are female, and 84% are between 20-59 years-old, see Table 2.

Table 2: Gender and age of survey and interview respondents

Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	Did not answer	Female	Male	Did not answer
Patients WITH pembrolizumab experience	0	5	0	0	0	2	3	0
Patients WITHOUT pembrolizumab experience	2	34	22	9	19	48	19	19
Caregivers	0	2	7	3	3	9	3	3
Total	**2**	**41**	**29**	**12**	**21**	**59**	**25**	**22**

The surveys designed by LC had a combination of multiple choice, rating and open-ended questions. There was also skipping logic that was built into the surveys allowing respondents to be asked questions that were only relevant to them. The open-ended responses to surveys and quotes obtained from the telephone interviews that reflected the sentiment of a majority were included verbatim in order to provide a deeper understanding of patient and caregiver perspectives.

From a patient's perspective, there are a number of symptoms associated with cHL that impact quality of life, which include fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough and mental/ emotional problems such as anxiety and difficulties with concentrating. Respondents also reported on aspects of their life negatively impacted by cHL, including ability to work, personal image, family obligations, intimate relations, friendships and ability to attend school. Most respondents indicated that current treatment options (e.g. ABVD, GDP, BEACOPP and MOPP/COPP, radiation, stem cell transplant, BV and surgery) work well in managing their cHL symptoms. LC noted that toxicity associated with their previous treatments were of great concern to many respondents; specifically, fatigue, "chemo-brain", peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility and lung damage were the most commonly reported. LC also indicated that respondents also experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). In the current sample LC noted that 93% of respondents had been treated with at least one line of conventional and 16% of respondents had received ≥ 3 lines of therapy. Respondents' expectations about the new drug under review were most importantly "effectiveness" followed by "minimal side effects" or "less side effects than current treatments". Respondents who have experience with pembrolizumab reported few side effects, and that they were tolerable. Some of the side effects reported with pembrolizumab included fatigue, cough, shortness of breath, nausea, itching, rash and joint pain. Reasons for beginning treatment with pembrolizumab included: no other treatment options available, progressed after stem cell transplant and fearing risk of toxicity associated with stem cell transplant and not responding to 3 previous lines of chemotherapy. The majority responded that pembrolizumab had positively impacted their health and well-being, notably no negative impacts on work/school, family obligations, friendships, intimate relations, activities or travel had been experienced.

Please see below for a summary of specific input received from LC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with classical Hodgkin Lymphoma

According to LC, 70% (n = 64/91) of patient respondents 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.

LC indicated that respondents with HL reported that the symptoms associated with their disease could significantly impact their quality of life. Of particular note, the most commonly reported symptoms include: fatigue or lack of energy (72%), enlarged lymph nodes (68%), drenching night sweats (44%), itching (43%), and persistent cough (38%). Other symptoms affecting quality of life for > 10% of respondents included unexplained weight loss, loss of appetite, trouble breathing, fever and chills and chest pain. Ongoing fatigue (constant, lasting fatigue or waves of fatigue) was also reported by 63% of survey respondents.

LC also examined which aspects of patients' lives had been NEGATIVELY impacted by cHL. Notably, the majority of patient respondents (61%) indicated that HL had a negative impact on their ability to work. Additional responses are summarized in Table 3.

Table 3: Effect of HL on day-to-day life of patients		
Aspect of life NEGATIVELY impacted by cHL	**# of respondents**	**% of respondents**
Ability to work	51	61%
Personal Image	39	47%
Family obligations	38	46%
Intimate relations	31	37%
Friendships	30	36%
Ability to attend school	13	16%
None of these	11	13%

Many respondents also reported that their quality of life was negatively affected by mental and emotional problems associated with their disease (Table 4).

Table 4: Effect of cHL on current quality of life of patients		
Symptom or problem related to HL	**# of respondents**	**% of respondents**
Anxiety/worry	42	48%
Problems concentrating	32	37%
Loss of sexual desire	29	33%
Stress of diagnosis	25	29%
Difficulty sleeping	25	29%
Memory loss	25	29%
Depression	20	23%
None of these	10	11%

Below are some of the key comments gathered from three (3) respondents to help illustrate the impacts in regards to their experience with cHL:

- *"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."* Female, 21-39, USA
- *"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 uni, 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."* Female, 21-39, Australia

- *"I almost feel like I suffer from ptsd from this experience. I went into remission for about a year and then had a recurrence. I'm always worried it might come back. If I smell alcohol swabs - like they use before taking blood or administering chemo - my mind goes right back to treatment days - and that's more than 25 years ago."* Female, 50-59, Canada

3.1.2 Patients' Experiences with Current Therapy for classical Hodgkin Lymphoma

LC reported that all patient respondents had previously received treatment or were currently undergoing treatment. Of the 73 patients who provided responses regarding their treatments, 93% had been treated with at least one line of conventional chemotherapy and 16% of respondents had received ≥3 lines of therapy. The most common conventional chemotherapy regimen received was ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) (81%), followed by GDP (gemcitabine, dexamethasone, cisplatin) (10%), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) (8%), and MOPP/COPP (mechlorethamine/cyclophosphamide, vincristine, procarbazine, prednisone) (5%). Other types of treatment individuals had received included radiation therapy (50%), autologous stem cell transplant (26%), brentuximab-vedotin (14%), surgery (10%), allogeneic stem cell transplant (4%), nivolumab (1%), and CAR-T therapy (1%).

In terms of treatment phases, LC indicated that of 85 respondents, indicating their treatment phase, 60% are in remission following their most recent line of therapy, 27% have been in remission for longer than 5 years and 15% of respondents had previously relapsed after one or more lines of therapy.

When LC asked respondents to rate their level of agreement with the statement "My most recent therapy could manage my Hodgkin lymphoma symptoms", on a 10-point scale; 10 = strongly agree, 72% of respondents gave a rating of ≥7, indicating that their most recent treatment was able to manage most or all of their HL symptoms.

Regarding side effects of current treatments, LC noted that toxicity associated with their previous treatments were of great concern to many respondents. The most common side effects respondents experienced during their HL treatments are listed in Table 5. In particular, respondents noted that nausea/vomiting (25/50; 50%), fatigue (23/50; 46%), and hair loss (11/50; 22%) were the most difficult side effects to tolerate. Many respondents (66) also experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). Fatigue (65%), "chemo-brain" (59%), peripheral neuropathy (32%), loss of menstrual periods (23%), thyroid dysfunction (18%), sterility (15%) and lung damage (14%) were the most commonly reported.

Table 5: Side effects of current cHL therapies

Side effect	# of respondents (total = 74)	% of respondents
Fatigue	70	95%
Hair loss	67	91%
Nausea/vomiting	65	88%
Mouth sores	51	69%
Peripheral neuropathy	39	53%
Low platelets	36	49%
Anemia and/or neutropenia	34	46%
Diarrhea	33	45%

Table 5: Side effects of current cHL therapies		
Side effect	**# of respondents (total = 74)**	**% of respondents**
Skin rashes/severe itching	29	39%
Loss of menstrual periods	26	35%
Breathing difficulties	23	31%
Infections	23	31%
Back pain	22	30%
Cough	20	27%
Irregular heartbeat	15	20%
Bowel obstruction	12	16%
Viral reactivation (e.g. shingles)	9	12%

LC asked respondents to rate how specific aspects of their treatment impacted their quality of life (Table 6).

Table 6: Negative impact of specific aspects of treatment				
Aspect of treatment	**Weighted average**	**% who rated 7-10 (significant impact)**	**% who rated Not applicable**	**Total number of responses**
Treatment-related fatigue	7.5	80%	0%	74
Ability to tolerate treatment	6.6	59%	0%	74
Infusion reaction	6.3	55%	8.5%	71
Infusion time	6.3	54%	6.8%	74
Number of clinic visits	6.2	59%	0%	73
Number of infections	4.3	22%	10%	73
Frequency of infections	4.0	15%	11%	74

LC also asked respondents to rate the negative impact of previous treatments on specific aspects of day-to-day life (Table 7).

Table 7: Negative impact of previous treatments on quality of life				
Aspect of life	**Weighted average**	**% who rated 7-10 (significant impact)**	**% who rated Not applicable**	**Total number of responses**
Ability to attend school	8.86	24%	66%	74
Ability to work	7.89	69%	14%	74
Travel	7.47	75%	7%	73
Activities	7.35	76%	1%	74
Intimate relations	7.08	68%	5%	71
Family obligations	6.14	55%	3%	74
Friendships	5.76	54%	0	74

Below are some key comments by four (4) respondents regarding experience with current therapies:

- *"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."* Female, 21-39, USA
- *"My short term memory from chemo is very bad on some days, which effects me at work and home. I'm constantly tired, I work full time and have 4 children. One of whom I was pregnant with when diagnosed."* Female, 21-39, UK
- *"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."* Female, under 20, USA
- *"Unable to work due to long-term side effects of chemotherapy. Pain and muscle weakness. I'm constantly exhausted, dialed from my stem cell transplant, have issue taking care of my toddler without help."* Female, 21-39, USA

LC also examined how difficult it was for patients to access treatment in their own community: The majority, 59/74 (79%) of individuals, were able to access treatment in their own community. For those who could not access treatment in their own community (n=15), 73% lived in a community without a cancer centre, or the treatment was not available in their province (20%) or country (7%). The most commonly reported financial impact of treatment was absence from work or school (48/70; 69%). Other financial burdens included parking (40%), cost of medications (30%), and travel to and from appointments (29%).

Below are some key comments by two (2) respondents regarding treatment access:

- *"Medications cost me over $80,000 over the last 7 years to help deal with side-effects of chemo. I am now on long-term disability, because I cannot work."* Female, 20-39, Canada
- *"Absence from work caused me to get into debt, first and second time."* Female, 50-59, UK

Furthermore, LC enquired about patients' choice of treatment. Respondents were asked how important it is for them and their physician to have a choice in deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 signifying not important as long as there is at least one treatment choice, to 10 signifying as extremely important to have a choice of treatment. LC reported that 70/85 (82%) of respondents rated the importance as 7, 8, 9 or 10, with a weighted average of 8.5. Of 85 respondents, 54% reported that they would take a drug with known side effects, potentially serious, if their doctor recommended it was the best choice for them (No = 2%; I don't know = 44%), indicating that many would be willing to tolerate significant side effects if the treatment is effective.

3.1.3 Impact of classical Hodgkin Lymphoma and Current Therapy on Caregivers

There were fifteen (15) caregiver respondents who completed the survey to address the impact on day-to-day life and challenges caregivers face with this type of cancer. Respondents were asked to rate on a scale of 1 (no impact) to 10 (very significant impact) how caring for the person with HL has impacted their day-to-day life. Please see Table 8 below for significant impacts on caregivers' daily activities.

Table 8: Effects of caregiving on quality of life	
Daily activity (Total responses = 15)	**7-10 (significant**
Ability to concentrate	10 (67%)
Contribute financially to household	9 (60%)
Travel	9 (60%)
Attend to household chores	8 (53%)
Volunteer	8 (53%)
Spend time with family and friends	7 (47%)
Exercise	5 (33%)
Fulfill family obligations	4 (27%)

Below are some key comments as described by three (3) caregiver respondents:

- *"My 20 year old son was diagnosed with cHL. This last year has been a nightmare. Family, friends don't call or even know what to say. We are left alone, while everyone's life continues." Female, 40-59, USA*
- *"I was pregnant with twins while caring for my man and we did what we had to do and we stuck together. It was hard to be away from our older kids when he was receiving treatments but nurses in oncology dept. are angels." Female, 20-39*
- *"I've become a caregiver. Scheduling my daughter's appointments, managing her medicine. Taken over her care. She was in between jobs at diagnosis and her prospects for a new job has significantly decreased. We support her financially now." Female, over 60, Canada*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with pembrolizumab

Based on no experience using the drug:

Regarding respondents' expectations about the new drug under review: "effectiveness" was most important to 31/44 (70%) individuals. A large number of patients (57%) also reported that "minimal side effects" or "less side effects than current treatments" was very important to them.

3.2.2 What Experiences Have Patients Had To Date with pembrolizumab?

Based on experience using the drug:

LC reported that five (5) patient respondents who have experience with pembrolizumab completed the survey and three (3) of these patient respondents were also interviewed for this submission. All five (5) patient respondents provided the date they began taking pembrolizumab as noted in the Table 9 below:

Table 9: cHL patients with pembrolizumab experience						
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

In terms of previous therapies, all five (5) patients had received at least 2 prior lines of conventional chemotherapy and three (3) patients had received 5 or more lines of therapy. Previous chemotherapy regimens included ABVD (n=5), GDP (n=3), GVD (n=2), COPP (n=1), DHAP (n=1), Bendamustine (n=1), and revlimid (n=1). Four (4) patients had undergone an autologous stem cell transplant, one (1) had undergone an allogeneic stem cell transplant and two (2) had received treatment with brentuximab vedotin prior to beginning treatment with pembrolizumab.

LC asked respondents about their reasons for beginning treatment with pembrolizumab. These included: no other treatment options available (n=1), progressed after auto-transplant and did not want to risk the potential toxicity of an allo-transplant (n=2), hoping for remission in order to proceed to allo-transplant (n=1), did not respond to 3 previous lines of chemotherapy and did not want to undergo an auto-transplant (n=1).

LC also enquired about which cHL symptoms were managed by pembrolizumab. Four (4) of five (5) patient respondents (80%) 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. One (1) patient respondent reported that their fatigue was not resolved by pembrolizumab.

When LC asked about side effects experienced with pembrolizumab all five (5) patients felt that side effects were well-tolerated, see Table 10.

Table 10: Side effects experienced with pembrolizumab

Side effect	Number of responses
Fatigue	1 (20%)
Cough	2 (40%)
Shortness of breath	3 (60%)
Nausea	1 (20%)
Itching	1 (20%)
Rash	1 (20%)
Loss of skin pigmentation	0
Decreased appetite	0
Headache	0
Constipation	0
Joint pain	2 (40%)
Back pain	0
Diarrhea	0
None of these	1 (20%)
Other (fever)	1 (20%)

LC asked patients if they would take this drug again, if their doctor thought it was the best choice, knowing the potential side effects. All five (5) individuals responded “yes”.

Also when prompted to compare how pembrolizumab compared to previous therapies, with respect to side effects, two (2) respondents 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.”* Male, 31, Canada

- *"It has greatly improved everything - I feel "normal" again. With chemo I always felt sick."* Male, 24, Canada

LC also asked respondents about patients' day-to-day life and quality of life with pembrolizumab. The majority of patients reported that pembrolizumab had no negative impact on work/school, family obligations, friendships, intimate relations, activities or travel. One (1) respondent reported experiencing lasting fatigue (that she thought may have been due to the drug) and that it limited her somewhat in these aspects of her life. Two (2) respondents reported that they were able to begin working (1 full-time; 1 part-time) for the first time since they began treatments for HL.

Below are some key comments described by four (4) respondents when asked how pembrolizumab has changed their 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."* Male, 31, Canada

- *"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."* Female, 27, Canada

- *"Other than the lasting joint pain, I feel like I'm back to normal. Sometimes I forget everything I went through."* Male, 24, Canada

- *"Everybody should be able to take this drug instead of going through chemo. It has been so much better for me."* Male, 20-39, USA

3.3 Additional Information

None provided

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from five of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- New treatment option for relapsed or refractory classical Hodgkin Lymphoma (cHL)
- Clarity on eligible patients

Economic factors:

- New treatment option
- Chair time

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that there is no standard of care for patients with refractory cHL or for patients who have relapsed after three or more lines of therapy. PAG identified that brentuximab vedotin is used for relapsed cHL.

After failure of brentuximab vedotin, chemotherapy with palliative intent, best supportive care and clinical trials are options. For patients who have failed autologous stem cell transplant and are eligible for transplant, the goal of treatment would be induction therapy to achieve remission for allogeneic transplant.

4.2 Factors Related to Patient Population

There is an unmet need for relapsed or refractory cHL. PAG is seeking clarity on the place in therapy of pembrolizumab. The number of previous therapies that patients in KEYNOTE-087 trial have received is unclear.

PAG is seeking information on whether other subtypes of HL also have overexpression of PD-L1 and if so, whether pembrolizumab would be appropriate for the other subtypes of HL.

PAG is seeking clarity on the use of pembrolizumab for cHL in patients who have not previously been treated with brentuximab vedotin. PAG noted that there is an ongoing trial (KEYNOTE-204) comparing pembrolizumab with brentuximab vedotin for brentuximab vedotin naïve patients.

