pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Nivolumab (Opdivo) for Non-Small Cell Lung Cancer

June 3, 2016

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Bristol-Myers Squibb** compared nivolumab to docetaxel (primary comparator) and to erlotinib and pemetrexed (secondary analysis) for squamous and non-squamous patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have failed at least one chemotherapy regimen. Two economic evaluations were conducted: 1) squamous NSCLC patients; and 2) non-squamous NSCLC patients. Pemetrexed is a comparator only for the non-squamous NSCLC population.

Table 1. Submitted Economic Model	
Nivolumab for the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have failed at least one prior platinum-based chemotherapy treatment.	*This is aligned with the two patient populations modelled: squamous and non-squamous NSCLC populations.*
Type of Analysis	*Cost Utility Analysis and Cost Effectiveness Analysis*
Type of Model	*Partitioned-survival model with 3 health states: progression free, progressed disease and death. These were used for the re-analysis estimates provided by the pCODR Economic Guidance Panel (EGP) in this report.* *To deal with structural uncertainty, the manufacturer also provided 2 Markov models (one for squamous NSCLC and one for non-squamous NSCLC)*
Comparator	*The primary comparator is docetaxel, which was compared to nivolumab in two head-to-head randomized clinical trials (Checkmate 017: squamous NSCLC patients; and Checkmate 057: non-squamous NSCLC patients).* *Erlotinib and pemetrexed for non-squamous NSCLC patients and erlotinib for squamous NSCLC patients were also compared to nivolumab based on indirect treatment comparisons.* *The Clinical Guidance Panel (CGP) did not consider erlotinib as an appropriate comparator as erlotinib is only relevant to a small sub-set of NSCLC patients.*
Time Horizon	*10 years (base case)*
Perspective	*Government*
Cost of nivolumab	*Nivolumab costs $782.22 per 40mg vial or $1,955.56 per 100mg vial.* • *At the recommended dose of 3 mg/kg of body weight every 2 weeks, nivolumab costs* o *$293.33 per day (no wastage)* o *$335.24 per day (with wastage)* o *$8213.35 per 28-day course (no wastage)* o *$9386.68 per 28-day course (with wastage)*

Cost of docetaxel*	*Docetaxel costs $11.42 per mg. (Cost is for both generic and brand name docetaxel)* • *At the recommended dose 75 mg/per m^2 every 3 weeks, docetaxel costs* o *$69.36 per day* o *$1,942.00 per 28-day cycle*
Cost of erlotinib*	*Erlotinib costs $68.00 per tablet.* • *At the recommended dose 150mg once daily, erlotinib costs* o *$68.00 per day* o *$1,904.00 per 28-day cycle*
Cost of pemetrexed*	*Brand Name pemetrexed costs $5.50 per mg.* • *At the recommended dose 500mg/m^2 every 3 weeks, pemetrexed costs* o *$222.62 per day* o *$6,233.33 per 28-day cycle* *Generic pemetrexed costs $0.83 per mg.* • *At the recommended dose 500mg/m^2 every 3 weeks, pemetrexed costs* o *$33.67 per day* o *$942.66 per 28-day cycle*
Model Structure	*This partitioned survival model was comprised of three health states: progression free; progressed disease and death. Trial data were extrapolated over time using statistical distributions.*
Key Data Sources	• *Two head-to head phase III clinical trials (Checkmate 017 and Checkmate 057) to compare nivolumab and docetaxel in terms of efficacy, impact on health-related quality of life, adverse events, and to derive treatment patterns after progression.* • *Indirect treatment comparisons to derive PFS and OS associated with other comparators (e.g. pemetrexed and erlotinib)* • *Utility data based on EQ-5D collected in Checkmate 017 and Checkmate 057; literature-based utility data used in sensitivity analyses* • *Resource utilization from the UK and expert opinion* • *Costing from Ontario and literature*
**Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. 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 IMS Health Canada Inc.*	

1.2 Clinical Considerations

According to the **pCODR Clinical Guidance Panel (CGP)**, the comparisons versus docetaxel and pemetrexed are appropriate.

- Relevant issues identified included:
  - The CGP did not consider erlotinib to be a relevant comparator as it has an increasingly limited clinical use in this patient population.

