pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Nivolumab (Opdivo) for Squamous Cell Carcinoma of the Head and Neck

August 31, 2017

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FUNDING

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by **Bristrol-Myers Squibb,** compared nivolumab (Opdivo) monotherapy with investigator's choice: **cetuximab, docetaxel, methotrexate** for the treatment of patients with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).

Table 1. Submitted Economic Model

Funding Request	Bristrol-Myers Squibb is requesting reimbursement for nivolumab for the treatment of patients with SCCHN with disease progression on or after platinum therapy. This aligns with the patient population that the economic model is built on.
Type of Analysis	Cost effectiveness and cost utility analysis
Type of Model	Partitioned-survival model
Comparator	Base-case analysis was performed for cetuximab, docetaxel and methotrexate.
Time Horizon	10 years
Perspective	Publicly funded health care system in Canada
Cost of nivolumab	Nivolumab costs $782.22 per 40mg vial or $1,955.56 per 100mg vial. • At the recommended dose of 3mg per kg every 2 weeks, the cost of nivolumab is: o $293.33 per day (no wastage) o $307.30 per day (with wastage) o $8213.35 per 28-day course (no wastage) o $8604.44 per 28-day course (with wastage)
Cost of docetaxel*	At the list price docetaxel costs $12.13 mg. • At the recommended dose of 40 mg/m^2 every week, docetaxel costs o $117.81 per day o $3298.68 per 28-day course
Cost of methotrexate*	At the list price methotrexate costs $8 per 25mg. • At the recommended dose of 60 mg/m^2 IV every week, methotrexate costs o $4.66 per day o $130.56 per 28-day course
Cost of cetuximab*	At the list price cetuximab costs $7.58 per 2mg • At the recommended dose of 250mg/m2 IV infusion once weekly, cetuximab costs: o $229.96 per day o $6,498.75 per 28-day cycle
Model Structure	The model was comprised of 3 health states: pre-progression, progression (or post-progression), and death. Transitions between these health states were driven by the CheckMate 141 trial, but the base-case survival benefits were based on parametric models.
Key Data Sources	The efficacy and safety parameters were based on the CheckMate 141 trial. Fully parametrical models were used to extrapolate

	survival beyond the trial period. It was an assumption that the OS benefit seen during the trial period can be extrapolated beyond the trial period.
**Drug costs for all comparators in this table are based on costing information under license from QuintilesIMS concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of QuintilesIMS. Price Soucre: IMS Delta PA accessed on June 5, 2017*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison between nivolumab group and investigators' choice is appropriate. Based on the available clinical evidence, the CGP concluded that

- there is a net clinical benefit to nivolumab in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck treated with evidence of cancer progression after at least one line of prior chemotherapy based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival as well as HRQoL benefit for nivolumab compared with investigators' choice of docetaxel, methotrexate, or cetuximab.
- Cetuximab is however not routinely available in Canada nor does it have regulatory approval in this setting
- Adverse event profiles were better for nivolumab than control chemotherapy.
- The Clinical Guidance Panel considered these results generalizable to patients with treated and controlled brain metastases, patients with controlled HIV and hepatitis B and C infection provided the infection was under control and treatment decision was at the discretion of their treating physician, patients with mucosal squamous cell carcinomas arising from any head and neck subsite (except EBER-positive nasopharynx and primary skin cancers), including those of slightly poorer performance status (ECOG 2), and those with multiple lines of prior chemotherapy.

Summary of registered clinician input relevant to the economic analysis
Registered clinician input was not received for this review.

Summary of patient input relevant to the economic analysis
Canadian Cancer Survivor Network (CCSN) provided input on nivolumab (Opdivo) for the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults.

From a patient's perspective, pain or discomfort, fatigue, trouble swallowing, sleep deprivation, depression affect their quality-of-life and the ability to enjoy life. As such, trouble swallowing, dry mouth, pain or discomfort, teeth problems, and fatigue are important symptoms of head and neck cancer that are most important to control for patients.

