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Reimbursement Recommendation

Nivolumab Plus Ipilimumab (Opdivo Plus Yervoy)

Indication: Opdivo (nivolumab), in combination with ipilimumab, for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma

Sponsor: Bristol Myers Squibb Canada Co.

Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Opdivo Plus Yervoy?

Canada's Drug Agency (CDA-AMC) recommends that Opdivo plus Yervoy be reimbursed by public drug plans for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) if certain conditions are met.

Why Did CDA-AMC Recommend Reimbursement?

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) determined that Opdivo plus Yervoy demonstrates acceptable clinical value versus tyrosine kinase inhibitors (TKIs) (sorafenib and lenvatinib), and immunotherapies (atezolizumab plus bevacizumab, and durvalumab plus tremelimumab) in adults with HCC at an advanced stage when it can no longer be surgically removed (unresectable or advanced). This determination was enough for pERC to recommend that Opdivo plus Yervoy be reimbursed.

Given that Opdivo plus Yervoy is expected to be an alternative to TKIs or currently available immunotherapies, acceptable clinical value refers to at least comparable value versus TKIs and immunotherapies. Evidence from a clinical trial (CheckMate 9DW) showed that treatment with Opdivo plus Yervoy likely results in patients living longer (improved overall survival [OS]) compared with sorafenib and lenvatinib at 24 months in patients with unresectable or advanced HCC. Evidence from an indirect treatment comparison suggested better OS with Opdivo plus Yervoy compared to other immunotherapies (atezolizumab plus bevacizumab, and durvalumab plus tremelimumab) after 6 months in adults with unresectable or advanced HCC.

Opdivo plus Yervoy was considered an alternative immunotherapy option that may offer a clinical benefit for some patients beyond 6 months of treatment. A key limitation of the evidence is the absence of information identifying which patients are at a higher risk of death in the first 6 months of treatment.

Which Patients Are Eligible for Coverage?

Opdivo plus Yervoy should only be covered for the first-line treatment of adults with unresectable or advanced HCC who have Child-Pugh score class A and good performance status. Opdivo plus Yervoy should not be covered if the patient has been previously treated for unresectable or advanced HCC.

Summary

What Are the Conditions for Reimbursement?

Opdivo plus Yervoy should be prescribed by and managed under the care of clinicians with expertise in managing unresectable or advanced HCC. Reimbursement should be for a maximum of 2 years of treatment. Reimbursement should be discontinued if the cancer becomes worse or there are unacceptable side effects. The total treatment cost of Opdivo plus Yervoy should not exceed that of treatment with the least costly immunotherapy comparator.

Important economic feasibility must be addressed for health systems to be able to adopt Opdivo plus Yervoy due to the magnitude of uncertainty in the budget impact.

Review Background

- **Disease background:** Hepatocellular carcinoma is liver cancer that starts in the cells that make up the body of the liver. Patients identified emotional distress, loss of independence, disruption to employment and family life, and reduction in quality of life as the negative impact of hepatocellular carcinoma. In 2023, the estimated incidence of liver and intrahepatic bile duct cancer in Canada was 4,700 new cases, and the estimated mortality was 3,500 deaths.
- **Indication and reimbursement request:** Nivolumab (Opdivo) in combination with ipilimumab has been approved by Health Canada for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma. The sponsor is seeking reimbursement for this patient population.
- **Drug under review:** Nivolumab is a PD-1 inhibitor. It is administered by IV infusion, and the dosage recommended in the product monograph is 1 mg/kg every 3 weeks along with 3 mg/kg of ipilimumab, also administered intravenously, for up to a maximum of 4 doses. After completing the maximum 4 doses of combination therapy, nivolumab is administered as a single drug until disease progression or unacceptable toxicity, or for up to 2 years. The dosage recommended in the product monograph is 240 mg every 2 weeks, or 480 mg every 4 weeks for the single drug phase.
- **Treatment costs:** At the submitted price of $782.22 per 40 mg/4 mL vial, the 28-day cycle cost of nivolumab is expected to be $2,086 per patient in the first four 28-day cycles (combination phase) and $9,387 in subsequent cycles (single-agent phase), based on the Health Canada–recommended dosage. At the submitted price of $5,800.00 per 50 mg/10 mL vial, the 28-day cycle cost of ipilimumab is expected to be $38,667 per patient in the combination phase, based on the Health Canada–recommended dosage. Therefore, the 28-day cycle cost of nivolumab plus ipilimumab is expected to be $40,753 per patient in the first 4 cycles (combination phase) and then $9,387 in subsequent cycles (single-agent phase).

