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pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Nivolumab (Opdivo) plus Ipilimumab (Yervoy) for Advanced Renal Cell Carcinoma

August 30, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Bristol-Myer Squibb compared nivolumab in combination with ipilimumab to sunitinib for patients with locally advanced or metastatic renal cell carcinoma (mRCC) and an intermediate to poor prognosis with clear-cell component. An overview of the submitted model is provided in Table 1.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Intermediate/poor risk patients with previously untreated, advanced or metastatic renal cell carcinoma This aligns with the patient population modelled. The patient population in the model was based on the patient population in CheckMate-214 which included patients with mRCC and an intermediate to poor prognosis with clear-cell component.
Type of Analysis	CEA, CUA
Type of Model	Partitioned-survival
Comparator	Sunitinib
Year of costs	2017
Time Horizon	15-year
Perspective	Canadian public healthcare payer
Cost of Nivolumab plus Ipilimumab	Nivolumab costs $1,956.00 per 100mg vial and $782.22 per 40 mg vial. At the recommended dose of 3 mg/kg every 3 weeks for the first 4 doses, over 12 weeks, nivolumab costs • $195.56 per day • $5,475.57 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 Ipilimumab costs $23,200.00 per 200 mg vial and $5,800 per 50 mg vial. At the recommended dose of 1 mg/kg every 3 weeks x 4 doses, ipilimumab costs • $386.67 per day • $10,826.67 per 28-day course
Cost of Sunitinib ** Price Source: Ontario Drug Benefit*	Sunitinib costs $64.42 per 12.5 mg capsule. At the recommended dose of sunitinib of 50 mg once daily, the cost of sunitinib is $257.66 per day and $7214.56 per 28-day course.
Model Structure	The three health states used in the partitioned survival model were progression free (PF); progressed disease; and Death.
Key Data Sources	CheckMate-214 a phase III RCT which compared nivolumab plus ipilimumab to sunitinib in patients with mRCC • Clinical efficacy and safety (Overall survival; Progression free survival; Time to discontinuation; Time to progression; Utilities; Frequency of adverse events) Costs • Drug costs from IMS/Brogan Delta PA and health care resources from Schedule of Benefits in Ontario, or from literature

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The CGP considered that sunitinib and pazopanib are the standard treatment options in the first-line setting. Temsirolimus is considered an acceptable first line treatment option in patients with poor risk criteria. The submitter only included sunitinib in their economic analysis. The CGP acknowledged that temsirolimus is not used frequently in Canada and agreed the result with sunitinib are generalizable to those expected with pazopanib.

Relevant issues identified included:

- Unknown appropriate sequencing of subsequent agents. *This was not addressed in the economic evaluation as all subsequent therapies were combined (i.e., not separated by line of therapy).*
- Immune-mediated reactions occurred more frequently with nivolumab-ipilimumab. *The economic evaluation did not include immune-mediated reactions as they did not meet the 2% threshold used for drug-related grade 3 or higher.*
- *It is reasonable to administer nivolumab as a weight based dose of 3mg/kg up to 240mg every 2 weeks or 6mg/kg up to 480mg every 4 weeks.*
- *Health related quality of life was an exploratory outcome in the trial and descriptive analysis were presented. It is unclear if minimally important differences were met.*

Summary of registered clinician input relevant to the economic analysis

- It was noted that nivolumab-ipilimumab would be used specifically for the intermediate/poor risk population because other treatments are effective in better prognosis patient populations. *The economic evaluation included only intermediate/poor risk patients.*
- It should also be noted that the dosing of ipilimumab in RCC is 1mg/kg which is much better tolerated than other studies in other disease sites (e.g. the dose used for metastatic melanoma is 3mg/kg). *The economic evaluation incorporated the dosing schedule of 1 mg/kg for ipilimumab.*
- They identified that if nivolumab-ipilimumab was given first line, then nivolumab monotherapy would not be funded in second/third line, but if sunitinib or pazopanib was given first line, then nivolumab monotherapy could be given for subsequent lines. *The economic evaluation addressed this consideration with incorporation of subsequent therapies.*

Summary of patient input relevant to the economic analysis

- When considering new therapies, respondents indicated a need for new drugs, or new drug combinations that result in fewer side effects as being of great priority. *The economic evaluation addressed this through incorporation of the frequency of and disutility associated with adverse events experienced in the CheckMate-214 trial.*
- Respondents would like to have drug treatments that combat the negative impact RCC has on quality of life. *The economic evaluation addressed this through incorporation of quality of life measures from the CheckMate -214 trial.*