4.3 Factors Related to Dosing

The dose is 200mg for cHL in the funding request and the KEYNOTE-087 trial. PAG noted trials suggest that weight based dose of 2mg/kg and 200mg fixed dose are similar. Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight

based dose for cHL given the high cost of fixed dose compared to weight based dose for patients weighing less than 100kg. In addition, as pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing.

4.4 Factors Related to Implementation Costs

Pembrolizumab would be an additional line of therapy. As pembrolizumab is an intravenous therapy, additional resources would be required to prepare and administer pembrolizumab.

4.5 Factors Related to Health System

Pembrolizumab would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. As pembrolizumab is a high cost drug and requires monitoring of immune-mediated reactions post-infusion, PAG noted that smaller outpatient cancer centres may not have the expertise and resources to administer pembrolizumab. This is a barrier for those patients who will need to travel to larger cancer centres that have the resources and expertise to administer pembrolizumab.

4.6 Factors Related to Manufacturer

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided: One joint submission from four clinicians submitted on behalf of the Hematology Drug Advisory Committee at Cancer Care Ontario and one group input from six oncologists across five provinces: British Columbia, Manitoba, Newfoundland, Ontario and Quebec.

Overall the oncologists providing input agreed that this indication and funding will only affect a very small number of patients and that there is currently no standard of care in relapsed/refractory patients with cHL. Two of the key benefits identified by both clinician groups was the encouraging response rate and good safety profile of pembrolizumab. An unmet need was identified by both groups. Pembrolizumab would be used in patients with refractory/relapsed cHL past autologous stem cell transplant (auto-SCT) and brentuximab vedotin (BV) and patients who are ineligible for transplant and have no access to BV. In patients who are eligible for allogeneic stem cell transplant (allo-SCT), this drug may replace conventional chemotherapy to provide a bridge to transplant. In patients who have chemo-refractory cHL, but who are BV-naïve, PD1 inhibitors may replace BV in patients who would not be able to tolerate BV (e.g. baseline neutropenia or neuropathy). The clinicians also noted that PDL1 testing would not be required.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for Hodgkin Lymphoma

The clinicians in both groups agreed that there is currently no standard of care in relapsed/refractory patients with cHL. Treatment options include:

- Palliative cytotoxic chemotherapy and or radiation therapy
- Allogeneic stem cell transplant
- Compassionate access to another anti PD-L1 agent – nivolumab

One clinician group providing input noted that allo-SCT is an option in young and fit patients that have a suitable donor. However, conventional chemotherapy regimens seldom provide adequate tumour control for a sufficient duration of time to allow for a graft versus lymphoma effect. Only patients, who have a complete remission or very good partial remission are allo-SCT candidates. Notably, allo-SCT is only potentially curative in 30% of these patients. The group of clinicians cautioned that allo-SCT is toxic and has a 20% treatment-related mortality at 2 years.

5.2 Eligible Patient Population

The clinicians in both groups agreed that this indication and funding will only affect a very small number of patients. One group of clinicians estimated that 90% and 80% of patients with limited stage and advanced stage cHL, respectively, are cured with the current standard of care. While HL is the most common lymphoma in adolescents and young adults, it remains a relatively uncommon lymphoma overall. Thus, it is estimated that only 25-35 patients per province per year would be eligible for anti-PD1 therapy such as pembrolizumab.

The other clinician group providing input noted that only patients with reasonable performance status can be considered for treatment with pembrolizumab after failure of both auto-SCT and BV. In this population Pembrolizumab may provide a treatment bridge to potential allogeneic stem cell transplant. Further, this clinician group expected a natural drop off rate in patients on BV after auto-SCT who would not receive subsequent treatment. It was anticipated that the majority of patient needing access to pembrolizumab would be the non-transplant eligible patients.

5.3 Identify Key Benefits and Harms with Pembrolizumab

Two of the key benefits identified by both clinician groups was the encouraging response rate and good safety profile of pembrolizumab.

One clinician group providing input noted in particular that pembrolizumab could be used as a bridge to allogeneic stem cell transplant and estimated a PFS benefit of 63% at 9 months. These clinicians also valued the safety profile observed in the Keynote-087 study, with the majority of adverse events being of grade 1 and 2 toxicities with minimal grade 3 or 4 toxicities. It was noted that experience is growing in using this class of drugs in terms of recognizing and managing some of the adverse events.

The other group of clinicians estimated that pembrolizumab provides good tumor control in > 90% of patients, with little to no side effects in 95% of patients. In particular, it was noted that the quality of life dramatically improves with pembrolizumab to a level that is comparable to the quality of life state prior to cHL diagnosis. One of the clinicians in this group communicated personal experience with treating eleven (11) cHL patients with pembrolizumab: In my experience in treating 11 patients with pembrolizumab, 8 have returned to work full time or part time, as early as 2 months having initiated their therapy. Although in the literature, it is estimated that 20% of patients obtain a complete response, the duration of response in these patients has not yet been reached. At our centre, 5/11 patients attained a CR, and 4/5 patients have maintained a CR while being off pembrolizumab for over 6 months. The follow up time in all of these patients is short. There is, however, hope that some patients may actually be cured with this approach, given that Hodgkin has the highest responses to PD1 inhibitors, and that 20% of patients with melanoma are cured with pembrolizumab.

The clinicians providing input across 5 provinces identified the following patient population for whom pembrolizumab should not be used:

- Patients with auto-immune diseases or who have had a prior reaction to nivolumab should not receive pembrolizumab because of the potential life-threatening immune related toxicities observed in approximately 5% of patients.
- Pregnancy is an absolute contra-indication to receive pembrolizumab

5.4 Advantages of Pembrolizumab Over Current Treatments

Both groups identified an unmet need that pembrolizumab would be able to fulfill.

One clinician group providing input responded that pembrolizumab may facilitate a bridge to auto or allo-SCT and fulfill an unmet need. However, the oncologists noted that it was unknown if progression free survival with pembrolizumab at 12 months post auto-SCT was superior to current available treatments.

The other group of clinicians providing input advocated that without a doubt, anti-PD1 inhibitors, such as pembrolizumab, are the most active therapies in patients with chemotherapy and BV-refractory cHL. There is no other class of drugs that has demonstrated this type of efficacy in terms of overall response rates (approximately 70%) and duration of response, which is not yet reached in patients who have achieved a CR. Even patients with stable disease benefit by having their lymphoma symptoms controlled by this drug. Hence, this novel class of therapy fulfills an unmet clinical need in a patient population that can return to work and contribute to the Canadian economy. In fact, >90% of patients do not experience severe adverse events (i.e. grade 3 or 4 adverse events) and thus do not require additional medications such as growth factor support, antibiotics or admission to hospital. In patients who have chemo-refractory cHL but who

are BV-naïve, PD1 inhibitors have a more favourable side effect profile compared to BV, which is associated with neutropenia, occasionally requiring G-CSF support, and neuropathy. Both of these side effects are the main causes of discontinuation of the drug.

5.5 Sequencing and Priority of Treatments with Pembrolizumab

One clinician group indicated that for the majority of younger patients this drug would be used after auto-SCT and BV failure. They noted that this drug would also address an unmet need in Ontario, where BV is not available as a treatment for older patients who are not eligible for auto-SCT. These clinicians anticipated this drug to be active in this older population as well, similarly to what is reported in the Keynote-087 phase II trial.

The other clinician group noted that patients whose cHL has relapsed past ASCT and BV have no other option that is comparable to anti-PD1 inhibitors. Therefore this class of drugs will not replace any existing standard of care. In patients who are eligible for allo-SCT, these drugs may replace conventional chemotherapy to provide a bridge to transplant. In patients who are chemo-refractory cHL, but who are BV-naïve, PD1 inhibitors may replace BV in patients who would not be able to tolerate BV (e.g. baseline neutropenia or neuropathy)

5.6 Companion Diagnostic Testing

One clinician group providing input noted that PDL1 expression did not appear to be a requirement for treatment with pembrolizumab for this submitted indication. It was noted that the phase 2 Keynote-087 study reported that only 0.6% patients had no staining for PDL1 expression. The clinicians explained that this meant that most patients will have some level of PDL1 expression in this recurrent cHL patient population. The clinicians concluded that based on the Keynote-087 study, it was not clear if PDL1 testing would even be required.

The other clinician group providing input noted there are no specific tests that would be necessary prior to administrating a PD1 inhibitor to a patient with relapsed/refractory cHL. The clinicians estimated that over 98% of cHL express PDL1, the ligand for PD1. Thus it was noted that the level of PDL1 by immunohistochemistry is not a reliable biomarker of response.

5.7 Additional Information

None provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of pembrolizumab in the following patient populations:

- Patients with classical Hodgkin Lymphoma (cHL) who failed to achieve a response or progressed after autologous stem cell transplant (ASCT) and have relapsed after treatment with or failed to respond to brentuximab vedotin (BV) post-ASCT, and
- Patients with cHL who did not receive ASCT and have relapsed after treatment with or failed to respond to BV.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of pembrolizumab should be included.**	1) Patients who progressed after/failed to respond to ASCT and subsequent BV 2) Patients who are ineligible for ASCT and have relapsed after or failed to respond to BV <u>Subgroups:</u> • Sex (male vs. female) • Age • ECOG performance status • Bulky disease (≥ 10 cm) • Prior BV failure • Best response to brentuximab (CR or PR vs. SD vs. PD vs. Unk) • Prior systemic therapies (yes vs. no) • Prior therapies (1 vs. 2 vs. 3 vs. 4 vs. ≥5) • Refractory to the most recent therapy (yes vs. no) • Prior autologous stem-cell transplantation (yes vs. no)	Pembrolizumab	**<u>Cohort 1 and Cohort 2</u>** Chemotherapy • Gemcitabine • Vinblastine • Vinorelbine • COPP (cyclophosphamide, vincristine, procarbazine, prednisone) Best supportive care	<u>Primary</u> • **OS** • **PFS** • **HRQoL** <u>Secondary</u> • ORR • Complete remission • Partial remissions • DOR • DCR <u>Safety</u> • AEs • SAEs • WDAEs

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	• Transplantation ineligible (yes vs. no) • Refused transplantation (yes vs. no) • PD-L1 tumour expression			

Abbreviations: cHL = classical Hodgkin lymphoma; **CR** = complete response; **PR** = partial response; **SD** = stable disease; **PD** = progressive disease; **Unk** = unknown; **ECOG**=Eastern Cooperative Oncology Group Performance Status; **WHO PS** = World Health Organization Performance Status; **HRQoL**=Health related quality of life; **RCT=**randomized controlled trial; **SAE**=serious adverse events; **AE**=adverse events; **WDAE**=withdrawals due to adverse events**; DCR**=disease control rate; **ORR**=objective response rate; **DOR=**duration of response; **BV** = brentuximab vedotin; **ASCT** = autologous stem cell transplant

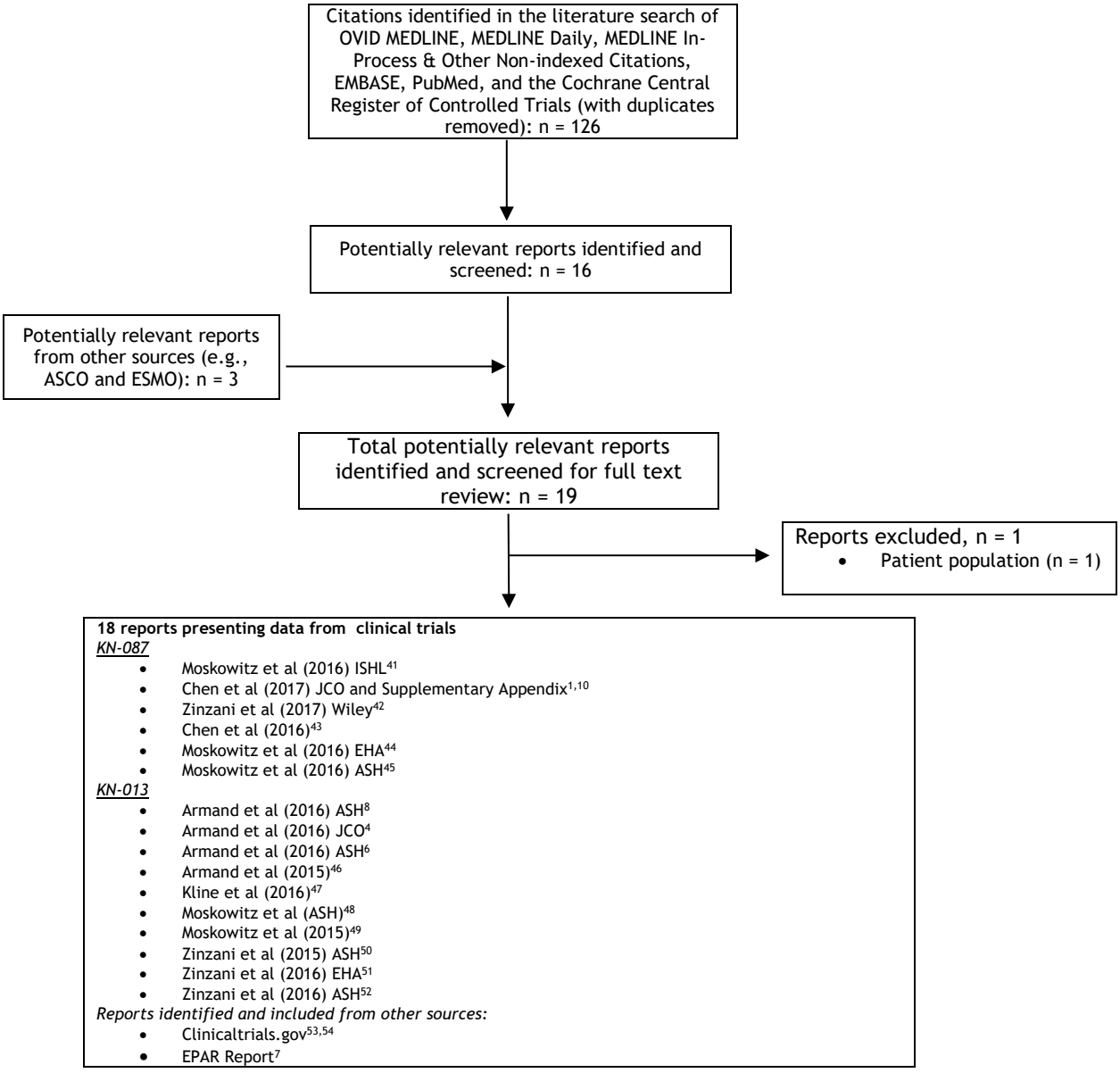
Notes:
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).
**Dose escalation trials were excluded but mixed design clinical trials (i.e. trials with a dose escalation phase followed by an efficacy-determining phase in which the intervention is administered at the same dose and schedule to all patients) were included if data were reported separately for the two phases of the trial.

6.3 Results

6.3.1 Literature Search Results

Of the 126 potentially relevant reports identified, two nonrandomized trials (KEYNOTE-087 [KN-087] and KEYNOTE-013 [KN-013]), reported in 18 citations, were included in the pCODR systematic review.[1,4,6,8,10,41-52] One report was excluded because of the patient population. Additional reports related to the KN-087 and KN-013 studies were obtained from the Submitter[11] and other resources.[7,53,54]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data was also obtained through requests to the Submitter by pCODR [NMA Report[11], Clinical Rationale,[11] Health Canada Module 2.5,[11] Health Canada Module 2.7.3,[11] Health Canada Module 2.7.4[11] and Health Canada Module 2.7.6,[11] Checkpoint Response[11] and Updated KN-087 Results[11]

6.3.2 Summary of Included Studies

Two non-randomized trials met the selection criteria of this review (KN-087 [n = 210] and KN-013 [n = 31]). KN-087 was a phase II, single-arm trial that assessed the effect of pembrolizumab in three patient cohorts with relapsed or refractory (R/R) cHL. The three cohorts consisted of patients who had (1) received ASCT and subsequent BV therapy; (2) received salvage chemotherapy and BV and were ineligible for ASCT due to chemoresistance; and (3) received ASCT and were BV-naïve.[1] For the purpose of this pCODR Review, the efficacy estimates of Cohort 3 from KN-087 will not be presented because it does not align with the funding request. KN-013 trial was a single-arm, multi-cohort, open-label phase 1b trial that assessed the effect of pembrolizumab in patients with R/R cHL who had disease progression on or after the treatment with BV.[4] Key characteristics of the trial are summarized in Table 4.

