CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Nivolumab (Opdivo) for Adjuvant Melanoma

March 7, 2019

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

DISCLAIMER ii
FUNDING ii
INQUIRIES iii
TABLE OF CONTENTS iv
1 ECONOMIC GUIDANCE IN BRIEF 1
1.1 Submitted Economic Evaluation 1
1.2 Clinical Considerations 2
1.3 Submitted and EGP Reanalysis Estimates 5
1.4 Detailed Highlights of the EGP Reanalysis 6
1.5 Evaluation of Submitted Budget Impact Analysis 7
1.6 Conclusions 8
2 DETAILED TECHNICAL REPORT 9
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 10
REFERENCES 11

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Bristol-Myers Squibb compared Nivolumab to high-dose IFN and observation as adjuvant therapy for patients with resected (absence of disease) Stage III-IV melanoma.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Nivolumab for patients with resected Stage III-IV melanoma with no evidence of disease (request is consistent with submission)
Type of Analysis	Cost Utility Analysis (per QALY), and Cost Effectiveness Analysis (per LY)
Type of Model	Partitioned-survival decision analytic model
Comparator	Nivolumab versus 2 comparators: 1. Observation (placebo as a proxy) 2. High dose interferon
Year of costs	2018
Time Horizon	10 years
Perspective	Canadian health care system perspective
Drug Cost of Nivolumab Source: pCODR	Nivolumab costs $782.22 per 40 mg vial, or equivalently $1, 955.56 per 100mg vial. At the recommended dose of 3 mg/kg IV every 2 weeks for up to 1 year, for an annual cost of $96,062 (based on average CM238 patient weight and rate of discontinuation) Cost per day: $263; 28-day cost: $7,369
Drug Cost of High-dose interferon Source: Ontario Drug Benefit Formulary	High-dose interferon costs $218.76 for 15MU, $364.60 for 25MU, or $729.19 for 50MU. At the recommended dose of 20 MU/m^2 5 days per week for 4 weeks, 10 MU/m^2 3 days per week for 48 weeks the average annual cost of high dose interferon is $31,889.65 (based on the average CM238 patient surface area and rate of discontinuation). Cost per day: $87; 28-day cost: $2,446
Drug Cost of Observation	Zero
Model Structure	Partitioned survival model built on 3 health states: 1. Recurrence free 2. Post-recurrence 3. Death Overall survival (OS) and recurrence-free survival curves were estimated to determine the proportion of patients in each health state every 28 days
Key Data Sources	CheckMate 238 (CM238) trial comparing Nivolumab versus Ipilimumab, and CA184-029 trial comparing Ipilimumab versus observation, were pooled using indirect analysis to provide estimates of Nivolumab versus high-dose interferon or observation. Clinical outcomes included: OS, recurrence-free survival, time to discontinuation, time to recurrence, adverse event rates, utility values.

	OS estimates for Nivolumab was estimated indirectly based on a published relationship of OS to recurrence-free survival for stage II/III melanoma.[1]
MU: million units	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of Nivolumab to observation, which is the most commonly adopted practice, is the most appropriate comparator for systemic therapy in the Canadian healthcare. The submitter also provided a comparison of Nivolumab to high-dose interferon (IFN); however, because of toxic side effects associated with its use, the CGP noted that it is used sparingly. Based on this input from the CGP, the EGP has only presented analysis for the comparison between Nivolumab and observation.

Relevant issues identified included:

- Recurrence-free survival is an acceptable outcome from which to infer a net clinical benefit for effectiveness.
    - This was addressed in the economic evaluation with costs and effects incurred for changes from recurrence-free heath states
- The incremental overall survival benefit between Nivolumab and Ipilimumab is unknown as the trial data are not yet mature, while the overall survival benefit between Ipilimumab and observation is known. Based on the CGP, the benefit of Nivolumab for recurrence-free survival may lead to benefit of overall survival.
    - The overall survival benefit between Nivolumab and observation was estimated indirectly in the economic evaluation, where this evidence is not as strong as direct trial evidence. The uncertainty of this overall survival benefit was addressed by +/10% of the mapping parameters of correlation equation parameters (constant, beta) as sensitivity analyses (Result: +/- <$4,000/QALY).
- The CGP appraised the NMA (where multiple studies existed which could be linked by a common comparator: Ipilimumab and IFN) and Bucher ITC analysis (where only a single study could be linked to another single study, also Ipilimumab and observation). The results of an NMA suggested that adjuvant treatment with Nivolumab was associated with a significant reduction in the risk of cancer recurrence, distant metastasis or death as compared to interferon or watchful observation/placebo; however, there were no statistically significant differences in recurrence-free survival observed between Nivolumab and other active treatment in the study population. In addition, Nivolumab had a similar safety profile compared with placebo, but treatment with Nivolumab was associated with statistically significantly lower risks of Grade 3 or 4 adverse events and discontinuation due to adverse events, as compared with interferon. Effect of Nivolumab on health-related quality of life relative to placebo was examined in an indirect treatment comparison analysis, and the between-group differences were not statistically significant, suggesting comparable quality of life for patients received Nivolumab and placebo.
- The CGP felt that the target patient population for the use of Nivolumab may include: BRAF-wild type and BRAF-mutated, cutaneous and mucosal melanoma but not ocular melanoma, and age <18 (on an individual basis). Patients should not be excluded based on 5 other clinical factors (ECOG >1, pre-existing immune-mediated illness, lymph node dissection, PD-L1 testing, prior adjuvant systemic therapy), but be excluded for the metastatic (relapsed) setting.
    - Specific subgroups were not addressed in the economic evaluation, which was built on the clinical evidence of CM238 trial where the 5 other clinical factors above were used as exclusion criteria for enrolment. The budget impact analysis was non-specific and included all cases of stage III and IV melanoma.

- The introduction of Nivolumab as adjuvant treatment to surgery for patients with completely resected melanoma offers a clinically meaningful benefit in recurrence-free survival, and fills a need that at present is unmet.
    - The economic model was constructed to evaluate the incremental cost relative to incremental time less spent in the different health states (recurrence-free state, a recurred disease state, or dead), as well as the effect of adverse events on quality of life.
- Resource utilization. The CGP felt that optimal treatment would mirror the schedule and dosage supported by the CM238 trial, but also recognized that clinicians may wish to adopt the use of a "capped dose," or adopt a 28-day treatment schedule, on an individual basis.
    - The change in dosage was not addressed in the base case of the economic evaluation, but addressed in a sensitivity analysis.

Summary of registered clinician input relevant to the economic analysis
Two clinician inputs were provided: one from an individual oncologist and one from a group of five oncologists associated with Cancer Care Ontario (CCO).

- The comparator high-dose IFN has little benefit with significant toxicity, which is presumably why it is rarely used globally. The toxicities listed were quite substantial, including fever, flu-like symptoms, myelosuppression, liver toxicity, and depression.
    - The economic evaluation considered available treatments such as high-dose IFN and the associated adverse events with this therapy, as well the more common standard of care observation.
- Patient selection was identified as an important issue:
    - The CCO group verified that the patient population in the request for funding of Nivolumab met the needs of the clinical practice setting, but noted that only patients who were stage IIIb and higher, based on the AJCC 7th edition staging system, were included in the clinical trial.
- The second submission from an individual oncologist noted that, considering the risk of metastatic relapse is higher for stage IIc patients than for stage IIIa patients, one can expect the indication to possibly include the higher risk group. Notably, the CGP advised that only patients with completely resected regional lymph node metastases Stage IV melanoma should be eligible for treatment with nivolumab in the adjuvant setting.
- The CCO group submission also verified that prescribing this drug to patients with histologically confirmed melanoma and metastases to regional lymph nodes or surgically resected distant metastases was appropriate. Further, they noted that complete dissection should not be a requirement to receive treatment with Nivolumab citing an article by Faries MB. et al.[2] This was supported by the CGP.
    - The economic evaluation did not address patient selection and the economic model was populated with the patient characteristics of the CM238 trial. In addition, the budget impact analysis included stage II patients which could relapse to stage III resected melanoma.)
- Both of the clinician input submissions conveyed that this treatment is very important and should be used in patients who are stage III, or stage IV having undergone resection, as progression to stage IV is a palliative situation. The current standard of care has minimal benefit, therefore creating a high unmet need for the treatment of melanoma.

