pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Nivolumab (Opdivo) for Metastatic Renal Cell Carcinoma

September 1, 2016

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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.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by** Bristol Myer Squib compared nivolumab to everolimus for patients with locally advanced or metastatic renal cell carcinoma (RCC) who have received at least 1 prior anti-angiogenic therapy. An overview of the submitted model is provided in Table 1

Table 1. Submitted Economic Model	
The funding request	For the treatment of patients with advanced or metastatic renal cell carcinoma who have received prior systemic therapy. This aligns with the patient population that the model was built around. The patient population in the model was based on the patient population in CheckMate 025 which included patients with locally advanced or metastatic clear cell RCC who had previous treatment with 1 or 2 previous anti-angiogenesis agents.
Type of Analysis	Cost Utility Analysis, Cost-effectiveness analysis
Type of Model	3 health state partitioned-survival model
Comparator	Nivolumab vs. Everolimus
Year of costs	*2015*
Time Horizon	*10 years*
Perspective	*Government*
Cost of nivolumab.	*Nivolumab costs $782.22 per 40mg vial or $1,955.56 per 100mg vial.* • At the recommended dose of 3mg per kg every 2 weeks, the cost of nivolumab is: o *$293.33 per day (no wastage)* o *$307.30 per day (with wastage)* o *$8213.35 per 28-day course (no wastage)* o *$8604.44 per 28-day course (with wastage)*
Cost of everolimus*	Everolimus costs $196.55 per 10 mg tablet • At the recommended dose of 10 mg per day, the cost of everolimus is: o $196.55 per day o $5503.40 per 28-day course
Model Structure	The model was comprised of 3 health states: 1) Alive no progression; 2) Alive post progression; 3) Dead. Overall survival curves and progression free survival curves were used to determine the proportion of patients that would be in each of the health states every 28 days.
Key Data Sources	*CheckMate 025, a phase 3 RCT trial which compared nivolumab to everolimus in patients with renal cell carcinoma previously* • *Overall survival* • *Progression free survival* • *Time to Discontinuation* • *Time to Progression* • *Adverse Event rates*

Table 1. Submitted Economic Model	
	• *Objective response rate* • *Utility values by health state (unpublished data)* *BMS Canada* • *Unit cost of nivolumab* *Ontario Exceptional Access Program* • *Unit cost of everolimus*
**Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.* *Drug cost calculations are based on an average cost per course based on 28 days of therapy unless otherwise noted. Dosing calculations assume a weight of 70 kg and a body surface area (BSA) of 1.7 m² when required.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison to everolimus is appropriate.

Relevant issues included:

- The CGP stated that overall survival benefit of nivolumab compared to everolimus observed in CheckMate 025 was both statistically significant and clinically meaningful. This survival benefit was incorporated in the economic analyses as overall survival predictions based on data from CheckMate 025.
- The CGP noted that nivolumab was very well tolerated and had a significant benefit in quality of life compared to everolimus. This was addressed in the economic analysis as it incorporated the quality of life benefit of time free of progression and on differences in adverse events between nivolumab and everolimus.

Summary of patient input relevant to the economic analysis

Patients considered the chances of long term stability of disease, improvement in physical condition, and quality of life as extremely important outcomes for nivolumab. The long term stability of disease was addressed in the model as it considered both overall survival and progression free survival. The model formally considered quality of life as the primary outcome of the model was quality adjusted life years. Patients who had experience with nivolumab stated that nivolumab was much easier to tolerate than other kidney cancer medications they had used. The impact of serious adverse events on quality of life for nivolumab and everolimus was incorporated in the model.

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

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for nivolumab which are relevant to the economic analysis:

- Nivolumab is an intravenous drug infused every 2 weeks while current standard of care is an oral medication given in the community. This was addressed in the economic evaluation by assigning an administration cost of $89.04 for each nivolumab infusion and a dispensing fee of $9.83 per 28 day prescription fee for everolimus. The delivery of oral oncology medications varies by province and dispensing fees could range from zero (provided by Cancer agency) to considerably more than $9.93.

