



# pan-Canadian Oncology Drug Review Final Economic Guidance Report

## Nivolumab (Opdivo) for Metastatic Melanoma

April 1, 2016

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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Background

This is a review of nivolumab for patients with advanced metastatic melanoma. The submitter originally submitted an economic analysis that compared nivolumab against ipilimumab, dabrafenib+trametinib, dacarbazine and vemurafenib for the first line treatment of patients with metastatic melanoma. However, upon the request of pCODR's Provincial Advisory Group (PAG), revision of review scope may be considered by pCODR in very limited instances, based on jurisdictional input, feasibility to conduct the revised review and clinical importance. An expansion of scope was considered for the use of nivolumab monotherapy for the treatment of patients with previously treated metastatic melanoma.

### *Nivolumab Monotherapy for Previously Treated Advanced Melanoma*

All three criteria for scope modification were met in this case and the scope of the review was expanded to include patients with previously treated advanced melanoma. The economic analysis for the treatment of patients with previously treated disease was provided by Bristol-Myers Squibb through this process.

Below we provide separate reviews for the first and second line submissions.

### Nivolumab for Previously Untreated Advanced Melanoma

The economic analysis submitted to pCODR by Bristol-Myers Squibb compared nivolumab to ipilimumab, dabrafenib+trametinib, dacarbazine and vemurafenib for patients with previously untreated metastatic melanoma. No distinction based on BRAF mutation was made in the patient population for nivolumab (although the treatment comparator would, for some treatments, vary depending on BRAF mutation status). Nivolumab (3mg/kg every 2 weeks), ipilimumab (3mg/kg every 3 weeks) and dacarbazine (1000mg/m<sup>2</sup> every 3 weeks) are administered intravenously, while vemurafenib (960mg oral twice daily), dabrafenib (150mg twice daily) and trametinib (2mg once daily) are administered orally. Based on the advice of the Clinical Guidance Panel (CGP) that dacarbazine is no longer a relevant comparator, and the lack of direct evidence comparing nivolumab with dabrafenib+trametinib and vemurafenib, we did not conduct any scenario analyses for these treatments. In addition, the CGP indicated that pembrolizumab is likely to become an important comparator for this population; however, no direct randomized controlled trial evidence currently exists comparing pembrolizumab with nivolumab. Therefore it was also not considered in any scenario analysis.

**Patients** considered the following factors as important for the review of nivolumab which could be relevant for the economic analysis: milder side effects compared to existing therapies, reduction of the progression of the disease and improved survival. Side effects and symptoms that were also considered important were anxiety, fear, depression and gastrointestinal issues. The patients providing input also stressed the importance of having access to an effective medication once other medications are no longer effective. Input provided by patient advocacy groups also noted the burden on caregivers, which was however not taken into account in the submitted economic analysis.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for nivolumab:

- According to the PAG the comparison with dacarbazine is inappropriate as it is no longer used in clinical practice for first line treatment of metastatic melanoma.

- PAG provided input on the necessity for direct comparisons of the effectiveness and cost-effectiveness of alternative treatments in metastatic melanoma.
- The PAG also stressed the importance of a guidance strategy for metastatic melanoma.
- PAG mentioned that the administration process for nivolumab (once every two weeks) and the length of treatment (until disease progression) may be important barriers in implementation.
- Wastage, training on the use on the new treatment, lower incidence of side effects, and the high cost of nivolumab are all factors that need to be addressed in the model, based on the PAG input.

Drug wastage and drug related costs were addressed in the model. Nivolumab is available in 40mg vials with a cost of \$782.22 or 100mg vials with a cost of \$1,955.56 and when administration costs are taken into consideration the cost is 19.56 per mg. At the recommended dose of 3mg/kg once every 14 days and by taking wastage into consideration, the average cost per 28-day course is \$8,604 or \$2,151 per week. Sensitivity analysis was conducted around the absence of wastage.

