CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pembrolizumab (Keytruda) for Squamous Non-Small Cell Lung Cancer

January 3, 2020

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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.
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Merck compared pembrolizumab in combination with carboplatin and paclitaxel chemotherapy to carboplatin and paclitaxel chemotherapy alone for patients with squamous metastatic non-small cell lung cancer. An additional analysis also compared pembrolizumab in combination with carboplatin and paclitaxel chemotherapy to pembrolizumab monotherapy for patients with squamous metastatic non-small cell lung cancer and high levels of PD-L1≥50%. This matches the submitter's funding request.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel chemotherapy for the treatment of patients with untreated metastatic, squamous NSCLC. It should be noted that nab-paclitaxel is not approved in Canada for the treatment of metastatic squamous NSCLC. The model only considered pembrolizumab in combination with carboplatin and paclitaxel.
Type of Analysis	Cost-utility analysis and cost-effectiveness analysis.
Type of Model	Partitioned-survival model
Comparator	**Primary comparison:** Carboplatin combined with paclitaxel. **Additional comparison (among PD-L1≥50% patients only):** Pembrolizumab monotherapy
Year of costs	2018
Time Horizon	10 years
Discount rate	1.5% (for both costs and utilities)
Perspective	Canadian publicly-funded health system
Cost of Pembrolizumab *Price source: Merck Canada Inc.*	• $4,400 per 100mg vial • Cost per dose: $8800.00 • Cost per 28 days: $11,733
Cost of chemotherapy ** Price Source:* *Carboplatin: INESSS Avis au ministre, Giotrif (June 2014)* *Paclitaxel: INESSS Avis au ministre, Avastin (June 2016)*	Carboplatin: • $18.80 per 150 mg vial • $56.39 per 450 mg vial • Cost per dose (645 mg): $87.41 • Cost per 28 days: $116.55 Paclitaxel: • $5.27 per 30 mg vial • $17.56 per 100 mg vial • Cost per dose (200 mg/m^2): $64.36 • Cost per 28 days: $85.81
Model Structure	Model was composed of three health states: progression-free survival (PFS), progressive disease (PD) and death (Figure 1).

Key Data Sources	**Primary comparison:** Model effectiveness parameters were estimated from KN407 patient-level data for time on treatment (ToT), PFS based on blinded independent review and overall survival (OS) up to year 1. SEER used for OS extrapolation beyond year 1. **Additional comparison:** Indirect treatment comparison of KN407 with KN042.

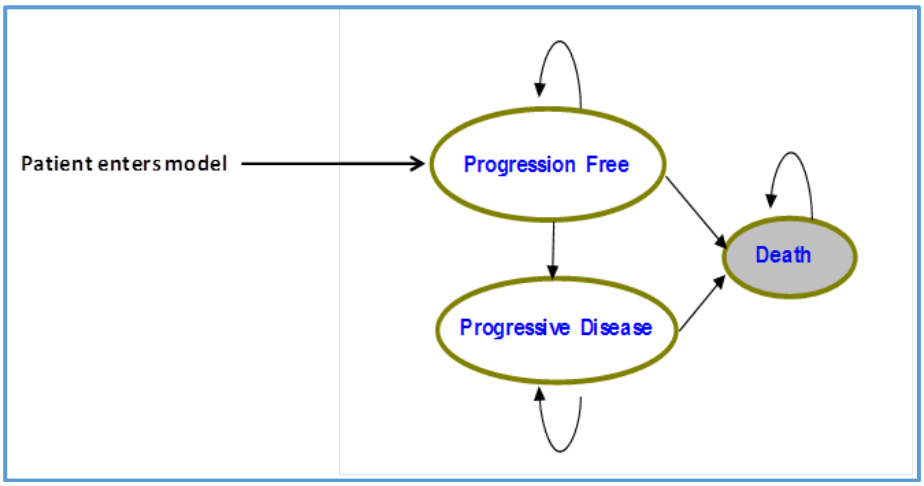

Figure 1: Transition Diagram for cohort Simulation Model Health Outcomes

1.2 Clinical considerations

According to the pCODR Clinical Guidance Panel (CGP), the primary comparison of pembrolizumab + chemotherapy vs. chemotherapy is appropriate. The CGP considered that pembrolizumab + chemotherapy vs. pembrolizumab monotherapy is also a clinically relevant comparator for PD-L1 TPS≥50% patients. The submitter did include this comparison in the additional economic analysis.

