CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Initial Economic Guidance Report

# Nivolumab (Opdivo) for Hepatocellular Carcinoma

November 29, 2018

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# 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.

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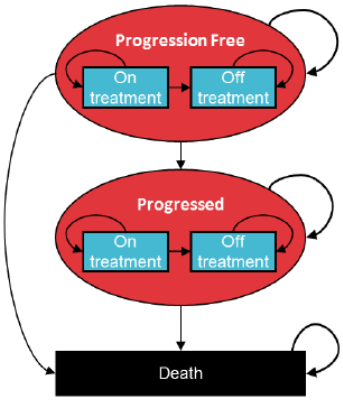
# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by **Bristol-Myers Squib** compared nivolumab (Opdivo) to best supportive care (BSC) as second-line treatment for patients with hepatocellular carcinoma (HCC) that have received prior treatment with sorafenib. The indication under review by pCODR is for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma who are intolerant to or have progressed on sorafenib therapy. Table 1 summarizes the submitted economic model.

**Table 1. Submitted Economic Model**

| | |
|---|---|
| **Funding Request/Patient Population Modelled** | Nivolumab as monotherapy for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic HCC that are intolerant to or have progressed on sorafenib therapy.<br><br>The modeled patient population was Canadian adults with advanced hepatocellular carcinoma (HCC) that have received prior treatment with or are intolerant to sorafenib. |
| **Type of Analysis** | *CUA & CEA* |
| **Type of Model** | *A three state (pre-progression, post-progression and death) partitioned-survival with weekly cycle length* |
| **Comparator** | *Base Case: Best Supportive Care (BSC)*<br><br>*Scenario analysis: Regorafenib* |
| **Year of costs** | *2016 Canadian dollars* |
| **Time Horizon** | *Lifetime* |
| **Perspective** | *Government (public payer perspective)* |
| **Cost of Nivolumab** | Nivolumab costs $782.22 per 40mg vial and $1,955.56 per 100mg vial, or $19.556 per mg.<br><br>In the model, the base case analysis used the method of moments technique to calculate the average number of vials for each administration of nivolumab.<br><br>At the recommended dose of 3mg per kg every two weeks, Nivolumab costs:<br>• $4,474.52 per 14-day course<br><br>This calculation was based on average body weight of 69.59 kg +/- 14.58kg, each administration use two 100 mg vials plus 0.72 40 mg vials and accounted for $391.24 of wastage. |
| **Cost of Best Supportive Care** | The submitted model assumed zero drug cost for BSC. |
| **Cost of Regorafenib** | Regorafenib costs $6,115.51 per pack of 40 mg 84 |

| | |
|---|---|
| | tablets. |
| **Model Structure** | *A partitioned survival model with three discrete health states was developed to evaluate the cost-utility of nivolumab in patients with HCC. The 3 health states were: progression-free (on/off treatment), progressed (on/off treatment), and death. It was assumed that any survival benefit could be extrapolated beyond the follow-up period and be adequately captured using parametric survival models. Expected (mean) values for costs and effects were obtained from probabilistic analysis.*<br>  <br> |
| **Key Data Sources** | *CheckMate 040[1], an ongoing, multicentre, non-comparative (single-arm), dose escalation and expansion trial (Phase 1/2) for nivolumab, BRISK-PS[2] for BSC, and RESORCE[3] for regorafenib. The comparison of nivolumab with BSC and regorafenib was informed by a manufacturer-sponsored indirect treatment comparison (ITC)* |

## 1.2 Clinical Considerations

**According to the pCODR Clinical Guidance Panel (CGP)**, the comparison of nivolumab to best supportive care is appropriate. Regorafenib was also recognized as a relevant comparator. The Submitter included this comparison as scenario analysis in the submitted model.
Relevant issues identified included:

- The CGP concluded that there ***may be*** a net overall clinical benefit with the use of nivolumab in patients with sorafenib-refractory or intolerant advanced HCC, with Child-Pugh Class A hepatic reserve and an ECOG performance status of 0-1.
- The response rate observed in the CheckMate 040 study was associated with an encouraging overall survival benefit. Clinicians reported that objective response rates are rarely observed in patients with hepatocellular carcinoma treated with systemic therapies.
- In HCC, tumor objective response rates have not been validated as a surrogate endpoint for overall survival.
- The overall survival observed in this non-comparative, single arm trial is encouraging but it is in context of comparison to historical data. Given the size of the study and the lack of a comparative arm, interpretation and generalizability is limited.
- An improvement in overall survival has not been established.