- Although the manufacturer provided an indirect treatment comparison of nivolumab versus pemetrexed, the CGP concluded that there was a high degree of uncertainty with the results due to several limitations in the analyses (see Section 7 of the Clinical Guidance Report for details). Therefore, the EGP did not provide re-analysis estimates for this secondary analysis.
- The CGP was uncertain as to the clinical benefit of continuing treatment beyond progression which occurred in nearly 20% of patients in both studies. The CGP did however acknowledge that treatment beyond progression should be done at the discretion of the treating physician. The EGP explored the impact of treatment beyond progression in their re-analysis estimates by using data from the two clinical trials.

Summary of patient input relevant to the economic analysis

Patients considered the following factors important in the review of nivolumab: improvement in quality of life and survival, better side effects profile, convenience of use, and fewer treatment visits reducing the burden for patient and care provider.

- The economic model submitted by the manufacturer takes into account quality of life, progression free survival and overall survival as well as adverse events.
- Convenience of use (e.g. 1 hour treatment every 2 weeks with nivolumab instead of 3-6 hours every 3 weeks) was not incorporated in the model.
- As per pCODR guidelines, the perspective of the model was that of the publicly funded healthcare system and did not consider patient or caregiver time costs.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for nivolumab: size of the eligible population, generalizability of the trial data and factors related to dosing, drug wastage, the high cost of nivolumab, indication creep and the potential for future indications.

- PAG expressed some concerns regarding the generalizability of the trials (Checkmate 017 and Checkmate 057) as the trials only included patients with ECOG performance status 0 and 1 who were previously treated with platinum-based doublet chemotherapy. However, the CGP was comfortable in generalizing the results to patients with ECOG 2 performance status. As such the economic results should also apply to this population.
- PAG expressed concerns that some cancer centres with a large number of NSCLC patients may not have the resources to accommodate the more frequent administration of nivolumab compared to docetaxel. This was not addressed in the economic model or the budget impact analysis (BIA).
- PAG also expressed concerns for the incremental costs due to drug wastage. This is addressed in the economic model and the BIA where an option for drug wastage is available.
- PAG expressed concerns regarding the treatment duration associated with nivolumab which ranged from 1 to 48 months in the trials. Although the base case model assumes that patients discontinue treatment after disease progression, a sensitivity analysis was performed by the manufacturer based on treatment duration.
- PAG mentioned that some smaller outpatient cancer centres may not have the expertise and resources to administer nivolumab or treat serious adverse events. This was not addressed in the economic model or the BIA.
- Finally, PAG noted that the high cost of nivolumab and large potential budget impact will be barriers to implementation. PAG noted that nivolumab is undergoing trials for other tumor sites.

1.3 Submitted and EGP Reanalysis Estimates

The main assumptions and limitations, in no order of importance, with the submitted economic evaluation were:

- **Extrapolation of PFS and OS using short term data:** Using trial data the manufacturer extrapolated PFS and OS over a time horizon of 10 years. Based on the feedback of the Clinical Guidance Panel, previous pCODR analyses of pemetrexed for maintenance therapy in NSCLC, and compared to other published economic evaluations (Jakael et al. 2013, Greenhalgh et al. 2015), a 5-year time horizon is deemed more appropriate for this population.
- **Treatment duration:** The base case analyses assume that treatment duration is determined by length of PFS. However, 21% patients in Checkmate 017 and 24% of patients in Checkmate 057 continued nivolumab treatment after progression for a mean duration of 2.9 months and 2.8 months, respectively.
- **Utility data:** The utility data associated with progression free (PF) and progressed disease (PD) considered in the manufacturer's base case analyses were collected in Checkmate 017 (PF = 0.789 and PD = 0.674) and Checkmate 057 (PF = 0.784 and PD = 0.748) for the squamous and non-squamous NSCLC populations, respectively. Similar to other cancer trials, these utility data, for which details have not yet been published, are characterized by a relatively low completion rate of the EQ-5D (e.g. percentage of patients with EQ-5D baseline data and at least one post-baseline visit ranging from 64% to 72% in Checkmate 017) and potential self-selection bias (e.g. patients continuing to complete their EQ-5D after disease progression may have better health status than those not completing the EQ-5D). In particular, the utility values associated with PD are relatively high compared to other published utility data for NSCLC (Nafees et al. 2008, Chouaid et al. 2013 and Lewis et al. 2010). Due to the uncertainty associated with the utility data derived from Checkmate 017 and Checkmate 057, the EGP considered that the base case analyses should be based on a range of different set of utility values: 1) trial data; and 2) published data. Although utility values of Nafees et al (2008) were used by the manufacturer (PF = 0.673 and PD = 0.473), the EGP used data from Chouaid et al (2013) for their re-analyses as these utilities were generated with the EQ-5D, Canadian patients were included in this study, and the data are presented by line of therapy (i.e. PF utility value associated with 2nd line of 0.74 and PD utility value associated with 3rd line/4th line of 0.46).
- **Body weight and body surface area (BSA):** The manufacturer uses, in the base case, an average body weight of 70 kg and a BSA of 1.7 m^2 rather than using the weight and BSA recorded in the trials (e.g. for Checkmate 017: mean body weight of 75.2 kg and mean BSA of 1.87 m^2).
- **Drug wastage:** The manufacturer base case analysis assumes no drug wastage. As mentioned by the Provincial Advisory Group (PAG), vial sharing may not always be possible. Dose is based on weight and there are two vial sizes available to help address drug wastage. Pharmacist opinion estimated that wastage will generally be low in the range of 5-10% in large centres. 10% was used as the basis for ECP re-analyses.

