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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pembrolizumab (Keytruda) for Classical Hodgkin Lymphoma

January 5, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Merck Canada Inc.** compared pembrolizumab to gemcitabine in patients with relapsed/ refractory classical Hodgkin Lymphoma for two populations.

- Cohort 1: Patients 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; OR
- Cohort 2: Patients who did not receive an ASCT and have relapsed after treatment with or failed to respond to BV.

These target populations are based on the inclusion/exclusion criteria for cohorts 1 and 2 within KN-087.

Table 1 Submitted Economic Model

Funding Request/Patient Population Modelled	*The two target populations as defined above are based on the inclusion/exclusion criteria of cohorts within the KN-087 trial.*
Type of Analysis	*CEA & CUA*
Type of Model	*Two models were submitted:* - *Markov state transition. Markov model was submitted as base case due to lack of data and extrapolation over long term.* - *Partitioned survival (presented as a scenario analysis)*
Comparator	*Gemcitabine (as proxy for chemotherapy)*
Year of costs	*2017*
Time Horizon	*20 years*
Perspective	*Government (public payer perspective)*
Cost of pembrolizumab	*Pembrolizumab costs $4,400 per 100mg* • *At the recommended dose of 200mg every 3 weeks, pembrolizumab costs:* o *$ 419.05 per day* o *$ 11733.33 per 28-day*
Cost of gemcitabine * **	*Gemcitabine costs $270 per 1000mg* • *At the recommended dose of 1000mg/m2; three times (days 1, 8 and 15) per 28 day cycle, gemcitabine costs:* o *$ 49.18 per day* o *$ 1377.00 per 28-day course*
Model Structure	*A Markov state transition model using transition probabilities to simulate the flow of cohort patients between health states over time. Three sets of transition probabilities were used: progression free to progressive disease, progression free to death and progressive disease to death.*
Key Data Sources	*KN-087: an open-label, single-arm, multi-cohort phase II trial of pembrolizumab in R/R cHL. Primary*

	endpoint was ORR, with secondary endpoints of PFS and OS.

** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA– accessed on August 15 , 2017*
*** In response to feedback by the submitter the dosage as well as calculations of the cost per day and the cost per 28-day course of gemcitabine have been revised. These changes, however, have no impact on the EGP's initial reanalysis estimates as the EGP did not use the estimates provided in this table, but exclusively used the gemcitabine price and dosage estimates that were provided by the submitter.*

In their feedback, the submitter commented that the initial pCODR recommendation reports a cost of gemcitabine of $270 per 1000mg and was retrieved from QuintilesIMS DeltaPA database. However, this cost was not used in the EGP Reanalysis of their ICER estimate. The data used in the pCODR recommendation should be consistent and therefore, pCODR's cost of gemcitabine should be used in the economic model and the EGP estimated ICER should be updated to reflect that cost (modifying the cost of gemcitabine changes the ICER to 186,439/QALY). In response to the submitter's feedback, the EGP noted that the EGP's initial reanalysis estimates are based exclusively on the gemcitabine price and dosage estimates provided by the submitter within the Excel model and do not reflect the price informed by QuintilesIMS DeltaPA database.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of pembrolizumab to gemcitabine is appropriate.

- Relevant issues identified included:
    - The CGP agree that there is a net clinical benefit to pembrolizumab, compared to 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.
    - The comparison of pembrolizumab to gemcitabine is appropriate for the requested patient population given the absence of randomized phase III data.
    - The follow up of the clinical trials informing the comparative efficacy is relatively short and additional data on longer term toxicities and PFS outcomes are awaited.
    - 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 CGP agreed that pembrolizumab has a favourable toxicity profile compared to chemotherapy. Adverse events were considered in the model and applied as a once-off cost at model start.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians noted that pembrolizumab fills a gap in treatment for these patients and provides good tumour control. It was also recognized that there is little long-term data on these patients. Further, pembrolizumab has a good safety profile. Both progression-free survival and adverse events were incorporated into the model.