- The toxicities observed with nivolumab in this patient population were expected and manageable compared to those observed in larger studies of other tumor types.
- Nivolumab offers a potentially clinically effective therapy in a disease setting where the available options are limited.
- The lack of a comparative arm in CheckMate 040 is a major barrier to estimating the effectiveness of nivolumab in this patient population.

**Summary of registered clinician input relevant to the economic analysis**
The clinicians providing input reported an unmet need among patients with HCC and that nivolumab would be useful. However, as the current review is based off of a phase 1/2 trial, the clinician input questioned whether this was appropriate. The opinion of the clinicians emphasized that the decision to approve nivolumab for use among patients should be based on phase three clinical data.

**Summary of patient input relevant to the economic analysis**
Patient input noted that currently, sorafenib is the only available treatment for patients with advanced stage HCC, however, the drug comes with many side effects and reduces their quality of life. Patient contacts reported having limited treatment options, and that they value new and better treatment options. The economic model used best supportive care as a comparator which would be considered an appropriate management strategy. A scenario analysis was also considered comparing nivolumab to regorafenib, a treatment option that was recently recommended for funding.

**Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis**
PAG considered the following factors would be important to consider if implementing a funding recommendation for nivolumab which are relevant to the economic analysis:

- Nivolumab is administered intravenously; chemotherapy chair time and nursing resources would be required to administer nivolumab
- PAG is seeking clarity on treatment duration and guidance on whether retreatment with nivolumab would be appropriate
    - Treatment with nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. The median duration of treatment among the 2L cohort was 5.26 months, and the median number of treatment cycles was 12 (range, 1-41).
- PAG is seeking whether there is information to guide sequencing of nivolumab and regorafenib in patients who have failed first line sorafenib.
    - The model did not assume treatment after nivolumab, however patients were allowed to be treated beyond progression. The CGP noted that other therapies are available after treatment with nivolumab, but there is currently no evidence to guide the sequencing of available treatments.
- PAG is seeking clarification that the dosing strategy of 3mg/kg up to maximum of 240mg, administered every two weeks, and other dosing strategies (e.g. 480mg every 4 weeks) would be appropriate for HCC, as with other cancers.
    - The 480mg every 4 weeks doing strategy was not included in the economic model and could not be explored.

## 1.3 Submitted and EGP Reanalysis Estimates

According to the economic analysis that was submitted by **Bristol-Myers Squibb** when nivolumab is compared with the best supportive care:

- The extra cost of nivolumab is $159,461(ΔC). Costs considered in the analysis included drugs, disease management, and adverse events.

- The extra clinical effect of nivolumab is 0.99 quality-adjusted life years and 1.13 life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, and utilities.

The submitter estimated that the incremental cost-effectiveness ratio was $161,944 per QALY. The submitter also submitted a scenario analysis of nivolumab is compared with regorafenib. When compared with regorafenib, the submitter estimated that the incremental cost-effectiveness ratio was $135,584 per QALY.

The EGP used the model submitted by **Bristol-Myers Squibb** and performed reanalyses. Detailed tables reporting the results of the EGP Reanalysis were provided in Section 1.4. The EGP estimates differed from the submitted estimates. Comparison between the submitted model and EGP reanalysis results was provided in **Table 2**.

**Table 2. Submitted and EGP Estimates for Nivolumab versus BSC**

| Estimates (range/point) | Submitted | EGP Reanalysis Lower Bound | EGP Reanalysis Upper Bound |
|---|---|---|---|
| ΔE (LY) | 1.13 LYs | 0.66 LYs | N/A |
| Progression-free | 0.32 | 0.29 | |
| Post-progression | 0.81 | 0.37 | |
| ΔE (QALY) | 0.99 QALYs | 0.47 QALYs | N/A |
| Progression-free | 0.28 | 0.22 | |
| Post-progression | 0.71 | 0.25 | |
| ΔC ($) | $159,461 | $91,831 | N/A |
| ICER estimate ($/QALY) | $161,944 | $193,458 | N/A |
| N/A = not available due to uncertainty of the efficacy data, the upper bound is not estimable | | | |