Ipilimumab costs \$5,800 and \$23,200.00 per 50 mg and 200mg vials, respectively. At the recommended dose of 3 mg/kg every 3 weeks, the cost of ipilimumab is \$9,667 per weekly cycle. This cost includes the cost of wastage. Vemurafenib weekly cost for a dose of 960mg was \$2,606, while dabrafenib and trametinib were \$1,773 and \$2,030 for doses of 150mg and 2mg/kg respectively.

### Nivolumab for Previously Treated Advanced Melanoma

The economic analysis submitted by Bristol-Myers Squibb for the treatment of patients with previously treated advanced melanoma compared nivolumab to investigator's choice of chemotherapy (dacarbazine or paclitaxel+carboplatin). No distinction based on BRAF mutation was done in the patient population. Nivolumab, dacarbazine, carboplatin, and paclitaxel are all administered intravenously.

According to the **pCODR Clinical Guidance Panel (CGP)** the comparisons were appropriate.

Drug wastage and drug related costs were addressed in the model. Nivolumab is available in 40mg vials with a cost of \$782.22 or 100mg vials with a cost of \$1,955.56 and when administration costs are taken into account the cost is 19.56/mg. At the recommended dose of 3mg/kg once every 14 days and by taking wastage into consideration, the average cost per 28-day course is \$8,604.

Dacarbazine costs \$190 per 600mg vial and on a dosing regimen of 1000mg/m<sup>2</sup> every 3 weeks the average cost per 28 day course is \$1,012. Paclitaxel costs \$325 per 30mg vials and on a dosing regimen of 175mg/m<sup>2</sup> every 3 weeks, the average cost per 28 day course is \$4,768. Finally carboplatin costs \$231 per 150mg vials and on a dosing regimen of 700mg/m<sup>2</sup> every 3 weeks the average cost per 28 day course is \$2,772. The submitter assumed that 56% of the control group would be using carboplatin-paclitaxel combination, while the rest would be on dacarbazine.

## 1.2 Summary of Results

### Nivolumab for Previously Untreated Advanced Melanoma.

The EGP's best estimate of the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) is between \$120,851/QALY and \$198,776/QALY when nivolumab is compared with ipilimumab in previously untreated advanced melanoma patients.

However, the EGP considers that there is a large degree of uncertainty around the estimates of clinical effectiveness for nivolumab due to assumptions regarding overall survival (see note following the section on EGP reanalyses, below).

The incremental cost-effectiveness ratio was based on an estimate of the extra cost ( $\Delta C$ ) and the extra clinical effect ( $\Delta E$ ). The EGP's best estimate of:

- the extra cost of nivolumab is between \$104,067 and \$145,608 ( $\Delta C$ ). The main factors influencing estimates of cost were the drug costs, the assumptions regarding survival, time horizon and the time to treatment discontinuation.
- the extra clinical effect of nivolumab is between 0.515 and 0.893 QALYs ( $\Delta E$ ). The main factors affecting the clinical effect estimates were the sources of evidence for overall survival, and the assumptions made in the extrapolation of the benefit in a lifetime horizon.

The estimates provided by the EGP are based on the model submitted by Bristol-Myers Squibb Canada and reanalyses conducted by the EGP. The EGP modified inputs related to time to treatment discontinuation, time horizon, cost of treatment alternative, and the input source of and modelling approach to overall survival.

In particular:

- The EGP assumed that treatment discontinuation in the nivolumab arm will follow a similar pattern as that observed in the Checkmate-067 trial [1], which randomized patients with previously untreated advanced melanoma to treatment with nivolumab, ipilimumab, or nivolumab plus ipilimumab. This was considered by the CGP as a more reasonable alternative to the submitter's assumption of treatment until disease progression. Hence, under the EGP's assumption a number of patients would likely continue with treatment even after disease progression. The justification of this assumption is related to the mechanism underlying the effect of immunotherapies whereby some patients may experience "pseudoprogression," which would technically meet the RECIST criteria for disease progression, but would not be true disease progression. When this modification is made, the extra cost and effect of nivolumab is \$123,608 and 0.861 QALYs, resulting in an increase in the ICER to \$143,564/QALY
- In addition to the assumption above, the EGP assumed treatment discontinuation for ipilimumab will follow the same pattern as in the Checkmate-067[1], where patients could be discontinuing treatment with ipilimumab before they reach the full 4 doses. When this modification is made, the extra cost and effect of nivolumab is \$125,670 and 0.861 QALYs, resulting in an increase in the ICER to \$145,937/QALY.

