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CADTH Reimbursement Recommendation

Tremelimumab (Imjudo) in Combination With Durvalumab (Imfinzi)

Indication: For the first-line treatment of adult patients with unresectable hepatocellular carcinoma who require systemic therapy

Sponsor: AstraZeneca Canada Inc.

Recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Imjudo in Combination With Imfinzi?

CADTH recommends that tremelimumab (Imjudo) in combination with durvalumab (Imfinzi) should be reimbursed by public drug plans for the treatment of patients with unresectable hepatocellular carcinoma (HCC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Imjudo in combination with Imfinzi should only be covered to treat adult patients who have confirmed liver cancer that cannot be removed by surgery, are classified as Child-Pugh score class A, and require systemic therapy. Patients should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

What Are the Conditions for Reimbursement?

Imjudo in combination with Imfinzi should only be reimbursed as first-line treatment and should not be given in combination with other systemic anticancer drugs. Imjudo in combination with Imfinzi should be prescribed by clinicians with expertise and experience in treating unresectable HCC. In addition, the price for Imjudo in combination with Imfinzi should be reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a phase III clinical trial showed that treatment with Imjudo in combination with Imfinzi allows patients to live longer and without further tumour growth.
- Imjudo in combination with Imfinzi meets patients' needs by offering another treatment that works, increasing the length of time that a patient is living after the start of their therapy, and having manageable side effects. Additionally, Imjudo in combination with Imfinzi addresses an unmet need for patients with unresectable HCC who are at a higher risk of bleeding and who are not eligible for treatment with atezolizumab in combination with bevacizumab.
- Based on CADTH's assessment of the health economic evidence, Imjudo in combination with Imfinzi does not represent good value to the health care system at the public list price. Therefore, a price reduction is required.
- Based on public list prices, Imjudo in combination with Imfinzi is estimated to cost the public drug plans $18,402,899 over the next

Summary

3 years. However, the actual budget impact is uncertain given the difference between the sponsor's estimate and CADTH's estimate.

Additional Information

What Is Hepatocellular Carcinoma?

HCC is the most common type of primary liver cancer, which occurs when tumour cells form in the tissues of the liver. HCC classically develops and grows in silent fashion, which makes it difficult to detect before the development of the later stages of the disease. The majority of liver tumours found in people at later stages are determined to be unresectable, which means the tumour cannot be removed with surgery. HCC is a severe form of liver cancer that represents approximately 72% of liver cancers in Canada. It is estimated that 3,500 new patients will be diagnosed with primary liver cancer and 1,650 Canadians will die from this disease in 2022.

Unmet Needs in Hepatocellular Carcinoma

Despite the currently available treatments for HCC, new treatment options are needed to delay disease recurrence or worsening, prolong patient life, and improve quality of life.

How Much Does Imjudo in Combination With Imfinzi Cost?

Treatment with Imjudo in combination with Imfinzi is expected to cost approximately $34,320 in the first 28-day cycle and $11,733 per 28-day cycle thereafter. This is due to the 1-time, upfront dose of Imjudo.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that tremelimumab in combination with durvalumab be reimbursed for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC) who require systemic therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, randomized, open-label, sponsor-blind, multicentre, global study (HIMALAYA; N = 1,324, including 393 patients in the tremelimumab in combination with durvalumab group and 389 patients in the sorafenib group) demonstrated that treatment with tremelimumab in combination with durvalumab resulted in added clinical benefit in adult patients with unresectable hepatocellular carcinoma. The HIMALAYA study showed that treatment with tremelimumab in combination with durvalumab was associated with a statistically significant and clinically meaningful improvement in overall survival (OS) with a median OS of 16.4 months (95% CI, 14.2 to 19.6 months) in the tremelimumab in combination with durvalumab group compared to 13.8 months (95% CI, 12.3 to 16.1 months) in the sorafenib group (hazard ratio [HR] = 0.78; 96.02% CI, 0.65 to 0.93; P = 0.0035). The OS rate at 36 months was 30.7% (95% CI, 25.8% to 35.7%) in the tremelimumab in combination with durvalumab group and 20.2% (95% CI, 15.8% to 25.1%) in the sorafenib group. The HIMALAYA trial showed that objective response rate (ORR) was 20.1% in the tremelimumab in combination with durvalumab group and 5.1% in the sorafenib group (odds ratio [OR] = 4.69; 95% CI, 2.85 to 8.04). The median time to onset of response from randomization was 2.2 months (interquartile range [IQR], 1.8 to 4.0 months) in the tremelimumab in combination with durvalumab group and 3.8 months (IQR, 1.9 to 8.4 months) in the sorafenib group. The safety profile of tremelimumab in combination with durvalumab was consistent with the known safety profile of other immuno-oncology checkpoint inhibitors and was considered manageable. Tremelimumab in combination with durvalumab addresses an unmet need for patients with unresectable HCC who are at a higher risk of bleeding and are not eligible for atezolizumab in combination with bevacizumab.