6.3.2.1 Detailed Trial Characteristics

Relevant summary information on trial characteristics may also be provided in a table format that can be used in section 2.1.3. When multiple trials are included in a systematic review, this section should compare and contrast the trials.

[Table 4]: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study name KEYNOTE-087 NCT02453594 **Characteristics** Nonrandomized, multicentre, single-arm, Phase II trial **Sample size** N = 210 **Locations** 51 sites in 13 countries, including United States (11 sites), Japan (7 sites), France (4 sites), Israel (4 sites), Russia (4 sites), United Kingdom (4 sites), Australia (2 sites), Germany (2 sites), Greece (2 sites), Hungary (2 sites), Sweden (2 sites), Canada (1 site) and Norway (1 site). **Patient Enrolment Dates** 24-Jun-2015 to 02-Mar-2016 **Data cut-off** 25-Sept-2016 **Funding** Merck	Key Inclusion Criteria: • R/R de novo cHL • Failed to achieve a response to, progressed after, or be ineligible for ASCT • Failed to achieve a response or progressed after treatment with BV or may be BV naïve • ECOG performance status of 0 or 1 • Measurable disease • Adequate organ function Key Exclusion Criteria: • Diagnosis of immunosuppression or received immunosuppressive therapy within 7 days of first study dose • Treatment with a monoclonal antibody within 4 weeks before first study dose • Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks before first study dose • Prior allogeneic hematopoietic SCT within the past 5 years • Clinically active CNS or pneumonitis • Active autoimmune disease requiring systemic treatment in past 2 years • Prior therapy targeting T-cell co-stimulation or checkpoint pathways • Known active HIV, HBV or HCV	Intervention: Pembrolizumab (200mg Q3W) Comparator: There was no comparator	Primary: ORR by BIRC Secondary: ORR by SI DOR by BIRC and SI CRR by BIRC and SI PFS by BIRC and SI OS Safety HRQoL

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study name KEYNOTE-013 NCT01953692 **Characteristics** Nonrandomized, multicohort, single-arm, Phase Ib trial **Sample size** N = 31 **Locations** 5 sites in 4 countries, including United States (2 sites), Canada (1 site), Italy (1 site) and France (1 site). **Patient Enrolment Dates** December-2013 to Sept-2014 **Data cut-off** 3-June-2016 **Funding** Merck	Key Inclusion Criteria: • Confirmed diagnosis of R/R cHL • Relapsed after, were ineligible, or refused ASCT • Received prior BV therapy • ECOG performance status of 0 or 1 • Adequate organ function Key Exclusion Criteria: • Active or past documented autoimmune disease • Clinically active CNS • Have ILD, second malignancy or HIV • Received previous treatment with checkpoint or T-cell costimulatory blockade, systemic immunosuppressive therapy within 7 days, or allogenic SCT within 5 years of first study dose	Intervention: Pembrolizumab (10 mg/kg Q2W) Comparator: There was no comparator	Primary: CRR by BIRC Secondary: Safety ORR by BIRC DOR by BIRC PFS by BIRC OS
Abbreviations: **R/R** = relapsed or refractory; **cHL** = classical Hodgkin lymphoma; **ASCT** = autologous stem cell transplant; **BV** = brentuximab vedotin; **ECOG** = Eastern Cooperative Oncology Group; **CNS** = central nervous system; **HIV** = Human Immunodeficiency Virus; **HBV** = Hepatitis B; **HCV** = Hepatitis C; **ILD** = interstitial lung disease; **Q3W** = every three weeks; **Q2W** = every two weeks; **SCT** = stem cell transplant; **BIRC** = blinded independent review committee; **SI** = study investigator; **ORR** = objective response rate; **DOR** = duration of response; **CRR** = complete response rate; **PFS** = progression-free survival; **OS** = overall survival; **HRQoL** = health-related quality of life			

a) Trial

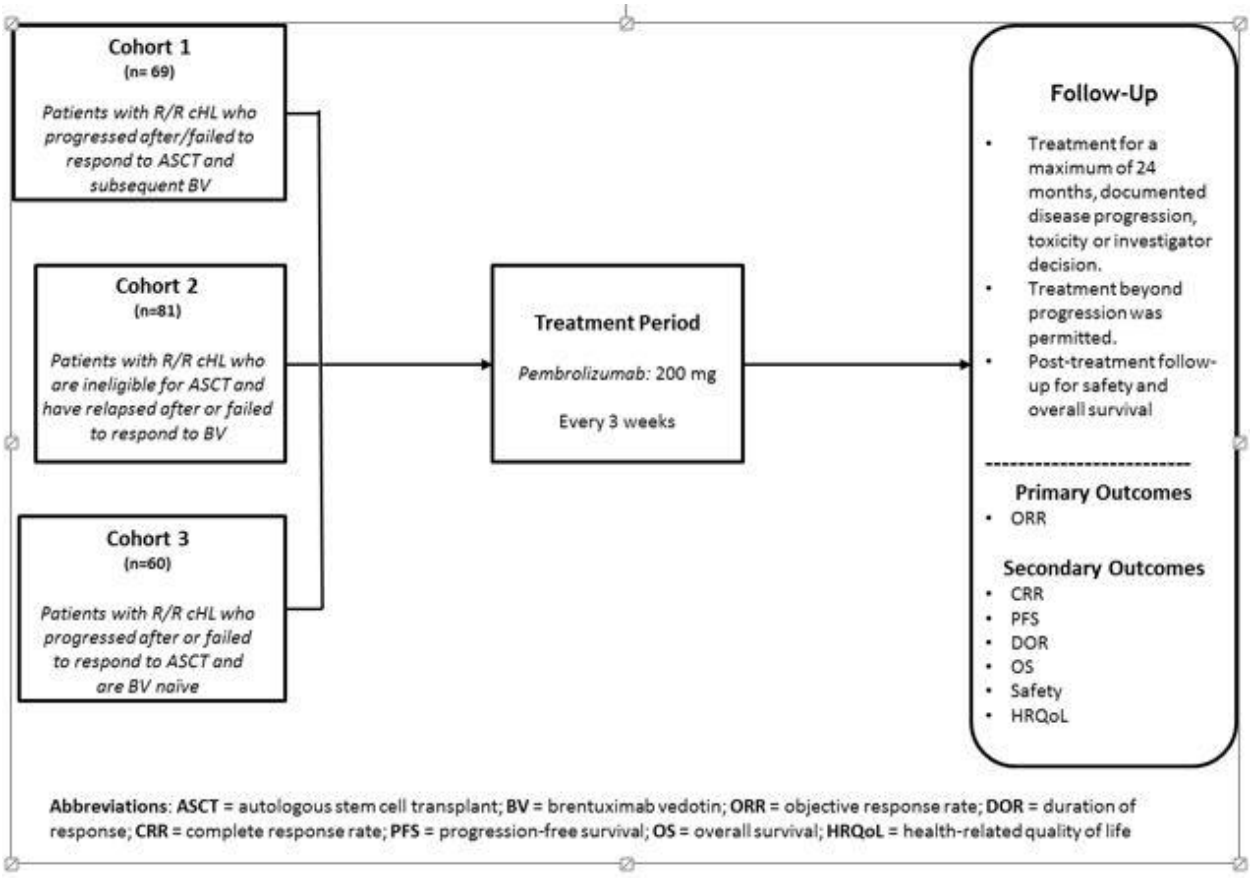
KEYNOTE-087

KN-087 was a multicentre, single-arm, nonrandomized phase II trial (Table 4). The objective of the trial was to assess the effect of pembrolizumab in three patient cohorts with R/R cHL. In this trial, "relapsed disease" was classified as disease progression after response to the most recent therapy while "refractory disease" was classified as failure to achieve complete remission or partial response to the most recent therapy.[1] The trial was composed of three patients cohorts, which included patients who had 1) failed to achieve a response or progressed after ASCT and had relapsed after treatment with or failed to respond to BV post-ASCT; 2) not received ASCT and had relapsed after treatment with or failed to respond to BV; and 3) failed to respond to, or progressed after ASCT, and had not received BV post-ASCT. The trial was funded by Merck and it was conducted in 51 sites within 13 countries, including Canada.

Patients were included in the KN-087 trial if they met the following criteria: adult patients with R/R cHL; had measureable disease; an ECOG performance status of 0 or 1; and adequate organ function.[1] Patients were excluded if they had: a diagnosis of immunosuppression or recipient of immunosuppressive therapy within 7 days of the first study dose; treatment with a monoclonal antibody within 4 weeks before first study dose; prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks before first study dose; prior allogeneic hematopoietic SCT within the past 5 years; clinically active central nervous system or pneumonitis; active autoimmune disease

requiring systemic treatment in past 2 years; prior therapy targeting T-cell co-stimulation or checkpoint pathways; and active HIV, HBV or HCV.

Figure 2: The study design of KEYNOTE-087



Data Source: CREATED BY pCORD METHODS

Figure 2 represents the study design of KN-087. The trial was composed of three phases: 1) the treatment phase, 2) the second course phase and 3) the follow-up phase.[55] These phases will be described in greater detail, more specifically:

Treatment Phase[55]

- Patients were treated with pembrolizumab (200 mg/m^2) for a maximum of 24 months or until disease progression, intolerable toxicity or investigator decision.
- Patients were assessed for response every 12 weeks using computed tomography (CT) using the Revised Response Criteria for Malignant Lymphoma (RRC).
- Patients were also assessed with positron emission tomography (PET) at week 12 and 24 to confirm complete remission (CR) or disease progression.
- Antitumour activity was evaluated by a blinded independent review committee (BIRC).
- Patients with CR could stop receiving pembrolizumab after a minimum of 6 months and after ≥ two doses of pembrolizumab post-CR.

Second Course Phase (Retreatment Period for Post-Complete Remission Relapse Only)[55]

- Patients could receive an additional 17 cycles of pembrolizumab beyond initial progression if they met the following criteria:
    - Stopped initial trial therapy after having confirmed CR by study investigator,
    - Received at least 24 weeks of pembrolizumab before discontinuing treatment and had at least two treatments beyond the date of initial CR,
    - Had disease progression as assessed by the study investigator after stopping initial pembrolizumab treatment,
    - Did not receive any anti-cancer therapies after initial pembrolizumab therapy,
    - Had an ECOG performance status of 0 or 1 and adequate organ function.
- Patients who had CR and were treated for up to two years with pembrolizumab could also receive an additional 17 cycles of pembrolizumab.

Follow-up Phase[55]

- Patients who discontinued for reasons other than disease progression were followed up every 12 weeks.
- Patients who achieved CR as assessed by the investigator and experience disease progression as determined by the study investigator could receive retreatment with pembrolizumab by entering the second course phase.
- Patients who had confirmed disease progression or started a subsequent therapy were followed up for survival until death, withdrawal or the end of the study.

The primary outcome in KN-087 was objective response rate (ORR) as assessed by BICR. Other secondary outcomes include: ORR as assessed by the study investigator, duration of response (DOR) as assessed by BICR and the study investigator, complete response rate (CRR) as assessed by BICR and the study investigator, progression free-survival (PFS), overall survival, safety and health-related quality of life (HRQoL).

The trial was designed to have ≥ 93% power to detect an ORR of ≥ 35% in cohort 1 and 3 compared with a fixed controlled rate of 15% and an ORR of ≥ 20% in cohort 2 compared with a fixed controlled rate of 5% using a one-sided significance level of α=0.025.[1] The protocol stated that there was no adjustment for multiplicity with the expectation of ORR as assessed by a BICR in each of the three cohorts.[55] All other efficacy analyses were considered explanatory.

The trial allowed for an interim analysis to be conducted in each cohort in order to determine futility.[55] The interim analysis was planned to occur when 30 patients in each cohort had reached the week 12 response assessment or they had discontinued treatment prior to week 12.[55] The interim analysis for cohort 1 and 2 was performed on 1-Feburary-2016[43,44] and on 8-April-2016 for cohort 3.[41]

The primary analysis was planned to occur when the last patient in each cohort had reached the week 12 response assessment or they had discontinued study therapy. This analysis was carried out on 27-June-2016.[45] Based on a protocol amendment, another efficacy analysis was conducted on 25-Sept-2016. This analysis occurred at the point when the last patient in each of the cohorts had reached the response assessment at week 24 or they had discontinued treatment.[1,3] A post-hoc analysis was presented on 31-December-2016 to provide an updated analysis for PFS.[1] Manufacturer also provided an updated analysis using the data cut-off of 21-March-2017. This analysis represents 6 months of additional follow-up from the 25-Sept-2016 cut-off. However, the results from this updated analysis will not be presented due to disclosure issues.[11]

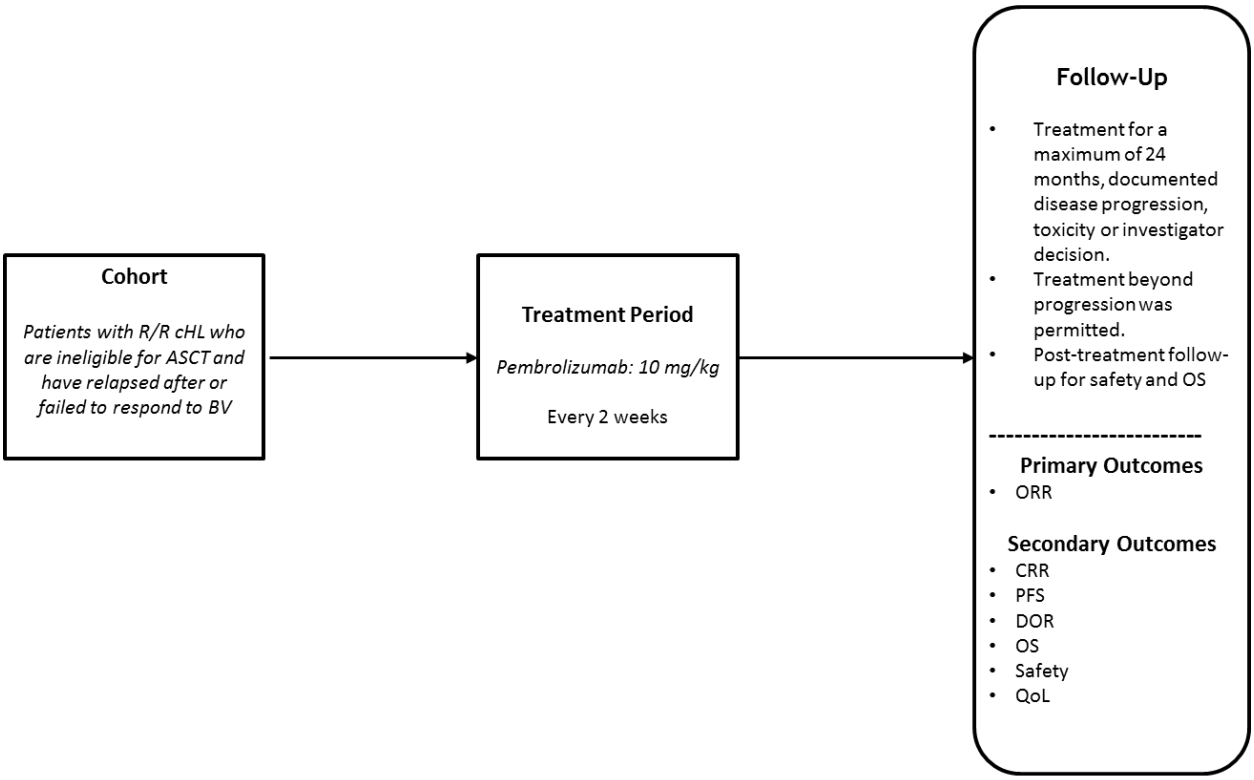
The Manufacturer reported that only one protocol amendment had occurred during the trial.[3] The following changes were made to the protocol: an update to the definitions of cohorts 1 to 3; added guidelines for grade 2 infusion reactions; removed the allowance for radiotherapy during the study; revised the interim analysis instructions; updated power calculation language; and modified the PFS analyses.[7]

KEYNOTE-013

KN-013 was a multicohort, open-label, single-arm, nonrandomized phase Ib trial (Table 4). The primary objective of the trial was to assess the effect of pembrolizumab in five patient cohorts with select hematological malignancies. However, for this pCODR Review, only the results of cohort 3 will be presented. Cohort 3 was composed of patients with R/R cHL who had disease progression on, or after, treatment with BV.[4] The trial was funded by Merck and it was conducted in five sites within four countries, including Canada.

