PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pembrolizumab (Keytruda) for Metastatic Melanoma

November 16, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The review for pembrolizumab was first submitted to pCODR assessing Pembrolizumab alone on patient outcomes compared to standard care or best supportive care in treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy. In accordance with the pCODR Procedures, the pCODR Provincial Advisory Group (PAG) requested additional information on pembrolizumab (Keytruda) which extend beyond the submitted scope of the review. The request by PAG expressed a need for pembrolizumab in ipilimumab naïve patients. Revision of review scope may be considered by pCODR in very limited instances, based on jurisdictional input, feasibility to conduct the revised review and clinical importance. All three criteria for scope modification were met in this case and the scope of the review was expanded to include patients naïve to ipilimumab treatment. The economic analysis for the first line review was provided by Merck through this process.

Patients naïve to ipilimumab treatment (First/Second Line Therapy)

The economic analysis **submitted to pCODR by Merck Canada/Oncology** compared pembrolizumab to ipilimumab (IPI) in advanced melanoma patients that have not previously received IPI treatment. In this model, BRAF+ patients could have previously been treated with BRAF/MEK inhibitors. Both pembrolizumab (2mg/kg dose use in the economic model) and ipilimumab are administered intravenously every 3 weeks. Scenario analyses comparing pembrolizumab with vemurafenib or dabrafenib in first line for BRAF+ patients were included, however, given the limitations and great uncertainty in the efficacy data presented through a network meta-analysis for pembrolizumab vs. BRAF/MEK inhibitors, the EGP did not provide re-analysis estimates for this comparison. A Canadian health care perspective was adopted. The model was built under the assumption that patients would not receive any other active treatment following progression.

According to the **pCODR Clinical Guidance Panel (CGP),** the comparisons were appropriate. Based on input from the CGP, the 2mg/kg every 3 weeks, which is the Health Canada approved dose for pembrolizumab, is likely to be used in the clinical setting. The CGP also commented that multiple trials have shown a lack of a dose-response relationship with pembrolizumab. Therefore EGP did not consider other doses or dosing regimens of pembrolizumab in their re-analysis.

Patients considered the following factors important in the review of pembrolizumab, which could be relevant to the economic analysis: cost effectiveness of the treatment as an early option compared to Ipilimumab or BRAF inhibitors, drug dosing, drug wastage, and patient time & cost to travel to larger centres with more expertise in monitoring reactions post-infusion. This last factor is not considered in the submitted analysis and EGP's re-analysis as the analysis uses a government payer perspective.

The **Provincial Advisory Group (PAG)** reinforced the same factors already mentioned by the patients as important and added the lack of long-term safety and efficacy data to be considered if implementing a funding recommendation for pembrolizumab. Additionally, PAG was seeking comparison with nivolumab and BRAF inhibitors in all lines of therapy. In the KEYNOTE-006 trial, Ipilimumab-naive patients with a BRAF mutation could have previously been treated with BRAF inhibitors. Only the comparison with BRAF inhibitors in first line was included in the model but was considered to produce uncertain estimates given the lack of clinical studies and great degree of uncertainty.

Drug wastage and drug related costs were addressed in the model, and the change in the vial size to 100 mg alone is expected to increase the incremental cost by approximately 40% in any scenario tested without a vial sharing program. The submitted analysis was conducted from a Ministry of Health Perspective, which is appropriate for submission to pCODR. The extrapolations on long-term data and duration of treatment were explored in the model and a subsequent reanalysis, and shown to be very important drivers of the cost effectiveness result.

Pembrolizumab costs $2200.00 per 50mg vial; and at the recommended dose of 2mg/kg once every 21 days, the average cost per day in a 28-day course of pembrolizumab is $293.33 and the average cost per 28-day course is $8,213.34. Based on information from the submitter, the vial size of pembrolizumab will transition to a 100mg liquid vial in the near future. The sensitivity analysis conducted by the submitter and the EGP to incorporate the introduction of the 100mg vial is based on the assumption that a 100mg vial costs $4400.00 per vial.