The two modifications above were considered essential for the model to be realistic and were therefore carried over throughout the modifications below.

- Time to treatment discontinuation in the previous two scenarios was assumed to follow a lognormal distribution. The EGP assessed the sensitivity of the economic analysis on this assumption by applying a log-logistic distribution to extrapolate the time to treatment discontinuation. With this modification, the extra cost and effect of nivolumab is \$117,551 and 0.857 QALYs respectively, resulting in an increase in the ICER to \$137,150/QALY.
- Overall survival data from the CheckMate 067 trial [1] were not mature by the time of the submission and therefore the submitter relied on other sources to inform the estimates for overall survival. In particular, for short-term estimates of overall survival, the economic analysis used data from the KEYNOTE 006 trial, which compared pembrolizumab to ipilimumab as first-line therapy for patients with metastatic melanoma. Long-term survival for the nivolumab and the ipilimumab arms was based on a study by Schadendorf et al [2] which indicated that overall survival with ipilimumab seems to plateau over longer follow up times. The short term data on survival from the KEYNOTE 006 trial[3] on the use of pembrolizumab, which was used as proxy for nivolumab, were not considered by the EGP as enough to justify the assumption made by the submitter that nivolumab (or pembrolizumab) would have a similar pattern of long-term mortality as ipilimumab. A conservative estimate was made where the EGP assumed a distribution with a decreasing pattern of survival such as the log-logistic distribution. When this modification is made, the extra cost and effect of nivolumab is \$122,350 and 0.615 QALYs, resulting in an ICER of \$198,776/QALY.
- Similar to previous submissions in advanced melanoma, the EGP made the assumption that the time horizon of 20 years is too long given the uncertainties around the model parameters. The EGP instead relied on a time horizon of 10 years which in previous submissions (ipilimumab, pembrolizumab) has been considered a good balance between uncertainty and a longer-term horizon. When this modification is made, the extra cost and effect of nivolumab is \$103,186 and 0.603 QALYs with an ICER of \$171,189/QALY
- A combination of the reduced time horizon and the assumption of a log-logistic distribution for the extrapolation of overall survival was made by the EGP. When both modifications were made, the extra cost and effect of nivolumab was \$102,154 and 0.515 QALYs resulting in an ICER of \$198,232/QALY
- Ipilimumab is being adopted currently by most of the provinces for first-line treatment of metastatic melanoma. However, as per pERC's recommendation at the time of evaluation of ipilimumab a significant improvement in the cost-effectiveness should be achieved by the provinces through price negotiations. The EGP made the assumption that provinces have succeeded in negotiating a 20% discount on ipilimumab, similar to assumptions made in previous pCODR reviews (pembrolizumab). When this modification is made, the extra cost and effect of nivolumab is \$145,608 and 0.861 QALYs with an ICER of \$169,091/QALY
- In addition to the scenario above, the EGP assumed that provinces will be successful in negotiating a 20% discount on nivolumab, similar to ipilimumab. When this assumption is made, the extra cost and effect of nivolumab is \$104,067 and 0.861 QALYs, resulting in an ICER of \$120,851/QALY