Patients identified a need for effective treatments that prolong life, improve quality of life, and have manageable side effects. pERC concluded that tremelimumab in combination with durvalumab met some of the patients' needs by offering an additional effective treatment option, improving OS, and having manageable side effects. Patients identified a need for treatments that maintain quality of life; although the frequency of treatments would be reduced compared to atezolizumab in combination with bevacizumab, no definitive conclusion could be reached regarding the effects of tremelimumab in combination with durvalumab on health-related quality of life (HRQoL) because the results were based on a large amount of missing data in both groups.

Using the sponsor-submitted price for tremelimumab and durvalumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for tremelimumab in combination with durvalumab compared with sorafenib was $265,036 per quality-adjusted life-year (QALY) gained. At this

ICER, tremelimumab in combination with durvalumab is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for the indicated population. A price reduction is required for tremelimumab and durvalumab to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Tremelimumab in combination with durvalumab should be reimbursed in the first-line treatment of patients aged 18 years or older who meet all the following criteria: 1.1. confirmed unresectable HCC 1.1.1. no longer amenable to local therapies (e.g., transarterial chemoembolization or surgery) 1.2. Child-Pugh score class A 1.3. good performance status 1.4. require systemic therapy.	Evidence from the HIMALAYA study demonstrated that treatment with tremelimumab in combination with durvalumab, when compared with sorafenib, resulted in added clinical benefit for adults with confirmed HCC, preserved liver function, and ECOG PS of 0 or 1.	pERC acknowledged that clinicians may consider using tremelimumab in combination with durvalumab for patients with an ECOG PS greater than 1 at their discretion.
2. Patients are ineligible for treatment with tremelimumab in combination with durvalumab if they have any of the following: 2.1. received any prior systemic therapy for unresectable HCC 2.2. severe autoimmune or inflammatory disorders.	No evidence of efficacy of tremelimumab in combination with durvalumab in patients who meet these ineligibility criteria was identified. These criteria align with the HIMALAYA study population and clinical experts' input.	—
Discontinuation		
3. Treatment with tremelimumab in combination with durvalumab should be discontinued upon the occurrence of any of the following: 3.1. loss of clinical benefit 3.2. unacceptable toxicity.	In the HIMALAYA study, treatment was permitted beyond disease progression if the patient was clinically stable and was deriving clinical benefit. According to clinical experts, treatment with tremelimumab in combination with durvalumab should be discontinued if there is disease progression or intractable severe immune-related adverse effects.	Based on the clinical experts' opinion, in clinical practice, tumour imaging assessment (multiphasic CT and MRI) would be performed every 3 to 4 months to assess response to treatment.
Prescribing		
4. Tremelimumab in combination with durvalumab should be prescribed by clinicians with expertise and experience in treating unresectable HCC.	This helps ensure that tremelimumab in combination with durvalumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
5. Tremelimumab in combination with durvalumab should not be reimbursed if given in combination with other systemic anticancer drugs.	There is no evidence of treatment with tremelimumab in combination with durvalumab and other systemic anticancer drugs.	—
Pricing		
6. A reduction in price	The ICER for tremelimumab in combination with durvalumab is $265,036 per QALY gained when compared with sorafenib. A price reduction of 50% would be required for tremelimumab in combination with durvalumab to achieve an ICER of $50,000 per QALY gained compared to sorafenib.	—
Feasibility of adoption		
7. The feasibility of adoption of tremelimumab in combination with durvalumab must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

ECOG PS = Eastern Cooperative Oncology Group Performance Status; HCC = unresectable hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