- PAG raised concerns about incremental costs incurred due to drug wastage for nivolumab. There was particularly concern over drug wastage in smaller centers where nivolumab may be administered to one patient in a given day. PAG noted that any unused portion would be discarded because the stability of the reconstituted drug would be poor. This is addressed in the economic analysis as the model includes the option of assuming drug wastage when estimating the cost of nivolumab. The manufacturer's budget impact analysis does assume drug wastage (no vial sharing between patients).
- The treatment duration of nivolumab is unknown since it is given until progression of disease. The model addresses this by using the actual time to drug discontinuation observed in CheckMate 025 to model the duration of drug treatment.
- The high cost and large budget impact of nivolumab will be a barrier to implementation. The BIA provides an estimate of the budget impact of funding nivolumab for 2nd and 3rd line treatment of RCC.

1.3 Submitted and EGP Reanalysis Estimates

The main cost drivers of the manufacturer's model were initial drug acquisition costs, assumed average patient weight and the assumption that there would be no drug wastage. Patient weight was important to the model because the dose of nivolumab provided to patients is dependent on the weight of the patient. Other inputs to the model that affected estimates of costs were subsequent treatment costs, administration costs and the costs of adverse events. The main drivers of the clinical outcomes of the model including estimated QALY's were the overall survival curves used to estimate survival for the two treatment groups over time, the time horizon used in the model and the utility values assigned to patients over the duration of the model time horizon. Other model variables that impacted clinical outcomes predicted by the model included were progression free survival curves, adverse event rates and disutility values for adverse event rates.

Overall, the assumptions made in the model and related input variables were mostly reasonable and appropriate. Most of the key model variables were based on data from the Checkmate 025 trial which compared nivolumab to everolimus in the patient population of interest. However there were a few concerns and limitations of the model which are listed below in order of importance.

- **Average patient weight:** In the base case analysis the average patient weight is assumed to be 70kg. However, the mean weight of patients in CheckMate 025 was 82.4kg (provided by manufacturer). This is likely more representative of the mean weight of the patient population being evaluated. The average patient weight was changed to 82.4kg in the EGP reanalysis. The submitter disagreed with the EGP's use of the average patient weight from the trial and indicated that patient weight based on the Canadian gender distribution would be more appropriate. The EGP agreed that there does appear to be a greater percentage of males in the CheckMate 025 study compared to the percentage of males in new cases of kidney cancer cases in Canada in 2015. However the clinical data for the economic evaluation from CheckMate 025 are based on the distribution of male and female patients included in the trial. Therefore an average patient weight based on that observed in CheckMate 025 is more appropriate for use in the EGP's re-analysis estimates.
- **Time Horizon:** The base case time horizon of the manufacturer's model is 10 years. Overall survival is extrapolated well beyond the time horizon of the trial. According to the Kaplan Meir curves in the trial publication, the longest follow-up for overall survival was approximately 2.5 years. The EGP considered that the 10 year time horizon may overestimate the incremental QALYs accumulate for nivolumab compared to everolimus. There are some data to support that the model's predictions of 5 year overall survival for

nivolumab may be reasonable. An update of a single arm Phase 1 dose escalation study (CA-209-003) found 5 year overall survival for nivolumab to be 34%. This compares to 5 year overall survival of 21% that is predicted in the submitted model. In addition, the clinical panel felt that the similar progression free survival (4.6 months nivolumab group vs 4.4 months everolimus group) but the significant difference in overall survival (25.0 months vs 19.6 months; HR 0.73 95% CI 17.6 to 23.1) suggested the potential for overall survival to be driven by a small group of longer term survivors. Substantial truncation of the time horizon would impact the model's ability to account for these potential long term benefits. The clinical guidance panel felt that the long term overall survival estimates from the model seem clinically reasonable. Therefore, the time horizon was not changed in the EGP reanalysis.