Ipilimumab costs $5,800 and $23,200.00 per 50 mg and 200mg vials, respectively. At the recommended dose of 3 mg/kg every 3 weeks for a 28 day cycle, the cost of ipilimumab is $1160.00 per day and 32,480.00 per 28 day cycle.

Ipilimumab-treated Patients (Second/Third Line Therapy)

The economic analysis **submitted to pCODR by Merck Canada/Oncology** also compared pembrolizumab to chemotherapy monotherapy (dacarbazine (DTIC)), or best supportive care (BSC) for patients with advanced melanoma (unresectable stage III and stage IV) refractory to ipilimumab. In this model, all patients had previously been treated with ipilimumab and, if BRAF mutation positive, a BRAF/MEK inhibitors. Both pembrolizumab (2mg/kg dose use in the economic model) and dacarbazine are administered intravenously and every 3 weeks. Paclitaxel+ carboplatin regime was used as a modification to the main analysis. Second line use of BRAF/MEK inhibitors were not modeled in the submitted analysis. The CGP also confirmed that patients will receive BRAF/MEK drugs at some point during their therapy, either before or after immune checkpoint inhibitors, thus the exclusion of BRAF/MEK drugs from the EGP's analysis is reasonable for this model.

According to the **pCODR Clinical Guidance Panel (CGP),** the comparisons were appropriate. Based on input from the CGP, the 2mg/kg every 3 weeks, which is the Health Canada approved dose for pembrolizumab, is likely to be used in the clinical setting. The CGP also commented that multiple trials have shown a lack of a dose-response relationship with pembrolizumab. Therefore EGP did not consider other doses or dosing regimens of pembrolizumab in their re-analysis.

Patients considered the following factors important in the review of pembrolizumab, which are relevant to the economic analysis: treatment as an early line treatment and appropriateness of dacarbazine as alternative, lack of comparative data with ipilimumab in case of first line therapy, drug dosing, drug wastage, cost-effectiveness compared to other treatments available, and patient time cost to travel to bigger centres with more expertise in monitoring reactions post-infusion.

The **Provincial Advisory Group (PAG)** reinforced the same factors already mentioned by the patients as important and added the lack of long-term safety and efficacy data to be considered if implementing a funding recommendation for pembrolizumab. Additionally, PAG was seeking comparison with nivolumab and BRAF inhibitors in all lines of therapy. Neither of those drugs was considered as a comparator in the model for Ipilimumab-treated patients due to lack of clinical studies in this population. In the KEYNOTE-002 trial,

patients were previously treated with ipilimumab and, if BRAF mutation positive, had previously being treated with BRAF inhibitor.

The use of pembrolizumab earlier in the course of disease was addressed by expanding the scope of the original submission, and the model for patients naïve to ipilimumab treatment was added to this review. The drug wastage and drug related costs were addressed in the model and it was estimated that with the change in the vial size to 100 mg, the wastage will increase by 64%, and the cost-effectiveness ratio of the new treatment in any scenario will be increased by around a similar proportion. The submitted analysis was conducted from a Ministry of Health Perspective, which is appropriate for submission to pCODR. The extrapolations on long-term data were explored in the model and a subsequent reanalysis, and proved to be a very important driver of the cost effectiveness results.

Pembrolizumab costs $2200.00 per 50mg vial; and at the recommended dose of 2mg/kg once every 21 days, the average cost per day in a 28-day course of pembrolizumab is $293.33 and the average cost per 28-day course is $8,213.34. Based on information from the submitter, the vial size of pembrolizumab will transition to a 100mg liquid vial in the near future. The sensitivity analysis conducted by the submitter and the EGP to incorporate the introduction of the 100mg vial is based on the assumption that a 100mg vial costs $4400.00 per vial.