Summary of patient input relevant to the economic analysis
Patients would like individualized treatment options that will offer disease control, with fewer side effects. Patients with experience with pembrolizumab noted that it improved their quality of life and reported few side effects. Both adverse events and quality of life were incorporated into the model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for pembrolizumab which are relevant to the economic analysis:

Enablers
- New treatment option that fills an unmet need for relapsed or refractor classical HL.
- Flat dosing, with no wastage given two vial sizes.
- Administered in an outpatient chemotherapy center.

Barriers
- Additional chair time.
- High cost drug.
- Requires monitoring of immune-mediated reactions post-infusions. Note that treatment-specific monitoring was not included in the model.

Other
- The dose in the funding request is for flat dosing of 200mg, which matches that of 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.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	1.16	0.933	N/A
Progression-free	1.23	1.086	
Post-progression	-0.07	-0.153	
ΔE (QALY)	1.04	0.898	N/A
Progression-free	1.05	0.95	
Post-progression	-0.02	-0.06	
ΔC ($)	$169,475	$177,046	N/A
ICER estimate ($/QALY)	**$163,544**	**$197,055**	**N/A**

The main assumptions and limitations with the submitted economic evaluation were:

- There was no comparative effectiveness data to inform the economic model. Therefore, a naïve indirect comparison was done. However, in this comparison, the manufacturer did not adjust for baseline factors that could be potential effect modifiers. Further, the manufacturer did report that there were baseline differences in age, ECOG score, presence of B symptoms, lymph nodes,

bulky disease and early relapse. These differences and the lack of adjustment for these factors could impact both the magnitude of the effect and the generalizability of the results.

- Gemcitabine was chosen as a proxy for all chemotherapies in the comparator arm. The assumption was made that all chemotherapies would be equal in effectiveness and only the cost of gemcitabine was used in the economic model.

- The model assumes that patients in the progression-free state are at the **same** risk of death from other causes as the general population, once matched on gender and age. The CGP noted that this is not a reasonable assumption for this patient population.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- Pembrolizumab treatment duration: based on PFS curve (and not on time on treatment curve in base case). Using a time on treatment curve to determine treatment duration includes only those who stay on the drug, with no treatment discontinuations with a maximum number of 35 cycles—regardless of progression status. Though using the PFS curve to determine time on treatment may include the cost of those who discontinue early, the CGP indicated that there are patients who stay on pembrolizumab beyond the maximum time period of 24 months, and using the PFS curve allows us to a more conservative approach to costing pembrolizumab for all patients. Further, the indication of pembrolizumab is to treat until progression, and therefore aligns with using the progression-free survival curve to determine time on treatment. Given that we cannot modify median treatment duration, using the progression-free survival approach to model time on treatment is more conservative than the use of the time on treatment curve.
- ***Time horizon: 10 years (and not 20 years in submitted base case).*** The CGP stated that it is highly unlikely that patients would live beyond 10 years, and there is no data to inform the long term survival of this patient population. Though shortening the time horizon does not affect mortality rates, it truncates the accrual of benefits, which at this time are unknown, over the long term.
- In their feedback to the initial recommendation, the submitter commented that while a time horizon less than 20 years seems reasonable, the time horizon should be longer than the 10 years proposed by the EGP as the time horizon of 10 years chosen by the EGP in its reanalysis appears to be too short. The EGP maintains its choice in selection of the 10-year time horizon for the following reasons.
    - There are little long-term data to inform overall survival for cHL patients. When examining the data based on the study by Cheah et al.[3], addressing overall survival of patients whose lymphoma progressed after ASCT and subsequent BV for cHL patients, the CGP noted that it is "unreasonable to assume that patients whose cHL progresses after a checkpoint inhibitor that was given after failure of BV will live longer". According to the Cheah et al.[3] paper, when considering the death rate of approximately 15% per year for overall survival after failure of BV, more than 70% of the patients died within 5 years of failure; therefore, a 10-year time horizon, according to the CGP, remains optimistic for this patient population.
    - The CGP also felt that it is reasonable to assume patients who are receiving pembrolizumab in this setting will do worse than patients included in the Cheah et al.[3] paper; that is, patients will have shorter overall survival because patients who receive pembrolizumab will have an additional treatment due to an additional progression.

- In terms of the reference of the submitter to the pCODR recommendation of BV for HL, the EGP chose a time horizon of 15 years (shortened from the submitted base case of 20 years). However, the CGP commented that patients receiving pembrolizumab for cHL in the setting of the current review would have even shorter survival than patients receiving BV for HL.