Adult patients were included in the trial if they had: confirmed diagnosis of R/R cHL; relapsed after, ineligible or refused ASCT; received treatment with BV; ECOG performance status of < 2; and adequate organ function.[4] Exclusion criteria included: active or past documented autoimmune disease; clinically active central nervous system; ILD; secondary malignancy; HIV infection; received prior treatment with a checkpoint or T-cell costimulatory blockade; systemic immunosuppressive therapy within 7 days or allogeneic STC within 5 years of first study dose.[4]

Figure 3. Study design of KEYNOTE-013



Abbreviations: **ASCT** = autologous stem cell transplant; **BV** = brentuximab vedotin; **ORR** = objective response rate; **DOR** = duration of response; **CRR** = complete response rate; **PFS** = progression-free survival; **OS** = overall survival

Figure 3 represents the study design of KN-013. The trial was composed of three phases: 1) the treatment phase, 2) the second course phase and 3) the follow-up phase.[5] These phases will be described in greater detail, more specifically:

Treatment Phase[5]

- Patients were treated with pembrolizumab (10 mg/kg) for a maximum of 24 months (i.e. 35 doses) or until disease progression, intolerable toxicity or investigator decision.
- Patients were assessed for response after 12 weeks, and then 8 weeks thereafter using CT and PET.
- Antitumour activity was evaluated by BIRC using the International Harmonization Project (IHP) criteria.
- Patients who had radiological progressive disease could remain on therapy until their progressive disease was confirmed by a follow-up scan or if they were still receiving clinical benefit. Clinical stability was defined as:
    - Absence of symptoms and signs indicating clinically significant progression of disease.
    - No decline in ECOG performance status.
    - Absence of rapid progression of disease or progressive tumor at critical anatomical sites requiring urgent medical intervention.
- Patients with a CR could stop receiving pembrolizumab after a minimum of 6 months and after more than two doses of pembrolizumab post-CR.

Second Course Phase (Retreatment Period for Post-Complete Remission Relapse Only)[5]

- Patients were eligible to continue receiving pembrolizumab (i.e. 17 cycles) if they met the following criteria:

- Stopped initial trial therapy after having confirmed CR,
- Received at least 24 weeks of pembrolizumab before discontinuing treatment and had at least two treatments beyond the date of initial CR,
- Had disease progression as assessed by the study investigator after stopping initial pembrolizumab treatment,
- Did not receive any anti-cancer therapies after initial pembrolizumab therapy,
- Had an ECOG performance status of 0 or 1 and adequate organ function.

Follow-up Phase[5]

- Patients who discontinued for reasons other than disease progression were followed up every 8 weeks.
- Patients who achieved CR and experienced disease progression as determined by the study investigator could receive retreatment with pembrolizumab by entering the second course phase.
- Patients who had confirmed disease progression or started a subsequent therapy were followed up for survival until death, withdrawal or the end of the study.

The primary outcome of the trial was complete response rate (CRR) as assessed by BIRC using the IHP criteria. Other secondary outcomes include: safety, ORR, DOR, PFS and overall survival. The trial required a sample size of 25 patients to have 80% power to detect a 20% improvement in CRR using a one-sided significance level of α=0.05.[5] It is not clear how the multiplicity of secondary outcomes was controlled.

The protocol stated that an interim analysis could be performed if fewer than 10 patients had been enrolled six months after the first patient had been treated.[5] The protocol reported that the power calculation did not take the interim analysis into account.[5] Although an earlier analysis was presented on 27-October-2015[4], the Manufacturer noted that it corresponds to a preliminary analysis of the KN-013 data. This analysis does not represent a formal interim analysis and there were no statistical adjustments made for this analysis.[3] The primary analysis was planned to occur after 10 patients had reached the week 12 assessment, and the analysis was conducted at the 3-June-2016 cut-off date.[5,6] In addition, a later data cut-off occurred at 27-Sept-2016.[8]

The Manufacturer reported that the protocol had been amended six times.[3] The protocol was amended for the primary reasons: 1) update inclusion and exclusion criteria, dose modification table, supportive care for AEs, criteria for early termination, and define the extent of treatment (duration); 2) remove one cohort; 3) add one cohort; 4) add two cohorts and to dose all new patients with 200 mg every 3 weeks; 5) add one cohort; and 6) update one exclusion criterion.[3]

b) Populations

The patient characteristics of KN-087 are presented in Table 5. The median age of the patient population was 35 years (range: 18 to 76), 53.8% were male, 51.0% had an ECOG performance status of 1, 88.1% were white, 16.7% had not received treatment with BV and 36.2% had prior radiation therapy.[7,11] The most common subtype of cHL was nodular sclerosing HL (80.5%) followed by mixed cellularity HL (11.4%). All patients had refractory disease or relapsed after more than three lines of therapy (100%). The majority of patients (83.3%) had previously failed or relapsed after treatment with BV (cohort 1: 100%, cohort 2: 100% and cohort 3: 41.7%).[7] Patients in cohorts 1 and 3 all were post-ASCT while none of the patients in cohort 2 had received ASCT.[7] Patients received a median of 4 previous lines of systemic therapy (range: 1 to 12) [chen].[7]

Table 5. Baseline characteristics for patients enrolled in KEYNOTE-087

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	69		81		60		210	
Gender								
Male	36	(52.2)	43	(53.1)	34	(56.7)	113	(53.8)
Female	33	(47.8)	38	(46.9)	26	(43.3)	97	(46.2)
Age (Years)								
<65	69	(100.0)	66	(81.5)	57	(95.0)	192	(91.4)
>=65	0	(0.0)	15	(18.5)	3	(5.0)	18	(8.6)
Mean	37.0		42.3		36.8		39.0	
SD	10.9		17.4		13.4		14.5	
Median	34.0		40.0		32.0		35.0	
Range	19 to 64		20 to 76		18 to 73		18 to 76	
Race								
American Indian Or Alaska Native	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.5)
Asian	7	(10.1)	4	(4.9)	1	(1.7)	12	(5.7)
Black Or African American	2	(2.9)	2	(2.5)	3	(5.0)	7	(3.3)
Missing	1	(1.4)	1	(1.2)	1	(1.7)	3	(1.4)
Multi-Racial	2	(2.9)	0	(0.0)	0	(0.0)	2	(1.0)
White	57	(82.6)	73	(90.1)	55	(91.7)	185	(88.1)
Ethnicity								
Hispanic Or Latino	6	(8.7)	5	(6.2)	3	(5.0)	14	(6.7)
Not Hispanic Or Latino	48	(69.6)	65	(80.2)	48	(80.0)	161	(76.7)
Not Reported	4	(5.8)	7	(8.6)	4	(6.7)	15	(7.1)
Unknown	11	(15.9)	4	(4.9)	5	(8.3)	20	(9.5)

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Race Group								
White	57	(82.6)	73	(90.1)	55	(91.7)	185	(88.1)
Non-White	11	(15.9)	7	(8.6)	4	(6.7)	22	(10.5)
Missing	1	(1.4)	1	(1.2)	1	(1.7)	3	(1.4)
US Region								
US	13	(18.8)	20	(24.7)	19	(31.7)	52	(24.8)
Ex-US	56	(81.2)	61	(75.3)	41	(68.3)	158	(75.2)
Disease Subtype								
Classical Hodgkin Lymphoma- Nodular Sclerosis	55	(79.7)	65	(80.2)	49	(81.7)	169	(80.5)
Classical Hodgkin Lymphoma- Mixed Cellularity	9	(13.0)	10	(12.3)	5	(8.3)	24	(11.4)
Classical Hodgkin Lymphoma- Lymphocyte Rich	4	(5.8)	1	(1.2)	3	(5.0)	8	(3.8)
Classical Hodgkin Lymphoma- Lymphocyte Depleted	0	(0.0)	4	(4.9)	1	(1.7)	5	(2.4)
Missing	1	(1.4)	1	(1.2)	2	(3.3)	4	(1.9)
ECOG Performance Status								
0	29	(42.0)	44	(54.3)	29	(48.3)	102	(48.6)
1	39	(56.5)	37	(45.7)	31	(51.7)	107	(51.0)
2	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)
Prior Lines of Therapy Group								
>= 3	68	(98.6)	78	(96.3)	36	(60.0)	182	(86.7)

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Prior Lines of Therapy Group								
< 3	1	(1.4)	3	(3.7)	24	(40.0)	28	(13.3)
Prior Lines of Therapy								
Subjects with data	69		81		60		210	
Mean	4.6		4.0		3.5		4.0	
SD	1.7		1.7		1.8		1.7	
Median	4.0		4.0		3.0		4.0	
Range	2.0 to 12.0		1.0 to 11.0		2.0 to 10.0		1.0 to 12.0	
Refractory or Relapsed After 3 or More Lines								
Yes	69	(100.0)	81	(100.0)	60	(100.0)	210	(100.0)
Time of relapse since SCT failure Group								
>=12 months	37	(53.6)	0	(0.0)	7	(11.7)	44	(21.0)
<12 months	32	(46.4)	0	(0.0)	53	(88.3)	85	(40.5)
Missing	0	(0.0)	81	(100.0)	0	(0.0)	81	(38.6)
Time of relapse since SCT failure (Months)								
Subjects with data	69		0		60		129	
Mean	30.4				6.3		19.2	
SD	40.0				11.8		32.5	
Median	12.6				1.9		7.9	
Range	2.5 to 247.9				0.4 to 76.0		0.4 to 247.9	
Brentuximab Use								
Yes	69	(100.0)	81	(100.0)	25	(41.7)	175	(83.3)

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Brentuximab Use								
No	0	(0.0)	0	(0.0)	35	(58.3)	35	(16.7)
Prior Radiation								
Yes	31	(44.9)	21	(25.9)	24	(40.0)	76	(36.2)
No	38	(55.1)	60	(74.1)	36	(60.0)	134	(63.8)
Bulky Lymphadenopathy								
Yes	5	(7.2)	12	(14.8)	3	(5.0)	20	(9.5)
No	64	(92.8)	69	(85.2)	57	(95.0)	190	(90.5)
Baseline B Symptoms								
Yes	22	(31.9)	26	(32.1)	19	(31.7)	67	(31.9)
No	47	(68.1)	55	(67.9)	41	(68.3)	143	(68.1)
Baseline Bone Marrow Involvement								
Yes	3	(4.3)	5	(6.2)	3	(5.0)	11	(5.2)
No	66	(95.7)	75	(92.6)	57	(95.0)	198	(94.3)
Missing	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.5)
(Database Cutoff Date: 27JUN2016).								

Data Source: EPAR Report[7]

KEYNOTE-013

The baseline characteristics of KN-013 are presented in Table 6.[11] The median age of the patient population was 32 years (range: 20 to 67), 58.1% were male, 54.8% had an ECOG performance status of 1, 93.5% were white and 41.9% had prior radiation therapy.[4,11] Most patients had nodular sclerosing HL (96.8%).[4] All patients in the trial had refractory disease or relapsed after more than three lines of therapy (100%) and had failed or relapsed after BV treatment (100%).[4] The majority of patients (74.2%) had previously failed or relapsed after ASCT and 25.8% were ineligible for ASCT.[4,11] Patients received a median of 5 previous lines of systemic therapy (range: 2 to 15).[11]

The Health Canada Modules stated that the categorization of “refractory” or “relapsed” were mutually exclusive.[11] Patients were classified as “refractory” if their best response to more than one line of prior therapy was stable disease or disease progression (N = 27). On the other hand, patients were classified as “relapsed” if they relapsed after more than three prior lines of therapy and were not refractory (N =4).

Table 6: Baseline characteristics of KEYNOTE-013 patients

	MK-3475 10 mg/kg	
	n	(%)
Subjects in population	31	
Gender		
Male	18	(58.1)
Female	13	(41.9)
Age (Years)		
< 65	29	(93.5)
>= 65	2	(6.5)
Mean	34.4	
SD	12.1	
Median	32.0	
Range	20 to 67	
Race		
Multiple	1	(3.2)
Null	1	(3.2)
White	29	(93.5)
Ethnicity		
Hispanic Or Latino	2	(6.5)
Not Hispanic Or Latino	25	(80.6)
Not Reported	4	(12.9)
Race Group		
White	29	(93.5)
Non-White	1	(3.2)
Missing	1	(3.2)
US Region		
US	16	(51.6)
Ex-US	15	(48.4)
Disease Subtype		
Nodular Sclerosis Hodgkin Lymphoma	30	(96.8)
Mixed Cellularity Hodgkin Lymphoma	1	(3.2)
ECOG Performance Status		
[0] Normal Activity	14	(45.2)
[1] Symptoms, but ambulatory	17	(54.8)
Prior Lines of Therapy Group		
>= 3	30	(96.8)
< 3	1	(3.2)

	MK-3475 10 mg/kg	
	n	(%)
Prior Lines of Therapy		
Mean	6	
SD	3	
Median	5	
Range	2 to 15	
Baseline Transplant Status		
Transplant Failed	23	(74.2)
Transplant Ineligible	8	(25.8)
Refractory or Relapsed After 3 or More Lines		
Yes	31	(100.0)
Brentuximab Use		
Yes	31	(100.0)
Prior Radiation		
Yes	13	(41.9)
No	18	(58.1)
Bulky Lymphadenopathy		
Yes	9	(29.0)
No	18	(58.1)
Unknown	3	(9.7)
Missing	1	(3.2)
Baseline B Symptoms		
Yes	10	(32.3)
No	20	(64.5)
Missing	1	(3.2)
Baseline Bone Marrow Involvement		
Yes	1	(3.2)
No	26	(83.9)
Missing	4	(12.9)
(Database Cutoff Date: 03JUN2016).		

Data Source: Health Canada Module 2.7.3[11]

c) Interventions

KEYNOTE-087

Treatment Dosing Schedule

All patients received an intravenous (IV) 200mg dose of pembrolizumab every three weeks for a maximum of 24 months or until disease progression, unacceptable toxicity or investigator decision.[1]

Dose delays, reductions or modifications

Treatment with pembrolizumab was withheld if drug-related toxicities and severe or life-threatening adverse events (AEs) occurred [protocol]. In addition, dosing interruptions were allowed if medical or surgical events, not related to pembrolizumab, occurred.[55] Patients could return to their therapy within three weeks of the scheduled interruption unless specified by the study investigator.[55]

KEYNOTE-013

Treatment Dosing Schedule

All patients received an IV 10 mg/kg dose of pembrolizumab every two weeks for up to 2 years or until disease progression or unacceptable toxicity.[54]

Dose delays, reductions or modifications

Treatment with pembrolizumab was withheld if drug-related toxicities and severe or life-threatening AEs occurred.[5] In addition, dosing interruptions were allowed if medical or surgical events, not related to pembrolizumab, occurred.[5] Patients could return to their therapy within three weeks of the scheduled interruption unless specified by the study investigator.[5]

d) Patient Disposition

KEYNOTE-087

The patient disposition for KN-087 is presented in Figure 4. Two hundred and ten patients were enrolled in the trial and received at least one dose of pembrolizumab (cohort 1: 69, cohort 2: 81 and cohort 3: 60). At the 25-Sept-2016 data cut off, 42.9% of patients discontinued their assigned therapy while 57.1% of patients were still receiving treatment.[1] More patients in cohort 2 discontinued (55.6%) as compared to those in cohort 1 (37.7%) or cohort 3 (31.7%).[1] The most common reasons for discontinuation were progressive disease (cohort 1: 14.5%, cohort 2: 24.7% and cohort 3: 21.7%) and complete response (cohort 1: 7.2%, cohort 2: 8.6% and cohort 3: 1.7%). More patients in cohort 2 discontinued due to physician's decision (8.6%) than those in cohort 1 (4.3%) and cohort 3 (3.3%).