Therapies for head and neck include: cisplatin, radiotherapy + cetuximab, paclitaxel, carboplatin, carboplatin + paclitaxel, cisplatin + 5 FU (Fluorouracil), and cetuximab. Common side effects of current therapies include: fatigue, loss of appetite, hair loss, and constipation. Other reported side effects include: nausea, hypothyroidism, peripheral neuropathy, low blood count, trismus, and infection. Patient respondents indicated that they would like nivolumab to: reduce side effects from current medications/treatments, stop disease progression, better control symptoms, and have ease of use. According to CCSN, patients struggling with disease progression and uncertainly about the future are willing to tolerate fairly significant side effects.

According to CCSN, head and neck cancer patients are both physically and psychologically impacted by living with advanced cancer. CCSN reports that 51% of respondents experience pain

or discomfort and 42% of respondents experience fatigue. As well, a total of 72% of respondents experience trouble swallowing and 26% of respondents were sleep deprived and experience depression and 19% of respondents experience anxiety.

CCSN expressed that all of these problems and issues affect their quality-of-life and the ability to enjoy life.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation on nivolumab for Squamous Cell Carcinoma of the Head and Neck (SCCHN):

Clinical factors:

- Indication creep into first line setting and other types of head and neck cancers
- PAG identified that there is no standard of care for recurrent or platinum-refractory SCCHN. In most province, cetuximab is not funded as palliative treatment of platinum-refractory SCCHN. Single agent chemotherapy such as docetaxel, paclitaxel, methotrexate, gemcitabine, vinorelbine and etoposide is often used after platinum chemotherapy.

Economic factors:

- Indefinite treatment duration
- PAG noted that there is a small number of patients with refractory SCCHN.

1.3 Submitted and EGP Reanalysis Estimates

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

- Comparator: In summary, the key assumption that has the most impact on the results of the economic evaluation is the cost of treatment with cetuximab in the comparator arm of the base case results, which is not consistent with Canadian clinical practice. The potential cost impact of this treatment is important as it resulted in significantly underestimated ICER. The EGP was, however, able to modify this input in the model by excluding cetuximab from the investigators' choice arm. Nevertheless, the survival benefit obtained from the clinical trial included 15 patients (of the total of 121 patients) which received cetuximab, but based on input from the Clinical Guidance Panel, it is assumed that the inclusion of cetuximab in the clinical effect estimates will have a minimal impact on the global effect estimates.

- Time horizon: Another important factor was the time-horizon of 10 years which was considered to be too long by the CGP and EGP, as patients with this condition have a median survival of less than 10 months. Additionally, there is an uncertainty related to the magnitude of long term benefit, between nivolumab and investigators' choice, which is unknown and cannot reasonably be estimated. The submitted model allowed the EGP to evaluate the impact of this factor.
- Utilities: Furthermore, the CGP and EGP agreed that the utilities used in the submitted model were overestimated, as the inputs used are higher than utilities seen in similar patients with this condition. The model allowed the EGP to perform several re-analyses around utilities.
- Duration of treatment: The CGP and EGP noted uncertainty related to the duration of treatment with nivolumab as the trial allowed for patients to be treated beyond progression. Furthermore, uncertainty remained related to subsequent therapy utilization and duration of subsequent therapy. The EGP was able to provide a reanalysis calculating treatment cost based on time to treatment discontinuation. The submitted model however did not allow the EGP to conduct re-analysis for the other factors.

- Nivolumab Dosing: In other indications, nivolumab is administered at a flat dose of 240 mg. Although there is currently no evidence to support the use of a flat dose, the CGP acknowledged that, in the future and where appropriate, a similar approach may be adopted for the current indication under review. The EGP therefore conducted one way sensitivity analysis based on the flat dose of 240mg, which corresponds to an average body weight of 80kg at 3mg/kg. Other average body weights were also tested to explore the impact of body weigh on the ICER and the EGP agreed this factor has a major impact on ICER. These analysis can be found in the detailed report.
- Overall survival: Finally, the survival benefit was estimated using fully parametric models. The submitter retained that parametric models were appropriate. While the model provided by the submitter did allow the EGP to change the parametric estimation method, it did not allow for other strategies, such as using the KM curve for the duration of the trial followed by the use of parametric modeling after the study end date. Ultimately, the model assumes that survival benefit observed during the trial period will be maintained during the extrapolation period. Using a shorter time horizon period decreases the impact of this assumption.
- The EGP performed several re-analyses and these results are presented in Table 2 and 3.