Dacarbazine costs $200.20 per 600 mg per vial. At the recommended dose of 200–250 mg/m² IV days 1-5 every 21-28 days, the cost of dacarbazine is $20.26 – $33.76 per day and $567.230 – $945.39 per 28 day cycle.

1.2 Summary of Results

Patients naïve to ipilimumab treatment

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $114,389/QALY and $151,369/QALY when pembrolizumab is compared to ipilimumab in Ipilimumab-naïve patients.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect measured as QALY (ΔE). The EGP's best estimate of:

- the extra cost of pembrolizumab is between $56,320 and $63,060 per patient. The main factors influencing estimates for cost were treatment duration, drug cost (pembrolizumab and ipilimumab) and vial size.
- the extra clinical effect of pembrolizumab is between 0.37 and 0.55 QALYs per patient over a 10-year time horizon. The main factors influencing the clinical effect estimates were the sources of evidence for overall survival (OS) used to extrapolate survival beyond progression.

In the ipilimumab naïve setting, the Economic Guidance Panel's best estimates were based on the model submitted by Merck Canada/Oncology and reanalyses conducted by the EGP. The EGP, in consultation with the CGP, modified inputs in the submitted model to reflect a more plausible clinical scenario. The following variations were made to the model to provide the EGP's best estimate (multivariate sensitivity analysis):

- Considering other sources of survival data (Korn algorithm). The EGP noted that long term OS was modelled using data from an ipilimumab study (Schadendorf et al) by

applying a HR function for pembrolizumab to the ipilimumab survival curves in Schadendorf et al. The EGP noted that the original ipilimumab data demonstrated a sustained separation in the tail of the survival curve, a benefit that is yet to be confirmed in the pembrolizumab study, and long term extrapolation on the original ipilimumab data is based on highly censored data. The EGP therefore used alternative sources of data to model long term survival for the pembrolizumab arm to account for this uncertainty. When this modification is made using data from the Korn algorithm, the extra cost and effect of pembrolizumab is $25,398 and 0.33 QALY, resulting in an increase in the ICER to $76,989 (base case $52,829/QALY)

- Decrease in the price of ipilimumab. The price of ipilimumab originally used in the model was referenced from the Ipilimumab submission to pCODR in Dec 2014. Given Ipilimumab has been recommended for funding and adopted by some provinces, it is likely that the price currently being paid is lower than the price used in this economic evaluation. As the price of the comparator has a very important effect on the incremental cost, the EGP explored the impact of a 20% price reduction for ipilimumab. When this modification is made, the extra cost and effect of pembrolizumab is $59,236 and 0.74 QALY, resulting in an increase in the ICER to $80,038 (base case $52,829/QALY).
- Canadian reference values for QALYs (progression free state: 0.79 /progressive disease state: 0.55). The submitted results used utility values from US, UK and EU scoring algorithms which appeared to be too high for this population after disease progression. The EGP instead used Canadian utility values that reflected various advanced melanoma health states and adverse events, elicited using standard gamble technique from general population. When this modification is made, the extra cost and effect of pembrolizumab is $39,099 and 0.69 QALY, resulting in an increase in the ICER to $56,603 (base case $52,829/QALY)
- Time Horizon of 10 years. The EGP, in consultation with the CGP, agreed that long-term data for this population is not yet mature to allow for far-reaching extrapolations based on long term data observed for ipilimumab trials, especially under the assumption that no active treatment will be given after pembrolizumab. When this modification is made, the extra cost and effect of pembrolizumab is $33,559 and 0.56 QALY, resulting in an increase in the ICER to $59,710 (base case $52,829/QALY)
- Vial size of 100 mg without a vial sharing program. The submitted indicated that the 50mg vial of pembrolizumab will be phased out in the near future and only the 100mg vial will be available. The EGP therefore only used the 100mg vial in their re-analysis estimates. When this modification is made, the extra cost and effect of pembrolizumab is $56,491 and 0.74 QALY, resulting in an increase in the ICER to $76,330 (base case $52,829/QALY)
- Treatment continuation up to 2 years, and 25% of patients after this point having a 12-month re-induction. The EGP noted that the submitted results assumed 50% of patients will go on to receive re-induction with pembrolizumab, once the 2 year treatment mark is reached. Based on input from the CGP, the EGP, reduced this to 25% in their best estimates as there is currently no evidence to determine what proportion of patients reach the 2 year treatment cut-off mark and subsequently go onto to re-induction. When this modification is made, the extra cost and effect of pembrolizumab is $31,986 and 0.74 QALY, resulting in an decrease in the ICER to $43,219 (base case $52,829/QALY)
- When the above parameters are combined the extra cost and effect of pembrolizumab is $56,320 and 0.37 QALY, resulting in the EGP's upper estimate of $151,369. When the above parameters are combined using the long term survival data used in the submitted base case results (long term ipilimumab data from Schadendorf et al), the