Figure 4. Patient disposition in the KEYNOTE-087 trial

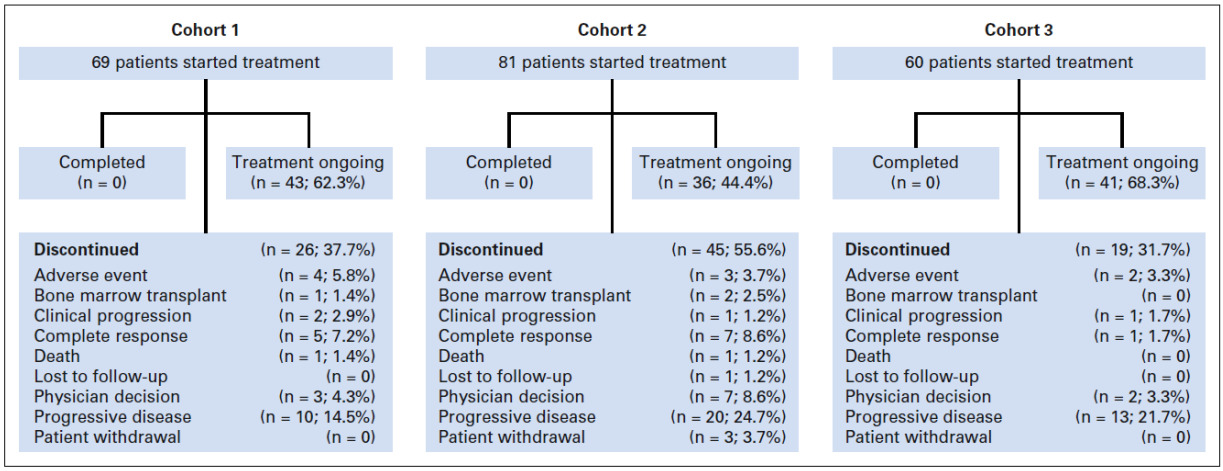


Fig 1. Patient disposition.

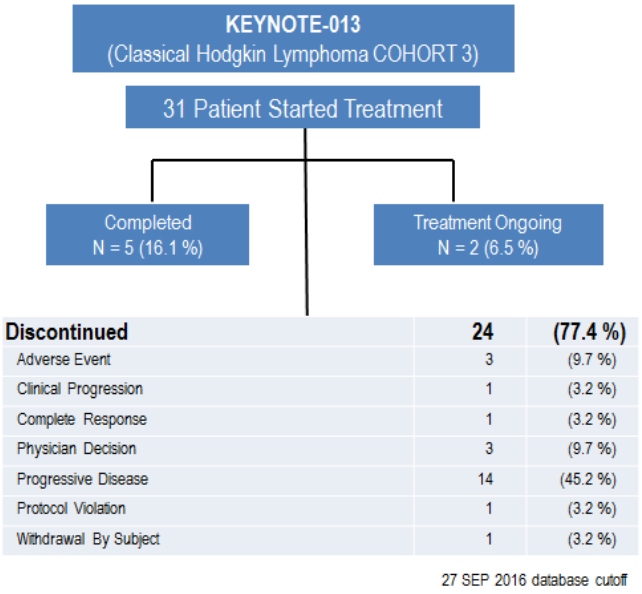
Data Source: Chen et al (2017) JCO.[1] Please note that the results of KEYNOTE-087 cohort 3 are beyond the scope of current Health Canada approval of pembrolizumab, and will not be considered.

One hundred and three major protocol deviations occurred during the trial. The majority of these deviations were due to informed consent and missed AE reports. No patients were excluded as a result of a protocol deviation.[3,7]

KEYNOTE-013

The patient disposition for the KN-013 trial is presented in Figure 5. Thirty-one patients were enrolled in the trial, and at the later 27-Sept-2016 data cut off, 74.2% of these patients had discontinued.[11] The primary reason for discontinuation was progressive disease (45.2%) followed by adverse event (9.7%) and physician decision (9.7%).[11]

Figure 5. Patient disposition in the KEYNOTE-013 trial



Data source: KEYNOTE-013 CONSORT diagram[11]

There were a total of 79 protocol deviations.[3]

e) Limitations/Sources of Bias

Two trials that assessed the effect of pembrolizumab in patients with R/R cHL were identified for this review, KN-087 (N = 201) and KN-013 (N =31). Specific aspects of trial quality are summarized in Table 7. The limitations that should be taken into consideration when interpreting the results of these trials, are presented below:

Table 7: Select quality characteristics of included studies of pembrolizumab in patients with R/R cHL

Study	Treatment vs. Comparator	Primary outcome	Required sample size[1,2]	Sample size	Randomization method[3]	Allocation concealment[4]	Blinding[4]	ITT Analysis[5]	Final analysis	Early termination	Ethics Approval
Keynote-87	Pembrolizumab (200 mg every 3 weeks)	ORR	180	210	Not randomized	No	No	No	No	No	Yes
Keynote-013	Pembrolizumab (10 mg/kg every 2 weeks)	CRR	25	31	Not randomized	No	No	No	No	No	Yes

Abbreviations: ORR = objective response rate; CRR = complete response rate; NR = not reported
1: The trial was designed to have ≥ 93% power to detect an objective response rate (ORR) of ≥ 35% in cohort 1 and 3 compared with a fixed controlled rate of 15% and an ORR of ≥ 20% in cohort 2 compared with a fixed controlled rate of 5% using a one-sided significance level of α=0.025.
2: The trial required a sample size of 25 patients to have 80% power to detect a 20% improvement in CRR using a one-sided significance level of α=0.05.
3: Patients enrolled in the trials were allocated by non-randomization and no stratification based on age, sex or other trials characteristics was used in the trial.
4: These were open-label trials and the sponsors, investigators and patients were unware of treatment status. However, outcomes were assessed in KN-087 using BIRC with RCC criteria and in KN-013 using BIRC with IHP criteria.
5: Patients were included in the efficacy analysis of KN-087 if they had received at least one dose of pembrolizumab while those in KN-013 were included if they had at least one post-baseline assessment.

- KN-087 and KN-013 were non-comparative studies. The single-arm, nonrandomized design makes interpreting the efficacy and safety events attributable to pembrolizumab challenging, since all patients with R/R cHL received the same treatment.

- Both KN-087 and KN-013 were single-arm, non-randomized, open-label trials. In open-label trials, the study investigator and the study participants are aware of their treatment status, which increases the risk of detection bias and performance bias. This has the potential to bias results and outcomes in favour of pembrolizumab if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. However, in order to mitigate the impact of this bias, the investigators used a blinded independent review committee to evaluate responses using standardized criteria for both trials. In addition, subjective outcomes (i.e. adverse outcomes and HRQoL) may be biased due to the open-label design.

- The adequacy of the ORR as a primary endpoint in KN-087 is unclear. Although ORR appears to be correlated with median overall survival, a statistical correlation does not necessarily equate to the prediction of a survival benefit from the response rate. Furthermore, the primary outcome in KN-013 was CRR as assessed by BIRC. The Clinical Guidance Panel stated that ORR would have been a more clinically meaningful outcome to measure, since partial responses to therapy in advanced HL are common, may reflect residual inactive disease and may be associated with prolonged disease control.

- The robustness of the preliminary overall survival and PFS results are limited due to short follow-up of the study populations and the lack of a randomized comparison treatment group in KN-087 and KN-013. The overall survival data should also be considered exploratory given the small sample sizes and no power calculation for PFS and overall survival.

- In KN-087, there was no adjustment for multiplicity with the exception of the primary outcome, objective response rate (ORR) as assessed by BICR, in each of the three cohorts.[55] All other efficacy analyses should be interpreted with caution because they are considered explanatory.

- In KN-087, HRQOL were collected using the EORTC QLQ-C30 and EQ-5D. The effect of pharmacological treatments on HRQoL is an important consideration when making treatment decisions. However, it should be noted that the HRQoL estimates were measured up to week 12, which may not represent an accurate picture of patients' experiences with pembrolizumab for a prolonged period of time. Additionally, the trial was non-randomized and the impact of pembrolizumab on patient's QoL in relation to other therapies is unknown. HRQoL data was not collected in KN-013.

- For the safety evaluation, it is important to note that since the data come from single-arm studies, it is difficult to estimate the contribution of the underlying disease on adverse reactions.

- There were a high degree of protocol deviations with 103 occurring in KN-087 and 79 in KN-013.[3] It is not clear what the magnitude or direction of the bias may have been due to these protocol deviations.

- Although the results of these trials indicate that there is a clinical benefit, there are many examples of anti-cancer regimens where the findings from phase II were not replicated in phase III trials.[9] However, there is an ongoing randomized, international, open-label phase III trial, KN-204 trial. KN-204 will assess the efficacy and safety of pembrolizumab as compared to BV in patients with R/R cHL. The trial will include the following R/R cHL patient populations: 1) those who have relapsed (disease progression after most recent therapy) or are refractory (failure to achieve CR or have PR to most recent therapy) cHL; or 2) those who have previously been treated with and responded to (achieved a CR or PR) to BV or BV-containing regimens and then experienced disease progression.[2]

- The effect of immunotherapies may not be adequately represented by antitumor activity measures since tumour response differs for other anticancer agents. This phenomenon, pseudo-progression, occurs in patients treated with immunotherapies, is characterized by radiologic disease growth which may be due to immune-related inflammation and not necessarily reflective of true disease progression. For instance, these patients may experience an initial increase in tumour size prior to it shrinking. This change in tumour size has the potential to be misinterpreted as disease progression. To account for pseudo-progression in the trials, patients who presented with disease progression and a stable clinical condition could continue to receive pembrolizumab at the discretion of the study investigator until repeated imaging that was performed 4-6 weeks later confirmed progression.[5,55]

- KN-087 and KN-013 assessed the effect of pembrolizumab in patients with R/R cHL. Other potentially relevant comparators were not assessed in this study (i.e. chemotherapy or BV). Of note, the Submitter has included a network meta-analysis which includes other comparators (such as gemcitabine and BV) which will be critically appraised later in the review and assessed by the Clinical Guidance Panel.[11]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

KEYNOTE-087

Efficacy analyses were performed in patients who had received ≥ 1 dose of pembrolizumab. Chen et al (2017) used a cut-off date of 25-Sept-2016, which represents a median duration of follow up of 10.1 months (range: 1.0 to 15.0 months).[1] This pCODR review will only present the efficacy results from cohorts 1 and 2 from KN-087 because they these cohorts were approved in the Health Canada Notification of Compliance with conditions. The results of cohort 3 are beyond the scope of this review. However, for secondary and exploratory outcomes, the pooled results of cohort 1, cohort 2 and cohort 3 will be presented. These estimates should be interpreted with caution because they may not be directly applicable to cohort 1 and cohort 2 due to uncertainty in the pooled estimates.

Objective Response Rate

The primary and secondary outcomes in the trial were ORR as assessed by BIRC and the study investigator using RCC criteria.[56] Chen et al (2017) defined the outcome as the proportion of patients who achieved CR or partial remission using RRC criteria at any time during the study.[1] Best overall response was defined as the best ORR from the first dose to first documented disease progression, death, or subsequent therapy (in the absence of disease progression).[1] For the assessment of CR, the authors stated that a post-treatment residual mass of any size was permitted if it was negative on PET imaging.

The point estimate of ORR and corresponding 95% confidence intervals (CIs) were estimated using the Clopper-Pearson method.[1] In addition, an exact binomial test was conducted versus a fixed control rate for each cohort. The trial was designed to have ≥ 93% power to detect an ORR of ≥ 35% in cohort 1 and 3 compared with a fixed controlled rate of 15% and an ORR of ≥ 20% in cohort 2 compared with a fixed controlled rate of 5% using a one-sided significance level of α=0.025.[55] Exploratory subgroups analyses, across all cohorts, were also planned and included: previous lines of therapy and by relapsed or refractory status.

Table 8 shows the results of ORR as assessed by BIRC for the 25-Sept-2016 data cut-off. The ORR for cohort 1 was 73.9% (95% CI: 61.9% to 83.7%), 64.2% (95% CI: 52.8% to 74.6%) for cohort 2 and 69.0% (95% CI: 62.3 to 75.2) for all patients.[1] Additionally, four patients in this analysis did not have any post-baseline assessments.[3]

Table 8: ORR estimates for Cohort 1, Cohort 2 and Cohort 3 at the 25-Sept-2016 data cut-off

Table 2. Best Overall Response by Blinded Independent Central Review

	Cohort 1 (n = 69) After ASCT/BV		Cohort 2 (n = 81) Ineligible for ASCT and Experienced Treatment Failure With BV		Cohort 3 (n = 60) No BV After ASCT		All Patients (N = 210)	
Response	No. (%)	95% CI†	No. (%)	95% CI†	No. (%)	95% CI†	No. (%)	95% CI†
Overall response rate	51 (73.9)	61.9 to 83.7	52 (64.2)	52.8 to 74.6	42 (70.0)	56.8 to 81.2	145 (69.0)	62.3 to 75.2
Complete remission*	15 (21.7)	12.7 to 33.3	20 (24.7)	15.8 to 35.5	12 (20.0)	10.8 to 32.3	47 (22.4)	16.9 to 28.6
Partial remission	36 (52.2)	39.8 to 64.4	32 (39.5)	28.8 to 51.0	30 (50.0)	36.8 to 63.2	98 (46.7)	39.8 to 53.7
Stable disease	11 (15.9)	8.2 to 26.7	10 (12.3)	6.1 to 21.5	10 (16.7)	8.3 to 28.5	31 (14.8)	10.3 to 20.3
Progressive disease	5 (7.2)	2.4 to 16.1	17 (21.0)	12.7 to 31.5	8 (13.3)	5.9 to 24.6	30 (14.3)	9.9 to 19.8
Unable to determine	2 (2.9)	0.4 to 10.1	2 (2.5)	0.3 to 8.6	0 (0)	—	4 (1.9)	0.5 to 4.8

Abbreviations: ASCT, autologous stem cell transplantation; BV, brentuximab vedotin.
*For complete remission, a residual mass was permitted for patients who had negative positron emission tomography scan results.
†On the basis of binomial exact CI method.

Data Source: Chen et al (2017) JCO.[1] Please note that the results of KEYNOTE-087 cohort 3 are beyond the scope of this review and will not be considered.

The results of ORR as assessed by the study investigator are presented in Table 9. The ORR for cohort 1 was 68.1% (95% CI: 55.8 to 78.8) while it was 66.7% (95% CI: 55.3 to 76.8) for cohort 2 and 68.1% (61.3 to 74.3) for all patients.[1]

Table 9. ORR as assessed by the study investigator using RCC criteria for cohort 1, cohort 2 and cohort 3

	Cohort 1 After ASCT/BV (n = 69)		Cohort 2 Ineligible for ASCT and Failed BV Therapy (n = 81)		Cohort 3 No BV After ASCT (n = 60)		All Patients (N = 210)	
	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*
Overall response rate	47 (68.1)	55.8-78.8	54 (66.7)	55.3-76.8	42 (70.0)	56.8-81.2	143 (68.1)	61.3–74.3
Complete remission†	22 (31.9)	21.2-44.2	23 (28.4)	18.9-39.5	18 (30.0)	18.8-43.2	63 (30.0)	23.9–36.7
Partial remission	25 (36.2)	25.0-48.7	31 (38.3)	27.7-49.7	24 (40.0)	27.6-53.5	80 (38.1)	31.5–45.0
Stable disease	13 (18.8)	10.4-30.1	16 (19.8)	11.7-30.1	11 (18.3)	9.5-30.4	40 (19.0)	14.0–25.0
Progressive disease	7 (10.1)	4.2-19.8	9 (11.1)	5.2-20.0	7 (11.7)	4.8-22.6	23 (11.0)	7.1–16.0
Unable to determine	2 (2.9)	0.4-10.1	2 (2.5)	0.3-8.6	-	-	4 (1.9)	0.5–4.8

*Based on binomial exact confidence interval method.
†For complete remission, a residual mass was permitted for patients who were negative on PET scanning.

Data Source: Chen et al (2017) JCO Supplementary Appendix.[1,10]

Chen et al (2017) performed three ORR subgroup analyses using all patients from KN-087; however, these analyses should be interpreted with caution due to small sample sizes. In the first subgroup, the effect on ORR was similar for patients who had received < 3 lines of therapy (ORR: 71.4% [95% CI: 51.3 to 86.8]; n = 28) or ≥ 3 lines of therapy (ORR: 68.7% [61.4 to 75.3]; n = 182).[10]

In the second subgroup analysis using all patients from KN-087, patients who were refractory to first-line therapy had a higher ORR (79.5% [95% CI: 68.4 to 88.0]; n = 73) than those who were BV naïve [71.4% (95% CI: 53.7 to 85.4); n = 35) or who were refractory to any therapy received (56.5% [95% CI: 34.5 to 76.8]); n = 23].[10]

Finally, patients who were refractory to at least one prior line of therapy had a higher ORR (ORR: 71.2% [95% CI: 63.7 to 77.9]; n = 170) than those who had relapsed after three or greater line of prior therapy (ORR: 67.8% [95% CI: 59.6 to 75.3]; n = 146).[10] This analysis included all patients enrolled in KN-087. Chen et al (2017) commented that analysis was not mutually exclusive and patients may belong to more than one category.