Relevant issues identified by the CGP included:

There is a net overall clinical benefit from the addition of pembrolizumab to carboplatin/(paclitaxel or nab-paclitaxel) in patients with advanced/metastatic squamous NSCLC. The KN407 trial (Paz-Ares, et al., 2018) demonstrates clear improvement in both OS (median OS 15.9 vs. 11.3 months, HR 0.64, 95%CI 0.49-0.85 p < 0.001) and PFS (median PFS 6.4 vs. 4.8 months, HR 0.56, 95%CI 0.45-0.70) for pembrolizumab + chemotherapy vs. chemotherapy alone (median follow-up 7.8 months).

The improved efficacy came with an acceptable safety profile with grade 3 or higher adverse events occurring in approximately equal numbers in both arms of the trial.

With respect to the pembrolizumab + chemotherapy vs. pembrolizumab monotherapy, there are methodological concerns (such as the small sample size, proportional hazards assumption not being met for OS and PFS for the KN-042 study, and the exclusion of patients from KN-024) raised in the indirect treatment comparison that limit the conclusions that can be drawn from that assessment.

Summary of registered clinician input relevant to the economic analysis

The clinicians providing input reported an unmet need in patients with PD-L1 TPS < 50% to improve the initial therapy and OS, and that pembrolizumab in combination with chemotherapy can lead to clinical benefit. On the other hand, the CGP supported having both the pembrolizumab + chemotherapy and the pembrolizumab monotherapy options available to patients with PD-L1 TPS ≥ 50% as these regimens have not yet been directly compared and it is so far unclear whether or not one regimen is superior to the other.

In the main analysis, the model only considered pembrolizumab + chemotherapy vs. chemotherapy regardless of patients' TPS status. In the additional analysis, the model compared pembrolizumab + chemotherapy vs. pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50%.

Summary of patient input relevant to the economic analysis

None of the patients that provided input received pembrolizumab + chemotherapy together as first line therapy for Squamous NSCLC. Patients recruited either had experience with pembrolizumab monotherapy or chemotherapy as first-line treatment.

The submitted economic model did consider three factors that were important and relevant to patients: survival, quality of life and adverse events.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG identified the following economic factors as being important to consider if implementing a funding recommendation for pembrolizumab + chemotherapy:

- **Clarity on the appropriate dosing schedule**. The CGP recognizes that prior decisions regarding pembrolizumab have recommended pembrolizumab dosing at 2mg/kg up to a maximum of 200mg. The CGP feels that it is beyond the scope of this review to reopen this decision. Thus, CGP notes that KN-407 uses the 200 mg flat dosing but that the Canadian health system has previously decided that this flat dosing yields equal outcomes to dosing 2mg/kg up to a maximum of 200mg. Complicating matters is that there is emerging data on dosing pembrolizumab at 400 mg flat dose every 6 weeks. Given the complexity of this topic the CGP recommends the pCODR review dosing and schedule for immune checkpoint inhibitors (ICIs) via a separate panel.

- **Clarity on the treatment duration and guidance on the appropriate stopping rules.** The CGP believes patients who complete two years of pembrolizumab and discontinue therapy without progression, should have the option for retreatment with pembrolizumab. The optimal duration of this retreatment is unknown. Whether restrictions should be placed on the timeframe between completion of therapy and documented disease progression (i.e. 6 months or more) is also unknown. Retreatment was not explored in the economic analysis.
- **Whether there are additional resources needed to monitor infusion reactions.** The submitted economic model had no explicit way of considering the impact of the additional resources needed to monitor infusion reactions. The submitted model did allow for a modification of administration costs. The EGP conducted scenario analyses under which administration costs were increased by 25% and by 50%.

