pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Nivolumab (Opdivo) with Ipilimumab (Yervoy) for Metastatic Melanoma

November 30, 2017

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The pCODR Expert Review Committee (pERC) deferred making a recommendation during the first deliberations on the submission of the combination of nivolumab plus ipilimumab (the Regimen) for the first-line treatment of patients with metastatic melanoma. pERC noted that a comparison between the Regimen and nivolumab monotherapy was a clinically important and relevant comparison. However, this comparison was not provided by the submitter. Therefore, pERC was unable to determine the cost–effectiveness of the Regimen in comparison to a relevant comparator, nivolumab monotherapy. As such, the deliberation by pERC on this review was deferred pending the provision of a cost-utility and cost-effectiveness analysis of the Regimen and nivolumab monotherapy. Additionally, the EGP had requested this comparison from the submitter on a number of occasions during the review, since the Clinical Guidance Panel (CGP) and the Provincial Advisory Group (PAG) had identified nivolumab monotherapy as a relevant comparator, but it was not provided at the time. Following the deferral of the pERC recommendation, the Submitter provided an updated economic analysis that included a cost utility analysis and cost-effectiveness analysis comparing the Regimen to nivolumab monotherapy.

The economic analysis **submitted to pCODR by Bristol-Myers Squibb** compared the expected costs and effects (quality adjusted life years, life years) of nivolumab in combination with ipilimumab (the Regimen), nivolumab, ipilimumab and pembrolizumab as a first-line treatment for patients with unresectable or metastatic melanoma, regardless of BRAF V600 mutation status.

In secondary analyses, the cost-effectiveness of Regimen was compared to other therapies indicated in the first-line setting for patients with BRAF V600 mutation-positive advanced melanoma (e.g. dabrafenib/trametinib and vemurafenib).

Table 1. Submitted Economic Model	
Funding Request/Patient Population Modelled	First-line treatment for patients with unresectable or metastatic melanoma .This is aligned with the funding request.
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.
Comparator	The comparators are nivolumab monotherapy and ipilimumab monotherapy, which were compared with Regimen (nivolumab in combination with ipilimumab) in a head-to-head randomized clinical trial (CheckMate 067; data cut off: September 2016). Regimen was also compared to pembrolizumab using an indirect comparison, as well as to dabrafenib/trametinib and vemurafenib for patients with BRAF V600 mutation-positive advanced melanoma based on naïve/unadjusted comparisons.

Table 1. Submitted Economic Model	
Time Horizon	20 years (base case; 10 and 15 years in sensitivity analyses)
Perspective	Government as payer
Cost of nivolumab plus ipilimumab*	Nivolumab costs $1,956.00 per mg for 100mg/10mL vial At the recommended dose of 1 mg/kg every 3 weeks for the first 4 doses, over 12 weeks, nivolumab costs • $65.19 per day • $1,825.23 per 28-day course • At the recommended dose of 3 mg/kg every 2 weeks, nivolumab single agent costs • $293.33 per day • $8,213.35 per 28-day course • At the recommended dose of 240 mg every 2 weeks, nivolumab costs • $335.24 per day • $9,386.69 per 28-day course Ipilimumab costs $23,200.00 per 200 mg/40 mL vial At the recommended dose of 3 mg/kg every 3 weeks x 4 doses, ipilimumab costs • $1,160.00 per day • $32,480.00 per 28-day course
Cost of nivolumab*	Nivolumab costs $1,956.00 per mg for 100 mg/10mL vial At the recommended dose of 3 mg/kg every 2 weeks, nivolumab costs • $293.33 per day • $8,213.35 per 28-day course • At the recommended dose of 240 mg every 2 weeks, nivolumab costs • $335.24 per day • $9,386.69 per 28-day course
Cost of ipilimumab*	Ipilimumab costs $23,200.00 per 200 mg/40 mL vial At the recommended dose of 3 mg/kg every 3 weeks x 4 doses, ipilimumab costs • $1,160.00 per day • $32,480.00 per 28-day course
Cost of pembrolizumab*	Pembrolizumab costs $2,200.00 per 50mg vial At the recommended dose of 2 mg/kg every 3 weeks, pembrolizumab costs • $293.33 per day $8,2133.33 per 28-day course