extra cost and effect of pembrolizumab is $63,060 and 0.55 QALY, resulting in the EGP's lower estimate of $114,389.

The EGPs range of estimates were substantially higher than the submitted estimates. However, the EGP consider its best estimates to still be limited by the uncertainty around long-term data (due to lack of a reliable source). The EGP also highlighted that the incremental cost for pembrolizumab is being derived from a comparison to an alternative drug that has a high cost (ipilimumab), therefore masking the high cost of pembrolizumab.

According to the economic analysis that was submitted by Merck Canada/Oncology, when pembrolizumab is compared with ipilimumab

- The extra cost of pembrolizumab is $39,099. Costs considered in the analysis included cost of treatment, adverse events management costs, disease management costs and terminal care costs.
- The extra clinical effect of pembrolizumab is 1.36 life years gained (LYG) or 0.74 quality adjusted life years (QALY). Clinical effects considered in the analysis included PFS, OS and utilities.

So, the Submitter estimated that, based on the submitted price the estimated incremental cost-effectiveness ratio of pembrolizumab (when compared to ipilimumab) is $28,749 per LY or $52,829 per QALY.

The submitter also provided estimates of cost-effectiveness for pembrolizumab compared to BRAF inhibitors as first line therapy. However, given the lack of direct comparative data and the limitations and considerable uncertainty identified in the results presented through a network meta-analysis for pembrolizumab vs. BRAF/MEK inhibitors, the EGP did not provide re-analysis estimates for this comparison. Please see a critical appraisal of the network meta-analysis in the Clinical Report (Section 7).

According to the economic analysis that was submitted by Merck Canada/Oncology, when pembrolizumab is compared with dabrafenib and based on the submitted price the estimated incremental cost-effectiveness ratio of pembrolizumab (when compared to dabrafenib) is $60,859 per QALY.

According to the economic analysis that was submitted by Merck Canada/Oncology, when pembrolizumab is compared with vemurafenib and based on the submitted price the estimated incremental cost-effectiveness ratio of pembrolizumab (when compared to vemurafenib) is $38,131 per QALY.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $586,833K/QALY and $903,678/QALY when pembrolizumab is compared to dacarbazine (DTIC) in patients refractory to ipilimumab. When pembrolizumab is compared to BSC the EGP's best estimate ranges from S700, 834/QALY to $1,859,069/QALY.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect measured as QALY (ΔE). The EGP's best estimate of:

- the extra cost of pembrolizumab is between $98K and $100K per patient. The main factors influencing changes cost is the cost of pembrolizumab and the time horizon
- the extra clinical effect of pembrolizumab is between 0.10 and 0.17 QALYs over the time horizon. The main factors influencing changes the clinical effect is the source of OS data for extrapolations of survival after progression, use of Canadian quality of life values for the health states and time horizon.