1.3 Submitted and EGP Reanalysis Estimates

Submitted estimates

Pembrolizumab + chemotherapy vs. chemotherapy:

According to the submitted base case economic analysis, the difference in cost (ΔC) between pembrolizumab + chemotherapy treatment and chemotherapy alone is $111,670. Costs considered in the analysis included drugs, disease management, and adverse events. The difference in clinical effectiveness (ΔE) between these two therapies amounts to 1.12 QALY. The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, and utilities. The submitter estimated that the incremental cost-effectiveness is $99,499/QALY.

The EGP identified limitations in the model submitted by Merck Inc as well as assumptions that limited its applicability to the Canadian context. The model's parameters were modified and then reanalyzed by the EGP. Parameters modified included the subsequent therapy options, modeling overall survival options, and extrapolation options. Detailed modifications are presented in Section 1.4 along with tables that detail the results of the EGP reanalysis. The EGP estimates differed from the submitted estimates. Summaries of the reanalysis of the pembrolizumab + chemotherapy vs. chemotherapy comparison performed by the EGP are given in Table 2. The EGP reanalyses in Table 2 followed from a probabilistic analysis (5,000 iterations) except for estimates of incremental life years, for which only deterministic estimates were reported by the model.

Table 2: Submitted and EGP estimates for pembrolizumab + chemotherapy vs. chemotherapy. EGP estimates are based on probabilistic reanalyses except where denoted as deterministic.

Estimates (range/point)	Submitted	EGP Reanalysis (Lower bound)	EGP Reanalysis (Upper bound)
ΔE (LY)*	1.41	0.62	NE
Progression-free*	0.85	0.65	NE
Post-progression*	0.56	-0.02	NE
ΔE (QALY)	1.12	0.49	NE
Progression-free	N/A	N/A	N/A
Post-progression	N/A	N/A	N/A
ΔC ($)	111,670	106,271	NE
ICER estimate ($/QALY)	99,499	216,280	NE

* Based on a deterministic reanalysis as probabilistic result not reported in model.
NE: not estimable
N/A: Not applicable

Pembrolizumab + chemotherapy vs. pembrolizumab monotherapy for PD-L1≥50%

According to the submitted base case economic analysis, the difference in cost (ΔC) between pembrolizumab + chemotherapy treatment and pembrolizumab monotherapy is $11,180. Costs considered in the analysis included drugs, disease management, and adverse events. The difference in clinical effectiveness (ΔE) between these two therapies amounts to -0.01 QALY. The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, and utilities. In this comparison, pembrolizumab + chemotherapy treatment is dominated (more costly, less effective) in the base case.

The EGP identified limitations in the model submitted by Merck Inc as well as assumptions that limited its applicability to the Canadian context. The model's parameters were modified and then reanalyzed by the EGP. Parameters modified include subsequent therapies options, modeling overall survival options, and extrapolation options. Detailed modifications are summarized in Section 1.4 along with tables that detail the results of the EGP reanalysis. The EGP estimates differed from the submitted estimates. Summaries of the reanalysis of the pembrolizumab + chemotherapy vs. pembrolizumab monotherapy comparison performed by the EGP are given in Table 3. The EGP reanalyses in Table 3 followed from a probabilistic analysis except for estimates of ΔE in terms of LY, for which only deterministic estimates were reported by the model.
Table 3: Submitted and EGP estimates for pembrolizumab + chemotherapy vs. pembrolizumab monotherapy among PD-L1>50% patients. EGP estimates are based on probabilistic reanalyses except where denoted as deterministic.

Estimates (range/point)	Submitted	EGP Reanalysis (Lower bound)	EGP Reanalysis (Upper bound)
ΔE (LY)*	0.08	0.05	0.08
Progression-free*	0.65	0.59	0.65
Post-progression*	-0.58	0.54	-0.57
ΔE (QALY)	-0.01	-0.07	-0.08
Progression-free	N/A	N/A	N/A
Post-progression	N/A	N/A	N/A
ΔC ($)	11,180	9,010	8,252
ICER estimate ($/QALY)	Pembrolizumab+ chemotherapy dominated (more costly, less effective)	Pembrolizumab+ chemotherapy dominated (more costly, less effective)	Pembrolizumab+ chemotherapy dominated (more costly, less effective)
* Based on a deterministic reanalysis as probabilistic result not reported in model.			