- ***Comparative effectiveness of pembrolizumab versus chemotherapy (gemcitabine).*** The data to inform this economic model was not from a head-to-head clinical trial but from an indirect comparison where adjustments for key baseline factors were not made, which could influence the magnitude of the effect and limit the generalizability of the results. As such, the EGP elected to use the lower 95% CI in its re-analysis given the uncertainty in the non-randomized data, to present a conservative estimate as the lower bound.
- In their feedback to the initial recommendation, PAG noted that without an upper bound for an ICER, pricing discussions may be challenging as it may be difficult to determine a cost-effective price. Although, the EGP acknowledged that without an upper bound for the ICER, pricing discussions may be challenging the EGP reiterated that it was not possible to place an upper bound on the ICER, given the lack of comparative effectiveness estimates and the poor quality of the indirect treatment comparison. The EGP maintained that given the uncertainty in the non-randomized data, it was a reasonable approach to use the lower 95% CI in its re-analysis to present a conservative estimate as the lower bound.

Table 3. Detailed Description of EGP Reanalysis

	ΔC	ΔE QALYs	ICUR (QALY)	
Baseline	$169,475	1.04	**$163,544**	-----
EGP's Reanalysis for the Best Case Estimate - Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Treatment duration - PFS curve	$181,599	1.04	**$175,244**	$11,700
Time horizon - 10 years	$166,436	0.97	**$171,517**	$7,973
Hazard ratio pembrolizumab: gemcitabine lower 95% CI	$167,858	0.96	**$174,351**	$10,807
Best case estimate - lower bound	$177,046	0.90	**$197,055**	$33,511
EGP's Reanalysis for the Best Case Estimate - Upper Bound				
Not applicable				
Best case estimate - upper bound	**No upper bound given uncertainty in data**			N/A

1.5 Key highlight of EGP one-way scenario analyses

Table 4. Key highlight of EGP one-way scenario analyses

Variable	Base Case Value	Sensitivity Analysis Value	Δ costs	Δ effects	Result ($/QALY)	Δ from baseline ICER
Base case			$169,475	1.04	$163,544	------
Cost per cycle - pembrolizumab	$8,800	$6,600	$129,302	1.04	$124,777	-$38,767
Cost per cycle - pembrolizumab	$8,800	$4,400	$89,129	1.04	$86,010	-$77,534
Cost per cycle - pembrolizumab	$8,800	$2,200	$48,956	1.04	$47,243	-$116,301

1.6 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- The change in the number of pembrolizumab eligible patients.
- Inclusion of administration costs.
- Market share.

Key limitations of the BIA model include basing treatment duration on time on treatment for pembrolizumab, and not progression-free survival. Using a time on treatment curve to determine treatment duration includes only those who stay on the drug—regardless of progression status. This parameter was not able to be modified and explored by the EGP.

1.7 Conclusions

The EGP's best estimate of ΔC and ΔE for pembrolizumab when compared to standard of care is:

- **A minimum of $197,055/QALY with no upper bound**
- **Within this range, it is difficult to determine where the best estimate would lie, given the lack of comparative effectiveness data.**
- **The extra cost of pembrolizumab is at least $177,046. The factors that most influence ΔC are the treatment duration, the cost of pembrolizumab, and the selection of either Cohort 1 or Cohort 2 (not combined).**
- **The extra clinical effect of pembrolizumab is between 0.90 and unknown (ΔE). The factors that most influence ΔE are the time horizon, utilities and the selection of either Cohort 1 or Cohort 2 (not combined).**

Overall conclusions of the submitted model:

- *Given the lack of comparative effectiveness estimates and the poor quality of the indirect treatment comparison, it is difficult to place an upper bound on the ICER, or to have an idea of where the ICER would lay.*
- *Though there is consensus from the CGP that there is net clinical benefit with this drug, it is not possible to determine the upper bound of the magnitude of this benefit given the available data.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lymphoma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Pembrolizumab (Keytruda) for Classical Hodgkin Lymphoma. A full assessment of the clinical evidence of Pembrolizumab (Keytruda) for Classical Hodgkin Lymphoma is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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