In the ipilimumab refractory patients, the EGP's estimates were based on the model submitted by Merck Canada/Oncology and reanalyses conducted by the EGP. Modification were made to the submitted model inputs to provide estimates that better reflected plausible clinical scenarios, as determined with CGP input. Varied parameters that were incorporated into the EGP's range of estimates are presented below (multivariate sensitivity analysis):

- Overall Survival extrapolations after progression using similar data in both arms (Korn or Schadendorf/Ipilimumab data). EGP noted that long term OS was modelled using different sources of data for the different arms – Ipilimumab data for Pembrolizumab arm and Korn algorithm for Chemotherapy arm. This implicitly assumes that after disease progression and consequently treatment discontinuation, the disease trajectory will be dependent on the prior treatment received, which is not supported by any available data. Considering that patients in both arms previously received ipilimumab and the absence of long term data to support extended benefit with pembrolizumab, the EGP used the assumption that disease progression was independent of prior treatment, and therefore both arms were assigned same source of OS data. The EGP consider two scenarios:
    - Giving the 'extended benefit' on survival to patients in both arms using Schanderford data/Ipi studies
    - Considering that long term extrapolation on the original ipilimumab studies is based on highly censored data, the alternative sources of data to model long term survival is using data from the Korn algorithm,
- Canadian reference values for QALYs (progression free state: 0.79 /progressive disease state: 0.55) The submitted results used utility values from US, UK and EU scoring algorithms which appeared to be too high for this population after disease progression. The EGP instead used Canadian utility values that reflected various advanced melanoma health states and adverse events, elicited using standard gamble technique from general population.
- Time Horizon of 5 years. The EGP, in consultation with the CGP, agreed that long-term data for this population is not yet mature to allow for far-reaching extrapolations based on long term data observed for ipilimumab trials.
- Vial size of 100 mg without a vial sharing program. The submitted indicated that the 50mg vial of pembrolizumab will be phased out in the near future and only the 100mg vial will be available. The EGP therefore only used the 100mg vial in their re-analysis estimates.

	pembrolizumab vs dacarbazine		**pembrolizumab vs BSC**	
	ΔC and ΔE	ICER ($/QALY)	ΔC and ΔE	ICER ($/QALY)
Base case results	$110,454 and 0.91 QALY	$121,843	$119,557 and 0.94 QALY	$126,691

Overall Survival extrapolations based on Schanderford data/Ipi studies	$90,548 and 0.053 QALY	$1,693,423	$96,018 and a loss in effect of -0.07QALY	Dominated (more costly and less effective)
Overall Survival extrapolations based on Korn algorithm	$93,837 and 0.19 QALY	$492,344	$101,284 and 0.15 QALY	$653,771
Canadian reference values for QALYs	$110,454 and 0.75 QALY	$146,819	$119,557 and 0.79 QALY	$151,984
Time Horizon of 5 years	$95,129 and 0.52 QALY	$182,344	$103,301 and 0.52 QALY	$198,122
Vial size of 100 mg	$123,673 and 0.90 QALY	$136,424	$132,776 and 0.94 QALY	$140,698
Combination of all parameters	Lower estimate[1]: $100,617 and 0.17 QALY Upper Estimate[2]: $98,954 and 0.10 QALY	$586,833 $903,678	Lower estimate[1]: $108,211 and 0.15 QALY Upper Estimate[2]: $105,616 and 0.06 QALY	$700,834 $1,859,069
[1] Korn algorithm OS survival curves [2] Schanderford et al/ Ipilimumab studies OS survival curves				

The EGPs estimates were substantially higher than the submitted estimates. However, the EGP consider its best estimates to still be limited by the uncertainty around long-term data (due to lack of reliable source).

More specifically, the reanalysis conducted by the EGP using the submitted model showed that the main factor affecting the cost-effectiveness ratio was the use of different survival assumptions (and source of long-term data) between pembrolizumab and the comparator. When applying the assumption that the survival of patients is equal between the pembrolizumab and chemotherapy arms (same source of long-term data) once the disease progresses and treatment stops, the incremental cost-effectiveness ratio increased. The EGP's believes these results are mainly influenced by the manufacturer's use of different sources of data in each arm (Schadendorf data/Ipi studies for pembrolizumab, and Korn algorithm for dacarbazine) despite patients in both arms having previously failed ipilimumab treatment.