Complete Response Rate

CRR was defined as the proportion of patients who had a CR and it was assessed by BIRC and the study investigator using RRC.[55] The point estimates of CRR and corresponding 95% CIs were obtained using the Clopper-Pearson method. An exact binomial test was conducted versus a fixed control rate for each cohort.

Chen et al (2017) stated that the CRR as assessed by BIRC was 22.4% (95% CI: 16.9 to 28.6) for all patients in the trial (Table 8).[1] The CRR was similar for cohorts 1 and 2. In contrast, the CRR as assessed by the study investigator was higher for all patients (CRR: 30.0% [95% CI: 23.9 to 36.7]) (Table 9).[10]

Duration of Response

DOR as assessed by BIRC and the study investigator using RRC was defined as the time between first response to the date of first documented disease progression, death or last disease assessment (if disease progression did not occur) [protocol]. Kaplain-Meier estimates were used to determine DOR. At the 25-Sept-2016 data cut-off, the median DOR had not been reached for any of the three cohorts.[1]

Disease control rate (DCR) was not measured in the trial.

Progression-Free Survival

PFS was defined as defined as the time from first dose to first documented disease progression or death due to any cause, whichever occurred first.[7] PFS was estimated using nonparametric Kaplain-Meier curves. At the 25-Sept-2016, the six month PFS rate was 72.4% for all patients.[1] The authors also noted that at an ad-hoc data cut-off, 31-Dec-2016, the 9-month PFS rate was 63.4%.[1]

Overall Survival

Overall survival was defined as defined as time from first dose to date of death.[55] Overall survival was also estimated using nonparametric Kaplain-Meier curves. At the 25-Sept-2016, only four patients had died and median overall survival had not been reached.[1]

KEYNOTE-013

Patients were included in the efficacy analysis if they had at least one post-baseline assessment. The primary analysis occurred on 3-June-2016, which represents a median follow up of 24.9 months (range: 7.0 to 29.7).[6] There was an additional data cut-off of 27-Sept-2016 and this date corresponds to 29 months of follow-up.[8]

Complete Response Rate

The primary outcome in the trial was CRR as assessed by BIRC using the IHP criteria.[4] CRR was defined as having no evidence of disease, which was confirmed by patients being PET-negative.[5] The authors reported the point estimates of CRR with corresponding 95% CIs using a binomial distribution.[5] Although the trial was initially designed to use 90% CI with a one-side p-value, Regulatory bodies requested that a 95% CI to be consistent with other phase II trials.[3]

At the 3-June-2016 data cut-off, EPAR reported that six patients had a CR as assessed by BIRC (CRR: 19.4%, 90% CI: 8.8 to 34.7).[7] A similar CRR was reported at the 27-Sept-2016 data cut-off (CRR: 19%, 95% CI: 8 to 38).[7]

The authours performed a subgroup analysis at the 27-Sept-2016 data cut-off, where they grouped patients who had prior ASCT and received BV post-ASCT (n = 16), those who were ASCT ineligible and failed BV (n = 8) and those who had prior ASCT and had BV pre-ASCT (N = 7).[8] The CRR in the first subgroup was 19% (95% CI: 4 to 46; N = 3/16), the second subgroup was 25% (95% CI: 3 to 65; N = 2/8) and the third subgroup was 14% (95% CI: 0.4 to 58; N = 1/7).

Objective Response Rate

ORR as assessed by the BIRC using IHP criteria was a secondary outcome in the trial. It was defined as the proportion of patients who achieved either a CR or a PR. Armand et al (2016) defined best overall response as the best response during the period between the first dose and first efficacy assessment showing progressive disease, or in the absence of progressive disease, the last efficacy assessment before subsequent therapy.[4] In the protocol it was stated that the point estimates of ORR with corresponding 95% CIs were derived using a binomial distribution.[5]

The ORR as assessed by BIRC for all patients was 58% (90% CI: 39 to 76; N = 31) at the 27-Sept-2016 data cut-off.[8] The ORR for patients who had prior ASCT and received BV post-ASCT was 69% (95% CI: 41 to 89; N = 16), 38% (95% CI: 9 to 76; N = 8) for those who were ASCT ineligible and failed BV and 57% (95% CI: 18 to 80; N = 7) for those who had prior ASCT and had BV pre-ASCT.[8]

Duration of Response Rate

DOR was defined as the time between the first response to the date of first documented disease progression, or in the absence of disease progression, the last efficacy assessment before subsequent therapy.[4] The median time to response was 2.8 months (range: 2.4 to 8.6) at the 27-Sept-2016 data cut-off.[8] Furthermore, the authours stated that the median DOR had not been reached (range: 0.0 to 26.1+ months).

Disease control rate (DCR) was not measured in the trial.

Progression-Free Survival

PFS was an exploratory outcome and the PFS curves were measured using non-parametric Kaplan-Meier methods.[5] At the 27-Sept-2016 data cut-off, the median PFS as assessed by BIRC was 11.4 months (95% CI: 4.9 to 27.8).[8] The 6-month and 12-month PFS rates as assessed by BIRC were 66% and 48%, respectively.[8]

Overall Survival

Overall survival was an exploratory outcome and it was defined as time from first dose to date of death.[5] The median overall survival had not been reached at the 27-Sept-2016 data cut-off.[8] The 6-month and 12-month overall survival rates were 100% and 87%, respectively.[8]

Quality of Life

KEYNOTE-087

Two publications assessed patient related outcomes (PROs) in KEYNOTE-087.[1,10,57] HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) and the European Quality of Life Five Dimensions Questionnaire (EQ-5D). PROs were assessed every cycle, for the first five cycles of treatment, and then every 12 weeks thereafter until disease progression.[10] Measurements were also obtained at treatment discontinuation and at the 30-day safety follow-up. Patients were included in the analysis if they completed at least one HRQoL questionnaire.[7] Please note that the HRQoL estimates were pooled across the three cohorts in KN-087. The results presented here may not be directly applicable to cohort 1 and cohort 2 and should be interpreted with caution.

HRQoL was documented using a change from baseline at week 12. EPAR commented that this time point was used in order to "*…minimize loss of data due to death or disease progression and to allow for comparison in subjects still on treatment*."[7] Compliance rates were high for the EORTC QLQ-C30 and the EQ-5D instruments at baseline and at 12 weeks.[7] At this point in the review, the completion rates beyond 12 weeks have not been reported.

The change in EORTC QLQ-C30 global health status/QoL from baseline to week 12 is presented in Table 10. The baseline global health status/QoL was similar for all subgroups at week 1. At week 12, there was a net improvement in QoL among all patients as compared to baseline (mean = 8.6; standard error [SE] = 1.6).[10] The least-square (LS) mean difference between responders and non-responders at week 12 was 4.7 (95% CI: -0.20 to 9.66; p-value: 0.06).[10]

Table 10: Change in EORTC QLQ-C30 Global Health Status/QoL Score From Baseline to Week 12 Across Cohorts

	Baseline		Week 12		Change From Baseline at Week 12	
	n*	Mean (SD)	n*	Mean (SD)	n†	Mean (SE)
All cohorts	191	64.1 (21.4)	199	72.4 (19.4)	184	8.6 (1.6)
Responders (CR+PR)	112	63.7 (20.4)	121	74.0 (19.2)	110	10.4 (2.1)
Patients with stable disease	49	65.8 (23.0)	50	73.3 (18.9)	48	7.3 (3.2)
Patients with PD	30	62.8 (22.6)	28	64.0 (19.6)	26	3.5 (3.6)
Comparison	**Difference in LS Means‡ (95% CI)**				***P* Value**	
Responder *v* nonresponder§	4.7 (-0.20-9.66)				0.0600	

Abbreviations: CI, confidence interval; CR, complete response; LS, mean least squares mean; PD, progressive disease; PR, partial response; PRO, patient-reported outcome; SD, standard deviation; SE, standard error.
*n = Number of patients in all-patients-as-treated population with each time point observation.
†n = Number of patients in all-patients-as-treated population with baseline and week 12 observations.
‡Based on constrained longitudinal data analysis model with the PRO score as the response variable, study visit and ECOG (0 *v* 1 or 2) as covariates.
§Response by investigator review at week 12; patients with PD include patients without week 12 assessments.

Data Source: Chen et al (2017) JCO Supplementary Appendix[10]

The change in EQ-5D from baseline to week 12 for all patients is presented in Table 11. The baseline EQ-5D scores were similar for all subgroups at week 1. At week 12, there was an improvement in QoL among all patients as compared to baseline (mean = 8.4; SE = 1.4).[10] The LS mean difference between responders and non-responders at week 12 was 4.3 (95% CI: 0.11 to 8.59; p-value: 0.0443).[10]

Table 11: Change in EQ-5D From Baseline to Week 12 Across Cohorts

	Baseline		Week 12		Change From Baseline at Week 12	
	n*	Mean (SD)	n*	Mean (SD)	n†	Mean (SE)
All cohorts	201	70.3 (18.3)	199	78.3 (16.9)	191	8.4 (1.4)
Responders (CR+PR)	119	68.9 (18.1)	121	79.4 (16.9)	116	10.9 (1.8)
Patients with stable disease	49	72.5 (20.8)	51	78.6 (16.7)	49	5.4 (3.0)
Patients with PD	33	71.8 (15.3)	27	73.1 (16.9)	26	2.6 (2.7)
Comparison	**Difference in LS Means‡ (95% CI)**				***P* Value**	
Responder *v* nonresponder§	4.3 (0.11, 8.59)				0.0443	

Abbreviations: CI, confidence interval; cLDA, constrained longitudinal data analysis; CR, complete response; LS, mean least squares mean; PD, progressive disease; PR, partial response; PRO, patient-reported outcome; SD, standard deviation; SE, standard error.
*n = Number of patients in all-patients-as-treated population with each time point observation.
†n = Number of patients in all-patients-as-treated population with baseline and week 12 observations.
‡Based on cLDA model with the PRO score as the response variable, study visit and ECOG (0 *v* 1 or 2) as covariates.
§Response by investigator review at week 12; patients with PD include patients without week 12 assessments.

Data Source: Chen et al (2017) JCO Supplementary Appendix[10]

Table 12 presents the change from baseline in EuroQol EQ-5D utility score using the European algorithm at week 12. As observed previously, the utility score was similar across all subgroups at baseline and there was an improvement in QoL at week 12 (mean: 0.06; SE = 0.02).[10] The LS mean difference between responders and non-responders at week 12 was 0.07 (95% CI: 0.018 to 0.129; p-value: 0.0094).[10]

Table 12: Change From Baseline in EuroQol EQ-5D Utility Score at Week 12

	Baseline		Week 12		Change From Baseline at Week 12	
	n*	Mean (SD)	n*	Mean (SD)	n†	Mean (SE)
All cohorts	201	0.74 (0.22)	199	0.80 (0.21)	191	0.06 (0.02)
Patients who responded (CR+PR)	119	0.74 (0.22)	121	0.83 (0.21)	116	0.09 (0.02)
Patients with stable disease	49	0.78 (0.18)	51	0.81 (0.19)	49	0.03 (0.03)
Patients with PD	33	0.72 (0.24)	27	0.69 (0.24)	26	-0.02 (0.06)
Comparison	**Difference in LS Means‡ (95% CI)**				***P* Value**	
Responder vs nonresponder§	0.07 (0.018, 0.129)				0.0094	

Abbreviations: CI, confidence interval; cLDA, constrained longitudinal data analysis; CR, complete response; LS, mean least squares mean; PD, progressive disease; PR, partial response; PRO, patient-reported outcome; SD, standard deviation; SE, standard error.
*n = Number of patients in all-patients-as-treated population with each time point observation.
†n = Number of patients in all-patients-as-treated population with baseline and week 12 observations.
‡Based on cLDA model with the PRO score as the response variable, study visit and ECOG (0 *v* 1 or 2) as covariates.
§Response by investigator review at week 12; patients with PD include patients without week 12 assessment.

Data Source: Chen et al (2017) JCO Supplementary Appendix[10]

KEYNOTE-013

HRQoL was not collected in KEYNOTE-013.

Harms Outcomes

KEYNOTE-087

Patients were included in the safety analysis if they had received ≥ 1 dose of pembrolizumab. At the data cut-off, there were 210 included in the safety analysis (cohort 1: 69; cohort 2: 81 and cohort 3: 60).[1] Chen et al (2017) reported that the median exposure to pembrolizumab was 8.3 months (range: 0.03 to 14.99) and patients received a median of 13 treatment cycles (range: 1 to 21 in cohorts 1 and 2, and 3 to 21 in cohort 3).[1]

Deaths

Chen et al (2017) reported that two deaths occurred during the treatment period, which were not considered treatment-related.[1] These deaths resulted from septic shock and acute graft-versus-host disease.[1]

All grades and grade 3 to 4 adverse events

The most common adverse events that occurred in the KN-087 trial are presented in Table 13. Chen et al (2017) reported that the most common grade 1 or 2 treatment-related adverse event (TRAE) that occurred in ≥ 5% of the safety population was hypothyroidism (11.9%) and pyrexia (10%).[1] Additionally, the most common grade 3 TRAE were neutropenia (2.4%), diarrhea (1%) and dyspnea (1%).[1] No grade 4 TRAEs occurred during the trial.

Table 13: Adverse events that occurred in ≥ 5% of the KEYNOTE-087 safety population

Table 3. Adverse Events Occurring in ≥ 5% of the Total Study Population

Adverse Event	All-Cause Adverse Events (N = 210) No. (%)			Treatment-Related Adverse Events (N = 210) No. (%)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
Pyrexia	49 (23.3)	2 (1)	0	21 (10)	1 (0.5)	0
Cough	44 (21)	1 (0.5)	0	11 (5.2)	1 (0.5)	0
Fatigue	40 (19)	2 (1)	0	18 (8.6)	1 (0.5)	0
Diarrhea	33 (15.7)	3 (1.4)	0	13 (6.2)	2 (1)	0
Vomiting	32 (15.2)	0	0	8 (3.8)	0	0
Nausea	28 (13.3)	0	0	12 (5.7)	0	0
Hypothyroidism	28 (13.3)	1 (0.5)	0	25 (11.9)	1 (0.5)	0
Neutropenia	7 (3.3)	4 (1.9)	2 (1)	6 (2.9)	5 (2.4)	0
Upper respiratory tract infection	27 (12.9)	0	0	7 (3.3)	0	0
Rash	23 (11)	0	0	16 (7.6)	0	0
Pruritus	23 (11)	0	0	8 (3.8)	0	0
Headache	22 (10.5)	1 (0.5)	0	13 (6.2)	0	0
Arthralgia	21 (10)	1 (0.5)	0	8 (3.8)	1	0
Constipation	20 (9.5)	0	0	6 (2.9)	0	0
Nasopharyngitis	19 (9)	0	0	2 (1)	0	0
Dyspnea	18 (8.6)	2 (1)	0	5 (2.4)	2 (1)	0
Back pain	16 (7.6)	1 (0.5)	0	4 (1.9)	0	0
Oropharyngeal pain	16 (7.6)	0	0	1 (0.5)	0	0
Asthenia	14 (6.7)	0	0	3 (1.4)	0	0
Myalgia	14 (6.7)	0	0	5 (2.4)	0	0
Sinusitis	13 (6.2)	0	0	1 (0.5)	0	0
Urinary tract infection	13 (6.2)	0	0	0	0	0
Insomnia	13 (6.2)	1 (0.5)	0	2 (1)	0	0
Nasal congestion	13 (6.2)	0	0	3 (1.4)	0	0
Bronchitis	12 (5.7)	1 (0.5)	0	2 (1)	0	0
Chills	12 (5.7)	0	0	5 (2.4)	0	0
Anemia	11 (5.2)	8 (3.8)	0	1 (0.5)	0	0
Muscle spasms	11 (5.2)	1 (0.5)	0	8 (3.8)	0	0

NOTE. Adverse events of any grade occurring in ≥ 5% of patients are shown. Two patients died as a result of graft-versus-host disease and septic shock, respectively, which were considered to be unrelated to treatment.