Table 2. Submitted base case and EGP re-analysis estimates of the ICER for the squamous population and Non-squamous populations.

Squamous population		
Estimates (compared to docetaxel)	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate ($/QALY), range/point	$151,560	$193,918 and $219,660
ΔE (QALY), range/point	0.66	0.44 and 0.50
ΔE (LY), range/point	0.82	0.60
ΔC ($), range/point	$100,168	$96,431
Non-squamous populations		
Estimates (compared to docetaxel)	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate ($/QALY), range/point	$133,520	$183,386 and $236,851
ΔE (QALY), range/point	0.64	0.34 and 0.44
ΔE (LY), range/point	0.78	0.52
ΔC ($), range/point	$84,918	$80,014

While pemetrexed is a relevant comparator, the CGP noted considerable uncertainty in the results of the indirect comparisons of nivolumab versus pemetrexed. Given the limitations and great uncertainty in the results presented through the indirect comparisons for nivolumab versus pemetrexed, the EGP did not provide re-analysis estimates for this comparison. The submitter, however, incorporated these estimates of effectiveness based on indirect treatment comparisons and provided cost-effectiveness estimates for nivolumab versus erlotinib and for nivolumab versus pemetrexed. Please see details on a critical appraisal of the presented network meta-analysis in Section 7 of the Clinical Guidance Report.

EGP Reanalysis

Squamous NSCLC

The **pCODR Economic Guidance Panel (EGP)** made the following changes to the model provided by the manufacturer for the squamous NSCLC population:

- Restricting model time horizon to 5 years
- Assuming 10% drug wastage
- Increasing nivolumab treatment duration to reflect that 21% of patients enrolled in Checkmate 017 received nivolumab for a mean duration of 2.9 months following disease progression
- Using average body weight (75.2 kg) and BSA (1.87 m^2) observed in Checkmate 017
- Due to the uncertainty associated with the utility data, 2 sources were used by the EGP. These were utility data derived from the trial and utility data based on Chouaid et al. 2013 (utility of 0.74 for PF and 0.46 for PD)
- All of the above inputs were used for the EGP's re-analysis estimates. Due to the uncertainty associated with the utility data, a range for the best estimate was calculated based on the two sources for utility data (i.e. trial versus literature)

Table 3: Detailed Description of EGP Reanalysis - Squamous NSCLC

	ΔC	ΔE	ICER	Δ from baseline submitted ICER
Baseline (Submitter's best case): nivolumab versus docetaxel	$100,168	0.66	$151,560/QALY gained	--
EGP Reanalysis				
1. Restricting model time horizon to 5 years	$85,543	0.50	$172,023	$20,463
2. Assuming 10% drug wastage	$101,427	0.66	$153,464	$1,904
3. Increasing nivolumab treatment duration to reflect that 21% of patients continued nivolumab treatment after initial progression for 2.5 months or 5 doses (versus an average 2.9 months as per trial data)	$104,408	0.66	$157,975	$6,415
4. Using mean weight (75.2 kg) and BSA (1.87 m^2) from trial rather than assuming a body weight of 70 kg and a BSA of 1.7 m^2	$106,805	0.66	$161,602	$10,042
5. Using alternative published source of utility data based on Chouaid et al. (utility of 0.74 for PF and 0.46 for PD)	$100,168	0.57	$175,531	$23,971
EGP's lower bound estimate combining re-analyses 1, 2, 3, 4 and utility data from Checkmate 017	$96,431	0.50	$193,918/QALY gained	$42,358
EGP's upper bound estimate combining re-analyses 1, 2, 3, 4 and 5 (using utility data from Chouaid et al. 2013)	$96,431	0.44	$219,660/QALY gained	$68,100