Table 2. Submitted and EGP Reanalysis Estimates

Estimates	Submitted	EGP Reanalysis (Docetaxel)		EGP Reanalysis (Methotrexate)		EGP Combined Re-Reanalysis[#]	
		Lower bound	Upper bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
ΔE (LY)	0.60	0.35	0.48	0.35	0.48	0.35	0.48
ΔE (QALY)	0.456	0.23	0.34	0.23	0.34	0.23	0.34
ΔC ($)	$27,988*	$33,802	$37,682	$41,403	$45,283	$37,602	$41,483
ICER estimate ($/QALY)	$61,411*	$109,743	$145,855	$131,880	$178,654	$120,811	$162,255

*The submitted results are based on an average of the ICER's derived from each comparison (i.e docetaxel, methotrexate and cetuximab).
[#] Combined analysis is composed of a comparison using docetaxel and methotrexate.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:
The following re-analyses have been performed by varying components of the model and were significant drivers of either the incremental effect or the incremental cost, such as survival, utilities and cost.

1. EGP noted that in the submitted model, the inclusion of cetuximab as a treatment choice, led to an overestimation of the cost of drug treatments in the comparator arm; with high impact on ΔC. As such, all the EGP re-analyses excluded this treatment option. In addition, as only 15 patients (of the total of 121 patients) received cetuximab the impact on survival estimates was minimal, and no further reanalyses were performed that included cetuximab.
2. The submitted model used a time horizon of 10 years. The CGP and EGP considered such a time horizon to be excessive for a population with a median survival of less than 10 months from first line treatment (Vermorken JB et al 2008). Additionally, one of the main assumption of this model was related on maintaining of the observed survival benefit between nivolumab and investigators' choice (from the trial) over the duration of the extrapolation. Using a shorter time horizon period decreases the impact of this assumption.

3. In patients with other conditions, nivolumab is available at a flat dose of 240 mg. CGP and EGP considered that this may also be considered appropriate for SCCHN patients, as such, re-analyses have been performed using the flat dose of 240mg for nivolumab.
4. Several re-analyses have been performed to reflect uncertainty related to the utility values. EGP noted that in the submitted model, treatment-specific utilities were derived from the trial, yet based on the CGP, the EGP considered these utilities (overall utilities: 0.789 responders and stable disease and 0.718 progressed disease; and treatment-specific utilities: nivolumab group: 0.789 responders; 0.789 stable disease; 0.718 progressed disease; investigators' choice group: 0.763 responders; 0.763 stable disease; 0.659 progressed disease) to be high for this specific population. As such, the EGP considered 2 re-analyses: 1) use of the same treatment-specific utilities as the comparator group for nivolumab group, except for the responsive disease state. In this state, the utilities were: 0.798 for nivolumab and 0.763 for comparator; 2) replacing PD utility value with 0.53, as reported in other studies (1, 2).
5. A reanalysis was performed to assess impact of treatment cost. As such, time to treatment curve was used to determine the treatments' cost was calculated based on the duration of treatment equal to the time to treatment discontinuation, as opposite to the calculation of the treatment duration equal to PFS.
6. Several parametric models have been tested by the EGP to test the impact of the choice of parametric distribution for PFS and OS on the ICURs. Yet, a small impact of this factor was observed on the ICURs.
7. The final three parameters used for lower bound and upper bound were: time-horizon (2nd point), utilities (4th point) and duration of treatment (5th point).