Table 1. Submitted Economic Model	
Cost of dabrafenib	Dabrafenib costs $65.23 per 75 mg capsule At the recommended dose of 150 mg twice daily, dabrafenib costs • $260.93 per day • $7,306.10 per 28-day course
Cost of trametinib	Trametinib costs $298.70 per 2mg capsule At the recommended dose of 2 mg once daily, trametinib costs • $298.70 per day • $8,363.60 per 28-day course
Cost of vemurafenib	Vemurafenib costs $34.14 per 240 mg tablet At the recommended dose of 960 mg twice daily, vemurafenib costs • $136.54 per day • $3,832.18 per 28-day course
Model Structure	This partitioned survival model was comprised of three health states: progression free; progressed disease and death. Trial data were extrapolated beyond the trial period using survival distributions.
Key Data Sources	• One head-to head phase III clinical trial (CheckMate 067) to compare Regimen, nivolumab monotherapy and ipilimumab monotherapy in terms of efficacy, treatment duration and adverse events. • Indirect treatment comparisons and naïve comparisons were used to compare Regimen versus the other comparators. • Canadian-based utility data from a sample of 87 healthy respondents from the general population living in Toronto and Vancouver (using the standard gamble technique to assign utility values to various health states in melanoma; Hogg et al. 2010 used in base case analysis (EQ-5D utility data collected in CheckMate 067 used in sensitivity analysis). • One Canadian expert opinion was used to derive/validate the healthcare resource utilization. • Costing from Ontario and Canadian literature data (e.g. end of life costs).
Note: *Drug costs for all comparators in this table are based on costing information from IMS Brogan accessed on November 25, 2016. *Assuming an average body weight of 70 kg.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP) and the EGP, the comparisons versus ipilimumab and nivolumab are appropriate.

Based on the clinical trials, the CGP concluded that the combination therapy (the Regimen) provides a clinically meaningful improvement in PFS (Hazard Ratio [HR]: 0.42; p<0.001) and OS (HHR: 0.55; p<0.0001) over ipilimumab monotherapy. However, when compared to nivolumab monotherapy, the CGP could not draw any firm conclusions as the analyses comparing Regimen and nivolumab monotherapy were only descriptive, unplanned and underpowered in CheckMate-067. Furthermore, the trial was not designed to compare the Regimen to the nivolumab monotherapy treatment group. The CGP concluded that "numerically there may be a trend favoring the combination of nivolumab plus ipilimumab over nivolumab monotherapy with respect to PFS" (i.e. HR: 0.74; 95%CI, 0.60 to 0.92)" but "there is no difference between the combination and nivolumab monotherapy in terms of OS" (HR: 0.88; 95%CI, 0.69 to 1.12)." The CGP noted that this analysis must be interpreted with caution. Although the manufacturer provided an indirect treatment comparison (ITC) of Regimen versus pembrolizumab, "the CGP and Methods team agreed that the comparative efficacy of nivolumab plus ipilimumab and pembrolizumab is uncertain given the substantial heterogeneity in the studies (CheckMate 067, KEYNOTE 002 and KEYNOTE 006) and patient characteristics among the included studies in the indirect treatment comparison." (Refer to Section 1.2 and Section 7 of the Clinical Guidance Report for more details). The CGP also concluded that "the effect of nivolumab plus ipilimumab compared to other targeted agents in BRAF mutation-positive carriers is unknown" (Refer to Section 1.2 and Section 7 of the Clinical Guidance Report for more details). As a result, the EGP did not undertake re-analysis estimates for the comparisons against pembrolizumab, dabrafenib/trametinib and vemurafenib.

The PAG provided feedback on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that the combination of nivolumab plus ipilimumab was not compared against pembrolizumab, previously recommended by pCODR as first line immunotherapy over ipilimumab, independent of BRAF mutation status. Pembrolizumab has been implemented as first line, standard of care therapy in most Canadian jurisdictions. Ipilimumab is no longer a valid comparator in Canada and nivolumab is recommended only for BRAF wild type tumors. Pembrolizumab is the most relevant standard of care for advanced melanoma as it is recommended for patients independent of BRAF status and it has a more favorable administration schedule. PAG noted that there were concerns with the use of an indirect comparison against pembrolizumab. However, clinicians have repeatedly indicated that pembrolizumab and nivolumab are considered clinically/therapeutically equivalent. In response to PAG's feedback, the CGP acknowledge that at the time the CheckMate-067 trial was designed, ipilimumab was an appropriate comparator. However, PD-inhibitors, such as pembrolizumab and nivolumab have recently become available in the first line setting for patients with metastatic melanoma who are treatment naive. Specifically, pembrolizumab is available in the first line setting independent of BRAF mutation status and nivolumab is available for patients with BRAF wildtype disease based on provincial funding criteria. It is unlikely that there will be future direct comparative trials comparing the efficacy of pembrolizumab and the combination of nivolumab and ipilimumab. The submitted ITC sought to compare the clinical effectiveness of the combination of nivolumab plus ipilimumab compared to pembrolizumab. This was used to inform the Submitter's economic analysis comparing the combination of nivolumab plus ipilimumab to pembrolizumab. However, due to the substantial heterogeneity in the patient characteristics in the included studies in the indirect treatment comparison, the CGP and Methods team re-iterate that there is uncertainty in the comparative efficacy estimates. Therefore, without reliable estimates of the efficacy of the combination of nivolumab plus ipilimumab compared to pembrolizumab, the EGP could not provide reanalysis estimates for this comparison.