**Table 3. Submitted and EGP Estimates for Nivolumab versus Regorafenib (Scenario Analysis)**

| Estimates (range/point) | Submitted | EGP Reanalysis Lower Bound | EGP Reanalysis Upper Bound |
|---|---|---|---|
| ΔE (LY) | 0.70 | 0.37 | N/A |
| Progression-free | 0.06 | 0.02 | |
| Post-progression | 0.64 | 0.35 | |
| ΔE (QALY) | 0.70 | 0.25 | N/A |
| Progression-free | 0.09 | 0.02 | |
| Post-progression | 0.61 | 0.24 | |
| ΔC ($) | $94,754 | $40,442 | N/A |
| ICER estimate ($/QALY) | $135,584 | $159,708 | N/A |
| N/A = not available due to uncertainty of the efficacy data, the upper bound is not estimable | | | |

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

- Lack of direct comparative effectiveness estimates: There were no head-to-head clinical trials comparing nivolumab to the comparators included in this review. Indirect comparisons were done to compare nivolumab to relevant comparators including BSC and regorafenib. The ITC for nivolumab versus BSC used individual-patient level data and the ITC for nivolumab versus regorafenib used a match-adjusted indirect treatment comparison. However, the uncertainty generated from the ITC was not incorporated in the economic model, therefore there remains considerable uncertainty in relative efficacy between the two treatment arms. For OS, the results of the covariate-adjusted analysis and match adjusted indirect comparisons were consistent, and showed a statistically

significant treatment benefit for nivolumab compared to BSC/placebo and regorafenib. For PFS, a treatment benefit was shown for nivolumab that was marginally better than BSC/placebo; however, no difference in PFS was observed when nivolumab was compared to regorafenib. The pCODR Methods Team concluded the ITC results should be interpreted with caution considering a number of limitations associated with the ITCs that raise uncertainty in the treatment estimates obtained.

- Extrapolation of overall survival using short term data: The median follow-up in the Checkmate 040 trial was relatively short (median follow-up of 14.9 months, with insufficient long term follow up (overall survival data may be immature). An improvement in overall survival has not been established.

- Utilities: CGP/EGP identified that the utilities used in the model from the CheckMate 040 trial may be higher than what would be seen in patients outside of a clinical trial.

- Treatment duration of nivolumab: Treatment duration was modeled using either extrapolated PFS curve or the time to discontinuation curve. Time to treatment discontinuation data from CheckMate 040 were used to define the time on treatment (ToT) for nivolumab and regorafenib, respectively. There is possibility that patients will be on nivolumab for longer than was modeled. The EGP requested the submitter to model a longer treatment duration at the time of the Checkpoint meeting. However, the submitter responded that it was not appropriate to extend the treatment duration of nivolumab in the model. They noted that for the model base-case, time-on-treatment for nivolumab was modeled according to best practices using extrapolated time to discontinuation (TTD) data from the Checkmate 040 trial. In the CheckMate 040 trial, patients could be treated as long as clinical benefit was observed or until treatment was no longer tolerated by the patient (i.e., treatment could be continued after progression). In CheckMate 040, 78 of 145 patients (53.8%) were treated beyond progression (Database lock March 17, 2017). The submitter noted that the TTD data were relatively mature, therefore it is unlikely that the TTD extrapolation significantly underestimates the treatment duration likely to be observed in clinical practice. The EGP was unable to evaluate the effect of prolonged treatment on the extra cost in the submitted model, which may be one of main cost drivers in the model.

- Administration costs: The EGP felt that the administration costs accounted for in the model were underestimated. The submitter estimated the total administration costs were $54.25 biweekly for nivolumab, which included the clinical administration of nivolumab supervised by a clinician. The total administration costs for regorafenib were $20.50 every 21 days to a maximum of 6 services per patient per 12 month period, which included the cost of clinical management of oral chemotherapy. Both of these costs were sourced from the Ontario Schedule of Benefits. In the comparison to BSC, the only administration cost accounted for was a physician clinic cost. The EGP and CGP noted that this is not an adequate reflection of the actual resource costs. Several other administration costs that would be associated with administering nivolumab including 3 to 4 pharmacy personnel per dose per patient to do various safety checks and calculations, a nurse to do an IV start and set up the infusion and pump and monitor periodically over the course of the 30-60 minute treatment, and medical clerks who book follow-up appointments and tests. Sensitivity analyses were done on this parameter and it was determined that the impact of increasing the administration cost by 50% has a very minimal impact on the ICER. However, running a sensitivity analysis where the administration costs in the submitter's model are increased by 50% still highly underestimates the true costs.