Highlights of Input From Interested Parties

The patient groups (Liver Canada, The Canadian Cancer Survivor Network, Cholangio-Hepatocellular Carcinoma Canada, and the Colorectal Cancer Resource & Action Network) noted the following regarding impacts of the disease, unmet needs, and important outcomes:

- The debilitating symptoms of hepatocellular carcinoma include chronic pain, fatigue, significant weight loss, muscle wasting, and impaired mobility.
- The negative impacts of hepatocellular carcinoma are emotional distress, loss of independence, disruption to employment and family life, and reduction in quality of life.
- Important treatment outcomes include living longer, maintaining quality of life, minimizing adverse events, slowing cancer progression, and improving access to treatments.

- There is a need for additional treatment options, access to treatments with improved tolerability, and systemic changes to improve early detection, referral pathways, and equitable drug and testing access and to avoid disparities in survival and quality of life, particularly in rural communities.

The clinician groups (the Canadian Gastrointestinal Oncology Evidence Network and Ontario Health [Cancer Care Ontario] Gastrointestinal Cancer Drug Advisory Committee) and the clinical experts consulted by CDA-AMC noted the following regarding unmet needs arising from the disease and place in therapy for the drug under review:

- There is a need for additional treatment options with, for example, a higher chance of complete response and a higher likelihood of downstaging to curative therapy so that a patient may be able to stop treatment.
- The anticipated place in therapy of nivolumab plus ipilimumab would be as a first-line immunotherapy combination treatment option.

The participating public drug programs raised potential implementation issues related to considerations for initiation, renewal, discontinuation, and prescribing of therapy; generalizability of trial populations to broader populations; care provision issues; system and economic issues; and potential need for a provisional funding algorithm.

Recommendation

With a vote of 10 in favour to 6 against, pERC recommends that nivolumab plus ipilimumab be reimbursed for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma only if the conditions listed in Table 1 are met.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Nivolumab in combination with ipilimumab should be reimbursed for the first-line treatment of adult patients with unresectable or advanced HCC who meet all the following criteria: 1.1. Confirmed unresectable HCC 1.2. Child-Pugh score class A 1.3. Good performance status.	Evidence from the CheckMate 9DW study demonstrated that treatment with nivolumab in combination with ipilimumab resulted in at least comparable clinical benefit compared to lenvatinib or sorafenib for adults with unresectable or advanced HCC, preserved liver function, and ECOG PS of 0 or 1.	Treatment with nivolumab in combination with ipilimumab would be reasonable in the following scenarios at the discretion of the treating clinician: • patients with an ECOG PS of 2 • patients who had partial resection, but failure to remove all HCC • patients with HCC where there is evidence of residual disease that can no longer be treated by locoregional therapies. pERC noted that patients with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC were

Reimbursement condition	Reason	Implementation guidance
		excluded from the CheckMate 9DW trial and should not be considered eligible.
2. Patients are ineligible for treatment with nivolumab in combination with ipilimumab if they have received any prior systemic treatment for unresectable or advanced HCC.	There is no evidence for the efficacy of nivolumab in combination with ipilimumab in patients who have received any systemic therapy for unresectable or advanced HCC. These criteria align with the CheckMate 9DW study population.	Treatment with nivolumab in combination with ipilimumab would be reasonable for patients who had received locoregional therapy (which is not considered systemic therapy). For patients with HCC who are currently on other immunotherapy regimens (atezolizumab in combination with bevacizumab or durvalumab in combination with tremelimumab), whose disease has not progressed but who experience serious adverse effects (such as severe proteinuria or gastrointestinal perforation) or intolerance to their current treatment, it would be reasonable to consider switching to nivolumab in combination with ipilimumab on a limited time basis at the time of implementation.
Discontinuation		
3. Reimbursement of nivolumab plus ipilimumab should be discontinued upon occurrence of: 3.1. disease progression 3.2. unacceptable toxicity 3.3. a maximum of 2 years of treatment.	Patients in the CheckMate 9DW study were given treatment for a maximum of 2 years from the start of the study treatment.	pERC noted that the CheckMate 9DW study did not provide evidence about re-treatment with nivolumab plus ipilimumab because patients received treatment for a maximum of 2 years. However, pERC agreed with the clinical experts and advised that if treatment with nivolumab in combination with ipilimumab was discontinued before the completion of 2 years of therapy for reasons other than progression or after the completion of 2 years of therapy, patients may receive an additional year of treatment with nivolumab plus ipilimumab if progression occurs more than 6 months after stopping treatment. The additional year of treatment should include nivolumab plus ipilimumab for a maximum of 4 cycles, followed by nivolumab monotherapy. It would be reasonable to consider stopping treatment with ipilimumab and transitioning to nivolumab monotherapy earlier for patients who experience unacceptable toxicity.
Prescribing		
4. Nivolumab plus ipilimumab should be prescribed by and managed under the care of clinicians with	This is meant to ensure that nivolumab plus ipilimumab is prescribed for patients for whom it is appropriate and that	Due to the toxicities associated with nivolumab plus ipilimumab, particularly in the first year of treatment, pERC indicated

