CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pembrolizumab (Keytruda) Non-Small Cell Lung Cancer

August 23, 2017

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

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

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

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

TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

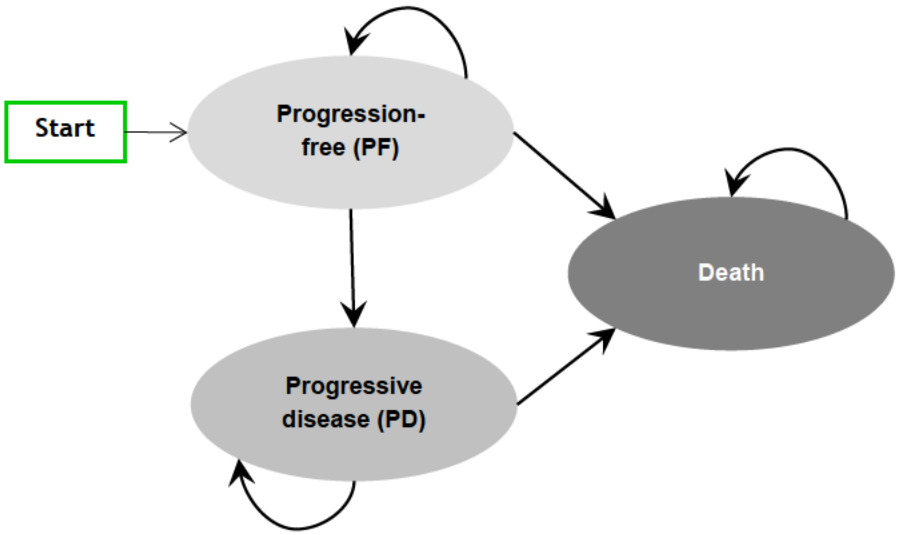
The economic analysis **submitted to pCODR by Merck Canada** compared pembrolizumab to platinum-based doublets for patients with previously untreated patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 ≥50%. Patients with EGFR sensitizing mutation and/or ALK translocation are excluded from the target population.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*The economic analysis matches with the funding request and the population in the trial.*
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival*
Comparator	*Standard of care, as defined by paclitaxel, carboplatin, pemetrexed, cisplatin, gemcitabine and other agents used in the Canadian setting*
Year of costs	*2016*
Time Horizon	*10 years*
Perspective	*Government*
Cost of pembrolizumab	• 200 mg every three weeks • $44.00 / mg • $8,800.00 / cycle of three weeks • $11,733.33 per 28-day course
Cost of standard of care: platinum-based doublet ** Price Source: IMS Brogan accessed March 3, 2017*	Based on weight of 70 kg and BSA 1.7m^2 Cisplatin + Pemetrexed • $2.70 per mg + $0.83 per mg At the recommended dose of cisplatin at 75 mg/m^2 every 21 days and pemetrexed at 500 mg/m^2 every 21 days, the cost is: • $50.06 per day • $1,401.67 per 28-day course Carboplatin + Pemetrexed • $1.33 per mg + $0.83 per mg At the recommended dose of carboplatin at AUC 5 or 6 every 21 days and pemetrexed at 500 mg/m^2 every 21 days, the cost is: • $65.33 per day • $1,829.32 per 28-day-course Cisplatin + Gemcitabine • $2.70 per mg + $0.22 per mg At the recommended dose of cisplatin at 75 mg/m^2 every 21 days and gemcitabine at

	1,250 mg/m^2 on days 1 & 8, every 21 days, the cost is: • $60.65 per day • $1,698.31 per 28-day course Carboplatin + Gemcitabine • $1.33 per mg + $0.22 per mg At the recommended dose of carboplatin at AUC 5 or 6 every 21 day and gemcitabine at 1,250 mg/m^2 on days 1 & 8, every 21 days, the cost is • $75.93 per day • $2,125.97 per 28-day course Carboplatin + Paclitaxel • $1.33 per mg + $0.19 per mg At the recommended dose of carboplatin at AUC 5 or 6 and paclitaxel at 200 mg/m^2 every 21 days, the cost is • $34.81 per day • $974.71 per 28-day course
Model Structure	*A three health state partitioned survival model where patients could transition at every one-week cycle. Patients begin in progression-free, and can move to either death, progressive disease or remain progression-free. Patients in progressive disease can move to death or remain in progression disease. See Figure 1.*
Key Data Sources	*Trial data from KN024* o *Note: overall survival data used in the economic model was taken from the second interim analysis after a median follow-up time of 11.2 months (May 9, 2016) and not the later data cut-off date after a median follow-up time of 19.1 months (January 5, 2017).*