Data Source: Chen et al (2017) JCO[1]

Adverse events of special interest

Chen et al (2017) defined immune-mediated adverse events (IMAE) as events with potentially drug-related immunologic causes regardless of treatment attribution.[1] The authors noted that 60 IMAEs and infusion related reactions occurred during the trial (Table 14).[1] The most common grade 1 or 2 IMAEs were hypothyroidism (13.3%) and infusion related reactions (4.8%). No grade 4 events occurred. The protocol stated that patients who had a grade ≥ 2 IMAE were treated with steroids and 23% of patients (n = 14/60) received systemic steroids for the treatment of their IMAE.[3]

Seven patients discontinued treatment from pembrolizumab because of an IMAE.[3] These events include: pneumonitis (n = 4), infusion related reaction (n = 2), cytokine release syndrome (n =1), myositis (n =1).[3] It should be noted that patients could have had more than one event.

Table 14: Immune-mediated adverse events and infusion-related reactions that occurred in the KEYNOTE-087 safety population

Immune-Mediated Adverse Events* and Infusion-Related Reactions	n (%)		
	Grade 1 or 2	Grade 3	Grade 4
Hypothyroidism	28 (13.3)	1 (0.5)	0
Infusion-related reaction	10 (4.8)	0	0
Hyperthyroidism	6 (2.9)	0	0
Pneumonitis	6 (2.9)	0	0
Cytokine release syndrome	5 (2.4)	1 (0.5)	0
Hypersensitivity	4 (1.9)	0	0
Colitis	1 (0.5)	1 (0.5)	0
Myositis	1 (0.5)	1 (0.5)	0
Iritis	1 (0.5)	0	0
Drug hypersensitivity	1 (0.5)	0	0
Enterocolitis	1 (0.5)	0	0
Iridocyclitis	1 (0.5)	0	0
Dermatitis psoriasiform	0	1 (0.5)	0

*Immune-mediated adverse events were defined as events with potentially drug-related immunologic causes, regardless of treatment attribution.

Data Source: Chen et al (2017) JCO Supplementary Appendix[10]

Adverse events leading to dose interruption, adjustment and discontinuation

Chen et al (2017) reported that nine patients (4.3%) discontinued treatment due to a TRAE.[1] The TRAEs included: myocarditis, myelitis, myositis, pneumonitis, infusion-related reactions and cytokine release syndrome.[1] In addition, 12.4% of all patients in KN-087 experienced a TRAE that led to a treatment interruption.

KEYNOTE-013

Patients were included in the safety analysis if they received at least one dose of pembrolizumab. At the 27-Sept-2016 data cut-off, there were 31 patients included in the safety analysis.[8] The Manufacturer reported that patients were exposed to pembrolizumab for a median of 239 days and received a median of 18 administrations.[3]

Deaths

Armand et al (2016) reported that no fatal drug related AEs occurred.[8]

All grades and grade 3 to 4 events

Twenty-one patients (68%) in the KEYNOTE-013 trial reported having a TRAE.[8] The most common TRAEs that occurred in ≥10% of the safety population were: diarrhea (20%) followed by hypothyroidism (13%), pneumonitis (13%), nausea (13%), fatigue (10%) and dyspnea (10%).[8] Nineteen percent of patients had a grade 3/4 TRAE. These AEs include: colitis (3%), axillary pain (3%), AST increased (3%), joint swelling (3%), nephrotic syndrome (3%) and back pain (3%).

Adverse events leading to dose interruption, adjustment and discontinuation

Armand et al (2016) reported that there were three AEs that lead to a discontinuation, and these include: one grade 3 nephrotic syndrome, one grade 2 interstitial lung disease and one grade 2 pneumonitis.[8]

6.4 Ongoing Trials

The pCODR systematic review identified one on-going trial. The details of the trial are presented in Table 1.

Table 1: Ongoing trial of pembrolizumab in patients with cHL[2,58]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study name KEYNOTE-204 NCT02684292 **Characteristics** Open-label, Phase III RCT **Estimated Sample size** N = 300 **Locations** Australia, Brazil, Canada, France, Germany, Israel, Italy, Japan, Poland, Sweden, United States **Patient Enrolment Dates** Recruiting **Estimated Primary Completion Date** 28-May-2018 **Funding** Merck	Key Inclusion Criteria: • Has relapsed (disease progression after most recent therapy) or refractory (failure to achieve CR or PR to most recent therapy) cHL. • Has responded (achieved a CR or PR) to BV or BV-containing regimens, if previously treated with BV. • Has measurable disease defined as ≥1 lesion that can be accurately measured in ≥2 dimensions with spiral CT scan or combined CT/ PET scan. Minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis. • Is able to provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival or newly obtained biopsy at Screening (Visit 1). • Has a performance status of 0 or 1 on the ECOG Performance Scale. • Has adequate organ function Key Exclusion Criteria: • Has hypersensitivity to the active substance or to any of the excipients in BV or pembrolizumab. • Is currently participating in or has participated in a study of an investigational agent and is currently receiving study therapy or has participated in a study of an investigational agent and has received study therapy or used an investigational device within 4 weeks of the first dose of study drug. • Has a diagnosis of immunosuppression or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. • Has had a prior mAb within 4 weeks prior to first dose of study drug in the study or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier. • Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy including investigational agents within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to a previously administered agent.	Intervention: Pembrolizumab (200mg Q3W for up to 35 cycles) Comparator: BV (1.8 mg/kg [maximum 180 mg per dose] for up to 35 cycles.)	Primary: OS PFS Secondary: ORR

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. • Has a known additional malignancy that is progressing or requires active treatment in the last 3 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy. • Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with the use of disease modifying agents, corticosteroids, or immunosuppressive drugs). • Has received prior therapy with an anti-programmed cell death-1 (anti-PD-1), anti-PD-ligand 1 (anti-PD-L1), anti-PD-L2, anti-CD137, or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody (including ipilimumab) or OX-40 (Tumor necrosis factor receptor superfamily, member 4 [TNFRSF4]), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. • Has a known history of HIV, tuberculosis, pneumonitis, active CNS metastases, HBV or HCV.		

Abbreviations: R/R = relapsed or refractory; cHL = classical Hodgkin lymphoma; ASCT = autologous stem cell transplant; BV = brentuximab vedotin; ECOG = Eastern Cooperative Oncology Group; CNS = central nervous system; HIV = Human Immunodeficiency Virus; HBV = Hepatitis B; HCV = Hepatitis C; ILD = interstitial lung disease; Q3W = every three weeks; Q2W = every two weeks; CR = complete response; PR = partial response; CET = computed tomography; PET = positron emission tomography; mAB = monoclonal antibody; AEs = adverse events

Data Source: Clinicaltrials.gov[2] and Zinzani et al (2016) ESMO[58]

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the indirect treatment comparison of pembrolizumab in patients with R/R cHL

Background

The pCODR-conducted literature search did not identify any RCTs that assessed the efficacy of pembrolizumab in patients with R/R cHL. Thus there is a lack of direct evidence comparing pembrolizumab to other anti-cancer therapies in the following cHL patient populations:

- Those who failed to achieve a response or progressed after ASCT, and relapsed after treatment with, or failed to respond to BV post-ASCT, and
- Those who did not receive ASCT and relapsed after treatment with or failed to respond to BV

Given the absence of head-to-head trials, the Manufacturer conducted a naive indirect treatment comparison (ITC).

The objective of this section is to summarize and critically appraise the submitted ITC that provides evidence for the efficacy of pembrolizumab versus active therapies in patients with R/R cHL.

Review of manufacturer's ITC

Objectives of manufacturer's ITC

The objective of the Manufacturers' ITC was to compare pembrolizumab to gemcitabine in patients with R/R cHL who have had disease progression after treatment with BV.

Study Eligibility and Selection Process

The Manufacturer conducted a systematic review to identify eligible studies (criteria in Table 1) for the ITC.[11]

Table 1: Population, interventions, and study design criteria for inclusion of studies

Criteria	Description
Population	Adult patients with cHL who are refractory after any line of therapy or who have relapsed after ≥ 3 prior lines of therapy
Interventions	*The following targeted drugs alone or as combinations with systemic chemotherapies:* Pembrolizumab Nivolumab Rituximab Lenalidomide Everolimus Vorinostat Panobinostat Ofatumumab Lucatumumab Brentuximab vedotin *The following systemic chemotherapies alone or in combinations:* Adriamycin (Doxorubicin) Bendamustine (Treakisym, ribomustin, levact, treanda, SDX-105) Bleomycin Carmustine (BCNU, BiCNU, Consium) Vinblastine Dacarbazine (DTIC) Etoposide (VP-16) Cyclophosphamide Ifosfamide (Ifex) Melphalan (Alkeran, Sarcolysin, Evomela) Mitoxantrone (Mitozantrone, Novantrone) Vincristine Procarbazine Cisplatin Cytarabine Gemcitabine Vinorelbine Oxaliplatin Mechlorethamine (Nitrogen mustard) *Other treatments in combination with chemotherapies:* Prednisone Methylprednisolone Dexamethasone
Comparators	Any
Outcomes	Overall survival Progression-free survival Objective response Complete response Partial response Treatment discontinuation due to AEs Serious (grade 3 and above) AEs (not used for study selection)
Study design	Randomized controlled trials Non-randomized clinical trials if needed for indirect comparisons and considered appropriate

Abbreviations: AE, adverse event; cHL, classical Hodgkin's lymphoma.

Data Source: NMA Report[11]

The following databases were searched for the systematic review: Embase, MEDLINE and Cochrane Register of Controlled Trials. The Scottish Intercollegiate Guidelines Network's (SIGN) filter for randomized-controlled trials was used in the Embase and Medline searches. The Manufacturer performed manual searches of clinicaltrials.gov and the proceedings from the American Society of Clinical Oncologists (2015, 2016) and American Society of Hematology (2014, 2015). The search was performed on 19-Oct-2016.[11]

The Manufacturer performed an additional search to locate observational studies that consisted of patients with R/R cHL who had progressed after BV. This search was done because of the lack of RCTs

that are conducted in this patient population and the lack of consensus on how patients should be treated once they fail BV therapy. The second search was performed on 2-December-2016 .[11]
The Manufacturer stated that two reviewers worked independently to screen titles, abstracts and full text articles. If any discrepancies occurred, the investigators used a third party to provide consensus. The two reviewers independently extracted data for the included studies and any discrepancies were resolved by a third reviewer. Table 2 presents the information that was extracted from each study. This includes details on study characteristics, interventions, baseline patient characteristics, and outcomes.[11] The Newcastle Ottawa Scale was used to assess the quality of the included studies.

Table 2: Study characteristics, interventions, patient characteristics, and outcomes that were extracted from included studies

Item	Data Extracted
Study characteristics	Author, year, journal Title of the publication Trial acronym Primary registration number or NCT number Trial phase Trial duration (year of initiation/completion) Study design (e.g., double blind, open label, multicenter, single-arm, etc.) Study setting (e.g., country, region, or any other available geographical identifiers) Number of subjects randomized Number of subjects completing the trial Analytical approach (intention-to-treat, modified intention-to-treat, per-protocol) Study inclusion criteria Study exclusion criteria
Interventions	Treatment dose Frequency of administration Method of administration Duration of administration
Baseline patient characteristics	Age Sex Ethnicity ECOG/WHO performance status Disease status or Disease stage or Clinical stage Bulky disease Pathological subtype International prognostic score or Hasenclever score B symptoms present Number of previous treatments Previous radiation therapy Previous autologous stem cell transplantation
Outcomes	Progression-free survival (as hazard ratio or Kaplan-Meier curve) Overall survival (as hazard ratio or Kaplan-Meier curve) Response proportion (overall, complete, partial, and stable disease) Adverse events (grade 3 or above, discontinuations)

Data Source: NMA Report[11]

Indirect treatment comparison methods

To determine whether an ITC was appropriate, the Manufacturer performed several steps. First, they explored compatibility of the included trials by comparing the study design, patient populations and study endpoints across the different trials.[11] Second, they assessed the distribution of treatment effect modifiers among all of the included trials.[11] Third, the Manufacturer also tested the proportional hazard assumptions for the different treatment comparisons.[11] This was achieved by visual inspection using log-log plots and testing the interaction between the treatment covariate and time covariate in the HR model.[3]

The Manufacturer reported that if the selected trials satisfied the assumptions of comparability, whereby the relative effects of a given treatment should be the same in all trials included in the ITC, then they would conduct a naïve ITC.[11] The Kaplan-Meier curves, from studies that had available independent-participant data (IPD), were estimated directly while the Kaplan-Meier curves from studies without IPD were digitalized.[11] The HRs were obtained using the Cox proportional hazard regression models.

The Manufacturer noted that they were unable to construct an NMA due to the lack of clinical data available for this patient population, and therefore, conducted a naïve treatment comparison.[11] The rationale for choosing this model was based on the fact that the Manufacturer was not able to adjust for all relevant confounders and the minimal differences between the adjusted and unadjusted ITC.[11]

The naïve ITC was performed using an outcome regression analysis, which is a regression model that can be applied to single-arm trials and when IPD is available for one of the trials. The regression model utilizes the outcome data from the intervention of interest and expresses the index intervention as a function of the relevant patient-reported factors. This index intervention was used as a common link to incorporate the effect estimates from the nonrandomized trials into the network. However, there is uncertainty using this type of model because it is unknown how unmeasured confounders will impact the outcome of interest.[11]

Results

Included studies

The systematic review identified a total of 10,359 citations.[11] Among these articles, 103 articles were included for title and abstract screening and 60 publications were excluded because of study design (N = 17), population (N = 28), outcomes (N = 4), interventions (N = 4) and for other reasons (N =7). Four citations from conference proceedings were included as well as data from the KN-87 CSR. Thus, a total of 43 publications were included in the initial search. The Manufacturer also performed another search to locate observational studies and identified two additional studies, which brought the total to 45 articles.[11]

To conduct an ITC that compared pembrolizumab versus gemcitabine, as a proxy for chemotherapy, in patients with R/R cHL who are refractory to BV treatment, the Manufacturer identified the following trials: KEYNOTE-087[1] and Cheah et al (2016).[12] Cheah et al (2016) was a retrospective database analysis that assessed subsequent therapies in 89 patients with disease progression after treatment with BV; however, patients were not excluded based on their age, ECOG performance status, prior allogenic SCT or comorbidities.[12] For the effect estimates of gemcitabine from Cheah et al (2016), the Manufacturer used response rates from 79 patients who received a subsequent treatment following progression on BV, which includes: the investigational agent (aka BV, N = 28), Gemcitabine (N = 15), Bendamustine (N=12), other alkylator (N=6), BV retreatment (N=6), Platinum based (N=4), ASCT (N=3) and other (N=5).[11,12] Since there is a lack of standard therapies for patients with R/R cHL post-BV, the Manufacturer assumed that all chemotherapies included in the Cheah et al (2016) analysis will have a similar clinical efficacy.[3] The pCODR CGP is in alignment with this assumption. Furthermore, although

Cheah et al (2016) was a retrospective cohort study, the PFS and OS rates were hand calculated using time to event data from electronic records.[12] Figure 1 shows a diagram of the ITC.[11] The originally submitted ITC used the 3-June-2016 cut-off date for KN-087. However, upon request from the Methods Lead, the ITC was updated to use the 25-Sept-2016 date.[11]

Trial characteristics

Details of the populations, interventions, comparators and outcomes used in KN-08,[1] KN-013[4] and Cheah et al (2016)[12] are reported in Table 3.