- Subsequent therapies were not included in the model. This was considered to be appropriate by the CGP. However, the CGP noted that other therapies are available after treatment with nivolumab, but there is currently no evidence to guide the sequencing of available treatments.

## 1.4 Detailed Highlights of the EGP Reanalysis

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

The EGP re-conducted several probabilistic scenario analyses. The EGP considered the following important factors with consulting with the clinical experts:

- Time horizon: The time horizon was shortened to 3 years from a lifetime in submitted base case. The time horizon was shortened to address the uncertainty in survival estimates based on extrapolation of short term trial data (14.9 months) and to reflect the clinical opinion of the CGP.
- Utilities: Used 0.76 for pre-progression; 0.68 for progressed. CGP/EGP identified that the utilities used in the model from the CheckMate 040 trial may be higher than what would be seen in patients outside of a clinical trial. Because of this, the regorafenib pCODR review was referenced, which addressed the same patient population. The pCODR Review Team for this review also determined that the utilities from the trial appeared overestimated, and two literature sources that reported utility values for the same patient population were found to be more appropriate. The same sources for the utilities were used in the EGP's reanalysis.[4,5] It was noted by the EGP that the utility in quality-adjusted life years generated in the post-progression state was higher than the pre-progression state. In the model, the time that patients spend in the progression-free state is relatively short compared to their survival, and patients could continue to be treated beyond progression.
- Data source of PFS and OS curves for comparison between nivolumab and BSC: Used RESORCE trial instead of BRISK trial. The BRISK trial was used as the data source for the ITC to generate PFS and OS curves for the BSC in the comparison of nivolumab and BSC in the original submission. The CGP felt that it would be more appropriate to use the RESORCE trial as the data source for the BSC PFS and BSC OS curve generation rather than using the BRISK trial because it may better reflect the BSC patient population.

Given the lack of comparative effectiveness estimates and the inability to evaluate the uncertainty from the indirect treatment comparison, it is not possible to place an upper bound on the ICER. It is difficult to have an idea of where the ICER would lie. There is also considerable uncertainty in the lower bound of the ICER due to certain parameters that the EGP was not able to explore (i.e. Testing the confidence interval of the hazard ratio for the treatment effect between nivolumab and the comparator, and extending the treatment duration past a certain cut-off). For example, if a different assumption about the treatment was made and it was extended for a longer period of time, then the EGPs ICER estimate would likely be underestimated. There was also a large difference in the ΔC ($) from the submitted model ($159,461) and the EGP's reanalysis ($91,831) when comparing nivolumab to BSC. The main reason for this difference is due to a large difference in the cost of nivolumab from shortening the time horizon to three years.The same large difference in the ΔC ($) occurred in the comparison of nivolumab to regorafenib primarily due to the shortened time horizon.

An estimate of the lower bound of the ICER is provided in **Table 4 and Table 5**. The EGP reran the probabilistic analysis to determine an estimate of the ICER for the following scenario:

- Time horizon of 3 years

- Utilities based on previous pCODR review of regorafenib as second-treatment for patients with hepatocellular carcinoma (HCC) following treatment with sorafenib
- Used RESORCE trial instead of BRISK trial as data source of PFS and OS curves for comparison between nivolumab and BSC
- Keep all the other parameters using the default value as set by the manufacturer

Based on 5,000 iterations, the EGP's best estimate of the lower bound of the ICER between nivolumab and BSC is $193,458 per QALY.

Based on 5,000 iterations, the EGP's best estimate of the lower bound of the ICER between nivolumab and regorafenib (scenario analysis) is $159,708/ QALY.