Discussion Points

- pERC acknowledged that at the time the HIMALAYA study was designed, sorafenib was the only approved treatment for patients with unresectable HCC who were ineligible for locoregional therapy or who had progressed after locoregional therapy and had not undergone prior systemic therapy. At the time the study was conducted, sorafenib was also considered standard of care therapy. pERC noted that sorafenib as the active comparator is consistent with the studies assessing other first-line therapies in unresectable HCC. However, pERC acknowledged that sorafenib is no longer the most common standard of care therapy and has been replaced by other therapies, such as atezolizumab in combination with bevacizumab and lenvatinib. As such, the results of the trial may not be directly generalizable to current standard of care. pERC noted, however, that sorafenib remains a treatment option for some patients (e.g., risk of bleeding, intolerant to lenvatinib or atezolizumab in combination with bevacizumab).
- pERC discussed that tremelimumab in combination with durvalumab would be suitable in patients with unresectable HCC and a higher risk of bleeding who would not be eligible for atezolizumab in combination with bevacizumab as tremelimumab in combination with durvalumab showed no increase in liver toxicity or risk of bleeding in the HIMALAYA study. pERC discussed that switching from atezolizumab in combination with bevacizumab to tremelimumab in combination with durvalumab should be event-driven for patients experiencing serious adverse effects, such as severe proteinuria and GI perforation, but only in the absence of disease progression.

- pERC noted that treatment with tremelimumab in combination with durvalumab would result in fewer clinic visits and less time in the clinic compared with atezolizumab in combination with bevacizumab because patients would be treated every 4 weeks with 1 drug except for the first cycle; for atezolizumab in combination with bevacizumab, patients are treated every 3 weeks and with 2 drugs. pERC discussed the fewer clinic visits and less time in the clinic, which could translate to less overall impact on chemotherapy units if patients were treated with tremelimumab in combination with durvalumab compared with atezolizumab in combination with bevacizumab.
- Two anchored matching-adjusted indirect comparisons (MAICs) submitted by the sponsor evaluated the efficacy and safety of tremelimumab in combination with durvalumab against other first-line treatments (atezolizumab in combination with bevacizumab, and lenvatinib) in patients with unresectable HCC. However, no conclusions could be drawn from the MAICs due to methodological limitations and imprecision in the effect estimates. As a result, the cost-effectiveness of tremelimumab in combination with durvalumab compared with atezolizumab in combination with bevacizumab and lenvatinib is uncertain. To account for this uncertainty, a greater price reduction than that noted in Table 1 may be required.
- pERC discussed the high upfront cost of tremelimumab in the first treatment cycle compared with existing treatment options, which will lead to immediate budgetary impacts to the system.
- pERC noted the difference in the budget impact estimated by the sponsor and by CADTH. There were 2 primary sources of uncertainty that led to this discrepancy. First, the sponsor overestimated the proportion of patients with HCC who have Barcelona Clinic Liver Cancer (BCLC) stage C disease at diagnosis. Second, the sponsor assumed that treatment with tremelimumab in combination with durvalumab would continue after disease progression, whereas clinical expert feedback elicited by CADTH indicated that, for all treatments, most patients would switch to a second-line therapy at the time of disease progression. This uncertainty should be accounted for during price negotiation and implementation.

Background

Primary liver cancer is one of the fastest-rising cancers in Canada, and it is estimated that 3,500 new patients will be diagnosed with primary liver cancer and 1,650 people living in Canada will die from this disease in 2022. According to Statistics Canada's Short-Term Cancer Prevalence in Canada 2018 report, the estimated 5-year prevalence of liver cancer is approximately 11.3 cases per 100,000 for both sexes. HCC is a severe form of liver cancer that represents approximately 90% of primary liver cancers globally and approximately 72% of liver cancers in Canada. HCC is the third-leading cause of cancer deaths worldwide, with a 5-year survival rate of only 20% in Canada. It is most commonly diagnosed in people older than 70 years and is 3 times more common in males than females. Due to the insidious nature of the disease, the majority of patients are diagnosed with advanced disease, with a median survival following diagnosis of approximately 6 to 8 months or 25% at 1 year. The predominant risk factors for HCC include chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV), misuse of alcohol or alcoholic

steatohepatitis, and nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. HCC is often diagnosed using noninvasive imaging, tissue biopsy, physical examination, or blood tests.