Summary of patient input relevant to the economic analysis
- Compared to previous treatments (Ipilimumab, IFN), patients seemed to prefer Nivolumab for its better tolerance and improved effectiveness.
    - Issues related to Nivolumab included the large number of hospital visits required for infusions, and the financial impact of having to take time off work for the drug, or having to pay for it out of pocket.

    - The healthcare payer was the only perspective considered in the economic evaluation and budget impact analysis; therefore, any costs borne by the patient were not considered.
- From a patient's perspective, mental health challenges including anxiety, depression and fear are common issues faced during the course of their disease. Patients indicated their condition as having a negative impact on their mental health. Physical symptoms such as, scarring, fatigue and lymphedema were reported by patients. The impact of patient's condition on their family and social life was also noted; family members also face anxiety regarding the lack of treatment options for their loved ones, in addition to facing financial stress due to costs of treatments.
    - (The patient's health-related quality of life was one of the main outcomes in the economic evaluation. Utility values were based on the EQ-5D scale which incorporates anxiety/depression as well as 4 other dimensions: limits on mobility, self-care, ability to perform usual activities, and pain/discomfort.
    - However, the effect on family's quality of life was not addressed, which follows CADTH guidelines.

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:

- Patient selection was identified as an issue for implementation with PAG. The AJCC (IIIa and IIIb classification) has changed since the CM238 trial and patients eligible for the Nivolumab trial would now be ineligible (and vice versa). To simplify, Health Canada changed the inclusion for the use of Nivolumab to include patients with completely resected melanoma with regional lymph node involvement.
- The trial included patients with BRAF-mutated melanoma, but there is no other evidence to guide treatment decision-making for the patient with completely resected, BRAF-mutated melanoma.
- There is evidence to support treating patients with Nivolumab who previously were treated with interferon-alpha or BRAF-directed agents as adjuvant to surgery, while there is no evidence to support treating patients with Nivolumab who were previously treated with a PD-1 immune checkpoint inhibitor (pembrolizumab) (or vice versa) in the adjuvant setting. Notably, there is currently no other immunotherapy reimbursed for use in the adjuvant setting for the population of interest.
- Time between surgery and initiation of Nivolumab as adjuvant treatment to surgery should be within 12 weeks. This is in alignment with the CheckMate 238 trial.
    - The economic model was populated with the patient characteristics of the CM238 trial, and did not address subgroup analysis.
- Re-initiation following treatment interruption due to adverse events. The decision to re-initiate treatment with Nivolumab as adjuvant therapy to surgery should be based on clinical judgment, but may be considered in certain circumstances. (The economic evaluation was based on the CM238 trial evidence which allowed resumption; if Grade 2 AE resolved in 3 months, or Grade 3 AE resolved in 7 days).
- Sequencing of current therapies. There is no data to guide subsequent treatment decision-making in the metastatic (relapsed) setting, following Nivolumab as adjuvant therapy. Clinicians may consider all of the options: BRAF-targeted agents, anti-CTLA-4 immune checkpoint inhibitor therapy, anti-PD-1 immune checkpoint inhibitor therapy, chemotherapy or experimental agents.
    - The economic evaluation included all post-protocol treatments which occurred in the CM238 trial, and modelled subsequent treatment based on the results of a survey of oncologists' typical practice patterns.
- Resources required to administer intravenous infusion, monitor and treat infusion related reactions and monitor and treat adverse events. PAG raised questions regarding clinic resource utilization, pertaining to infusion time, schedule of infusions, and weight-based versus fixed or capped dosing.

- The economic model did not address these questions in the base case analysis. Budget impact analysis included infusion time and drug administration resources.