Reimbursement condition	Reason	Implementation guidance
expertise in managing unresectable or advanced HCC.	adverse effects are managed in an optimized and timely manner.	that increased monitoring for immune-related adverse events (such as hepatitis) is likely required. pERC agreed with the clinical experts that subcutaneous nivolumab would be a reasonable alternative to IV nivolumab for the single-agent phase of the indication under review. pERC noted that jurisdictions may consider applying weight-based dosing to a cap for nivolumab maintenance and may dose at every 2 weeks or every 4 weeks, as clinically appropriate.
Pricing		
5. The total treatment cost of nivolumab plus ipilimumab should be negotiated so that it does not exceed that of treatment with the least costly immunotherapy comparator (i.e., durvalumab plus tremelimumab or atezolizumab plus bevacizumab) for the same indication.	Based on the committee's assessment of the evidence, no definitive conclusion could be drawn regarding the comparative efficacy and safety of nivolumab plus ipilimumab vs. durvalumab plus tremelimumab or atezolizumab plus bevacizumab due to the low certainty of the evidence submitted by the sponsor. Therefore, the total treatment cost of nivolumab plus ipilimumab should be no more than the least costly immunotherapy for the same indication.	—
Feasibility of adoption		
6. The economic feasibility of adopting nivolumab plus ipilimumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption.	—

ECOG PS = Eastern Cooperative Oncology Group Performance Status; HCC = hepatocellular carcinoma; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; vs. = versus.

[a]For the statement regarding the size of the price reduction required, band 1 = 1% to 24%, band 2 = 25% to 49%, band 3 = 50% to 74%, and band 4 = 75% or greater.

Rationale for the Recommendation

Clinical Value

Based on the totality of the clinical evidence, pERC concluded that nivolumab plus ipilimumab demonstrates acceptable clinical value compared with TKIs (sorafenib and lenvatinib) and immunotherapies (atezolizumab plus bevacizumab, and durvalumab plus tremelimumab) in adult patients with unresectable or advanced HCC. Given that nivolumab plus ipilimumab is expected to be an alternative to TKIs or currently available immunotherapies, acceptable clinical value refers to at least comparable value versus TKIs and immunotherapies.

Evidence from 1 phase III, open-label, sponsor-blind, randomized controlled trial (CheckMate 9DW) demonstrated that treatment with nivolumab plus ipilimumab likely results in added clinical benefit for patients with unresectable or advanced HCC compared with the investigator's choice of TKI (sorafenib or lenvatinib) in OS at 24 months. pERC noted that a detriment in OS was observed through the first 12 months when the Kaplan-Meier (KM) curves crossed; however, beyond 12 months, the curves remained separated, and at 24 months, nivolumab plus ipilimumab was likely associated with a clinically important increase in OS compared with sorafenib or lenvatinib. Results for progression-free survival (PFS) were similar in that the KM curves of PFS crossed between 9 and 12 months and remained separated in favour of nivolumab plus ipilimumab until 36 months.

Evidence from piecewise survival analyses of anchored simulated treatment comparisons (STCs) to other immunotherapies (atezolizumab plus bevacizumab, and durvalumab plus tremelimumab) suggested an improvement after 6 months in OS for the comparison between nivolumab plus ipilimumab and other immunotherapies (DUR + TRE: [redacted]; ATE + BEV: [redacted], but this is associated with some uncertainty due to imprecision (i.e., the 95% confidence intervals [CIs] included the null, suggesting the potential for little to no difference). Similarly, according to the results for PFS at 6 months and beyond, nivolumab plus ipilimumab was favoured over durvalumab plus tremelimumab and atezolizumab plus bevacizumab. Overall, there is low certainty in the STC results primarily due to limitations such as a violation of the proportional hazards assumption within some of the segments using the 6-month cut point and heterogeneity that could not be accounted for due to the lack of a common comparator across studies.