The PAG also provided feedback on pERC's Initial Recommendation that the combination was not compared against BRAF/MEK targeted agents, previously recommended by pCODR for first line treatment in patients with BRAF mutated disease. A number of jurisdictions do not allow sequencing of BRAF/MEK

inhibitors after immunotherapy, thus BRAF/MEK targeted agents are the first line standard of care for patients with BRAF mutated disease. Registered clinicians provided feedback on pERC's Initial Recommendation indicating that they disagree with the recommendation to limit funding to treatment naïve patients, as the clinicians strongly support the use of nivolumab plus ipilimumab either as a first line immunotherapy or second line post-BRAF targeted therapy. The latter would also be consistent with Ontario's funding for single agent immunotherapies. Furthermore, a patient group, Melanoma Network of Canada, provided feedback on pERC's Initial Recommendation that the combination therapy should be considered in second line as well as first line, for patients that have failed targeted therapies. In response to PAG's feedback, the CGP acknowledge that the current standard of treatment for patients with metastatic melanoma who are BRAF mutation positive are BRAF targeted agents (ex. trametinib, dabrafenib, vemurafenib) based on provincial funding criteria. The CGP are not aware of any trials evaluating the clinical effectiveness of BRAF targeted therapies and the combination in the treatment naïve metastatic melanoma setting. The CGP re-iterate that the submitter attempted to compare the effect of nivolumab plus ipilimumab compared to targeted agents in BRAF mutation-positive carriers in the submitted indirect treatment comparison. However, the submitter was unable to do so. Therefore, the comparative efficacy of the combination compared to targeted agents for BRAF mutation positive carriers is unknown. The submitter performed a naïve secondary economic analysis comparing the combination of nivolumab plus ipilimumab to BRAF targeted therapies. However, the EGP could not provide reanalysis estimates without reliable estimates of the efficacy of the combination of nivolumab plus ipilimumab and BRAF targeted therapies.

Summary of patient input relevant to the economic anaysis

Patients considered the following factors important: improvement in quality of life, reduction in disease progression, improved survival, and improved side effects profile. The majority of patients treated with Regimen (N unknown) reported that the combination therapy had eliminated the cancer or has stopped disease progression. The combination was described as challenging and the side effects needed to be managed by experienced oncologists.

- The economic model submitted by the manufacturer takes into account quality of life, progression free survival and overall survival, as well as adverse events.
- Adverse events were taken from CheckMate 067 and were assigned costs and dis-utilities.
- 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, although the burden on the caregivers was noted by patients.

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

PAG considered that the following factors would be important to consider if implementing a funding recommendation for Regimen: limited comparative data against PD-1 and other oral targeted therapies for BRAF mutative positive melanoma, uncertainty regarding post-progression treatments and sequencing, potential for substantial drug wastage, high cost of the combination therapy, uncertainty in the cost of monitoring and managing toxicities and unknown treatment duration.

- PAG expressed concern regarding the generalizability of CheckMate 067 as the trial only included patients with ECOG performance status (PS) 0 and 1. The CGP "noted that in routine clinical practice, most patients with advanced melanoma are ECOG PS 1 or 2. The CGP agreed that treatment may be reasonably extended to patients with ECOG PS 2 and that the decision to selectively treat patients with PS 2 should be left to the discretion of the treating oncologist." As such the economic results should also apply to this population.
- PAG also expressed concerns about the incremental costs due to drug wastage. This is addressed in the economic model and the BIA, which assumes no vial sharing in the base case scenario (a sensitivity analysis which assumed no drug wastage was performed by the manufacturer).