According to the economic analysis that was submitted by Merck Canada/Oncology, when:
Pembrolizumab is compared with dacarbazine,

- The extra cost (ΔC) of pembrolizumab is $110,454. Costs considered in the analysis included cost of treatment, adverse events management costs, disease management costs and terminal care costs.
- The extra clinical effect (ΔE) of pembrolizumab is 1.22 life years gained (LYG) or 0.91 QALY. Clinical effects considered in the analysis included PFS, OS and utilities

So, the Submitter estimated that, based on the submitted price the estimated incremental cost-effectiveness ratio is $90,536 per LY and $$121,843 per QALY.

And, when pembrolizumab is compared with BSC

- The extra cost (ΔC) of pembrolizumab is $119,557. Costs considered in the analysis included cost of treatment, adverse events management costs, disease management costs and terminal care costs.
- The extra clinical effect (ΔE) of pembrolizumab is 1.26 life years gained (LYG) or 0.94 QALY. Clinical effects considered in the analysis included PFS, OS and utilities.

So, the Submitter estimated that, based on the submitted price the estimated incremental cost-effectiveness ratio is $94,886 per LY and $126.691 per QALY.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the incremental cost-utility ratio (ICUR) differ from the Submitter's, what are the key reasons?

Patients naïve to ipilimumab treatment

The EGP estimates differ from those of the submitter due to the use of an entire new scenario by EGP as the main analysis as described further below. The price of ipilimumab, treatment duration, and a short-time horizon had the most impacts on the model. Given no sequential treatment was incorporated into the model, the extrapolation over a longer time horizon would just offset the initial costs of incorporating the drug in the arsenal of treatments without reflecting the actual clinical practice given the lack of optimal sequencing in this population. The magnitude of the effect on the ICUR of using other data sources for OS extrapolation, and change in vial size coming to the market were equally important.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

The EGP estimates differ from those of the submitter. The main factor influencing the EGP's re-analysis estimate was the use, by the EGP, of similar survival assumptions between arms for long term data after the trial period and following progression. In comparison the submitted results used different survival assumptions (and source of long-term data) in the pembrolizumab and comparator arms which resulted in a favourable ICER for pembrolizumab. The EGP also used Canadian utility values for calculating QALY and a shorter time horizon which impacted the model but less significantly than the assumptions for long term survival data.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Patients naïve to ipilimumab treatment

Factors important to patients were mostly addressed. The primary concern was with treatment as an early line therapy compared to alternatives other than chemotherapy. Extrapolations and uncertainty around survival expectations were addressed following requested for additional information by EGP and reanalyses. Drug dosing and wastage, side effects and quality of life were appropriately incorporated into the model allowing reanalyses and change in parameters to test different scenarios. Out-of-pocket patient cost with travel to receive treatment is a concern that is not addressed in an analysis from the perspective of a government payer. However, this perspective is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

Factors important to patients were mostly addressed. The primary concern with the use of pembrolizumab in an earlier line of therapy (ipilimumab naïve) and the appropriateness of dacarbazine as alternative was not available initially and was addressed through expansion of the scope of the review, which is addressed in a dedicated chapter, in which pembrolizumab is compared to ipilimumab.

Extrapolations and uncertainty around survival expectations were addressed through requests for additional information by EGP for their reanalyses. Drug dosing and wastage, side effects and quality of life were appropriately incorporated into the model allowing reanalyses and change in parameters to test different scenarios. Out-of-pocket patient cost with travel to treatment is a concern that is not addressed in an analysis from the perspective of a government payer. However, this perspective is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Patients naïve to ipilimumab treatment

Yes, the design and structure of the economic model was adequate. However, the assumptions and sources of data were considered inadequate by the EGP. EGP requested additional data and made adjustments to the submitted model to ensure more robust assumptions and more realistic scenarios for survival, dosing, wastage, and drug price. Uncertainty around survival was partially treated in the model.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