1.3 Submitted and EGP Reanalysis Estimates

The main cost driver of the manufacturer's model was the drug acquisition costs, which were assumed to be based on the same average patient weight and rates of discontinuation as for patients in the CM238 trial. Another key input, which affects long-term benefit, is the assumption that Nivolumab has an incremental OS benefit versus Ipilimumab, which in turn produces an indirectly estimated OS benefit versus observation. Without direct evidence for OS from the CM238 trial of Nivolumab versus Ipilimumab, which is still immature and not present at 2 years' follow-up, the submitted economic model assumed that OS can be predicted based on a mathematical relationship to recurrence-free survival. This assumption was based on a publication[1] which reported that RFS may be a reasonable surrogate for OS in this setting. A network meta-analysis was then used to combine the results of CM238 with the CA184-029 trial (comparing Nivolumab to observation) to determine the comparative efficacy of Nivolumab versus observation. However, CGP felt that a direct estimate of the OS comparing Nivolumab versus Ipilimumab would be preferable to a projected value for OS for Nivolumab, but commented that an RFS benefit leading to an OS benefit seemed logical in principle only. Similarly, the projection of the long-term duration of the benefit for OS and recurrence-free survival up to 10 years for Nivolumab is uncertain. Other inputs in the manufacturer's model had less impact on variation of the economic results: subsequent treatment costs, administration costs and the costs of adverse events, and utility values for health states and adverse events.

Overall, the assumptions made in the model and related input variables caused little variation in uncertainty analyses, and were reasonable and appropriate. Most of the key model variables were based on clinical data from the CM238 trial, which compared Nivolumab to Ipilimumab in the patient population of interest. However, there were a few concerns and limitations of the model; these are listed below in order of importance.

- The first factor is the assumption of the value for OS for Nivolumab. In the absence of direct OS data from the CM238 trial, which is still immature at this time, OS for the comparison of Nivolumab to ipilimumab was modelled as a fixed relationship to recurrence-free survival (RFS) (HR 0.71). Although there is evidence to suggest that RFS is a surrogate for OS[1], the EGP noted that there is some variation in the predictive formula used to map the relationship between RFS and OS where the relationship can vary by +/-30%. The mapping of OS from RFS was revisited to a more conservative estimate, given that indirect estimates from NMA and ITC estimates often overstate estimates derived from head-to-head comparisons.[3]
- A second major assumption is the extrapolation of the survival curves out to 10 years, based on 2 years of clinical data from CM238. Although the parametric predictions of RFS for Nivolumab and observation indicate continual divergence, the possibility that the overall survival benefit would extend for a shorter period beyond the trial, i,e., to 5 years, was assessed. This was considered to be appropriate by the CGP.
- A key driving factor for the economic analysis is the cost of the drug (over the one year of administration), which on average in Canadian prices, was $96,062 for Nivolumab. This is based on 36.1% of patients receiving full dosing all year, while the rest of the patients discontinued due to adverse events (AEs) or death. Because the percentage of patients who receive full dosage could change due to sampling variability, the EGP assessed the possibility that 50% of patients could receive full annual dosing.
- The cost of AEs was based on several assumptions, including number of AEs, resource utilization to treatment of AEs, and unit costs for AEs. The unit costs for AEs were obtained from international literature and may not reflect local pricing. The reanalysis included the use of Canadian costs for admissions.

- Another assumption that was altered was the choice of preference weights for the utilities generated from EQ-5D scales in the trial. In the reanalysis, the preference weights were changed to Canadian weights for different health states, which was similar to the submitted Scenario 1 for utility values.

Table 2. Submitted and EGP Estimates for Nivolumab vs Observation (A: Deterministic, B: Probabilistic)

A

Estimates (point)	Submitted	EGP Reanalysis - Upper
ICUR estimate ($/QALY)	$55,248	$93,493
ΔE (LY)	1.62	1.00
Recurrence-free	2.01	1.91
Post-recurrence	-0.39	-0.91
ΔE (QALY)	1.43	0.93
Recurrence-free	1.77	1.69
Post-recurrence	-0.34	-0.75
Adverse events	0.00	0.00
ΔC ($)	79,175	87,293

B

Estimates (point)	Submitted	EGP Reanalysis - Upper
ICUR estimate ($/QALY)	$55,791.94	$94,846
ΔE (LY)	1.61	0.98
Recurrence-free	NA	NA
Post-recurrence	NA	NA
ΔE (QALY)	1.42	0.92
Recurrence-free	NA	NA
Post-recurrence	NA	NA
ΔC ($)	$79,441	$87,191

NA: not available

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model for Nivolumab vs Observation:

1. Reduced the OS benefit between Nivolumab and Ipilimumab (from 0.71 to 0.907).
2. Benefit of overall survival limited to 5 years
3. Increased the cost of Nivolumab to represent 50% of patients with full annual dose
4. The cost of a bed day for admissions was changed to Canadian unit costs
5. Utility values were changed to Canadian preference weights for EQ-5D

Table 3. EGP Reanalysis Estimates (A: Deterministic, B: Probabilistic)

A

EGP's Reanalysis for the Best Case Estimate for Nivolumab vs Observation (deterministic)					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICUR ($/QALY)
1. Base case (deterministic)	$79,175	1.43	1.62	$55,248	---
2. HR-OS $_{\text{Nivo vs Ipil}}$=0.907 (from 0.71)	$78,626	0.97	1.08	$81,059	+$25,810
3. Cut-off survival benefit to 5 years	$81,338	1.31	1.48	$62,136	+$6,888
4. Percentage patients with full dose= 50% (from	$85,584	1.43	1.62	$59,720	+$4,472

36.1%)					
5. Canadian costs per bed day	$79,224	1.43	1.62	$55,282	+$35
6. Canadian weights for EQ-5D	$79,175	1.45	1.62	$54,547	-$701
Best case estimate – Upper (inclusion of parameters 2,3,4,5,6)					
EGP Best case – Upper	$87,293	0.93	1.00	$93,493	+$38,245
Best case estimate – Lower (inclusion of parameters 3,4,5,6)					
EGP Best case – Lower	$87,821	1.33	1.48	$66,082	+$10,834

B

EGP's Reanalysis for the Best Case Estimate for Nivolumab vs Observation (probabilistic)					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICUR ($/QALY)
Base case (probabilistic)	$79,441	1.42	1.61	$55,792	--
Best case estimate – Upper (inclusion of parameters 2,3,4,5,6)					
EGP Best case – Upper	$87,191	0.92	0.98	$94,846	+$39,054
Best case estimate – Lower (inclusion of parameters 3,4,5,6)					
EGP Best case – Lower	$87,974	1.31	1.45	$67,366	+$11,574

The probabilistic sensitivity analysis results for the EGP's best case estimates were similar to the deterministic results.

1.5 Evaluation of Submitted Budget Impact Analysis

The inputs that had the largest impact on the BIA based on the manufacturer's sensitivity analyses were average patient weight, market share multiplier, Canadian population, and the number of new cases diagnosed age 12+. The average patient weight was taken from the CM238 trial, and it is unclear if the treatment-eligible patients would have the same weight. On the other hand, it is likely that the size of the total Canadian population would not actually vary, while there is uncertainty in the number of new cases diagnosed age 12+ which is estimated using the UK estimate of '% 12+ population diagnosed with melanoma' =0.03%.

Key limitations of the BIA model include:

- The lack of Canadian epidemiology estimates for number of new cases of treatment eligible melanoma, i.e., stage III/IV absence of disease post-resection melanoma.
- Assuming that the drug acquisition cost for Nivolumab patients in the CM238 trial would be the same cost in the Canadian context, i.e, same patient weight, rate of discontinuation due to adverse events.

In the absence of available evidence on epidemiology to confirm these existing variations, the only input which was varied for a re-analysis was the cost of the drug acquisition. The cost of the drug varies by patient weight and rates of discontinuation. The typical dose is based on 36.1% of patients receiving full dosing all year, while the rest of the patients discontinued due to adverse events. Because the percentage of patients who receive full dosage could change due to sampling variability, we assessed the possibility that 50% of patients could receive full annual dosing. Over 3 years, this represents an increase in the cumulative budget impact of 13%.

1.6 Conclusions

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

- ICUR between $66,082/QALY and $93,493/QALY.
- Within this range, the best estimate would likely be: $93,493/QALY with a conservative OS benefit for Nivolumab vs Ipilimumab. If the manufacturer's assumption holds and there was an OS benefit of Nivolumab versus Ipilimumab HR-OS= 0.71, then the ICUR would be $66,082/QALY.
- The incremental cost was between $87,293 to $87,821, and was mostly driven by the cost of the drug. The drug cost was assumed to be based on giving the drug to patients with weight similar to the patients in the CM238 trial, while varying the percentage of patients receiving the full annual dosage between 36.1% (in the submission) and 50% (in the re-analysis). Based on this, the drug acquisition cost of Nivolumab could range from $96,062 and $102,856.
- The extra clinical effect of Nivolumab versus observation is between an additional 0.93 to 1.33 QALYs over a 10-year time horizon. The lower estimate is based on 2 extreme (upper limit) assumptions; a conservative OS benefit for Nivolumab versus Ipilimumab, and no additional survival benefits with Nivolumab beyond 5 years.
- The probabilistic sensitivity analysis results for the EGP's best case estimates were similar to the deterministic results.