- PAG also had questions regarding post-progression treatments and sequencing. The model has an option to include post-progression treatments and associated costs.
- PAG commented on the uncertainty in the cost of monitoring and managing toxicities. The model includes costs for the management of AEs based on the frequency observed in CheckMate-067.
- PAG commented on the unknown treatment duration with nivolumab. Based on CheckMate-067 trial data, the model used the time to discontinuing treatment curves to extrapolate duration of treatment with Regimen beyond the trial period. A 24-month treatment duration with Regimen was explored in a sensitivity analysis performed by the manufacturer and results indicated a decrease in the incremental cost-effectiveness ratio (ICER).

- The PAG provided feedback on pERC's Initial Recommendation that the economic analysis did not account for the re-initiation of single agent nivolumab (after discontinuation of the combination due to toxicities or after treatment break), which would likely occur in actual practice. The economic analysis did not account for the re-initiation of single agent nivolumab after discontinuation of the combination due to toxicities or after a treatment break. The CGP note that if discontinuation of the combination therapy was due to side effects from ipilimumab and not nivolumab, the re-initiation of nivolumab monotherapy would be reasonable in clinical practice.

- The PAG provided feedback on pERC's Initial Recommendation that the dose during the monotherapy phase is 3mg/kg. PAG is requesting guidance on whether 3mg/kg to maximum dose of 240mg to maximize drug cost efficiencies could be addressed as it may alter the economic analysis and budget impact analysis. A flat dose of 240mg for all patients would lead to higher drug costs. It is noted that nivolumab was studied and approved at a dose of 3 mg/kg every two weeks until disease progression or unacceptable toxicity, whichever occurs first. A flat dose of nivolumab has been approved for other indications; however, there is currently no evidence for flat dosing in the current indication. Therefore, the EGP did not conduct a reanalysis using the flat dose of 240 mg.

1.3 Submitted and EGP Reanalysis Estimates

Table 2: Submitted and EGP Estimates

Estimates (compared to nivolumab)	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate ($/QALY), range/point	$47,119	$6,601 and $72,128
ΔE (QALY), range/point	0.569	0.271 and 0.325
ΔE (LY), range/point	0.713	0.390
ΔC ($), range/point	$26,814	$2,144 (lower bound) and 19,532 (upper bound)

Table 3: Submitted and EGP Estimates

Estimates (compared to ipilimumab)	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate ($/QALY), range/point	$66,750	$86,758 and $116,541
ΔE (QALY), range/point	2.241	1.252 and 1.441
ΔE (LY), range/point	2,593	1.616
ΔC ($), range/point	$149,556	$125,019 (lower bound) and 145,958 (upper bound)

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

- **Extrapolation of OS using short term data:** Using trial data, the manufacturer extrapolates PFS and OS over a time horizon of 20 years. Using a long time horizon can lead to erroneous predictions of long term survival based on extrapolation of trial data with limited follow-up. While the updated CADTH guideline recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention (Page 31)", the guidelines also state that, in cases where that extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement may be used to justify the plausibility of extrapolation (Page 43). Based on the feedback of the CGP, previous pCODR assessments of similar treatments in previously untreated advanced melanoma and a recent publication authored by BMS (Bohensky et al. 2016), a 10-year time horizon is deemed more clinically plausible for a previously untreated metastatic melanoma patient population and a good balance between uncertainty and a long time horizon.
- **Treatment post progression:** The results presented by the manufacturer do not include post-progression treatment costs in the base case analysis. These analyses are rather presented in a scenario analysis based on the distribution of subsequent systematic treatments observed in CheckMate 067 following disease progression. The analyses indicate that subsequent treatment costs were lower with Regimen as fewer patients with Regimen continue on systematic therapies (i.e. 47% for Regimen versus 73% and 74% with nivolumab monotherapy and ipilimumab monotherapy, respectively). The analyses, including subsequent treatment costs, resulted in a much lower ICER for Regimen when compared to nivolumab monotherapy ($16,898/QALY gained compared to $47,119/QALY gained in the base case) and when compared to ipilimumab monotherapy (e.g. $59,149/QALY gained versus $66,750/QALY gained in the base case analysis).
- **Utility data:** The model has the option to use 2 different sets of utility data.
    - In the base case analysis, the utility data were derived from a sample of 87 healthy respondents from the general population living in Toronto and Vancouver (mean age of 46 years and 49% male) using the standard gamble technique to assign utility values to various health states in melanoma (Hogg et al. 2010). This study was presented at a conference in 2010 but the full study has not been published in a peer-review journal. This set of Canadian data was previously used in the EGP base case re-analysis of nivolumab monotherapy for advanced melanoma (March 2016).
    - The second set of utility data used by the manufacturer in a sensitivity analysis were based on the EQ-5D utility data collected in CheckMate 067, which was a multinational trial. Transferring utilities from other jurisdictions to Canada may result in bias.
    - While both sources of utility data are not ideal (e.g. none of these studies/data have been published and a critical appraisal is difficult), the 2 sets of utility data provide different results ($66,750/QALY gained in submitted base case analysis when comparing Regimen versus ipilimumab monotherapy and $74,103/QALY gained when using trial utility data). This illustrates the uncertainty associated with the utility data.
- **Body weight**: The manufacturer based its analysis on an average body weight of 70 kg. However, the mean body weight was 82 kg in CheckMate 067.

