CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy)

(Bristol-Myers Squibb)

Indication: First-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no known EGFR or ALK genomic tumour aberrations.

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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

AIC	Akaike information criterion
ALK	anaplastic lymphoma kinase
BIC	Bayesian information criterion
DoT	duration on treatment
EGFR	epidermal growth factor receptor
ICER	incremental cost-effectiveness ratio
KM	Kaplan-Meier
LY	life-year
Mb	megabase
mg	milligram
NI+PDC	nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy
NSCLC	non-small cell lung cancer
OS	overall survival
PDC	platinum-doublet chemotherapy
PD-L1	programmed death ligand-1
PEM	pembrolizumab
PFS	progression-free survival
QALY	quality-adjusted life-year

Executive Summary

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

Table 1: Submitted for Review

Item	Description
Drug product	Nivolumab (Opdivo; single-use vial for injection), to be used in combination with ipilimumab (Yervoy; vial for injection) and two cycles of platinum-based chemotherapy
Submitted prices	Nivolumab, 10 mg per mL, solution: $19.55 per mg ($782.22 per 40 mg vial) Nivolumab, 10 mg per mL, solution: $19.55 per mg ($1955.56 per 100 mg vial) Ipilimumab, 5 mg per mL, solution: $116.00 per mg ($5800.00 per 50 mg vial)
Indication	Adult patients with metastatic non-small cell lung cancer (NSCLC) with no known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations and no prior systemic therapy for metastatic NSCLC.
Health Canada approval status	NOC
Health Canada review pathway	Other expedited pathway – Project Orbis
NOC date	August 6, 2020
Reimbursement request	As per indication
Sponsor	Bristol-Myers Squibb Company
Submission history	Previously reviewed: Yes (nivolumab plus ipilimumab) Indication: patients with intermediate or poor-risk advanced renal-cell carcinoma based on the International Metastatic Renal Cell Carcinoma Database Consortium Recommendation date: November 1, 2018 Recommendation: Recommended with a price reduction to improve the cost-effectiveness of nivolumab to an acceptable level. Previously reviewed: Yes (nivolumab plus ipilimumab) Indication: patients with unresectable or metastatic melanoma regardless of BRAF status who are treatment-naïve, with ECOG performance status 0 – 1 and with stable rain metastases, if present Recommendation date: November 30, 2017 Recommendation: Recommended with a price reduction to improve the cost-effectiveness of nivolumab to an acceptable level. Previously reviewed: Yes (nivolumab) Indication: adults with advanced or metastatic NSCLC who progressed on or after chemotherapy Recommendation date: June 3, 2016 Recommendation: Recommended with a price reduction to improve the cost-effectiveness of nivolumab to an acceptable level.

ALK = anaplastic lymphoma kinase; BRAF = gene mutation; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations
Treatments	Nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy (NI+PDC)
Comparators	• platinum-doublet chemotherapy (PDC) comprising carboplatin + paclitaxel for squamous histology, and for non-squamous histology, carboplatin + pemetrexed or cisplatin + pemetrexed • pembrolizumab in combination with PDC for non-squamous histology comprising carboplatin + pemetrexed or cisplatin + pemetrexed (PEM+PDC) • pembrolizumab monotherapy for programmed death ligand 1 (PD-L1) was greater than or equal to 50% (PEM) • pembrolizumab in combination with carboplatin + paclitaxel or nab-paclitaxel for squamous histology (PEM+CHEM)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data sources	CheckMate 9LA trial, CheckMate 227 trial, indirect treatment comparison (ITC; KEYNOTE trials: 189, 024, 042, 407)
Submitted results for base case	• Based on the sequential analyses, NI+PDC was more costly and produced more QALYs than PDC, PEM, and PEM+CHEM, but was less costly and produced fewer QALYs compared to PEM+PDC. • NI+PDC was extendedly dominated through PEM and PEM+PDC (i.e., treatment has a higher incremental cost-effectiveness ratio when compared to the previous cost-effective treatment and the next more effective treatment) • NI+PDC is not among the optimal therapies (i.e., not on the efficiency frontier)
Key limitations	• The CADTH Clinical Review identified several limitations with the sponsor-submitted ITC, and concluded that applicability of the ITC results must be interpreted with caution. As such, CADTH placed greater focus on the direct comparative data from CheckMate 9LA. • Duration on treatment (DoT) in the model was assumed to equal each treatment's PFS curve. Trial-observed DoT for each comparator and feedback from clinical experts consulted by CADTH indicated that PFS provides an overestimation of the duration on treatment. • For the first 13 months, Overall Survival (OS) was modeled based on time to mortality data from the CheckMate 9LA study, thereafter, a lognormal parametric function fitted to 37 months of data from CheckMate 227 was applied for the remainder of the 20 year time horizon. According to the CADTH Clinical Review, it is unclear whether outcomes for patients from CheckMate 227 can be generalized to represent long term treatment outcomes for patients in CheckMate 9LA. • A weight-based approach for nivolumab was applied based on the sponsor's assumed dosing regimen of 4.5 mg per kg along with an assumption of 5% vial sharing for nivolumab and ipilimumab. The modeled dosage and vial sharing assumption did not align with the nivolumab product monograph and led to an underestimation of the cost per dose of nivolumab. • The sponsor's assumed drug prices for the chemotherapy component across comparators were inaccurate as they did not reflect 2020 estimates from the IQVIA Delta PA database. • The sponsor's assumptions regarding drug wastage for ipilimumab (5 to 10% at large administration centers) was felt to be substantially underestimated for ipilimumab based on clinical expert and CADTH-participating drug plan feedback. • CADTH encountered analytic limitations with the sponsor's model which applied fixed time to event distributions that limit the ability to apply stochastic analysis to these curves, limiting CADTH's ability to perform scenario analyses or test the sensitivity of the model to variations in these distributions.