Below are detailed tables describing the analyses conducted by the EGP on the submitter's base case models. Scenario analyses were conducted by changing one parameter in the model and running a probabilistic analysis. **Table 4** shows the EGPs analyses on the model for the comparison of nivolumab to BSC, and **Table 5** shows the EGPs analyses on the model for the comparison of nivolumab to regorafenib (scenario analysis).

**Table 4. Detailed Description of EGP Reanalysis for Comparison between Nivolumab and BSC**

| | ΔC | ΔE QALYs | ΔE LYs | ICUR (QALY) | Δ from baseline submitted ICER |
|---|---|---|---|---|---|
| Baseline (Submitter's best case) | $159,461 | 0.99 | 0.98 | $161,944 | ---- |
| LOWER BOUND | | | | | |
| *Time horizon - 3 years* | $92,634 | 0.49 | 0.57 | $190,800 | $28,856 |
| *Utilities - pre-progression: 0.76, progressed: 0.68* | $158,550 | 0.82 | 1.13 | $192,599 | $30,655 |
| *Data source for PFS and OS curves - RESORCE* | $159,675 | 1.14 | 1.31 | $140,263 | -$21,681 |
| Best case estimate of above 3 parameters | $91,831 | 0.47 | 0.66 | $193,458 | $31,514 |
| UPPER BOUND | | | | | |
| No upper bound given the uncertainty of the data | | | | | |

**Table 5. Detailed Description of EGP Reanalysis for Comparison between Nivolumab and Regorafenib (Scenario Analysis)**

| | ΔC | ΔE QALYs | ΔE Lys | ICUR (QALY) | Δ from baseline submitted ICER |
|---|---|---|---|---|---|
| Baseline (Submitter's best case) | $94,754 | 0.70 | 0.70 | $135,584 | -- |
| LOWER BOUND | | | | | |
| *Time horizon - 3 years* | $40,436 | 0.32 | 0.37 | $127,866 | -$7,718 |
| *Utilities - pre-progression: 0.76, progressed: 0.68* | $94,704 | 0.58 | 0.71 | $161,994 | $26,360 |
| *Data source for PFS and OS curves - RESORCE (same as base case but ran PSA again)* | $94,788 | 0.70 | 0.69 | $137,066 | $1,482 |
| Best case estimate of above 3 parameters | $40,442 | 0.25 | 0.37 | $159,708 | $24,124 |
| UPPER BOUND | | | | | |
| No upper bound given the uncertainty of the data | | | | | |

**Table 6. Results of one-way scenario analyses for price reductions of nivolumab, using EGP best estimate lower bound (Nivolumab versus BSC), probabilistic results (5,000 iterations)**

| | Price / nivolumab 40 mg vial | Price/nivolumab 100 mg vial | Δ costs | Δ effects | Result ($/QALY) | Δ from lower bound |
|---|---|---|---|---|---|---|
| List price | $782.22 | $1,955.56 | $91,831 | 0.47 | $193,458 | --- |
| -25% | $586.66 | $1,466.67 | $67,859 | 0.47 | $146,854 | -46,604 |
| -50% | $391.11 | $977.78 | $46,006 | 0.47 | $97,701 | -95,757 |
| -75% | $195.55 | $488.89 | $22,944 | 0.47 | $48,593 | -144,865 |

## 1.5 Evaluation of Submitted Budget Impact Analysis

The budget impact analysis (including wastage) is from a Canadian perspective, including only national values for the eligible patient population and the associated costs. The factors that most influence the budget impact include eligible population size, duration of therapy, drug cost and market share. The EGP identified a significant market share reduction assumption in year 2 and year 3 for nivolumab in the submitted BIA, which may potentially create a larger overall budget impact. The submitter's rationale for this was that they had made the assumption that the nivolumab will become first-line treatment for advanced HCC in the near future, which would cause the market share of nivolumab in the post-sorafenib setting to decline from Years 1 to 3. At this time, nivolumab in the first line setting for patients with advanced HCC is not available in Canada; a Phase 3 trial comparing nivolumab to sorafenib in the first-line setting is ongoing. Key limitations of the BIA model include population size, duration of therapy, drug cost and market share. It is difficult to determine how accurate the eligible population, duration of

therapy, and market share at this point of time. However, these parameters were able to be modified and explored by the EGP.