- Utility estimates from the Checkmate 066 trial [4], which compared nivolumab to dacarbazine in patients with previously untreated advanced melanoma, were used for the estimation of QALYs in the base case of the economic study. The Checkmate-066 study [4] was a multinational study with patients primarily from Europe, Canada and Latin America. Transferring utilities from other jurisdictions to Canada is likely to result in bias. To investigate the effect of such bias we assumed utilities from the Canadian population by using the Hogg et al 2010 study utility values. The Hogg et al[5] study has estimated the utility for patients with metastatic melanoma to be overall lower to that identified in the CheckMate-066 Study[4] (i.e. both in the progression free and post-progression states). When this modification is made, the extra cost and effect of nivolumab is \$125,670 and 0.893 QALYs with an ICER of \$140,756/QALY
- Note that due to the structure of the model submitted, a change in the time to treatment discontinuation has an effect on both the estimates of incremental costs and QALYs gained. That is associated with an assumed longer period in the progression-free state and therefore an increase in QALYs. To adjust for that we used the information on time to treatment discontinuation only for the estimation of costs. This resulted in extra cost and effect of \$125,670 and 0.852 QALYs with an ICER of \$147,500/QALY.
- Due to the uncertainty around overall survival we assumed that the evidence from the CheckMate 067 RCT [1] is the best source for extrapolation of survival in both treatment arms. We therefore fitted a parametric distribution to the CheckMate 067[1] data and extrapolated the survival probability over the whole time horizon (20 years). When this modification is made, nivolumab is associated with extra costs and effects of \$124,586 and 0.777 QALYs with an ICER of \$160,382/QALY.

The EGPs estimates differed from the submitted estimates.

**NOTE:** The most important component of model uncertainty is the assumption regarding overall survival. In particular, overall survival estimates that originated from the KEYNOTE-006 RCT, which compared pembrolizumab with ipilimumab as first line therapy of advanced melanoma. That RCT does not include nivolumab as a treatment alternative and the submitter assumed that the overall survival data for pembrolizumab is directly applicable to nivolumab. The EGP does not consider this an appropriate methodology and the extent of uncertainty around this assumption, although difficult to quantify, is very large.

According to the economic analysis that was submitted by Bristol-Myers Squibb, when nivolumab is compared with ipilimumab:

- the extra cost of nivolumab is \$80,234( $\Delta C$ ). Costs considered in the analysis included cost of treatment, administration costs, and adverse event management costs.
- the extra clinical effect of nivolumab is 0.852 QALYs ( $\Delta E$ ). The clinical effect considered in the analysis was based on extension of overall survival and utility improvements.

So, the Submitter estimated that the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) was \$94,176/QALY [ $\Delta C / \Delta E$ ]

The submitter also provided estimates of cost-effectiveness for nivolumab compared to vemurafenib, dacarbazine, and dabrafenib+trametinib for first line treatment of advanced melanoma. However, given the lack of direct comparative data, the limited use of some of these comparators in practice (e.g. dacarbazine), the EGP did not provide re-analysis estimates for these comparisons.

### Nivolumab for Previously Treated Advanced Melanoma.

The EGP's best estimate of the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) is between \$62,673/QALY and \$159,936/QALY when nivolumab is compared with investigator's choice of chemotherapy (ICC) in patients with previously treated advanced melanoma.

However, the EGP considers that there is a large degree of uncertainty around the estimates of clinical effectiveness for nivolumab relative to ICC due to the assumptions regarding overall survival (see note following the section on EGP reanalyses, below).

The incremental cost-effectiveness ratio was based on an estimate of the extra cost ( $\Delta C$ ) and the extra clinical effect ( $\Delta E$ ). The EGP's best estimate of:

- the extra cost of nivolumab is between \$108,921 and \$177,351. The main factors influencing estimates of cost were the drug costs, the assumptions around survival, time horizon and the time to treatment discontinuation
- the extra clinical effect of nivolumab is between 0.841 and 2.145 QALYs ( $\Delta E$ ). The main factors affecting the clinical effect estimates were the sources of evidence for overall survival, and the assumptions made in the extrapolation of the benefit in a lifetime horizon.

The EGP based these estimates on the model submitted by Bristol-Myers Squibb Canada and reanalyses conducted by the EGP. The EGP modified inputs related to time to treatment discontinuation, time horizon, cost of treatment alternative, source and modelling approach of overall survival.