Limitations

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

- **Treatment comparator I**: At present, the standard of care in Canada is that individuals with a PD-L1 TPS ≥ 50% are eligible to receive pembrolizumab monotherapy as 1L treatment. The primary comparison addresses the cost-effectiveness of giving pembrolizumab with chemotherapy as 1L therapy to squamous NSCLC regardless of TPS score. A more relevant decision problem in the Canadian context may be to compare treatment with pembrolizumab + chemotherapy vs chemotherapy for patients with TPS < 50%. This is especially important as: 1) the submitter's additional comparison suggests that pembrolizumab + chemotherapy is dominated (more costly, less effective) among patients with TPS ≥ 50% and, 2) CADTH HTA guidelines (Section 3 - Target Population) say that the economic evaluation should investigate sources of heterogeneity within the target population that may lead to differences in the effectiveness of the intervention. The EGP requested that the submitter provide a model in which pembrolizumab + chemotherapy for all patients is compared against the status quo in Canada, in which patients with TPS≥50% receive pembrolizumab monotherapy and patients with TPS<50% receive chemotherapy. The submitter declined to provide such a model, and considered this to be a different decision problem to the one posed by the current funding request.

- **Treatment comparator II**: In Canada, chemotherapy regimens other than those considered by the submitter can be used (e.g. cisplatin, carboplatin, gemcitabine, vinorelbine, paclitaxel and docetaxel). The CGP indicated to the EGP that the differences with other chemotherapy regimens are unlikely to significantly impact the analysis. However, including the other chemotherapy regimens used in Canada would have provided a more complete analysis, even if exploratory.

- **Subsequent therapies:** The subsequent therapies accounted for in the model in the base case assumed that nivolumab therapy is available as a second line treatment following a first line treatment that includes anti-PD-1/PD-L1 therapy. Nivolumab is not an option in Canada if anti-PD-1/PD-L1 therapy such as pembrolizumab is given in the first line. Of note, only the costs of subsequent therapies were included in the model, the clinical effect could not be altered.

- **Modeling pembrolizumab + chemotherapy OS:** The submitter's base case estimates assumed that OS for both the pembrolizumab + chemotherapy and the chemotherapy arms followed KN407 trial KM data for year 1. Mortality risks from the SEER database were used for years 2 to 13 for the chemotherapy arm. To estimate the OS in the pembrolizumab + chemotherapy arm for years 2 to 5, the relative risk of death of pembrolizumab + chemotherapy vs. chemotherapy from KN407 trial months 7-12 (=0.58)

was used to scale down the SEER mortality risk used for chemotherapy arm OS. The same SEER-based mortality risk used in chemotherapy arm beyond year 5 was used for the pembrolizumab + chemotherapy arm beyond year 5. The use of SEER data on mortality for the chemotherapy arm from year 2 onwards is a limitation as:

- SEER data contains US patients only. The survival of US patients may not be reflective of patients in the Canadian setting.
- The mortality risks derived from SEER data were up to 2014. The CGP indicated that these data may not capture the effect of second line immuno-oncology treatments available to patients who received chemotherapy as 1L. Thus, the SEER data may underestimate overall survival in the chemotherapy arm.
- To derive the mortality risk of the pembrolizumab + chemotherapy arm for years 2to 5, the submitter scaled down the mortality risk of the chemotherapy arm using a relative risk of death of 0.58 (standard error = 0.12) obtained from the 7-12 months of KN407 trial data. The submitter assumed that this relative risk is constant for years 2-5.
- Furthermore, when the relative risk was broken down by PD-L1 TPS subgroup, the relative risk of death in months 7-12 varied significantly. According to the submitter, these relative risks are 0.79 (0.31-1.93), 0.64 (0.31-1.34) and 0.45 (0.20-0.83) for PD-L1 ≥ 50%, PD-L1 1-49% and PD-L1 <1% respectively. In the view of the EGP, the use of a relative risk of 0.58 (standard error = 0.12) to derive the pembrolizumab + chemotherapy OS neglects a significant amount of uncertainty that may have a substantial impact on OS.