Overall conclusions of the submitted model:

- The economic model was sophisticated and uncertainty was exhaustively assessed.
- Comparing Nivolumab to observation, the ICUR could range between $66,082/QALY to $93,493/QALY.
- An important assumption is the presence or absence of an OS benefit of Nivolumab versus Ipilimumab, due to the immaturity of OS data from the CM238 trial. With a conservative OS benefit, the ICUR was reanalyzed to be $93,493/QALY, while if the incremental overall survival existed as presented in the submission, then the reanalyzed ICUR would be $66,082/QALY
- The economic model was based on characteristics of patients in the CM238 trial, which had specific inclusion criteria. CGP, registered clinicians, and provincial advisory groups indicated that the target population may be broader, but cost effectiveness may be similar.
- Based on the submitter's economic model, the ICUR for Nivolumab versus high dose IFN is lower ($35,716/QALY) than the ICUR when comparing Nivolumab versus observation ($55,248/QALY). At different willingness to pay thresholds, high dose IFN is rarely considered the most cost effective treatment.

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 nivolumab (Opdivo) for adjuvant melanoma. A full assessment of the clinical evidence of nivolumab (Opdivo) for adjuvant 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.

REFERENCES

1. Suciu S, Eggermont AMM, Lorigan P, et al. Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II-III Melanoma Adjuvant Therapy. J Natl Cancer Inst. 2018;110(1)
2. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N. et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med. 2017 Jun 8;376(23):2211-2222
3. Bucher HC, Guyatt GH, Griffith LE, Walter SD: The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997, 50: 683-691. 10.1016/S0895-4356(97)00049-8.
4. Tarhini A, Benedict A, McDermott D, Rao S, Ambavane A, Gupte-Singh K, Sabater J, Ritchings C, Aponte-Ribero V, Regan MM, Atkins M. Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost-effectiveness analysis. Immunotherapy. 2018 Oct;10(14):1241-1252. doi:10.2217/imt-2018-0085. Epub 2018 Sep 3. PubMed PMID: 30175642.
5. Mennini FS, Bini C, Marcellusi A, Del Vecchio M. Cost Estimate of Immune-Related Adverse Reactions Associated with Innovative Treatments of Metastatic Melanoma. Clin Drug Investig. 2018 Oct;38(10):967-976. doi:10.1007/s40261-018-0690-9. PubMed PMID: 30143953. (not freely available, pay journal $USD 49.95).
6. Meng Y, Hertel N, Ellis J, Morais E, Johnson H, Philips Z, Roskell N, Walker A, Lee D. The cost-effectiveness of Nivolumab monotherapy for the treatment of advanced melanoma patients in England. Eur J Health Econ. 2018 Nov;19(8):1163-1172. doi: 10.1007/s10198-018-0964-4. Epub 2018 Mar 9. PubMed PMID: 29524005.
7. Kohn CG, Zeichner SB, Chen Q, Montero AJ, Goldstein DA, Flowers CR. Cost-Effectiveness of Immune Checkpoint Inhibition in BRAF Wild-Type Advanced Melanoma. J Clin Oncol. 2017 Apr 10;35(11):1194-1202. doi:10.1200/JCO.2016.69.6336. Epub 2017 Feb 21. PubMed PMID: 28221865; PubMed CentralPMCID: PMC5791832.
8. Bohensky MA, Pasupathi K, Gorelik A, Kim H, Harrison JP, Liew D. A Cost-Effectiveness Analysis of Nivolumab Compared with Ipilimumab for the Treatment of BRAF Wild-Type Advanced Melanoma in Australia. Value Health. 2016 Dec;19(8):1009-1015. doi: 10.1016/j.jval.2016.05.013. PubMed PMID: 27987627.