In particular:

- The EGP assumed that treatment discontinuation in the nivolumab arm will follow a similar pattern as that observed in the Checkmate-037 trial [6], which compared nivolumab to investigator's choice of chemotherapy in patients with previously treated advanced melanoma. This was considered by the CGP as a more reasonable alternative to the submitter's assumption of treatment until disease progression. Hence, under the EGP's assumption a number of patients would likely continue with treatment even after disease progression. The justification of this assumption is related to the mechanism underlying the effect of immunotherapies whereby some patients may experience "pseudoprogression," which would technically meet the RECIST criteria for disease progression, but would not be true disease progression. When this modification is made, the extra cost and effect of nivolumab is \$177,351 and 2.145 QALYs, resulting in an increase in the ICER to \$62,673/QALY

- In addition to the assumption above the EGP assumed treatment to discontinuation for ICC will follow the same pattern as in the Checkmate-037[6]. When this modification is made, the extra cost and effect of nivolumab is \$176,659 and 2.145 QALYs, resulting in an increase in the ICER to \$82,350/QALY.

**The two modifications above were considered essential for the model to be realistic and were therefore carried over throughout the modifications below.**

- Time to treatment discontinuation in the previous two scenarios was assumed to follow a lognormal distribution. The EGP assessed the sensitivity of the economic analysis on this assumption by applying a log-logistic distribution to extrapolate the time to treatment discontinuation. When this modification is made, the extra cost and effect of nivolumab is \$173,786 and 2.144 QALYs respectively, resulting in an increase in the ICER to \$81,044/QALY
- Recent evidence from the CheckMate 066 trial[4] indicate that the two-year probability of treatment discontinuation remains high and decreases at a lower rate over time for treatment-naïve advanced melanoma patients. The submitted model might underestimate time to treatment discontinuation because it assumes a reduction that is steeper than observed in the CheckMate 066 trial [4]. The EGP adjusted the probability of PFS in such a way that better reflects the observed trend of PFS in the CheckMate-066 trial [4]. When this modification is made, the extra cost and extra effect of nivolumab is \$263,875 and 2.169 QALYs, resulting in an increase in the ICER to \$121,650/QALY
- Overall survival data were not mature by the time of submission and therefore the submitter relied on external sources of overall survival. In particular, the economic analysis used overall survival estimates from the CheckMate-066 trial [4], which compared nivolumab to ICC in patients with previously untreated advanced melanoma. Long term survival for nivolumab was based on a study by Schadendorf et al [2] which indicated that overall survival with ipilimumab seems to plateau over longer follow up times. The short term data on survival from the CheckMate 066 trial on the first-line use of nivolumab, which was used as a proxy for second- or later-line nivolumab, were not sufficient to justify an assumption that nivolumab in the second- or later-line would have a similar pattern of long-term mortality as ipilimumab . A conservative estimate was made where the EGP assumed a distribution with a decreasing pattern of long-term survival such as the log-logistic distribution. When this modification is made, the extra cost and effect of nivolumab is \$165,292 and 1.332 QALYs, resulting in an ICER of \$124,076/QALY.
- A combination of the reduced time horizon and the assumption of a log-logistic distribution for the extrapolation of overall survival was made by the EGP. When both modifications were made, the extra cost and effect of nivolumab was \$111,725 and 0.841 QALYs resulting in an ICER of \$132,809/QALY
- A combination of the reduced time horizon and the assumption of treatment discontinuation probability that follows the same trend as that of CheckMate 066[4] was made by the EGP. When both modifications were made, the extra cost and effect of nivolumab was \$141,819 and 0.887 QALYs resulting in an ICER of \$159,936/QALY
- Similarly to previous submissions in advanced melanoma, we made the assumption that the time horizon of 20 years is too long given the uncertainties around the model input parameters. We instead relied on a time horizon of 5 years which in previous submissions has been considered a good balance between uncertainty and long-time horizons in second/third line therapies in advanced melanoma. When this

modification is made, the extra cost and effect of nivolumab is \$111,902 and 0.879 QALYs with an ICER of \$127,297/QALY