EGP Reanalysis

The EGP re-analyzed the data by taking a shorter time horizon of 10 years, using a mean body weight of 82 kg as per trial data, different utility data and analyses with subsequent treatment costs following disease progression both included and excluded. A multi-way analysis combining a time horizon of 10 years and a mean body weight of 82 kg as per the CheckMate 067 trial data was used to determine a lower bound (i.e. when including subsequent treatment costs in the analysis and using utility data from

literature) and an upper bound (i.e. not including subsequent treatment costs and using utility data from trial).

Only detailed results of the EGP's re-analyses are presented to compare Regimen, nivolumab monotherapy and ipilimumab monotherapy. An analysis was also provided by the manufacturer based on an indirect treatment comparison (ITC) of Regimen and pembrolizumab. Due to the limitation of this ITC, the CGP concluded that "the comparative efficacy of nivolumab plus ipilimumab and pembrolizumab is uncertain given the substantial heterogeneity in the studies (CheckMate 067, KEYNOTE 002 and KEYNOTE 006) and patient characteristics among the included studies in the indirect treatment comparison. Additionally, the effect of nivolumab plus ipilimumab compared to other targeted agents in *BRAF* mutation-positive carriers is unknown." (Refer to Section 1.2 and Section 7 of the Clinical Guidance Report for more details). As a result, the EGP did not undertake re-analysis estimates for the comparisons against pembrolizumab, dabrafenib/trametinib and vemurafenib.

Table 4. EGP Reanalysis Estimates versus nivolumab monotherapy

Description of reanalysis comparing Regimen versus nivolumab	ΔC	ΔE	ICER QALY gained	Δ from baseline submitted ICER
Baseline (Submitter's best case versus nivolumab)	$26,814	0.569	$47,119	--
1. Restricting model time horizon to 10 years	$29,375	0.325	$90,438	$42,719
2. Including cost of immunotherapies and targeted therapies following disease progression.	$9,616	0.569	$16,898	-$30,221
3. Using 82 kg for the weight as per trial data (with 82 kg, 246mg are needed for the administration of Regimen: the Submitter assumed that 2*40mg vial + 2*100mg vials would be used for a total of 280mg; this means that 34 mg will be wasted).	$9,357	0.569	$16,443	-$31,276
4. Using 82 kg for the weight as per trial data (with 82 kg, 246mg are needed for the administration of Regimen: EGP assumed that 4*40mg vials + 1*100 mg vial would be used for a total of 260 mg meaning that 14mg would be wasted instead of 34 mg in the previous scenario).	$16,008	0.569	$28,130	-$19,589
5. Using utility data from trial	$26,814	0.518	$51,719	$4,000

Table 5: EGP Reanalysis for the Lower and Upper Bounds of the Estimate compared to nivolumab monotherapy

EGP's Reanalysis for the lower and upper bounds of the Estimate compared to nivolumab				
Description of Reanalysis	**ΔC**	**ΔE**	**ICER QALY Gained**	**Δ from baseline submitted ICER**
Baseline (Submitter's best case versus nivolumab)	$26,814	0.569	$47,119	--
EGP's lower bound estimate combining re-analyses 1, 2 and 4	$2,144	0.325	$6,601	-$40,518
EGP's upper bound estimate combining re-analyses 1, 4 and 5	$19,532	0.271	$72,128	$25,009