Figure 1. Model structure as provided by the submitter



1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison with cisplatin-based regimens is appropriate.

- Relevant issues identified included:
  - There is a net clinical benefit for patients.
  - Follow-up period for economic model at data cut-off of May 9, 2016 (median 11.2 months) is shorter than the later data cut-off date of January 5, 2017 (median 19.1 months). The follow-up period of 11.2 months is relatively short due to the trial stopping early.
  - Cross-over was allowed in the key clinical trial informing the economic model (KEYNOTE-024). 43.7% of the patients crossed over to receive pembrolizumab, which may limit the reliability of the survival data. Cross-over was not adjusted for in the submitted base case for the economic model, but was assessed in scenario analyses provided by the submitter
  - In addition to improvements in survival, serious adverse events were less frequent with pembrolizumab and pembrolizumab also increased the time to deterioration in quality of life.
  - The evidence is robust that for patients with NSCLC without sensitizing mutations, pembrolizumab is superior to standard first-line chemotherapy.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered the current treatment for patients with previously untreated metastatic NSCLC was platinum doublet chemotherapy. Clinicians surveyed felt that pembrolizumab provides improved response rate over chemotherapy for patients with PD-L1 >50%, based on the population of the clinical trial. Clinicians felt that pembrolizumab had a superior adverse event profile to current standard of care chemotherapy. These factors were all considered in the economic model.

Summary of patient input relevant to the economic analysis
Patients considered a non-chemotherapy treatment as very important, due to the high burden of chemotherapy regimens with adverse events and quality of life. Patients also valued the disease control

offered by treatment and increase in quality of life. These factors are all considered in the economic analysis.

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

- The 200mg flat dose in KEYNOTE-024 can increase the dose and cost for some patients, when compared to the weight-based dose of 2mg/kg used in KEYNOTE-010. Using a combination of the 2 mg/kg and the flat dose, where appropriate to minimize cost, would be ideal.
- High cost of pembrolizumab.
- The need to conduct EGFR, ALK and PD-L1 testing at time on diagnosis to ensure appropriate treatment.

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)	1.23	1.20	0.84
Progression-free	1.52	0.77	0.77
Post-progression	-0.29	0.425	0.07
ΔE (QALY)	0.99	0.96	0.67
Progression-free	NC	NC	NC
Post-progression	NC	NC	NC
ΔC ($)	$98,298	$107,632	$103,406
ICER estimate ($/QALY)	$99,392	$111,769	$154,273

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

- The assumption of a 10-year time horizon was felt to be reasonable by the CGP, as this population is previously untreated and there is evidence to suggest that patients with previously untreated metastatic NSCLC may live as long as 10 years.
- The use of SEER data from year 5.5 onwards is a limitation as SEER data contains patients with EGFR+ and ALK+ patients who tend to live longer. Further, the median survival of US patients is not reflective of patients in the Canadian setting.
- The KEYNOTE-024 clinical trial allowed for cross-over from standard of care chemotherapy to pembrolizumab. This cross-over, however, was not adjusted for in the base case economic model.
- The economic model is based on a median duration of follow-up of 11.2 months (and not the later data cut-off of 19.2 months). This relatively short follow-up was extrapolated to a 10-year time horizon.
- Utilities in the economic model, as collected in the KEYNOTE-024, were pooled between the two treatment arms. This method was considered conservative by the CGP as pembrolizumab is less toxic compared to chemotherapy.

1.4 Detailed Highlights of the EGP Reanalysis

Overall the ICER is: higher than what the submitter reported by: $12,377 - $54,881 / QALY.

