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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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 f	
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 = nonsmall cell lung cancer

Type of economic evaluation Cost-utility analysis Partitioned survival model 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 (PCC) comprising carboplatin + pacifitaxel for squamous histology, and for non-squamous histology, carboplatin + pacifitaxel for squamous histology comprising carboplatin + pemetrexed or cisplatin + pemetrexed (PEM+PDC) • pembrolizumab in combination with PDC for non-squamous histology comprising carboplatin + pemetrexed or cisplatin + pemetrexed (PEM+PDC) • pembrolizumab in combination with carboplatin + pacifitaxel or nab-pacifitaxel for squamous histology (PEM+CHEM) • pembrolizumab in combination with carboplatin + pacifitaxel or nab-pacifitaxel for squamous histology (PEM+CHEM) • pembrolizumab in combination with carboplatin + pacifitaxel or nab-pacifitaxel for squamous histology (PEM+CHEM) • pembrolizumab in combination with carboplatin + pacifitaxel or nab-pacifitaxel for squamous histology (PEM+CHEM) • pembrolizumab in combination with carboplatin + pacifitaxel or nab-pacifitaxel for squamous histology (PEM+CHEM) • perspective Caradian publicly funded health care payer Outcomes QAL		y of Economic Evaluation
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indocardie as they did not relieve 2020 estimates notif the RAVIA Deita I A database.		 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. 		centers) was felt to be substantially underestimated for ipilimumab based on clinical expert and
 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. 		distributions that limit the ability to apply stochastic analysis to these curves, limiting CADTH's ability

Table 2: Summary of Economic Evaluation

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)
	 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

Economic Review

Appendix 1: Cost Comparison Table

Appendix 2: Submission Quality



Appendix 3: Additional Information on the Submitted Economic Evaluation



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



Appendix 5: Submitted BIA and CADTH Appraisal

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