Following the posting of the pERC initial recommendation and receipt of feedback from eligible stakeholders, the submitter provided feedback on a number of re-analyses conducted by the EGP. First the submitter disagreed with the EGP's use of a 3 year time horizon in the estimation of the upper bound of the EGP's re-analysis estimates. The EGP in consultation with the CGP used a shorter time horizon because patients who progress after cisplatin-based chemotherapy are not expected to have prolonged survival. In addition, using parametric survival models for overall survival, the simulated proportion of patients still alive at 3 years is 11.8% and 2.0% in the nivolumab and the investigator's choice groups, respectively. Therefore, both the CGP and EGP agreed that a conservative model, based on a 3-year time horizon is appropriate.

The submitter also commented on the use of time to treatment discontinuation instead of the PFS curves to model the duration of treatment within the EGP's re-analysis. Given that patients could be treated with nivolumab beyond disease progression, the CGP supported the use of time to treatment discontinuation in the EGP's re-analyses.

Lastly, the submitter challenged the EGP's choice of utility estimates in its re-analysis which included a 10% reduction in the utilities used for the comparator group. To address the submitter's comment, the EGP conducted a literature review to identify utility values for this population. Two references on head and neck cancer patients were found, Noel CW et al 2015, Kularatna S et al 2016. Both reported values using the EQ-5D method. A 3rd reference was found with utility values for patients with squamous and non-squamous non–small cell lung cancer (NSCLC) that had been previously been treated with cisplatin-based chemotherapy, Chouaid C et al 2013. It was felt that the utilities for this patient population would be very similar to those of the recurrent SCCHN population. (Chouaid C et al 2013) Again, these utilities were generated with the EQ-5D and Canadian patients were included in this study. The EGP conducted a re-analysis using 0.53 as the utility value for the PD state. This value is the average of the utility values reported by Kularatna et al. in stage 3 and 4 SCCHN patients, and the same as the average utility values reported by Chouaid et al. in 2nd and 3rd/4th line PD NSCLC patients. The EGR was thus modified to

account for this change and the results are presented below. Notably, the results are not much changed from what was previously presented (upper range of EGP`s ICER increased by about $3.1K).

Table 3: Detailed Description of EGP Reanalysis				
	ΔC	ΔE	ICER	Δ from baseline submitted ICER
Submitted Base Case Results				
Baseline (Nivolumab vs. cetuximab)	$14,109	0.456	$30,957/QALY	----
Baseline (Nivolumab vs. docetaxel)	$30,816	0.456	$67,616/QALY	----
Baseline (Nivolumab vs. methotrexate)	$39,039	0.456	$85,661/QALY	----
Baseline (Nivolumab vs. combined cetuximab, docetaxel and methotrexate)	$27,988	0.456	$61,411/QALY	----
Key One-Way Sensitivity Analysis - Average body weight of 80Kg corresponding to a flat dose of 240 mg (3mg/kg)				
Flat dose (nivolumab vs docetaxel)	$37,183	0.46	$81,587	$20,176
Flat dose (nivolumab vs methotrexate)	$45,407	0.46	$99,631	$38,220
LOWER BOUND - Nivolumab vs. Docetaxel				
Time horizon 5 years	$28,098	0.37	**$75,996**	$14,585
Utilities (0.798 nivolumab; 0.763 comparator in responsive state)	$30,816	0.42	**$72,948**	$11,537
Duration of treatments calculated as time to treatment discontinuation	$40,950	0.46	**$89,853**	$28,442
Best case estimate of above 3 parameters	$37,682	0.34	$109,743	$48,332
LOWER BOUND - Nivolumab vs. Methotrexate				
Time horizon 5 years	$36,321	0.37	**$98,239**	$36,828
Utilities (0.798 nivolumab; 0.763 comparator in responsive state)	$39,039	0.42	**$92,414**	$31,003
Duration of treatments calculated as time to treatment discontinuation	$48,551	0.46	**$106,531**	$45,120
Best case estimate of above 3 parameters	$45,283	0.34	$131,880	$70,469
UPPER BOUND - Nivolumab vs. Docetaxel				
Time horizon 3y	$24,903	0.28	**$89,223**	$27,812
Utilities : PD utility = 0.53 in both nivolumab and comparator group	$30,816	0.36	$84,706	$23,295
Duration of treatments calculated as time to treatment discontinuation	$40,950	0.46	**$89,853**	$28,441