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

- PFS modeling of pembrolizumab: Though the Weibull curve had the lowest AIC and BIC for fit, upon visual inspection, a more realistic fit is the Generalised Gamma curve. This had the second lowest AIC, and the projection of those in the PFS beyond 5 years (close to no patients) was validated by the CGP. This is considered a conservative modeling approach using historical assumptions regarding 5 and 10 year PFS, given the lack of long-term data of patients on 1st line pembrolizumab.
- Use of SEER data beyond 5.5 years: SEER database may include patients beyond the scope of the population within the scope of the review. The use of SEER to control for modeling of overall survival beyond 5.5 years may overestimate the benefit of pembrolizumab on overall survival.
- Treatment effect of pembrolizumab: In the submitted base case, the treatment effect of pembrolizumab is modeled by OS projections. The EGP, with input from the CGP, felt that the treatment effect should gradually decline over time, reaching a hazard ratio of 1 at 260 weeks as a conservative upper bound best estimate.

Table 3. EGP Reanalysis Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	$99,298	0.99	$99,392	-----
EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
PFS modeling of pembrolizumab-Gamma curve	$107,796	0.99	$108,995	$9,603
No use of SEER data beyond 5.5 years for either treatment arm	$98,229	0.96	$102,005	$2,613
Best case estimate of above parameters	$107,632	0.96	$111,769	$12,377
UPPER BOUND				
PFS modeling of pembrolizumab-Gamma curve	$107,796	0.99	$108,995	$9,603
No use of SEER data beyond 5.5 years for either treatment arm	$98,229	0.96	$102,005	$2,613
No treatment effect of pembrolizumab beyond 260 weeks	$95,302	0.76	$125,430	$26,038
Best case estimate of all above parameters	$103,406	0.67	$154,273	$54,881

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis (increases the budget impact) include:

- Increasing the treatment rate to 10% from 5%;
- Not funding a 2L anti-PD-1;
- Increasing the treatment duration by 15%; and
- Increasing the PD-L1 testing rate by 10%

Key limitations of the BIA model include assumptions that are unknown, such as the impact of pembrolizumab on the treatment rate of patients and the treatment duration. These parameters were modified and explored by the EGP and impacted the magnitude of the BIA.

1.6 Conclusions

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

- Between $12,377/QALY and $54,881/QALY
- The extra cost of pembrolizumab is between $103,406 and $107,632 (ΔC). *The main factors that influence ΔC include the adjustment method for cross-over, the cost of pembrolizumab, and the population considered in the economic model treatment with pemetrexed).*
- The extra clinical effect of pembrolizumab is between 0.67 and 0.96 (ΔE). *The main factors that influence ΔE include the time horizon, the adjustment method for cross-over and the duration of treatment effect of pembrolizumab.*

Overall conclusions of the submitted model:

- *The submitter provided a well-designed, user-friendly, modifiable economic model. This allowed the EGP to examine various scenario analyses regarding assumptions for which no clinical evidence is available, such as treatment duration and long-term overall survival projections.*

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 NSCLC. A full assessment of the clinical evidence of pembrolizumab for NSCLC 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 pER pembrolizumab for NSCLC C 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

1. Reaume MN, Leighl NB, Mittmann N, et al. Economic analysis of a randomized phase III trial of gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer (Italian GEMVIN3/NCIC CTG BR14 trial). Lung Cancer. 2013;82(1):115-120

2. Goeree R, Villeneuve J, Goeree J, Penrod JR, Orsini L, Tahami Monfared AA. Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes. J Med Econ. 2016;19(6):630-644.

3. Verma S, Rocchi A. Economic evaluation of antiaromatase agents in the second-line treatment of metastatic breast cancer. Support Care Cancer. 2003;11(11):728-734.

4. Hellmann MD, Ma J, Garon EB, et al: Estimating long-term survival of PD-L1-expressing, previously treated, non-small cell lung cancer patients who received pembrolizumab in KEYNOTE-001 and -010. 2017 ASCO-SITC Clinical Immuno-Oncology Symposium. Abstract 77. Presented February 23, 2017.