Patients identified a need for treatments with improved tolerability, and clinicians identified a need for more effective treatment options that could lead to complete response and do not increase the risk of bleeding, or treatments that are potentially curative. pERC noted that nivolumab plus ipilimumab does not address these unmet clinical needs; however, it is an alternative immunotherapy option that may offer a clinical benefit for some patients beyond 6 months of treatment. pERC noted that a key limitation of the evidence is the absence of information identifying which patients are at a higher risk of mortality in the first 6 months of treatment.

Further information on the committee's discussion around clinical value is provided in the Summary of Deliberation section.

Developing the Recommendation

The determination of acceptable clinical value was sufficient for pERC to recommend reimbursement of nivolumab plus ipilimumab. As part of the deliberation on whether to recommend reimbursement, the committee also considered unmet clinical need, unmet nonclinical need, and health inequity. Information on this discussion is provided in the Unmet Clinical Need and Distinct Social and Ethical Considerations domains in the Summary of Deliberation section.

Because pERC recommended that nivolumab plus ipilimumab be reimbursed, the committee also deliberated on whether reimbursement conditions should be added to address important economic

considerations, health system impacts, or social and ethical considerations, or to ensure clinical value is realized. The resulting reimbursement conditions, with accompanying reasons and implementation guidance, are stated in Table 1.

Summary of Deliberation

pERC considered all domains of value of the deliberative framework before developing its recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, refer to Expert Committee Deliberation at Canada's Drug Agency.

The committee considered the following key discussion points, organized by the 5 domains of value.

Clinical Value

- **Appropriate comparators:** TKIs (lenvatinib) and immunotherapy regimens (atezolizumab plus bevacizumab, and durvalumab plus tremelimumab) were considered appropriate comparators for the drug under review. However, the immunotherapy options are most relevant given that the anticipated place in therapy for nivolumab plus ipilimumab is as an alternative immunotherapy treatment option.
- **Efficacy versus immunotherapies (atezolizumab plus bevacizumab, and durvalumab plus tremelimumab):** Comparisons to immunotherapy options were limited to indirect evidence that was assessed as evidence of low certainty. pERC reviewed evidence from piecewise survival analyses of anchored STCs to other immunotherapies (atezolizumab plus bevacizumab, and durvalumab plus tremelimumab). pERC concluded that the STCs suggested that nivolumab plus ipilimumab may result in improvements in OS and PFS beyond 6 months of treatment relative to durvalumab plus tremelimumab and atezolizumab plus bevacizumab. However, pERC also highlighted that treatment with nivolumab plus ipilimumab may also lead to higher mortality during the first 6 months of treatment. pERC noted that the certainty of this evidence was low due to methodological limitations, including violation of the proportional hazards assumption and lack of a common comparator across trials.
- **Efficacy versus investigator's choice of sorafenib or lenvatinib:** One randomized controlled trial (CheckMate 9DW; N = 668) demonstrated that treatment with nivolumab plus ipilimumab likely results in higher OS rates compared with sorafenib or lenvatinib, but this benefit is delayed. The median OS was 23.66 months (95% CI, 18.83 to 29.44 months) in the nivolumab plus ipilimumab group and 20.63 months (95% CI, 17.48 to 22.54 months) in the sorafenib or lenvatinib group. There was a violation of the proportional hazards assumption as evidenced by an early survival detriment with nivolumab plus ipilimumab relative to sorafenib or lenvatinib, which was addressed through prespecified supportive analyses (piecewise hazard ratio, unstratified Max-Combo test, and restricted mean survival time analyses) to account for the delayed effect. The absolute difference in the KM estimate of the probability of OS for nivolumab plus ipilimumab compared with sorafenib or

lenvatinib was [redacted], was –1.3% (–8.4% to 5.8%) at 12 months, and was 10.2% (95% CI, 2.5% to 18.0%) at 24 months. Results for PFS were similar and also handled through supportive, piecewise analyses. For PFS, the KM curves crossed between 9 and 12 months and remained separated in favour of nivolumab plus ipilimumab until 36 months. The median PFS (primary definition) was 9.07 months (95% CI, 6.60 to 10.51 months) in the nivolumab plus ipilimumab group and 9.20 months (95% CI, 7.89 to 11.07 months) in the sorafenib or lenvatinib group. The absolute difference in the KM estimate of the probability of PFS (primary definition) for nivolumab plus ipilimumab compared with sorafenib or lenvatinib was [redacted]. Lastly, nivolumab plus ipilimumab may improve health-related quality of life (HRQoL) based on the change from baseline in the Functional Assessment of Cancer Therapy–Hepatobiliary total score compared with sorafenib or lenvatinib, though the evidence was assessed as having low certainty.