- **Extrapolation of efficacy data:** The median follow-up in the KN-407 trial was relatively short (median follow-up was 7.8 months). Extrapolation for PFS, OS and treatment duration was estimated using Kaplan-Meier data, parametric distributions or a combination of both for 10 years. Extrapolation of survival over a 9 year period from a 7.8 month median follow-up study was judged by the EGP to be highly uncertain. The choice of extrapolation parametric fitting curves can impact the long-term OS significantly and can even lead to projections in which chemotherapy eventually yields a greater probability of OS than pembrolizumab + chemotherapy. To highlight the fact that uncertainty in the extrapolation of OS beyond the trial period could possibly lead to a more effective OS for chemotherapy alone, the EGP conducted sensitivity analyses using the 2nd best fitted extrapolation parametric fitting curves based on the submitted AIC and BIC information on PFS and OS.

  The submitter provided feedback on pERC's Initial Recommendation disagreeing with the examples of possible clinical scenarios that could contribute to combined immunotherapy/chemotherapy being less effective and more costly than chemotherapy alone as first line treatment. After further consultation with CGP, EGP have removed the possible clinical scenarios to align with the removal of the upper bound reanalysis originally included in the initial report.

  Furthermore, this extrapolation was made based on a trial population that had the option of receiving nab-paclitaxel instead of paclitaxel. Nab-paclitaxel is not approved in Canada for the treatment of metastatic squamous NSCLC. Therefore, the treatment given to the trial population is not fully representative of the treatment that would be given to the corresponding (metastatic squamous NSCLC) patient population in Canada.

- **Time-to-death utilities:** It is unclear whether using utilities based on time-to-death gives a better measure of quality of life than utilities based on progression status. In its response to the EGP's request to justify use utilities based on time-to-death, the submitter said that this approach "more finely and completely captures declines in health-related quality of life over time relative to use of utilities for health states of progression-free and progressed disease." Since there is no direct evidence to verify this claim, the EGP conducted a probabilistic scenario analysis in which utilities were based on progression status. It was found that basing utilities on progression-status increased the ICER by 13% with respect to that of the submitted base case.

- **Scenario analyses:** The submitter's scenario analyses were evaluated deterministically rather than probabilistically. Although this may not be in compliance with CADTH HTA guidelines, deterministic scenario analyses have been accepted in previous reviews.

- **PSA uncertainty:** The submitter's PSA assumed that several standard errors were 20% of the corresponding parameter's base value, hence not reflecting the true parameter uncertainty. This is not in compliance with CADTH HTA guidelines.

- **A lack of direct comparative effectiveness estimates**: there were no head-to-head clinical trials comparing pembrolizumab + chemotherapy vs. pembrolizumab monotherapy for patients with TPS ≥ 50% included in this review. In addition, data from the KN024 trial (comparing pembrolizumab monotherapy against chemotherapy for metastatic NSCLC TPS ≥ 50% patients) were not used in this ITC (see Clinical Guidance Report). Constant hazard ratios (HR)/time varying HR were derived based on an indirect treatment comparison (ITC) based on KN407 with KN042. These hazard ratios were applied to the modeled OS and PFS curves for pembrolizumab + chemotherapy to derive the OS and PFS curves for pembrolizumab monotherapy. Confidence intervals around the estimated HRs were wide due to the limited sample size of the subsets of patients from KN407 (n=146) and KN042 (n=181) included in the ITC. The analysis may not be powered to demonstrate a statistically significant difference between pembrolizumab-chemotherapy and pembrolizumab monotherapy.

1.4 Detailed Highlights of the EGP Reanalysis

Pembrolizumab + chemotherapy vs. chemotherapy

To address these limitations, the EGP made the following changes to the model:

- **Subsequent therapies:** From the Canadian public healthcare perspective, nivolumab may not be available as a 2L therapy in Canada following 1L treatment with pembrolizumab. For this reason, the EGP opted to replace the submitter's base case post-discontinuation regimen, which included 2L nivolumab, with the submitter's scenario analysis, which excluded this option from the possible 2L therapies available to patients in the pembrolizumab + chemotherapy arm.

- **Modeling pembrolizumab + chemotherapy OS:** The EGP determined that the limitations associated with the use of SEER data in modeling overall survival beyond year 1 (see section 1.3) may lead to an overestimation of the improvement in OS in the pembrolizumab + chemotherapy arm. The EGP performed re-analyses using the OS estimates provided by the submitter that were based on extrapolations of KN407 OS data from week 19 onwards.