Non-squamous NSCLC

The EGP made the following changes to the model provided by the manufacturer for the non-squamous NSCLC population:

- Restricting model time horizon to 5 years
- Assuming 10% drug wastage
- Increasing nivolumab treatment duration to reflect that 24% of patients enrolled in Checkmate 057 received nivolumab for a mean duration of 2.8 months following disease progression
- Using average body weight (72.7 kg) and BSA (1.82 m^2) observed in Checkmate 057
- Due to the uncertainty associated with the utility data, 2 sources were used by the EGP. These were utility data derived from the trial and utility data based on Chouaid et al. 2013 (utility of 0.74 for PF and 0.46 for PD)
- All of the above inputs were used for the EGP's re-analysis estimates. Due to the uncertainty associated with the utility data, a range for the best estimate was calculated based on the two source for the utility data (i.e. trial versus literature)

Table 4: Detailed Description of EGP Reanalysis – Non-squamous NSCLC

	ΔC	ΔE	ICER	Δ from baseline submitted ICER
Baseline (Submitter's best case): nivolumab versus docetaxel	$84,918	0.64	$133,520/QALY gained	--
EGP REANALYSES				
1. Restricting model time horizon to 5 years	$71,839	0.44	$164,651	$31,131
2. Assuming 10% drug wastage	$85,961	0.64	$135,161	$1,641
3. Increasing nivolumab treatment duration to reflect that 24% of patients continued nivolumab treatment after initial progression for 2.5 months or 5 doses (versus an average 2.8 months as per trial data)	$89,802	0.64	$141,201	$7,681
4. Using mean weight (72.65 kg) and BSA (1.82 m^2) from trial rather than from assuming weight of 70 kg and BSA of 1.7 m^2	$87,663	0.64	$137,837	$4,317
5. Using alternative published source of utility data based on Chouaid et al. (utility of 0.74 for PF and 0.46 for PD)	$84,918	0.48	$177,000	$43,480
EGP's lower bound estimate combining re-analyses 1,2, 3, 4 and using utility data from Checkmate 057	$80,014	0.44	$183,386/QALY gained	$49,866
EGP's upper bound estimate combining re-analyses 1, 2, 3, 4 and 5 (using utility data from Chouaid et al. 2013)	$80,014	0.34	$236,851/QALY gained	$103,331

1.4 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the size of the population, treatment duration associated with nivolumab, cost of nivolumab and drug uptake.

1.5 Conclusions

For the squamous NSCLC population, the lower and upper bounds of the EGP's best estimate of ΔC and ΔE for nivolumab when compared to docetaxel are:

- $193,918/QALY gained (lower bound) and $219,660/QALY gained (upper bound)
- The extra cost of nivolumab is $96,431. The factors that most influence the incremental costs compared to docetaxel are time horizon and nivolumab duration of treatment.
- Depending on the source of the utility data, the extra clinical effect of nivolumab is 0.44 QALYs (Chouaid et al., 2013) or 0.50 QALYs (trial data). The factors that most influence the incremental number of QALYs are time horizon and the utility values associated with disease free and progressed disease.

For the non-squamous NSCLC population, the lower and upper bounds of the EGP's best estimate of ΔC and ΔE for nivolumab when compared to docetaxel is:

- $183,386/QALY gained (lower bound) and $236,851/QALY gained (upper bound)
- The extra cost of nivolumab is $80,014. The factors that most influence the incremental costs compared to docetaxel are time horizon and nivolumab duration of treatment.
- Depending on the source of the utility data, the extra clinical effect of nivolumab is 0.34 QALYs (Chouaid et al. 2013) or 0.44 QALYs (trial data). The factors that most influence the incremental number of QALYs are time horizon and the utility values associated with disease free and progressed disease.

Overall conclusions of the submitted model:

- The model was well designed and short-term model projections were validated against trial data.
- The above EGP base case estimates are driven by the trial data (e.g. PFS and OS), a time horizon of 5 years and choice of utility data.
- Future research should focus on providing additional details: 1) the utility data associated with progression free and progressed disease from a Canadian perspective; 2) drug wastage; and 3) treatment patterns following progression.

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 Nivolumab (Opdivo) for Non-Small Cell Lung Cancer. A full assessment of the clinical evidence of Nivolumab (Opdivo) for Non-Small Cell Lung Cancer 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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