- **Harms and challenges with identifying patients most suitable for treatment with nivolumab plus ipilimumab:** pERC discussed the evidence for harms observed with treatment with nivolumab plus ipilimumab versus TKIs in the CheckMate 9DW study. No evidence for harms compared to other immunotherapies was included in the submission. Overall, patients in the nivolumab plus ipilimumab group experienced numerically more adverse events (AEs), serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), and immune-mediated AEs, particularly grade 3 or 4 AEs, than patients in the sorafenib or lenvatinib group. pERC noted the most common immune-related AE of any grade was hepatitis as well as the greater number of deaths due to study drug toxicity (per investigator assessment), most of which were related to liver toxicities, in the nivolumab plus ipilimumab group compared to TKIs. The product monograph for nivolumab advises early diagnosis and appropriate management to minimize potential life-threatening complications, and based on input from the clinical experts, pERC indicated that increased monitoring for liver toxicities would likely be required when considering treatment with nivolumab plus ipilimumab. Even with the increased monitoring, some of the committee members expressed significant concerns with safety during the first year of treatment with nivolumab plus ipilimumab, particularly due to the absence of information identifying which patients are at a higher risk of mortality. The committee also acknowledged these concerns may be mitigated based on input from clinical experts who suggested that the use of nivolumab plus ipilimumab will likely be limited to select patients in clinical practice at the discretion of the treating clinician; however, it was unclear how patients at lower risk of complications would be identified.
- **Clinical importance of treatment effects:** Patient group input indicated that patients want to live longer, maintain quality of life, minimize AEs, slow progression, and improve the ease of access to patients. Regarding quality of life, nivolumab plus ipilimumab may improve HRQoL compared with sorafenib or lenvatinib, but the clinical importance of the effect is uncertain. Based on expert input, a 5% difference in OS and PFS was considered clinically important. As previously noted in the results for nivolumab plus ipilimumab versus TKIs in the CheckMate 9DW study, a clinically important increase in mortality and progression was observed at 6 months, but a clinically important decrease

in mortality and progression was observed at 24 months. pERC concluded that the availability of an additional treatment option for unresectable or advanced HCC is important to patients, but acknowledged the variability of clinically important treatment effects with nivolumab plus ipilimumab over time. Accordingly, pERC emphasized the importance of involving patients in decisions regarding their treatment by disclosing the risks and benefits.

- **Certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach:** The assessment of OS (at 6 months, 12 months, and 24 months) and PFS (at 6 months and 12 months) was rated as low to moderate certainty due to serious or very serious risk of imprecision. The assessment of PFS at 24 months was rated as high certainty. The assessment of HRQoL (Functional Assessment of Cancer Therapy–Hepatobiliary total score) was rated as low certainty due to a very serious risk of study limitations (missing data and bias due to the open-label study design). Harms outcomes — patients with SAEs of any grade and patients with WDAEs — were rated as high and moderate certainty, respectively. The moderate rating was due to serious risk of imprecision.
- **Clinical value:** Based on the preceding considerations, the committee determined that nivolumab plus ipilimumab demonstrates comparable clinical benefit compared with TKIs and immunotherapy regimens.

Unmet Clinical Need

- **Severity of the disease:** pERC acknowledged that, in Canada, HCC is the most common type of liver cancer and was the sixth leading cause of cancer-related death in 2023, and that the 5-year net survival is 18%.
- **Availability of treatment options:** Current treatments improve survival and control disease progression, with immunotherapy options being more effective than TKIs.
- **Input on unmet clinical need:** Patients identified a need for treatments with improved tolerability, and clinicians identified a need for more effective treatment options that could lead to complete response and do not increase the risk of bleeding, or treatments that are potentially curative. The committee noted that nivolumab plus ipilimumab does not address these unmet clinical needs.

Distinct Social and Ethical Considerations

- **Input on unmet nonclinical need:** The committee acknowledged the patient group input on nonclinical needs, which include a need for systemic changes to improve early detection, referral pathways, and equitable drug and testing access, and to avoid disparities in survival and quality of life, particularly in rural communities.
- **Equity considerations:** Patient and clinician groups have identified that people from systemically marginalized communities (Indigenous people, people who have recently immigrated to Canada, and people experiencing low income) face barriers to diagnosis, care coordination, and access to novel therapies for HCC, which contribute to disease progression and poorer health outcomes.