- **Utility values:** The utility values assigned in the model were based on unpublished data from the CheckMate 025 trial using the EQ5D questionnaire. The utility values assigned to patients who are progression free were 0.887 with response and 0.835 without response. The utility value assigned to patients with progressed disease was 0.806. These utility values seem high given that these are patients with metastatic or advanced cancer. A study that measured general population utilities in the U.K. found that on average, general population utility for individuals aged between 55-64 was 0.80 while average general population utility scores for individuals between 65-74 was 0.78[1]. It is optimistic that patients with progressed advanced renal cell carcinoma would have similar utility scores than the general population. As a sensitivity analysis, the submitters assumed utility values of 0.69 for progression free patients and 0.61 for patients with progressed disease. This was based on the utility values used in a submission to NICE for their appraisal of axitinib for advanced renal cell carcinoma[2]. In the EGP reanalysis, a range of utility values are applied. These include the set of utility values for the progression free and post progression health states observed in CheckMate 025 and the utility values used for progression free (0.69) and post-progression (0.61) states in the NICE submission for axitinib. The submitter indicated that the use of utility values from the axitinib trial is not appropriate due to differences in the baseline patient characteristics between the two trials and the differing toxicity profiles of axitinib and nivolumab. However, in the absence of alternative published sources and given that the axitinib utility data were used as a sensitivity analysis in the manufactures cost-effectiveness analysis, the EGP was comfortable to use the results. The EGP was also concerned that the utility values used in the model (based on CheckMate 025 data) appeared to be high compared to what has been found in other studies conducted in similar populations. For example, and as stated originally, the post-progression utility in the axitinib submission (0.61) is much lower than that used in the current submitted model (0.81). The submitter further noted that due to the differences in the toxicity profile of axitinib and nivolumab, the use of utility values will significantly underestimate the quality of life gains with nivolumab. The EGP noted that, in the model, the quality of life impact of adverse events are captured through one-time dis-utilities associated with each type of adverse event. The utility values applied to the progression free and post progression health states are independent of both the specific treatment received and the adverse events associated with the treatment received. From the EGP's understanding, the utility data from CheckMate 025 were not based solely on patients receiving nivolumab. Finally, the EGP recognized the merits of using utility data from the same study upon which other model inputs are based. However, concerns remained regarding the health state utilities based on CheckMate 025 which seem higher than those seen in similar populations. To explore both ends of the uncertainty in the utility data, the EGP changed the reanalysis estimates to include both a lower bound and upper bound re-estimate of cost-effectiveness. In the lower bound estimate, health state utility values based on CheckMate 025 are used in the model. In the

upper bound estimate, health state utility values based on those used in the axitinib submission to NICE are used in the model.

- **Drug Wastage:** The base case model assumes vial sharing for nivolumab and therefore no drug wastage. However, some drug wastage in the healthcare system is likely. The provincial advisory group raised the cost impact of drug wastage for nivolumab as a concern. In the EGP reanalysis, it is assumed that drug wastage will occur.

Table 2. Provides a summary of the cost effectiveness results from manufacturer's analysis and from the EGP reanalysis

Table 2. Submitted and EGP Estimates			
Estimates	Submitted	EGP Reanalysis (lower bound)	EGP Reanalysis (upper bound)
ICER estimate ($/QALY), range/point	$131,349	$186,312	$242,521
ΔE (QALY), range/point	0.481	0.481	0.370
ΔE (LY), range/point	0.557	0.557	0.557
ΔC ($), range/point	$63,185	$89,625	$89,625

1.4 Detailed Highlights of the EGP Reanalysis

The following changes were conducted in the EGP reanalysis:

- Average patient weight changed from 70 kg to 82.4 kg based on average weight amongst CheckMate 025 patients
- Two sets of utility values were used in the EGP reanalysis to create a lower and upper bound estimate of cost-effectiveness. The lower bound estimate used health state utility values from CheckMate 025 (progression free with response=0.887. progression free no response=0.835, post-progression=0.806). The upper bound estimate of cost-effectiveness used health state utility values used in the axitinib manufacturers submission to NICE (progression free=0.69, post progression=0.61)
- Drug wastage was assumed in the model

The results of the reanalyses are provided in Table 3

Table 3 cost-effectiveness results from EGP reanalysis				
Description of Reanalysis	**Incremental Costs**	**Incremental QALYs**	**Incremental $/QALY**	**Change in $/QALY from base case**
Base case	$63,185	0.48	**$131,349**	
1. Change mean patient weight to 82.4 kg (from CheckMate 025)	$82,856	0.48	**$172,242**	$40,893
2. Assume drug wastage	$68,473	0.48	**$142,341**	$10,992
EGP lower bound estimate of cost effectiveness (includes changes in 1, 2 and using utility values from Checkmate 025)	$89,625	0.48	**$186,312**	$54,963