Best case estimate of above 3 parameters	$33,802	0.23	$145,855	$84,444
UPPER BOUND - Nivolumab vs. Methotrexate				
Time horizon 3y	$33,126	0.28	**$118,687**	$57,276
Utilities : PD utility = 0.53 in both nivolumab and comparator group	$39,039	0.36	$107,311	$45,900
Duration of treatments calculated as time to treatment discontinuation	$48,551	0.46	**$106,531**	$45,120
Best case estimate of above 3 parameters	$41,403	0.23	$178,654	$117,243

1.5 Evaluation of Submitted Budget Impact Analysis

The BIA was based on the Canadian healthcare perspective. The factors that most influence the budget impact analysis include the estimated market share as well as the proportion of patients eligible to receive nivolumab. Particularly, cetuximab had the majority of market share in reference scenario, which was considered inaccurate in the Canadian health care system. As cetuximab is not publicly reimbursed in Canada for this population, the EGP reanalysis considered the cetuximab market share to be 0% in both scenarios. The submitter provided several sensitivity analyses with difference market share for nivolumab, yet because of cetuximab's large reference market share the presented results are inaccurate. In the re-analysis, the EGP considered that docetaxel and methotrexate would have nearly half of the market share in reference scenario. In the treatment funded scenario, nivolumab would have half the market share, while docetaxel and methotrexate will share the other half. Based on this, the budgetary impact over 3 years will be almost double the submitter' estimate. Other market share scenarios were considered by the EGP which revealed small deviation.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for Nivolumab when compared to investigator's choice is:

- Between $120,811/QALY to $162,255/QALY. The EGP further notes that this range is uncertain given that the magnitude of long term benefit, between nivolumab and investigators' choice is unknown and cannot reasonably be estimated. The EGP anticipates that this is likely to have the biggest impact on the ICER.
- Within the provided range, the best estimate would likely be $162,255/QALY, which corresponds to the scenario with a time horizon of 3 years, utility values in the PD state derived from a literature review, and the duration of treatment equal to the time to treatment discontinuation. The EGP anticipates that this is likely to be higher if the flat dose of 240mg were adopted for this population.
- The extra cost of nivolumab is between $37,602 and $41,483. The duration of treatment is an important factor and when combined with a flat dose of 240mg, would result in an even higher cost.
- The extra clinical effect of nivolumab is between 0.23 QALY and 0.34 QALY. The factors that influence the clinical effectiveness are the time horizon and utility value in the PD state.

Overall conclusions of the submitted model:
Though the submitted model included many appropriate assumptions, the use of cetuximab as a treatment in the comparator arm was an important assumption that was not consistent with Canadian clinical practice. The potential impact of this treatment is important as the ICER was significantly

underestimated, as a result of its significant cost. Another important factor was the time-horizon which was considered to be excessive by CGP and EGP, as patients in this setting have a median survival of less than 10 months. Particularly, when the long-term benefit between nivolumab and investigators' choice is uncertain, as its unknown and cannot reasonably be estimated. The submitted model allowed the EGP to evaluate the impact of these two factors. Additionally, the CGP and EGP noted uncertainty related to the duration of treatment with nivolumab as the trial allowed for patients to be treated beyond progression. The EGP was able to provide a reanalysis calculating treatment cost based on time to treatment discontinuation, as opposite to the assumption that treatment duration is equal to PFS. Finally, nivolumab is currently used as a flat dose (240mg) for patients with other conditions. Based on CGP input, the EGP explored the impact of flat dosing in the current review. For the SCCHN patients this corresponds to an average body weight of 80kg at 3mg/kg, and the EGP agreed this had a large impact on the cost of nivolumab as well as the ICER.

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 Lymphoma/Myeloma 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-utility of Nivolumab for patients with recurrent or metastatic, squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum therapy. A full assessment of the clinical evidence of nivolumab compared with alternative treatments 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.

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