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 reimbursement recommendation for nivolumab-ipilimumab, which are relevant to the economic analysis:

- PAG is seeking information on comparison to pazopanib and temsirolimus or whether the trial results can be generalized to patients receiving other first line therapies. *The economic evaluation did not address comparisons to pazopanib and/or temsirolimus.*

- PAG has concerns with drug wastage, particularly with ipilimumab which is available in only one vial size. As ipilimumab is available as a 50mg vial, two 50mg vials would be required to prepare a 70mg dose for a 70kg patient and the part vial would be wasted. Drug wastage for nivolumab is minimized with vial sharing as nivolumab is indicated in many other cancers. *Wastage as well as no wastage (vial sharing) was incorporated for both ipilimumab and nivolumab.*
- PAG is seeking information on alternate dosing schedules for nivolumab in the nivolumab monotherapy phase. PAG is seeking guidance on the use of nivolumab 3mg/kg up to a maximum of 240mg every two weeks in the monotherapy maintenance phase, given that this dosing schedule has been adopted in other indications. *The option of weight-based dosing up to a 240 mg cap for nivolumab was considered.*
- Nivolumab and ipilimumab are intravenous therapies, where as pazopanib and sunitinib are oral therapies. *This was addressed in the economic evaluation by assigning an administration cost of $75.00 for each nivolumab infusion and a dispensing fee of $9.33 per 28 day prescription fee for sunitinib. The delivery of oral oncology medications varies by province and dispensing fees could range from zero (provided by Cancer agency) to considerably more than $9.33 (what was used in the reference case).*

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis	
		Lower	Upper
ΔE (QALY)	1.287	1.281	0.672
Progression-free	0.709	0.701	0.412
Post-progression	0.502	0.504	0.183
Disutility due to AE	0.077	0.117	0.117
ΔC ($)	148,320	149,283	171,992
ICER estimate ($/QALY)	**115,266**	116,539	255,796

The main assumptions and limitations with the submitted economic evaluation were:

- The ICUR was sensitive to time on treatment (and therefore treatment cost) using the TTD versus PFS curves for treatment groups. The uncertainty in this parameter was explored by the EGP.
- Notably, the CGP agreed that patients may continue to derive benefit from treatment beyond progression given the molecular mechanism of immunotherapies (ie., possible occurrence of pseudoprogression or late response in patients). Therefore, it is reasonable that patients may derive post progression benefit.
- The model was based on 25.2 months of follow-up data from the CheckMate-214 trial and extrapolating the treatment effect of nivolumab-ipilimumab over a 15 year time horizon. As the median overall survival of nivolumab-ipilimumab was not reached at the final OS data cut, the use of a 15 year time horizon assumes the treatment effect would continue indefinitely over the time horizon.
- The submitter did not provide further details on what was incorporated in the health state costs. Similar results for costs by treatment group were observed for drug administration and drug monitoring despite substantially higher unit costs for nivolumab-ipilimumab compared to sunitinib. The submitter did not provide a clinical or economic rationale for the resulting similar costs. Overall, varying health state and monitoring costs had small impacts on observed ICUR.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- **Distribution of subsequent therapies:** For the 54% of patients randomized to sunitinib and who received subsequent systematic therapy, the submitter assumed that 18% would go on to receive sunitinib in subsequent lines. The CGP considered that patients are unlikely to receive re-treatment with sunitinib. For the EGP reanalysis (lower and upper bound), no patients were assumed to receive subsequent treatment with sunitinib following first-line sunitinib treatment.
- **Truncate treatment effect:** The submitter assumed the treatment effect of nivolumab-ipilimumab would continue indefinitely for the entire 15 year time horizon. Given the short follow up period, the CGP agreed a decline in the treatment effect collected beyond the end of the trial period was reasonable. For the upper bound of the EGP reanalysis, the treatment effect for nivolumab-ipilimumab was further reduced from the end of the trial up to 5.
- **Determination of treatment costs:** The submitted base case analysis determines time on treatment (and therefore treatment costs) using the TTD curve. When treatment costs are determined using PFS (and not TTD), the ICUR increases significantly. The rationale for the large difference in results according to the submitter was that as patients in CheckMate-214 discontinued therapy prior to progression, the mean TTD is lower than that of mean PFS. Based on the trial data 30% of patients in the nivolumab plus ipilimumab group discontinued treatment due to study drug toxicity or adverse events unrelated to the study drug. Furthermore, as the CheckMate 214 trial allowed patients to be treated beyond RECIST defined progression, 28.5% of patients in the nivolumab plus ipilimumab group and 23.6% of patients in the sunitinib group were treated beyond progression. The CGP noted that the shorter TTD compared to PFS observed may be related to infusion reactions which would increase treatment discontinuation. Furthermore, more patients discontinued treatment with nivolumab-ipilimumab compared to sunitinib due to toxicity. Overall, given the uncertainty in the determination of time on treatment (and therefore treatment costs), for the upper bound of the EGP reanalysis, treatment cost determined by PFS for both treatment groups was considered. Notably, the CGP agreed that patients who discontinue treatment may continue to derive benefit given the mechanism of action of immunotherapies.
- **Utility values:** Based on input from the CGP, the utility values incorporated in the model, which were derived from the CheckMate 214 trial, seem high compared to the general population given these patients have advanced or metastatic cancer. Notably, quality of life was an exploratory outcome in the CheckMate 214 trial and only descriptive results were presented. Similarly, these values are higher than other studies conducted in similar populations. The submitter provided a scenario analysis using utility values from the NICE TA evaluation of sunitinib for mRCC. For the upper bound of the EGP reanalysis, utility values to reflect those used in the submission for NICE evaluation of sunitinib (0.77 for PF and 0.72 for PD) were included.