Table 3 cost-effectiveness results from EGP reanalysis				
Description of Reanalysis	**Incremental Costs**	**Incremental QALYs**	**Incremental $/QALY**	**Change in $/QALY from base case**
3. Change utility values: Progression Free: 0.69 Progressed Disease: 0.61	$63,185	0.37	**$170,976**	$39,627
EGP upper bound estimate of cost effectiveness, includes changes in 1, 2 and 3 (using utility values from axitinib NICE submission)	$89,625	0.37	**$242,521**	$111,172

- The listed price of everolimus was used in the economic analysis. Since this value may not reflect the actual cost paid by cancer agencies a sensitivity analysis was conducted assuming a reduction from the listed price of everolimus. The results of this sensitivity analysis are shown in Table 4.

Table 4. Sensitivity analysis on discount in the price of everolimus per 10mg tablet				
Description of Reanalysis	**Incremental Costs**	**Incremental QALYs**	**Incremental $/QALY**	**Change in $/QALY From base case**
Manufacturers base case model				
0% ($196.55)	$63,185	0.48	$131,349	
10% ($176.90)	$67,749	0.48	$140,837	$9,488
15% ($167.07)	$70,031	0.48	$145,582	$4,744
25% ($147.41)	$74,596	0.48	$155,070	$9,488
50% ($98.28)	$86,007	0.48	$178,791	$23,721
EGP lower bound estimate of cost-effectiveness				
0% ($196.55)	$89,625	0.37	$242,521	
10% ($176.90)	$94,189	0.37	$254,872	$12,351
15% ($167.07)	$96,471	0.37	$261,047	$18,526
25% ($147.41)	$101,035	0.37	$273,398	$30,877
50% ($98.28)	$112,446	0.37	$304,275	$61,754
EGP upper bound estimate of cost-effectiveness				
0% ($196.55)	$89,625	0.48	$186,312	$54,963
10% ($176.90)	$94,189	0.48	$195,800	$64,451
15% ($167.07)	$96,471	0.48	$200,545	$69,196
25% ($147.41)	$101,035	0.48	$210,033	$78,684
50% ($98.28)	$112,446	0.48	$233,754	$102,405

1.5 Evaluation of Submitted Budget Impact Analysis

The overall approach and assumptions of the BIA appears to be reasonable and appropriate. The BIA assumed a mean patient weight of 70kg. If a mean patient weight of 82.4 kg, as was

observed in CheckMate 025 is assumed instead, the three year cumulative budget impact of nivolumab would increase by 31% from the manufacturer's base case analysis.

1.6 Conclusions

- The EGP's lower bound and upper bound estimate of the incremental cost per QALY of nivolumab compared to everolimus is $186,312 and $242,521 respectively.
- The EGP's best estimate of the incremental cost of nivolumab compared to everolimus is $89,625. Incremental cost is most affected by acquisition costs of medication and the patient weight.
- The EGP's lower bound and upper bound estimate of the incremental QALY's gained with nivolumab compared to everolimus is 0.48 and 0.37 respectively. Incremental QALYs are most impacted by the overall survival estimates, the time horizon of the model and the health state utility values assigned to patients in the model.

Overall, the approach taken and the assumptions made in the submitted model were reasonable and appropriate. A few of the model variables values were changed to derive the EGP lower and upper bound cost effectiveness of nivolumab compared to everolimus. First, the average patient weight in the model was changed from 70kg to 82.4 kg to reflect the average patient weight in CheckMate 025. It was felt that this better represented the average patient weight for the population of interest. Though, they were derived from unpublished data from Checkmate 025, EGP felt that the utility values used in the submitted model were a bit too optimistic, given the population in the model were patients with advanced or metastasized RCC. Therefore, for the lower bound cost-effectiveness estimate, health state utility values from CheckMate 025 were used. However for the upper bound estimate of cost-effectiveness, health state utility values based on those used in a recent NICE evaluation of axitinib for advanced RCC were used. Finally, the EGP changed the assumption around drug wastage in the model to assume that there would be drug wastage (no vial sharing between patients).

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 Genitourinary 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 advanced or metastatic renal cell carcinoma (RCC). A full assessment of the clinical evidence of nivolumab (Opdivo) for advanced or metastatic renal cell carcinoma (RCC) 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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