- **Extrapolation of efficacy data**: Alternative parametric fitting curves were explored by the EGP for both the chemotherapy and the pembrolizumab + chemotherapy arms to guide the derivation of the lower and upper bound estimates based on the submitted AIC and BIC information. The EGP used the best fitting (exponential) OS curve, in terms of AIC and BIC, to derive the lower bound for the reanalysis. This parametric fitting curve choice was identical to the submitter's base case extrapolation. Under these extrapolations, 5-year survival is around 8% in the pembrolizumab + chemotherapy arm and 3% in the chemotherapy arm.

  The EGP judged that the extrapolation of OS over a 9 year period from a 7.8 month median follow-up study is highly uncertainty. Therefore, in order to attempt to derive the upper bound of the reanalysis, the EGP conducted sensitivity analyses using log-logistic extrapolation curves. This class of curve was

identified by the submitter as the next best fitting parametric function “based on AIC and BIC criteria with visual inspection”.

It was found that by only changing the chemotherapy OS extrapolation from the best (exponential) extrapolation to the second best (log-logistic) extrapolation, and keeping best fitting (exponential) curve for the pembrolizumab + chemotherapy OS, the conclusion of the analysis would change. Specifically, such reanalysis predicts that pembrolizumab + chemotherapy treatment is dominated (more costly, less effective).

The submitter provided feedback on pERC’s Initial Recommendation disagreeing with the EGP’s upper-bound reanalysis for pembrolizumab + chemotherapy versus chemotherapy. Specifically, the submitter did not agree with the modification of the chemotherapy arm log-logistic extrapolation stating it would not be plausible that chemotherapy OS would overtake pembrolizumab + chemotherapy around week 182 given the within-trial trend in efficacy observed based on KM data for each arm The EGP further consulted with CGP regarding the upper bound scenario and clinical plausibility that chemotherapy OS would overtake pembrolizumab + chemotherapy around week 182. The CGP agreed that OS in the chemotherapy arm is unlikely to be greater than pembrolizumab + chemotherapy OS (i.e. the CGP do not believe that pembrolizumab + chemotherapy can be less effective than chemotherapy alone). The EGP also believe that the ICER will likely be closer to the lower bound of the reanalysis, and have thus decided to remove the upper bound of the reanalysis originally included in the initial economic guidance report. Due to the uncertainty generated from the extrapolation of OS from the short follow up period of 7.8 months, the EGP was not able to estimate the upper bound of the ICER. Moreover, there remains high uncertainty in the lower bound estimate as the choice of parametric extrapolation can impact the results.

Based on 5000 iterations, the EGP’s estimate of the ICER of pembrolizumab + chemotherapy vs. chemotherapy has a lower bound of $216,280/QALY. The upper bound is not estimable. See Table 4.

Table 4: Detailed Description of EGP Reanalysis for pembrolizumab + chemotherapy vs. chemotherapy

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs*	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	**$111,670**	**1.12 QALY**	1.41 LY	**$99,499/QALY**	--
[LOWER BOUND]					
Best extrapolation of OS for both arms	$106,600.48	0.49	0.62	$216,951.66	$117,452.66
No 2L anti-PD-1/PD-L1 therapy following pembrolizumab therapy in 1L	$113,609.10	1.11	1.41	$102,798.87	$3,299.87
Best case estimate of above 2 parameters	$106,271	0.49	0.62	$216,280	$116,781
The upper bound is not estimable.					
* Based on a deterministic reanalysis.					

Pembrolizumab + chemotherapy vs. pembrolizumab monotherapy among PD-L1>50% patients

To address the identified limitations, the EGP made the following changes to the model:

- **Subsequent therapies:** From the Canadian public healthcare perspective, nivolumab may not be available as a 2L therapy in Canada following 1L treatment with pembrolizumab. For this reason, the EGP opted to replace the submitter's base case post-discontinuation regimen, which included 2L nivolumab, with the submitter's scenario analysis, which excluded this option from the possible 2L therapies available to patients in the pembrolizumab + chemotherapy arm.