Table 6. EGP Reanalysis Estimates versus ipilimumab

Description of reanalysis comparing Regimen versus ipilimumab	**ΔC**	**ΔE**	**ICER QALY gained**	**Δ from baseline submitted ICER**
Baseline (Submitter's best case versus ipilimumab)	$149,556	2.241	$66,750	--
1. Restricting model time horizon to 10 years	$123,121	1.441	$85,372	$18,662
2. Including cost of immunotherapies and targeted therapies following disease progression.	$132,525	2.241	$59,149	-$7,601
3. Using 82 kg for the weight as per trial data (with 82 kg, 246mg are needed for the administration of Regimen: the Submitter assumed that 2*40mg vial + 2*100mg vials would be used for a total of 280mg; this means that 34mg would be wasted).	$187,767	2.241	$83,805	$17,055
4. Using 82 kg for the weight as per trial data (with 82kg, 246mg are needed for the administration of Regimen: the EGP assumed that 4*40mg vials + 1*100 mg vial for a total of 260 mg would be used; this means that 14mg would be wasted instead of 34 mg in the previous scenario).	$175,861	2.241	$78,491	$11,741
5. Using utility data from trial	$149,556	2.018	$74,103	$7,353

Table 7: EGP Reanalysis for the Lower and Upper Bounds of the Estimate compared to Ipilimumab monotherapy

EGP's Reanalysis for the lower and upper bounds of the Estimate compared to ipilimumab				
Description of Reanalysis	**ΔC**	**ΔE**	**ICER QALY Gained**	**Δ from baseline submitted ICER**
Baseline (Submitter's best case versus ipilimumab)	$149,556	2.241	$66,750	--
EGP's lower bound estimate combining re-analyses 1, 2 and 4	$125,019	1.441	$86,758	$20,008
EGP's upper bound estimate combining re-analyses 1, 4 and 5	$145,958	1.252	$116,541	$49,791

1.1 Evaluation of Submitted Budget Impact Analysis

1.2 The overall approach for the budget impact analysis (BIA) appears reasonable and appropriate. Factors that most influence the BIA include the size of the population, treatment duration associated with Regimen, cost of Regimen and drug uptake. Conclusions

The lower and upper bounds of the EGP's best estimate of ΔC and ΔE for Regimen compared to nivolumab monotherapy are:

- $6,601/QALY gained (lower bound) and $72,128/QALY gained (upper bound)
- The extra cost of Regimen (the addition of nivolumab to ipilimumab) compared to nivolumab monotherapy is estimated to be $2,114 (when subsequent systematic treatment costs following progression are included) or $19,532 (when subsequent systematic treatment costs are excluded). The factors that most influence the incremental costs compared to nivolumab monotherapy are time horizon, patient weight and inclusion of subsequent systematic treatment costs following disease progression.
- Depending on the source of the utility data, the extra clinical effect of Regimen is 0.271 QALYs (trial data) or 0.325 QALYs (Hogg et al. 2010). The factors that most influence the incremental number of QALYs are time horizon and the utility values associated with disease free and progressed disease.

The lower and upper bounds of the EGP's best estimate of ΔC and ΔE for Regimen compared to ipilimumab monotherapy are:

- $86,758/QALY gained (lower bound) and $116,541/QALY gained (upper bound)
- The extra cost of Regimen (the addition of nivolumab to ipilimumab) compared to ipilimumab monotherapy is estimated to be $125,019 (when subsequent systematic treatment costs following progression are included) or $145,958 (when subsequent treatment costs following progression are excluded). The factors that most influence the incremental costs compared to ipilimumab are time horizon, patient weight and inclusions of subsequent treatment costs following disease progression.
- Depending on the source of the utility data, the extra clinical effect of Regimen is 1.252 QALYs (trial data) or 1.441 QALYs (Hogg et al. 2010). 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. Short-term model projections were compared against literature and trial data.

- The above EGP base case estimates are driven by the trial data (e.g. PFS and OS), a time horizon of 10 years, a body weight of 82 kg, choice of utility data and whether costs of systematic treatment following progression are included.
- Future research should focus on providing additional details: 1) the utility data associated with progression free and progressed disease in patients with metastatic melanoma from a Canadian perspective; and 2) treatment duration of Regimen and treatment patterns following disease 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 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 the combination of nivolumab plus ipilimumab for metastatic melanoma. A full assessment of the clinical evidence of the combination of nivolumab plus ipilimumab 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).

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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