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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

PEMBROLIZUMAB (KEYTRUDA)

(Merck Canada)

Indication:

For the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression [Combined Positive Score (CPS) ≥ 1] as determined by a validated test.

For the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

5-FU	platinum and fluorouracil
CPS	Combined Positive Score
CDR	CADTH Common Drug Review
fpNMA	fractional polynomial Network Meta-Analysis
HNSCC	head and neck squamous cell carcinoma
ICER	incremental cost effectiveness ratio
LY	life year
OS	overall survival
QALY	quality adjusted life year
R/M	metastatic or unresectable recurrent
SOC	standard of care

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Pembrolizumab (Keytruda), 100 mg vial
Submitted price	Pembrolizumab, 100 mg vial: $4,400
Indication	(i) For the first-line (1L) treatment of metastatic or unresectable recurrent (R/M) head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression [Combined Positive Score (CPS) ≥ 1] as determined by a validated test. (ii) For the 1L treatment of R/M HNSCC in combination with platinum and fluorouracil (5-FU) chemotherapy, in all adult patients.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	October 09, 2020
Reimbursement request	As per indication
Sponsor	Merck Canada Inc.
Submission history	Previously reviewed: Yes Pembrolizumab (Keytruda) has been reviewed for multiple indications at CADTH. The following indications were reviewed in 2020. Indication: for the treatment of patients with advanced renal cell carcinoma Recommendation date: April 2, 2020 Recommendation: recommended on the condition of cost-effectiveness being improved to an acceptable level. Indication: for the treatment of patients with metastatic squamous NSCLC Recommendation date: January 3, 2020 Recommendation: recommended on the condition of cost-effectiveness being improved to an acceptable level.

NOC = Notice of Compliance

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target populations	*Monotherapy:* Adult patients with R/M HNSCC whose tumours have PD-L1 expression (CPS ≥ 1) *Combination therapy:* All adult patients with R/M HNSCC
Treatments	*Monotherapy:* Pembrolizumab given alone (monotherapy) *Combination therapy:* Pembrolizumab + platinum (cisplatin/carboplatin) + 5-FU (combination therapy)
Comparators	• Platinum + 5-FU • Extreme regimen*:* cetuximab + platinum + 5-FU
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	15 years
Key data sources	KEYNOTE-048 trial and sponsor submitted fractional polynomial network meta-analysis (fpNMA) modelling relative efficacy of platinum + 5-FU to pembrolizumab
Submitted results for base case	*Monotherapy:* ICER = $68,875 per QALY vs platinum + 5-FU (ΔC = $68,744, ΔE = 0.9981 QALYs). Extreme regimen extendedly dominated. *Combination therapy:* ICER = $91,726 per QALY vs platinum + 5-FU (ΔC = $92,075, ΔE = 1.0038 QALYs). Extreme regimen extendedly dominated.
Key limitations	• The Extreme regimen is not a relevant comparator from a Canadian public health payer perspective, since cetuximab is not funded for this indication by participating plans. • The sponsor's preferred approach for extrapolating OS beyond the KEYNOTE-048 study resulted in an unrealistic number of patients still alive beyond 10 years. • The sponsor's base case analysis included no treatment effect waning. • The sponsor overestimated the number of patients receiving subsequent treatment. • The sponsor assumed that some patients would receive cetuximab as subsequent treatment following pembrolizumab. Since cetuximab is not funded in Canada for this indication, other (less expensive) subsequent treatments would be provided in Canadian clinical practice. • The sponsor's submitted Excel model was excessively complex. This reduced model transparency and made the task of validation difficult. Therefore, CADTH could not guarantee the model was free from error.
CADTH reanalysis results	• CADTH's reanalysis included the following changes: Extreme regimen removed as a comparator; exponential function used to extrapolate OS; 5-year treatment effect waning applied; number of patients receiving subsequent treatment reduced by 30%; and, subsequent treatment with cetuximab reallocated to platinum + 5-FU following treatment with pembrolizumab. • CADTH base case results: *Monotherapy:* ICER = $131,260 per QALY vs platinum + 5-FU (ΔC = $72,550, ΔE = 0.5527 QALYs) (1.9% of iterations below $50,000 per QALY) *Combination therapy:* ICER = $162,165 per QALY vs platinum + 5-FU (ΔC = $95,650, ΔE = 0.5898 QALYs) (0.6% of iterations below $50,000 per QALY) • For monotherapy and combination therapy an approximate price reduction of 49% and 67% respectively would be required to fall below a WTP threshold of $50,000 per QALY.

5-FU = platinum and fluorouracil, ICER = incremental cost-effectiveness ratio; LY = life-year; PSM = partitioned survival model; QALY= quality-adjusted life-year

Conclusions

CADTH undertook reanalyses to address several key limitations of the sponsor's model. CADTH's base case reanalysis included a more plausible extrapolation for long term OS, a consideration of 5 -year treatment effect waning, and a lower proportion of patients receiving subsequent treatment more closely aligned with that expected in Canadian practice. These corrections increased the ICER of pembrolizumab compared to the relevant comparator: platinum + 5-FU.

According to CADTH's reanalyses, the ICER for pembrolizumab monotherapy vs platinum + 5-FU in adult patients with R/M HNSCC whose tumours have PD-L1 expression (CPS ≥ 1) is $131,260 per QALY; while the ICER for pembrolizumab combination therapy vs platinum + 5-FU in all adult patients with R/M HNSCC is $162,165 per QALY. At a WTP threshold of $50,000 per QALY, a price reduction of 49% is required for pembrolizumab monotherapy to be cost-effective, while a price reduction of 67% is required for pembrolizumab combination therapy to be cost-effective.

It is important to note that CADTH was unable to address limitations stemming from the excessive complexity of the sponsor's model. As such, CADTH was unable to validate calculations in the model, and it is possible that further limitations exist beyond those identified , which may result in an underestimation of the true ICER for pembrolizumab.

Based on the sponsor's submitted BIA, the total incremental cost for reimbursement of pembrolizumab for R/M HNSCC is estimated to be [redacted] over three years. CADTH reanalysis suggests that the budget impact of introducing pembrolizumab to the market is underestimated, with the 3-year budget impact from the CADTH base case estimated at $151,370,606. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this economic information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 5: Submitted BIA and CADTH Appraisal

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

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