- The Checkmate 037 utility estimates were used for the estimation of QALYs in the base case of the economic study. The Checkmate-037 study was a multi-national study with patients primarily from Europe, Canada and Latin America. Transferring utilities from other jurisdictions to Canada is likely to result in bias. To investigate the effect of such bias we assumed utilities from the Canadian population by using the Hogg et al study utility values from 2010. The Hogg et al study[5] has estimated the utility for patients with metastatic melanoma to be overall lower to that identified in the CheckMate-066 Study (i.e. both in the progression free and post-progression states)When this modification is made, the extra cost and effect of nivolumab is \$177,351 and 1.874 QALYs with an ICER of \$94,626/QALY
- Note that due to the structure of the model submitted, a change in the time to treatment discontinuation has an effect on both the estimates of incremental costs and QALYs gained. That is associated with an assumed longer period in the progression-free state and therefore an increase in QALYs. To adjust for that, the EGP used the information on time to treatment discontinuation only for the estimation of costs. This resulted in extra cost and effect of \$177,351 and 2.12QALYs with an ICER of \$83,656/QALY.
- Due to the uncertainty around overall survival, we assumed that the evidence from the CheckMate 037 RCT [6] is the best source for extrapolation of survival in both treatment arms. We therefore fitted a parametric distribution to the CheckMate 037[6] data and extrapolated the survival probability over the whole time horizon (20 years). When this modification is made, nivolumab is associated with extra costs and effects of \$169,030 and 1.591QALYs with an ICER of \$106,231/QALY.

The EGPs estimates differed from the submitted estimates.

**NOTE:** The most important component of model uncertainty is the assumptions regarding overall survival. In particular, short-term overall survival estimates originated from the CheckMate-066 RCT, which compared nivolumab with ICC for first line therapy of advanced melanoma. The data from this first-line RCT were used to inform the effectiveness of nivolumab versus ICC in second/third line therapy. This assumption was based by the submitter on an earlier study suggesting that the line of therapy is not an effect modifier in advanced melanoma. However, this was a study published before the introduction of novel immunotherapies. The EGP does not consider this an appropriate methodology and the extent of uncertainty around this assumption, although difficult to quantify, is very large. However, the EGP acknowledges recent studies pointing towards the effectiveness of nivolumab regardless of previous treatment with ipilimumab (e.g. Johnson et al 2015[7]).

According to the economic analysis that was submitted by Bristol-Myers Squibb, when nivolumab is compared with ICC:

- the extra cost of nivolumab is \$108,921( $\Delta C$ ). Costs considered in the analysis included cost of treatment, administration costs, and adverse event management costs.
- the extra clinical effect of nivolumab is 2.12 QALYs ( $\Delta E$ ). The clinical effect considered in the analysis was based on extension of overall survival and utility improvements.

So, the Submitter estimated that the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) was \$51,295/QALY [ $\Delta C / \Delta E$ ]

### 1.3 Summary of Economic Guidance Panel Evaluation

**If the EGP estimates of  $\Delta C$ ,  $\Delta E$  and the ICER differ from the Submitter's, what are the key reasons?**

The EGP estimates for incremental cost, for both previously untreated and previously treated patients, differ from those of the submitter mainly due to differences in the assumption of treatment duration by the EGP in the main analysis. In addition, more conservative assumptions regarding the short- and long-term overall survival had a profound effect on the estimates for incremental effectiveness and incremental cost in the economic analysis.

**Were factors that are important to patients adequately addressed in the submitted economic analysis?**

Most factors important to patients were addressed. Side effects were taken into account in the model, the impact on progression free and overall survival was considered and the impact of the disease on quality of life was incorporated through the utility estimates. The health-related burden of the disease on the caregivers was not incorporated.

**Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?**

Yes, the design and structure of the economic model was adequate. However, the assumptions and sources of data were considered inadequate by the EGP. The EGP requested additional data and made adjustments to the submitted model to ensure more robust assumptions and more realistic scenarios for treatment duration, survival, dosing, and drug price.

**For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?**

The most important effect for which the EGP made adjustments was that associated with time to treatment discontinuation. The original assumption by the submitter was that once patients are progressing, physicians will terminate the treatment. However, there is evidence internally within the nivolumab trials as well as from other studies in the literature that response can occur after disease progression. For that reason the EGP relied on time to treatment discontinuation rather than time to progression as a measure of treatment duration.