- **Modeling pembrolizumab + chemotherapy OS:** The EGP determined that the limitations associated with the use of SEER data in modeling overall survival beyond year 1 (see section 1.3) may lead to an overestimation of the improvement in OS in the pembrolizumab + chemotherapy arm. The EGP performed re-analyses using pembrolizumab + chemotherapy OS estimates provided by the submitter that were based on extrapolations of KN407 OS data from week 19 onwards. OS for the pembrolizumab monotherapy arm was estimated by scaling pembrolizumab + chemotherapy OS by the constant hazard ratio estimates used in the submitter's base case

- **Extrapolation of efficacy data:** Alternative parametric fitting curves were explored by the EGP for the pembrolizumab + chemotherapy arm to guide the derivation of the upper bound estimates. Among these, the best fitting (exponential) and the second-best fitting (log-logistic) parametric curves (based on reported AIC and BIC) for the pembrolizumab + chemotherapy overall survival were tested by the EGP. Based on probabilistic analyses, under both extrapolation scenarios the model predicted very similar incremental utilities and costs in the pembrolizumab + chemotherapy arm compared to the pembrolizumab monotherapy army, yielding ΔE=-0.07 QALY, ΔC=$9,340 and ΔE=-0.08 QALY, ΔC=$8,582 for the exponential and log-logistic extrapolations, respectively. As in the submitted base case, pembrolizumab + chemotherapy is dominated (more costly, less effective) under both of these extrapolations.

Based on 5000 iterations, the EGP estimates that pembrolizumab + chemotherapy is dominated (more costly but less effective) in both the lower bound and upper bound scenarios tested. See Table 5.

Table 5: Detailed Description of EGP Reanalysis for pembrolizumab + chemotherapy vs. pembrolizumab monotherapy among PD-L1>50% patients

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs*	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	11,180	-0.01	0.08	Pembrolizumab + chemotherapy is dominated (more costly, less effective)	--
[LOWER BOUND]					
Best extrapolated pembrolizumab + chemotherapy arm OS	$9,340.42	-0.07	0.05	Pembrolizumab + chemotherapy is dominated (more costly, less effective)	
No 2L anti-PD-1/PD-L1 therapy following pembrolizumab therapy in 1L	$8,219.38	-0.08	0.08	Pembrolizumab + chemotherapy is dominated (more costly, less effective)	
Best case estimate of above 2 parameters	$9,010	-0.07	0.05	Pembrolizumab + chemotherapy is dominated (more costly, less effective)	
[UPPER BOUND]					
Pembrolizumab + chemotherapy arm OS second best extrapolation	$8,582	-0.08	0.08	Pembrolizumab + chemotherapy is dominated (more costly, less effective)	
No 2L anti-PD-1/PD-L1 therapy following pembrolizumab therapy in 1L	$8,219.38	-0.08	0.08	Pembrolizumab + chemotherapy is dominated (more costly, less effective)	
Best case estimate of above 2 parameters	$8,252	-0.08	0.08	Pembrolizumab + chemotherapy is dominated (more costly, less effective)	
* Based on a deterministic reanalysis.					

1.5 Evaluation of Submitted Budget Impact Analysis

The BIA is that of the Canadian public health care system and estimated the overall three-year Canadian budgetary impact of reimbursing pembrolizumab for the 1L treatment of patients with metastatic squamous non-small cell lung cancer in combination with carboplatin and paclitaxel or nab-paclitaxel. Note that nab-paclitaxel is not approved in Canada for the treatment of metastatic squamous NSCLC.

The factors that most influence the budget impact analysis are the shape of the pembrolizumab combination uptake curve(which determines the rate at which the pembrolizumab combination captures market share with respect to competing treatments), the inclusion of patients at stage IIIb, the percentage of patients referred to medical oncologists, the percentage of patients treated by medical oncologists, the time to peak share of pembrolizumab in combination, and a modification of the dose intensity.

1.6 Conclusions

- The EGP's best estimate of ΔC and ΔE for pembrolizumab + chemotherapy when compared to chemotherapy alone is:
    - Lower bound ΔC = $106,271
    - Upper bound ΔC = unknown
    - Lower bound ΔE = 0.49
    - Upper bound ΔE = unknown

  These ranges produced a lower bound on the ICER of $216,280/QALY. The upper bound is not estimable.