For advanced, unresectable HCC, the goal of treatment is to extend long-term survival, delay progression, and maintain and improve the patient's quality of life, and guidelines recommend the use of systemic targeted therapies. According to the clinical experts consulted by CADTH, systemic treatment options have improved over the past several years with the introduction of the combination of atezolizumab and bevacizumab, lenvatinib, and sorafenib as first-line systemic treatment options in Canada. The clinical experts consulted by CADTH identified a key limitation of the current first-line therapy with atezolizumab in combination with bevacizumab: patients with untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding are not candidates for this combination therapy. Therefore, upper endoscopy is indicated for patients with cirrhosis or high risk of bleeding.

The Health Canada indication for tremelimumab in combination with durvalumab is for the first-line treatment of adult patients with unresectable HCC who require systemic therapy, which generally aligns with the sponsor's requested reimbursement criteria. Tremelimumab is a selective, fully human immunoglobulin G2 antibody that blocks cytotoxic T lymphocyte–associated protein 4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumour immune activity. Durvalumab is an engineered monoclonal antibody that blocks the interaction of programmed cell death ligand-1 with its receptors PD-1 and CD80. The recommended dose of tremelimumab is 300 mg intravenously as a single priming dose in combination with durvalumab 1,500 mg IV for cycle 1 day 1, followed by durvalumab 1,500 mg IV as a single agent every 4 weeks.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, multicentre, randomized, open-label, sponsor-blind, global trial in patients with unresectable HCC
- patient perspectives gathered by 1 patient group, the Colorectal Cancer Resource & Action Network (CCRAN) in collaboration with the Canadian Cancer Survivor Network (CCSN), Canadian Liver Foundation (CLF), and GI Society
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with unresectable HCC
- input from 2 clinician groups, including the Canadian Gastrointestinal Oncology Evidence Network (CGOEN), and Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (GI DAC), and a clinician from the Alberta Health Services Cancer Care, University of Alberta.

Stakeholder Perspectives

Patient Input

CCRAN in collaboration with the CCSN, CLF, and GI Society, provided a collective patient input for this review. CCRAN is a national not-for-profit patient advocacy group championing the health and wellbeing of Canadians affected by colorectal cancer and those at risk of developing the disease. CCSN, CLF, and the GI Society thoughtfully collaborated with CCRAN to ensure that the perspectives of patients with advanced HCC and their caregivers are captured, represented, and well weaved in this submission. CCRAN gathered information for this review from in-depth interviews with 2 patients with HCC (both patients had experience with the currently available treatment of HCC; only 1 patient had experience with the drugs under review), a literature review, and online public forums for patient-reported outcomes.

According to the patient input received from CCRAN, HCC is the most common primary liver cancer. CCRAN noted that risk factors associated with HCC include cirrhosis, hepatitis B and C infections, and alcohol intake. Both patient interviews indicated that they had not been experiencing any symptoms at the time of HCC diagnosis. CCRAN indicated that a diagnosis and symptoms of HCC represent a substantial physiological and psychological burden for patients and their caregivers and can significantly affect their HRQoL. CCRAN pointed to various symptoms of HCC that affected their patients' quality of life and daily activities, including sleep disorders, sexual dysfunction, ascites, gynecomastia, pruritis, fatigue, muscle cramps, and lack of appetite even after treatment. Both patient respondents highlighted that the daily activities that were most commonly affected included the ability to work, participate in activities they enjoy, and spend time with family and friends. One of the interviewed patients (age = 92 years, female, age at HCC diagnosis = 71 years) found herself cycling through the same stages of cancer grief — anger, depression, guilt, anxiety, hopelessness, and fear — which hit her hard at the time of the initial diagnosis and subsequent relapse.

CCRAN indicated that patients with HCC expect the following key outcomes to be improved from any new drug or treatment: improved quality of life, prolonged survival, manageable side effects, maintenance of functionality, ability to engage in society and be contributing members of the workforce. According to the patient input received from CCRAN, HCC is a unique carcinoma because the majority of cases will develop in patients with cirrhosis; therefore, therapeutic options will be limited due to the patient's overall health status. CCRAN indicated that patients with early-stage HCC are preferred candidates for resection, transplant, and local ablation, whereas patients at intermediate stages may be candidates for transarterial chemoembolization, and those with advanced disease will receive systemic therapies. CCRAN noted that the current systemic treatments for HCC include atezolizumab in combination with bevacizumab, as well as lenvatinib, sorafenib, regorafenib, and cabozantinib. The limited treatment tolerability, in part due to the side effects, was highlighted by CCRAN as a major challenge to available systemic therapy for advanced HCC.