## 1.6 Conclusions

**The EGP's best estimate of ΔC and ΔE for nivolumab when compared to best supportive care is:**

- The ICER would likely be between $193,458/QALY and unknown.

- This unknown upper bound of the ICER provided by the EGP reflects a considerable amount of uncertainty present in the incremental benefit of nivolumab against BSC. It is difficult to estimate where the best estimate would likely be. The extra cost of nivolumab is between $91,831 and unknown (ΔC). The main factors that influence the ΔC of the best estimate are the cost of nivolumab and the time horizon. It should be noted that the EGP was unable to evaluate the effect of prolonged treatment on the extra cost in the submitted model, which may be one of main cost drivers.

- The extra clinical effect of nivolumab is between 0.47 and unknown (ΔE**)**. The main factors that influence ΔE are the data source choice for the OS curves for BSC, OS extrapolation model and a shortened time horizon. It should be noted that EGP was unable to evaluate the uncertainty of the indirect comparison in the submitted model, which may be one of the main clinical effect drivers.

**The EGP's best estimate of ΔC and ΔE for nivolumab when compared to regorafenib is:**

- The ICER would likely be between $159,708/QALY and unknown.

- This unknown upper bound of ICERs provided by the EGP reflects a considerable amount of uncertainty present in the incremental benefit of nivolumab against regorafenib. It is difficult to estimate where the best estimate would likely be.

- The extra cost of nivolumab is between $40,442 and unknown (ΔC). The main factors that influence the ΔC of the best estimate are the cost of nivolumab and the time horizon. It should be noted that the EGP was unable to evaluate the effect of prolonged treatment on the extra cost in the submitted model, which may be one of main cost drivers.

- The extra clinical effect of nivolumab is between 0.25 and unknown (ΔE). The main factors that influence ΔE are the data source choice for the OS curves for BSC, OS extrapolation model and a shortened time horizon. It should be noted that EGP was unable to evaluate the uncertainty of the indirect comparison in the submitted model, which may be one of the main clinical effect drivers.

**Overall conclusions of the submitted model:**

- **Model Structure**
    - The economic model structure and the parametric extrapolation are appropriate, however, the model did not consider the uncertainty generated from the indirect treatment comparison. The parametric curve selection by the submitter was based on goodness-of-fit (the curves with the lowest AIC and BIC values), visual inspection, and clinical plausibility through discussions with clinicians. The

parametric curves used in the Nivolumab versus BSC comparison were log-logistic for OS, generalised gamma for PFS, and gompertz for TTD.

- **Data Inputs**
    - There are no comparative effectiveness trials available. The effectiveness data used in the economic model were based on indirect treatment comparison.
- **Patient Input**
    - The factors relevant to patients were taken into consideration in the economic model.
- **Overall**

Overall, the model structure and the parametric extrapolation are appropriate, however, given the lack of comparative effectiveness estimates and the inability to evaluate the uncertainty from the indirect treatment comparison, it is not possible to place an upper bound on the ICER, and there is considerable uncertainty in the EGP's best estimate of the lower bound of the ICER. Because of this, it is difficult to estimate where the ICER would lie.

# 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 Gastrointestinal Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of nivolumab for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma who are intolerant to or have progressed on sorafenib therapy. A full assessment of the clinical evidence of nivolumab for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular 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 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. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 Jun;389:2492-502.

2. Llovet J, Decaens T, Raoul J, Boucher E, Kudo M et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS Study. J Clin Oncol. 2013 Oct;31(28); 3509-3516.

3. Bruix J, Qin S, Merle P, Granito A, Huang YH et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan;389(10064);56-66.

4. Leung HW, Liu CF, Chan AL. Cost-effectiveness of sorafenib versus SBRT for unresectable advanced hepatocellular carcinoma. Radiat Oncol. 2016;11:69.

5. Camma C, Cabibbo G, Petta S, Enea M, Iavarone M, Grieco A, et al. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. Hepatology. 2013;57(3):1046-54.

6. European Medicines Agency. Medicines – Withdrawn applications. Opdivo. 2018. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003985/wapp/Post-authorisation/human_wapp_000238.jsp&mid=WC0b01ac058001d128

7. European Medicines Agency. Questions and answers on the withdrawal of the marketing authorisation application for Opdivo (nivolumab). 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2017/09/WC500234787.pdf