Yes, the design and structure of the economic model was adequate. However, the assumptions and source of data were considered inadequately by the EGP. EGP was able to make adjustments in submitted model to ensure more robust assumptions on long-term survival, dosing, wastage, and drug price. Uncertainty around survival was not treated in the model.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

Patients naïve to ipilimumab treatment

The factor with the largest effect on the results is the treatment duration. There is some concern from the CGP that if patients are responding to treatment, some clinicians might consider continuing pembrolizumab treatment until disease progression rather than stopping the drug after 2 years, which would results in almost doubled the original ICUR. However, there is no data available on the benefit of treatment extend or re-induction, or proportion of patients extending treatment. Therefore, CGP recommend adherence to the trial protocol to treatment up to 2 years, and expect a small proportion of re-induction that might be individually discussed, similarly to the ipilimumab recommendation.

Secondly, the long-time horizon (20 years) assuming no subsequent sequential treatment for this population may offset the high initial cost of treatment without truly reflecting clinical practice and costs in the long-term. Previous input from the pCODR Melanoma Clinical Guidance Panel (pCODR review for Ipilimumab in both first and second line) reported five years as a reasonable time horizon for patients with advanced melanoma in last line of therapy, and 10-20 years in first line of therapy. In discussing with the CGP, it was noted that while a short time horizon might underestimate the potential long-term effects of immune therapy, there is currently no evidence to support that pembrolizumab will have a sustained long term benefit in a proportion of patients as was observed with other immunotherapies. Therefore, the EGP used a 10-year time horizon to provide a balance between underestimation of cost (no sub sequential treatment) and overestimation of long-term effect.

Moreover, having an already expensive comparator makes the incremental cost seem low. However, it is likely that since 2014 when ipilimumab became the first line therapy for this population, its price may have been driven down by market forces. A 20% decrease in ipilimumab price results in more than 50% increase in the pembrolizumab ICUR.

The use of different data sources for extrapolation in survival for both Ipilimumab and pembrolizumab treated patients also had an important effect on ICUR. The submitted base case analysis used Schadendorf data (Ipi studies) to extrapolate survival. These data present a plateau in survival (sustained survival benefit) after 5 years at around 20%. This was considered to be unsupported by long term data for pembrolizumab and associated with limitations due to high censoring of the data used for the original ipilimumab curves. In the reanalysis, when applying a different data source (Korn algorithm), the ICUR of pembrolizumab increased by >40%.

Other assumptions such as vial size and extrapolation of benefit of the drug after treatment discontinuation also have an important impact on the results.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

The factor with the largest effect on the results is the use of different sources of data in each arm (Schadendorf data/Ipi studies for pembrolizumab, and Korn algorithm for Dacarbazine) for the extrapolation on survival after the trial period, and after disease progression, despite patients in both arms having previously failed ipilimumab treatment. The Schadendorf data (Ipi studies), applied to extrapolate survival for the pembrolizumab arm, presents a plateau in survival (sustained survival benefit) after 5 years of around 20%, which was found to be implausible by EGP given the quality of the data (highly censored) and lack of long term follow up data to confirm a sustained long term effect in a proportion of patients. In the EGP's reanalysis, when adjusting this assumption to use the same data source for extrapolating long term survival after the disease progression in both arms (either Schadendorf data or Korn algorithm), the incremental cost for pembrolizumab were several times higher.

Secondly, high estimates of utility values for the progressive state of the disease derived from the trial are very discrepant from Canadian utility values for the same state (0.73 vs 0.55). This Canadian study investigated various advanced melanoma health states and adverse events, elicited using standard gamble technique from general Canadian population, which is deemed more appropriate. When applying Canadian utilities to the submitted model, this parameter alone decreased the previous 0.91 gain in QALY to 0.75.