- **Access in smaller or rural centres:** pERC discussed the potential challenges of managing treatment with nivolumab plus ipilimumab in smaller or rural settings across Canada, but also noted that treatment should be prescribed by a clinician with expertise in the delivery of dual immunotherapy, particularly due to the potential toxicities and risk of mortality. Acknowledging that the delivery of care may vary across Canada, pERC deferred to the jurisdictions to determine the most appropriate way to implement care based on their region.
- **Significant unmet nonclinical need or health inequity:** pERC indicated that nivolumab plus ipilimumab does not significantly address the nonclinical needs or health inequities, though pERC acknowledged that the fixed duration of treatment with nivolumab plus ipilimumab for a maximum of 2 years may reduce the burden of treatment for some patients relative to other immunotherapies, which are continued until disease progression or unacceptable toxicity.

Economic Considerations

- **Health impacts of nivolumab plus ipilimumab versus relevant comparators:** Due to limitations associated with the sponsor's submitted STC, the comparative effectiveness between nivolumab plus ipilimumab versus durvalumab plus tremelimumab and versus atezolizumab plus bevacizumab was deemed of low certainty. Therefore, no definitive conclusions could be drawn.
  - The comparison with lenvatinib or sorafenib is considered less relevant because clinical experts have indicated that these therapies are generally used only in patients who are not eligible for immune-oncology treatment.
- **Cost of nivolumab plus ipilimumab versus relevant comparators:** The total treatment cost of nivolumab plus ipilimumab is lower than that of durvalumab plus tremelimumab or atezolizumab plus bevacizumab. This difference is primarily attributable to the fixed treatment duration of nivolumab plus ipilimumab (maximum of 2 years), whereas other immuno-oncology therapies are administered until disease progression.
- **Key findings of the economic evaluation:** Due to limitations associated with the sponsor's submitted STC, the comparative effectiveness between nivolumab plus ipilimumab versus durvalumab plus tremelimumab and versus atezolizumab plus bevacizumab was deemed of low certainty. Therefore, the evidence of clinical benefit is too uncertain to estimate the price reduction needed to ensure cost-effectiveness of nivolumab plus ipilimumab in relation to durvalumab plus tremelimumab or atezolizumab plus bevacizumab.
- **Certainty of the evidence:** The STC used to inform the comparative effectiveness of nivolumab plus ipilimumab relative to durvalumab plus tremelimumab and versus atezolizumab plus bevacizumab was deemed of low certainty. The committee concluded that nivolumab plus ipilimumab demonstrates comparable clinical benefit and harms compared with immunotherapy regimens. In addition, the lack of long-term data introduced additional uncertainty in the magnitude of the benefit of nivolumab plus ipilimumab.

Impacts on Health Systems

Anticipated budget impact: It is estimated that 1,794 patients would be eligible for treatment with nivolumab plus ipilimumab over a 3-year period (year 1 = 577; year 2 = 601; year 3 = 616), of whom 199 are expected to receive nivolumab plus ipilimumab (year 1 = 29; year 2 = 84; year 3 = 86). The estimated budget impact of reimbursing nivolumab in combination with ipilimumab on the public drug plans in the first 3 years is estimated to be a savings of approximately $2 million, with a predicted expenditure of approximately $29 million on nivolumab plus ipilimumab (i.e., not accounting for the current expenditure on comparators). The actual budget impact will depend on the confidentially negotiated price of each comparator.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information (links to the full documents of the review can be found on the project webpage):

- the CDA-AMC review of the clinical and pharmacoeconomic evidence submitted by the sponsor, as well as relevant ethical issues related to nivolumab plus ipilimumab (refer to the main report and Supplemental Material document)
- the sponsor’s comments on the draft report and the CDA-AMC responses
- patients' perspectives gathered by 4 patient groups (joint submission), Liver Canada, the Canadian Cancer Survivor Network, Cholangio-Hepatocellular Carcinoma Canada, and the Colorectal Cancer Resource & Action Network (refer to the Patient and Clinician Group Input document)
- input from 2 clinician groups, the Canadian Gastrointestinal Oncology Evidence Network and Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (refer to the Patient and Clinician Group Input document)
- input from public drug programs that participate in the reimbursement review process (refer to the Supplemental Material document)
- input from 2 clinical experts, consulted by CDA-AMC, with expertise in the management of hepatocellular carcinoma.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice-Chair), Paul Agbulu, Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Michael Raphael, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: October 8, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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