Table 3. Patient Characteristics comparing KEYNOTE-087, KN-013 and Cheah et al (2016)

Characteristic		KEYNOTE-087, Cohort 1&2	KEYNOTE-087, Cohort 1	KEYNOTE-087, Cohort 2	KEYNOTE-013[44]	Cheah et al. (2016)[2]
Treatment		Pembrolizumab 200mg			Pembrolizumab 10mg/kg	BV then subsequent treatment
Number of patients		150	69	81	31	89[α]
Age (median)		37.5	34.0	40.0	32	32
Female (%)		71 (47.3%)	33 (47.8%)	38 (46.9%)	13 (42%)	46 (47%)
ECOG	0	73 (48.7%)	29 (42.0%)	44 (54.3%)	NR	33 (41%)
	1	76 (50.7)%	39 (56.5%)	37 (45.7%)	NR	44 (54%)
	2	1 (0.7%)	1 (1.4%)	0 (0.0%)	NR	3 (4%)
Baseline B symptoms		48 (32.0%)	22 (31.9%)	26 (32.1%)	NR	7 (8%)
Bulky Lymphadenopathy		16 (10.7%)	5 (7.2%)	11 (13.6%)	2 (6%)	15 (37%)
Bone marrow involvement		8 (5.3%)	3 (4.3%)	5 (6.2%)	NR	NR
Disease status – relapse		70 (46.7%)	46 (66.7%)	24 (29.6%)	21 (68%)	NR
Disease status – refractory		80 (53.3%)	23 (33.3%)	57 (70.4%)	10 (32%)*	NR
Previous BV therapy		150 (100%)	69 (100.0%)	81 (100.0%)	31 (100%)	89 (100%)
Prior radiation		52 (34.7%)	31 (44.9%)	21 (25.9%)	NR	NR
No. prior auto-SCT	1	NR	NR	NR	22 (71%)	NR
	≥ 2	NR	NR	NR		NR
Median no. of prior line of therapy		4	4	4	NR	4

*Calculated; [α] not all characteristics were available from this sample. BV: Brentuximab vedotin; ECOG: Eastern Cooperative Oncology Group; N/A: Not applicable; NR: Not reported; SCT: Stem cell transplant

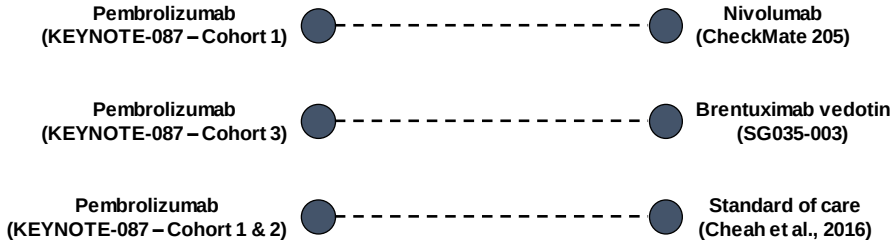
Data Source: NMA Report [11]

The Manufacturer justified the use of a naïve ITC because the baseline characteristics of the trial were comparable.[11] However, the Manufacturer did comment that there were differences baseline characteristics, such as: age; baseline B symptoms bulky lymphadenopathy and prior relapse (Table 3).[11] In addition, due to missing data, it is difficult to compare baseline characteristics between Cohort1&2 and Cheah et al (2016).[11,12]

Indirect Treatment Comparison

Despite the differences in the patient baseline characteristics and effect modifiers, the Manufacturer performed a naïve ITC comparing pembrolizumab to gemcitabine using an outcome regression method.[11] Figure 1 presents the ITCs comparing pembrolizumab to gemcitabine in Cohort1&2.[11]

Figure 1: Graphical representation of ITC of pembrolizumab (KN-087 Cohort 1&2) as compared to gemcitabine (Cheah et al [2016])



Data Source: NMA Report and Checkpoint Response.[3,11] Please note that the results of pembrolizumab vs. BV and pembrolizumab vs. nivolumab are beyond the scope of this review and will not be considered.

Estimates from KN0-87 were updated to the 25-Sept-2016 database lock.[1] The direct estimates of ORR, PFS, overall survival, duration of treatment and grade ≥3 AEs that were obtained from KN087[11] and Cheah et al (2016)[12] are presented in Table 4 and the Kaplan-Meier curves of PFS for pembrolizumab (KN-087 Cohort1&2[11]) and gemcitabine (Cheah et al [2016][12]) are presented in Figure 2.[11]

Table 4: The direct effect estimates of ORR, PFS, overall survival, duration of treatment and grade ≥3 AEs from the KN 087 and Cheah et al (2016) studies

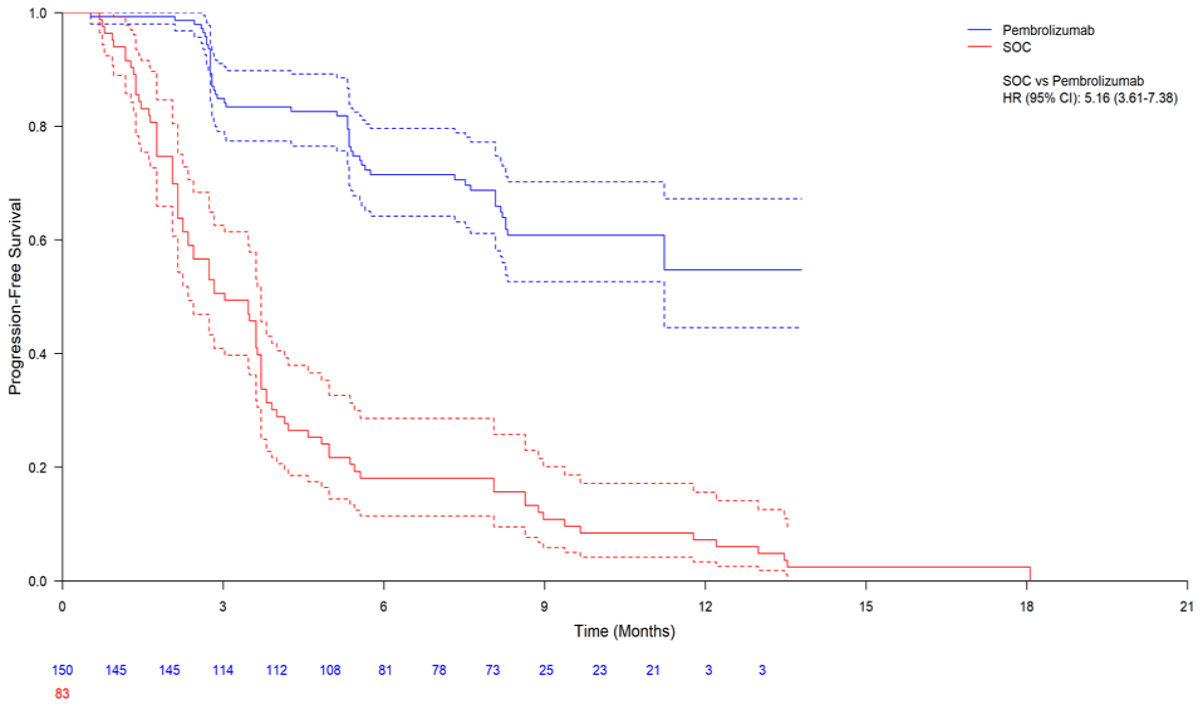
Characteristic	KEYNOTE-087 (Cohorts 1&2) (n=150)	Cheah et al. (2016) (n=89)
Follow-up duration, median (months)	7.1, June 2016 10.1, Sept 2016	25
ORR, %	68.7	34
OS, median (months)	NR	25.2
Survival rate, %	Not reported	Not reported
PFS, median (months)	13.7	3.5
Duration of treatment, median	10.8 months	Not reported
One or more grade ≥3 AEs, all-cause, %	26.0	Not reported

AE: Adverse events; ITC: Indirect treatment comparison; NR: not reached; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival

[a]June data base lock

Data Source: NMA Report[11]

Figure 2: Naïve Kaplan-Meier curves of PFS for pembrolizumab (KN-087 Cohort1&2) and gemcitabine (Cheah et al [2016])



Dashed lines represent confidence intervals

CI: Confidence interval; HR: Hazard ratio; PFS: Progression-free survival; SoC: standard of care

Source: Merck [45]

Data Source: NMA Report[11]

Using a naive ITC, the Manufacturer showed that gemcitabine was associated with shorter PFS as compared to pembrolizumab in patients from Cohort 1&2 (HR: 5.16, 95% CI: 3.61 to 7.38).[11] Although the Manufacturer collected information on OS, they were unable to provide an estimate from the ITC because OS was immature at both the 3-June-2016 and 25-Sept-2016 data cut-offs and would not provide reliable estimates.[11] In addition, ORR was higher in patients treated with pembrolizumab as compared to gemcitabine (OR: 4.22, 95% CI: 2.37 to 7.53).[11] Grade ≥ 3 AEs could not be estimated because these results were not reported in Cheah et al (2016).[7,11]

Critical Appraisal of the ITC

The quality of the ITC provided by the Submitter was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[59] Details of the critical appraisal are presented below.

Table 20: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions		Details and Comments‡
1.	Is the population relevant?	**Yes**. The indication for this review was to assess the efficacy and safety of pembrolizumab in patients with cHL who 1) failed to achieve a response or progressed after ASCT and have relapsed after treatment with or failed to respond to BV post ASCT (Cohort 1) or 2) did not receive an ASCT and have relapsed after treatment with or failed to respond to BV (Cohort 2).For the purpose of the ITC analysis, the Manufacturer pooled Cohorts 1 and 2 from KN-087. The Clinical Guidance Panel felt that this was appropriate given two baseline characteristics of the patient populations. Data was also obtained from a retrospective cohort (Cheah et al (2016)[7]), which was composed of 79 patients with disease progression after treatment with BV. Data was also obtained from a retrospective cohort (Cheah et al (2016)[7]), which was composed of 79 patients with disease progression after treatment with BV.
2.	Are any critical interventions missing?	**No.** The Manufacturer included all relative interventions for this patient population in the systematic review.
3.	Are any relevant outcomes missing?	**Yes, in part.** In the ITC, the Manufacturer calculated PFS, ORR and safety outcomes. The Manufacturer was unable to assess OS because of immature data. HRQoL was not considered for this analysis.
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The settings of the two included trials were similar.
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** The Manufacturer provided a summary of the systematic literature review process used in the ITC.[11] In the summary, the Manufacturer took adequate steps to ensure an unbiased selection of studies for inclusion in their analysis. They described the information sources they used, their search strategy, their study selection criteria, duplicate data extraction and risk of bias assessment.
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** The Manufacturer stated that a standard NMA approach was not feasible because of an absence of RCTs in this patient population. Thus they performed a naïve ITC using an outcome regression model.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**No**. The Manufacturer assessed the quality of included studies using the Newcastle-Ottawa Scale. However, Cheah et al (2016) was a retrospective cohort study and the PFS and OS rates were hand calculated using time to event data from electronic records.[7] Thus the reliability and robustness of these estimates are uncertain.
8.	Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No**. The Manufacturer captured all the relevant information.
9.	Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** The Manufacturer provided a qualitative assessment of heterogeneity (Table 3); however, the Methods team felt that performing a subgroup analysis and a test for difference would have been more informative. The Manufacturer noted that there were differences in the following baseline characteristics: age, baseline B symptoms, bulky lymphadenopathy, prior radiotherapy, refractory disease and previous BV therapy, ECOG score, lymph nodes and early

ISPOR Questions		Details and Comments‡
		relapse. In addition, some of the included studies did not report on relevant patient characteristics.
10.	If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes.** The Manufacturer reported that there were differences in baseline characteristics. They also stated that they did not adjust for baseline factors and this assumption could be a source of bias in the analysis.
11.	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Not applicable**. No RCTs were included in the ITC.
12.	If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable**. There was no closed loop.
13.	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable**. There was no closed loop.
14.	With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**No.** The Manufacturer performed a naïve ITC and did not attempt to adjust the imbalance of treatment effects across trials.
15.	Was a valid rationale provided for the use of random effects or fixed effect models?	**Not applicable**.
16.	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable**.
17.	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**No.** Subgroup analysis or meta-regression analysis were not performed; however, the Methods Team does recognize that assessment of heterogeneity may have been difficult due to a limited number of studies included in the ITC.
18.	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes**. This representation was presented in Figure 2.
19.	Are the individual study results reported?	**Yes.** The submitter provided the baseline characteristics of the trials used in the ITC as well as the effect estimates of PFS and overall survival as well as ORR and AEs.
20.	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Not applicable.**
21.	Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** The manufacturer provided the hazard ratio and 95% CI of PFS that was obtained from the indirect comparison between pembrolizumab vs gemcitabine.
22.	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**

ISPOR Questions		Details and Comments‡
23.	Is the impact of important patient characteristics on treatment effects reported?	**No.**
24.	Are the conclusions fair and balanced?	The ITC Report provided by the Manufacturer did not make any strong conclusions in their report. The ITC performed by the Manufacturer showed that gemcitabine shortened PFS as compared to pembrolizumab (HR: 5.16, 95% CI, 3.61 to 7.38). ORR was higher in patients treated with pembrolizumab as compared to gemcitabine. Grade ≥ 3 AEs could not be assessed because it was not reported in Cheah et al (2016). In addition, OS could not be derived from the ITC because OS estimates were immature in KN-087. However, these claims were weakened because of the differences in patient inclusion criteria across the different trials and potential effect modifiers that were not adjusted for in the naïve ITC. Furthermore, the Manufacturer did not include any other patient important outcomes in their indirect comparison, and therefore, it is difficult to determine the overall benefit of pembrolizumab in Cohort 1&2.
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**

HRQoL = health-related quality of life; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; ORR = objective response rate; PFS = progression-free survival.
† Adapted from Jansen et al[59]
‡Bolded comments are considered a weakness of the ITC.

Conclusion

The Manufacturer submitted a naive ITC that compared pembrolizumab to gemcitabine in patients who progressed after ASCT and BV. The results of the naïve ITC indicate that treatment with gemcitabine was associated with a detrimental effect on PFS (HR: 5.16, 95% CI, 3.61 to 7.38) as compared to pembrolizumab. Likewise, ORR was higher in patients treated with pembrolizumab as compared to gemcitabine. However, grade ≥ 3 AEs could not be assessed because the results were not reported in Cheah et al (2016).[7] On the other hand, the effect estimates of overall survival were not assessed in the ITC because the results from KN-087 were immature.

Although the ITC suggests that pembrolizumab associated with improved efficacy and safety as compared to gemcitabine, these results should be interpreted with caution. Cheah et al (2016) was a retrospective cohort study and the PFS and OS rates were hand calculated using time to event data from electronic records.[7] Since this was a retrospective analysis of time to event data - the reliability and robustness of these estimates are uncertain. Furthermore, the overall conclusions of the ITC are very limited because of substantial heterogeneity in the studies and patient characteristics among the included studies. Finally, the Manufacturer performed a naïve ITC and there was no attempt to adjust for any differences among the trials included in the analysis. Thus the treatment effect estimates from the ITC may be overestimated because other aspects of the included studies (i.e. patient populations, interventions or outcomes) may have biased the reported effect.[13] Given these limitations, the comparative efficacy of pembrolizumab versus gemcitabine is uncertain.

8 COMPARISON WITH OTHER LITERATURE

None identified

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on pembrolizumab for cHL. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lymphoma Clinical Guidance Panel is comprised of 3 medical oncologists.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** June 2017**, Embase** 1974 to 2017 July 14**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Line #	Searches	Results
1	(pembrolizumab* or lambrolizumab* or Keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475 or 1374853-91-4 or DPT0O3T46P).ti,ab,ot,kf,kw,hw,rn,nm.	5004
2	Hodgkin Disease/ or Hodgkin*.ti,ab,kf,kw. or ((lymphoma* or lymphogranuloma* or granuloma*) and malignan*).ti,ab,kf,kw.	251719
3	1 and 2	342
4	3 use pmez	61
5	3 use cctr	20
6	*pembrolizumab/	965
7	(pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475).ti,ab,kw.	2813
8	Hodgkin Disease/ or Hodgkin*.ti,ab,kw. or ((lymphoma* or lymphogranuloma* or granuloma*) and malignan*).ti,ab,kw. or Reed-Sternberg*.ti,ab,kw.	251500
9	(6 or 7) and 8	199
10	9 use oemezd	126
11	10 and conference abstract.pt.	35
12	limit 11 to yr="2012 -Current"	35
13	10 not 11	91
14	4 or 5 or 13	172
15	remove duplicates from 14	118
16	15 or 12	153

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#5	Search #4 AND publisher[sb] Filters: English	8
#4	Search #1 AND #2 Filters: English	59
#3	Search #1 AND #2	62
#2	Search Hodgkin Disease[mh] OR Hodgkin*[tiab] OR ((lymphoma*[tiab] OR lymphogranuloma*[tiab] OR granuloma*[tiab]) AND malignan*[tiab])	101134

#1	Search pembrolizumab [Supplementary Concept] OR 1374853-91-4[rn] OR DPT0O3T46P[rn] OR pembrolizumab*[tiab] OR lambrolizumab*[tiab] OR keytruda*[tiab] OR MK-3475[tiab] OR MK3475[tiab] OR Merck-3475[tiab] OR Merck3475[tiab] OR Sch-900475[tiab] OR Sch900475[tiab]	920

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Keytruda/pembrolizumab, Hodgkin Lymphoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Keytruda/pembrolizumab, Hodgkin Lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Keytruda/pembrolizumab, Hodgkin Lymphoma - last 5 years

Literature Search Methodology

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017July14) with In-process records & daily updates via Ovid; Embase (1974-2017July14) via Ovid; The Cochrane Central Register of Controlled Trials (June 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pembrolizumab, Keytruda and Hodgkin Lymphoma.

No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of October 5, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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