Finally, time horizon is another factor influencing the cost-effectiveness results. Previous input from the pCODR Melanoma Clinical Guidance Panel (Ipilimumab EGP report) reported five years as a reasonable time horizon for patients with advanced melanoma. The submitter used a 10 year time horizon for the base case results. This parameter alone decreases the observed QALY gain from the previous 0.91 to 0.52, and increases the ICUR from the previous $121K/QALY to $182K/QALY (49%).

No other assumptions or parameters had a substantial impact on the results compared to the ones above.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Patients naïve to ipilimumab treatment

No. EGP would consider using a different data source for OS extrapolations (due to highly censored data used for the reference base case), lower drug price for the comparator, Canadian utility values, 100mg vial size and a shorter time horizon.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

No, the estimates of clinical effect were not adequate. The submitter used different data sources for long term extrapolation of survival in the treatment and comparison arms despite the fact that all patients previously failed ipilimumab therapy in both arms. The survival extrapolations for pembrolizumab was also mostly based on data from Schadendorf et al (pooled OS data from ipilimumab-treated patients with advanced melanoma - phases I/II/III), which has its limitations as the data is highly censored. The EGP was able to show the impact of using the same data source in both arms for survival extrapolation after disease progression. The EGP also considered using Canadian utility values and a shorter time horizon to be more appropriate.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

Patients naïve to ipilimumab treatment

The BIA_model was found to be the most sensitive to pembrolizumab's market share, treatment duration, patient weight and number of cases of advanced melanoma.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

A number of sensitivity analyses were conducted, and the model was found to be the most sensitive to pembrolizumab's market share, treatment duration, and number of cases of melanoma.

Market share was based on a market database and took into account first and second line choices, however, since there is no stablished guidelines regards to the optimal sequence of therapies in melanoma, the market share can change rapidly.

What are the key limitations in the submitted budget impact analysis?

Patients naïve to ipilimumab treatment

The reference case considered the use of the 50mg vial sizes without vial sharing. Change in vial size to 100 mg would add another 13% increase in the budget impact.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

The reference case considered the use of the drug within a vial sharing program with maximum wastage of 10% and 50mg vial sizes. The EGP noted that the 50mg vial will transition to a 100mg liquid vial format in the near future which may impact on wastage. Reanalyses in the BIA assuming the vial size change to the 100mg vial without a vial sharing program increases the incremental budget in 11%.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

Patients naïve to ipilimumab treatment

- Long-term data on potential benefits of pembrolizumab on survival after disease progression and treatment discontinuation.
- A comprehensive probabilistic sensitivity analysis that encapsulates all sources of uncertainty (including around long-term survival, independent of the data source utilized for extrapolations, utility values and comparator price).
- Incorporation of cost and consequences of subsequent treatments in this population.

Previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

- A more comprehensive, objective, and transparent treatment of extrapolation beyond the clinical trial data.
- A comprehensive probabilistic sensitivity analysis that encapsulates all sources of uncertainty (including around long-term survival).
- Long-term data on residual benefits of pembrolizumab on survival after disease progression and treatment discontinues.

Is there economic research that could be conducted in the future that would provide valuable information related to pembrolizumab for Patients naïve to ipilimumab treatment or Ipilimumab-treated patients?

A key parameter that affects the economic profile of this type of treatment is the lasting impact on long-term survival. Little evidence is available whether the studied treatment will affect survival once the disease is in a progressive state (and the drug is discontinued). This will require a dedicated survival analysis with time zero being the start of the progressive disease and the outcome of interest being mortality.

Also, there is lack of evidence on long-term quality of life data in melanoma patients especially after the disease progression, when treatment is discontinued.

2 DETAILED TECHNICAL REPORT – IPILIMUMAB NAÏVE PATIENTS

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 DETAILED TECHNICAL REPORT – IPILIMUMAB TREATED PATIENTS

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.

4 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Melanoma 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 metastatic melanoma. A full assessment of the clinical evidence of pembrolizumab (Keytruda) for metastatic melanoma 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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