- The submitter's estimate of the ΔC for pembrolizumab + chemotherapy vs. chemotherapy is $99,499. The main factor that influences the difference in ΔC is the extrapolated OS estimate, which predicts a shorter expected time during which patients receive pembrolizumab and hence lower drug acquisition costs. Specifically, under the submitter's base case estimated OS, the difference in expected time in the progression-free state is 10.21 months. In the EGP's reanalysis, this difference was revised down to 7.75 months.

  The submitter's estimate of the extra clinical effect of pembrolizumab + chemotherapy vs. chemotherapy is 0.63 QALYs greater than the EGP's estimate. The main factor causing this difference is the shortened estimated overall survival that is obtained when an extrapolation model is used for the OS.

- The EGP's best estimate of ΔC and ΔE for pembrolizumab + chemotherapy when compared to pembrolizumab monotherapy (among PD-L1>50% patients) is:
    - Lower bound ΔC = $9,010
    - Upper bound ΔC = $8,252
    - Lower bound ΔE = -0.07
    - Upper bound ΔE = -0.08

  Pembrolizumab + chemotherapy is dominated under both the lower bound and upper bound scenarios.

- The submitter's estimate of the ΔC for pembrolizumab + chemotherapy vs. pembrolizumab monotherapy is $11,180. The main factor that influences the difference in ΔC is the extrapolated OS estimate, which predicts a shorter expected time during which patients receive pembrolizumab and hence lower drug acquisition costs. Specifically, under the submitter's base case estimated OS, the difference in expected time in the progression-free state is 7.83 months. In the EGP's reanalysis, this difference was revised down to between 7.06 and 7.83 months.

- The submitter's estimate of the extra clinical effect of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy is between 0.08 and 0.09 QALYs greater than the EGP's estimate. The main factor causing

this difference is the shortened estimated overall survival that is obtained when an extrapolation model is used for the OS.

Overall conclusions of the submitted model:

- **Model Structure**
  - The economic model structure and the parametric extrapolation are appropriate. However, the model was not able to generate results for the potentially more clinically relevant comparison of pembrolizumab + chemotherapy for all patients regardless of TPS score vs the status quo, in which patients with TPS ≥ 50% receive pembrolizumab monotherapy and patients with TPS < 50% receive chemotherapy.
- **Data Inputs**
  - Extrapolating the overall survival up to 10 years creates significant uncertainty in total accumulated costs and utilities.
  - There are no direct trials to compare the clinically relevant treatment regimens for patients with PD-L1 TPS ≥ 50% (pembrolizumab + chemotherapy vs. pembrolizumab monotherapy). The effectiveness data used in the economic model were based on indirect treatment comparisons and efficacy assumptions.
- **Patient Inputs**
  - The factors relevant to patients were taken into consideration in the economic model.

- **Overall**
  The model structure and parametric extrapolation methodology are correct. However, it was difficult for the EGP to adequately assess the ICER of the pembrolizumab + chemotherapy vs. chemotherapy comparison due to a lack of long-term OS data. It was also difficult for the EGP to adequately assess the ICER for pembrolizumab + chemotherapy vs. pembrolizumab monotherapy due to a lack of a direct trial for comparison and due to the fact that the indirect treatment comparison was not adequately powered for statistical significance. It is of note that data from the KN024 trial, which compared pembrolizumab monotherapy against chemotherapy among TPS≥50% patients, was not included in the ITC.

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 Lung 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 for Squamous NSCLC. A full assessment of the clinical evidence of [drug name and indication] 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.

REFERENCES

Hatswell, A. J. et al., 2014. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. *Health Qual Life Outcomes,* Volume 12, p. 140.

Kim, A., Devine, B. & Roth, J. A., 2019. Cost-effectiveness of first-line pembrolizumab plus chemotherapy for metastatic squamous non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology,* 37(15_suppl), pp. e20703-e20703.

Paz-Ares, L. G. et al., 2018. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. *N Engl J Med,* Volume 379, pp. 2040-51.