Table 3: Detailed Description of EGP Reanalysis

EGP's Reanalysis for the Best Case Estimate				
Description of Reanalysis	ΔC	ΔE	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$148,320	1.287	$115,266	--
LOWER BOUND				
Subsequent therapies, patients treated with sunitinib do not receive	$149,283	1.281	$116,539	+$1,273

subsequent treatment with sunitinib				
UPPER BOUND				
Subsequent therapies, patients treated with sunitinib do not receive subsequent treatment with sunitinib	$149,283	1.281	$116,539	$1,273
Truncate treatment effect: declines from 24 to 60 months	$112,071	0.732	$153,006	$36,467
Treatment duration determined by PFS for both treatment groups	$213,532	1.288	$165,820	$49,281
Utility values to reflect those used in submission for NICE evaluation of sunitinib (0.77 for PF and 0.72 for PD)	$147,331	1.169	$126,081	$9,542
Best case estimate of above five parameters	**$171,992**	**0.672**	**$255,796**	**+$140,529**

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the number of treatment lines considered (first-line only or up to three lines), eligible patient population, treatment duration of nivolumab-ipilimumab, and market share of nivolumab-ipilimumab. Considering only first-line treatment (as the budget is partially reduced by a lower use of nivolumab in second-line) and increasing several factors (eligible patient population size, duration of treatment with nivolumab-ipilimumab, and market share of nivolumab-ipilimumab) increased the budget impact.

Limitations of the BIA model as identified by the submitter include the data sources for duration of treatment, inclusion of dosing regimens according to the product monograph only, dosing of nivolumab, wastage, and exclusion of any treatment that could be used in first-line that does not have Health Canada approval. The treatment duration, dosing of nivolumab, and wastage were able to be modified and explore by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for nivolumab plus ipilimumab when compared to sunitinib is:

- Between $116,539/QALY and $255,796/QALY
- The wide range in the upper and lower bound reflects uncertainty in the ICUR, overall the EGP felt the ICUR likely lies closer to the upper bound.
- The extra cost of nivolumab plus ipilimumab is between $149,283 and $171,992 (ΔC). The main factors that influence the incremental costs are the time on treatment (and therefore treatment costs) and cost of nivolumab.
- The extra clinical effect of nivolumab plus ipilimumab is between 0.672 QALYs and 1.281 QALYs (ΔE). The main factor that influence the incremental effects is the assumptions on long term treatment effect.

Overall conclusions of the submitted model:

- Overall, the approach taken and most of the assumptions made in the submitted economic evaluation were reasonable and appropriate.
- However, a limitation of the economic model was that it did not consider subsequent therapies by line of therapy (i.e., second or third-line), however, CheckMate-214 did not capture subsequent therapies per line of therapy. The model also did not incorporate immune-mediated reactions that are known to occur with nivolumab plus ipilimumab.

- If one accepts that the treatment effect of nivolumab plus ipilimumab would decline over time, patients in the sunitinib group would not receive re-treatment with sunitinib, time on treatment is more likely to follow PFS not TTD which was longer, and lower utility values for patients with mRCC, then the ICUR is closer to the upper bound of $255,796/QALY. Based on input from the CGP, the EGP notes that the ICER is likely closer to this upper bound.

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 plus ipilimumab for renal cell carcinoma. A full assessment of the clinical evidence of nivolumab (Opdivo) plus ipilimumab (Yervoy) for advanced renal cell carcinoma 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 information redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

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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