Component	Description
	• The sponsor did not include atezolizumab-based therapies as relevant comparators.

CADTH reanalysis results	• CADTH reanalyses included: the exclusion of the indirect comparators; using product monograph dosing for nivolumab; no vial sharing for nivolumab or ipilimumab; revised approach for modeling DoT; OS extrapolations exclusively based on CheckMate 9LA data; and revised drug prices for pemetrexed, cisplatin, carboplatin, and paclitaxel. CADTH was unable to address uncertainty associated with the sponsor's indirect treatment comparison, methodological limitations in the derivation of survival outcomes for select comparators, or the omission of relevant treatment comparators.
	  ○ NI+PDC vs. PDC: $146,239 per QALY (incr. costs, $73,063; incr. QALYs, 0.50)
	  ○ At a WTP threshold of $50,000 per QALY, NI+PDC had a 0% chance of being cost-effective. NI+PDC would require a price reduction of at least 28% to be considered cost-effective.
	• CADTH undertook a scenario analysis to estimate the cost-effectiveness of NI+PDC compared with PDC, PEM, PEM+CHEM, and PEM+PDC. Based on the sequential analyses, NI+PDC remained extendedly dominated through PEM and PEM+PDC.

ALK = anaplastic lymphoma kinase; DoT = duration on treatment; EGFR = epidermal growth factor receptor; incr. = incremental; ITC = indirect treatment comparison; LY = life-year; NI+PDC = nivolumab plus ipilimumab and two cycles of platinum-based chemotherapy; NSCLC = non-small cell lung cancer; OS = overall survival; PDC = platinum-doublet therapy; PD-L1 = programmed death ligand 1; PEM = pembrolizumab monotherapy; PEM+PDC = pembrolizumab plus platinum-doublet based chemotherapy, PEM+CHEM = pembrolizumab plus chemotherapy; PFS = progression-free survival; PSM = partitioned survival model; QALY= quality-adjusted life-year; vs. = versus

Conclusions

The clinical effectiveness of nivolumab plus ipilimumab in combination with platinum-doublet chemotherapy (NI+PDC) relative to other currently available treatments is limited to a direct comparison between NI+PDC and platinum-doublet chemotherapy (PDC), which suggests NI+PDC is associated with improved overall survival and progression-free survival. As there is currently no direct trial evidence that compares NI+PDC to current standards of care, specifically immunotherapy-based treatments, for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer with no known epidermal growth factor receptor or anaplastic lymphoma kinase genomic tumour aberrations, and no high-quality indirect evidence, the relative effectiveness of NI+PDC remains unknown.

CADTH undertook reanalyses to address limitations in the sponsor's submission, including: the exclusion of indirect comparators; using a dose for nivolumab per the product monograph; an assumption of no vial sharing for nivolumab or ipilimumab; revised approach for modeling DoT; and, OS extrapolations exclusively based on CheckMate 9LA data. According to the CADTH reanalysis comparing NI+PDC versus PDC, which was exclusively based on evidence from the CheckMate 9LA trial, NI+PDC was more costly (incremental cost, $73,063) and more effective (incremental QALYS, 0.50), yielding an incremental cost-effectiveness ratio of $146,239 per quality-adjusted life-year gained. A price reduction of 28% is required to achieve an ICER of $50,000 per QALY. CADTH also undertook a scenario analysis to estimate the cost-effectiveness of NI+PDC compared with PDC and other relevant comparators (pembrolizumab monotherapy, pembrolizumab plus chemotherapy, pembrolizumab plus platinum-based chemotherapy (PEM+PDC)) using the sponsor's indirect treatment comparison results. Based on a sequential analysis in this scenario; NI+PDC is extendedly dominated through PEM and PEM+PDC.

The cost-effectiveness for NI+PDC remains uncertain for patients with squamous histology, non-squamous histology, PD-L1 expression level ≥1%, or PD-L1 expression level <1%. However, NI+PDC is the most expensive treatment option available and is not likely to be considered cost-effective compared with the modeled comparators (i.e., PEM+PDC, pembrolizumab plus chemotherapy, pembrolizumab monotherapy, and PDC).

Based on the sponsor's submitted budget impact analysis, introducing NI+PDC was associated with an estimated cost saving of $7,663,351 over the first three years. CADTH reanalyses estimated that the budget impact of introducing NI+PDC for the modelled indication could range from a saving $83,230,349 in the first three years to an incremental cost of $20,508,252.

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.

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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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