Additionally, the time horizon assumed by the submitter (20 years) may offset the high initial cost of treatment without truly reflecting the overall survival benefits expected in the real world. Previous pCODR reviews of ipilimumab and pembrolizumab as first and as subsequent-line treatments have suggested that 5 years is a reasonable time horizon for patients with advanced melanoma receiving a last line of therapy, and 10-20 years in patients receiving first-line therapy. Given that there is no evidence of sustained long-term survival for nivolumab, the EGP used a 10-year time horizon for first-line and a 5-year horizon for second/third-line therapy to provide a balance between underestimation of cost (no subsequent treatment) and overestimation of long-term effect.

The findings of the submission for the previously untreated setting for nivolumab, and subsequent EGP review, need to be evaluated in light of the fact that the main comparator ipilimumab, is itself a treatment alternative that was found to have a high and highly uncertain ICER in a previous pCODR review [8].

Last, but not least, both the previously untreated and the previously treated nivolumab submissions relied on estimates of short- and long-term overall survival that were either from a different treatment option (previously untreated) or from a different patient population (previously treated). Although some of the uncertainty associated with this assumption was explored in reanalyses, the EGP feels that the residual uncertainty is considerable and that any recommendation for both previously untreated and previously treated settings should be done after taking into consideration the absence of any evidence from an RCT for nivolumab's relative overall survival benefit. Any survival benefit identified in this submission is based on very strong assumptions.

**Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?**

No. The EGP would consider a different source for short-term overall survival (namely the CheckMate037 and CheckMate067 Trials), treatment discontinuation, Canadian utility values and more conservative extrapolations of long-term survival.

## 1.4 Summary of Budget Impact Analysis Assessment

**What factors most strongly influence the budget impact analysis estimates?**

The submitter provided an updated BIA model which was designed to capture the effect of nivolumab in both the previously untreated and previously treated settings. Given that the BIA was not specific to the population of interest (i.e. patients previously treated with nivolumab), the EGP considered this analysis needs to be modified to capture the effect of nivolumab for patients previously treated with ipilimumab. The BIA was found to be sensitive with respect to the disease prevalence, the assumption of treatment duration, the current market share, as well as assumptions on the proportion of that market share that will be captured by nivolumab. The base case estimate of the BIA was that introduction of nivolumab will result in overall cost-savings due to a reduced use of ipilimumab, but as noted earlier, this analysis included both the previously untreated and the previously treated settings and reanalysis would be required to answer the question about the previously treated setting only.

**What are the key limitations in the submitted budget impact analysis?**

The submitted BIA was found to have a number of flaws as well as limitations.

For both the previously untreated and the previously treated settings, the submitter has assumed in the model that every patient will receive 4 doses of ipilimumab. However according to the CheckMate-067 trial [1], the average number of doses received, based on the submitted BIA report is 3.1. By adjusting the model with the more appropriate (i.e., lower) estimate of ipilimumab treatment doses, nivolumab is not cost-saving. In addition, the skewed distribution of time to treatment discontinuation implies that an estimate that is purely based on average duration is likely to underestimate the expected budget impact.

Overall the EGP believes that the submitted BIA for nivolumab significantly underestimates the budget impact.

## 1.5 Future Research

**What are ways in which the submitted economic evaluation could be improved?**

Both long- and short-term overall survival for the treatment of interest (previously untreated) and the population of interest (previously treated) are required.

Both models would benefit from a more appropriate distributional fit on progression free/time to treatment discontinuation parameters.

Utility values that originate from a Canadian setting, are representative of the population and are recent would provide valuable input to the model.

**Is there economic research that could be conducted in the future that would provide valuable information related to Nivolumab for first and second/third line treatment?**

A key parameter for which no available information exist in the submitted models is overall survival. Although evidence on short term overall survival will become available once the CheckMate 067[1] and 037 RCTs [6] are completed, evidence of long-term survival of nivolumab and the relative effect of the treatment beyond progression is scant.

Also, there is lack of evidence on long-term Canadian utilities in patients advanced melanoma especially after treatment discontinuation.

## 2 DETAILED TECHNICAL REPORT - FIRST LINE TREATMENT

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 DETAILED TECHNICAL REPORT - SECOND/THIRD LINE TREATMENT

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

## 4 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Melanoma 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 for metastatic melanoma. A full assessment of the clinical evidence of nivolumab for metastatic melanoma 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](http://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](http://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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