One of the interviewed patients (age = 74 years, male, age at HCC diagnosis = 68 years) had experience with treatment with the drug under review after transarterial chemoembolization, which negatively affected his quality of life. The patient respondent, who resided in Cranbrook, British Columbia, had access to tremelimumab in combination with durvalumab through a clinical trial. That patient respondent indicated

that the drug under review had promising and durable treatment results, with no side effects other than an occasional skin rash. He also mentioned that tremelimumab in combination with durvalumab helped him regain functionality and livelihood, which reduced the burden on his caregivers and loved ones. CCRAN advocated for tremelimumab in combination with durvalumab to be approved for the indication under review and suggested that it will help alleviate the gaps in current HCC therapy.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of unresectable HCC.

The clinical experts consulted by CADTH for this review stated that the treatment goals for patients with unresectable HCC include prolonging life and delaying progression. They mentioned that treatments have improved in the past several years with the introduction of lenvatinib, which has better efficacy and lower toxicity than sorafenib, and atezolizumab in combination with bevacizumab. However, the benefits of current treatments have been incremental. Moreover, atezolizumab in combination with bevacizumab is limited to patients who have had a recent upper endoscopy and were found not to have symptomatic varices. The clinical experts noted that tremelimumab in combination with durvalumab would be indicated as first-line therapy for patients who would currently be indicated for atezolizumab and bevacizumab, and that choice of therapy would depend on clinician and patient preference. They also mentioned it may be indicated for patients who had started tyrosine kinase inhibitor therapy and had progressed or experienced severe toxicity.

The clinical experts agreed that tremelimumab in combination with durvalumab would be recommended for patients with unresectable HCC with preserved liver function (Child-Pugh A), good performance status (potentially up to Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 2), and who are not indicated for local therapy, such as transarterial chemoembolization. They mentioned that patients who were on tyrosine kinase inhibitors and/or other therapies but had severe side effects leading to permanent discontinuation would also be eligible for tremelimumab in combination with durvalumab. Patients who are not candidates for other immune checkpoint inhibitors would not be candidates for tremelimumab in combination with durvalumab.

The clinical experts mentioned that, in clinical practice, imaging would be obtained every 3 months to assess response to treatment. The most important outcomes are prolonged survival, delayed progression, disease control, and maintained quality of life with low toxicity profile. The clinical experts noted that tremelimumab in combination with durvalumab should be discontinued if there is disease progression or intractable severe immune-related adverse effects. According to the clinical experts, tremelimumab in combination with durvalumab can be administered in most systemic therapy suites in which cancer patients receive

chemotherapy and immunotherapy. Administration of this therapy can be supervised by most medical oncologists experienced in treating HCC.

Clinician Group Input

The clinician group input was obtained from 2 clinician groups, including the CGOEN represented by 6 clinicians, and Ontario Health (Cancer Care Ontario) GI DAC represented by 5 clinicians, and from a clinician from the Alberta Health Services Cancer Care, University of Alberta.

CGOEN indicated that with modern systemic therapy, downsizing of disease has led to newer options for local regional treatments of the liver (i.e., stereotactic radiation, embolization, ablation, resection, or transplant). CGOEN highlighted that patients with HCC may have an increased bleeding risk due to the underlying liver disease and the vascular nature of the disease itself, and therapy that does not increase this risk will be key in this area. The clinician groups agreed that given a good safety profile, tremelimumab in combination with durvalumab will be another first-line HCC treatment option, especially for patients with hypertension or varices, or when upper GI endoscopy is not available. The clinician from the University of Alberta indicated that tremelimumab in combination with durvalumab may become the preferred first-line immunotherapy option for treatment of patients with unresectable HCC. CGOEN and the clinician form the University of Alberta noted that patients receiving tremelimumab in combination with durvalumab would have fewer clinic visits and less time in the clinic because they would be treated every 4 weeks and essentially with 1 drug except for the first cycle, whereas for atezolizumab in combination with bevacizumab, patients are treated every 3 weeks and with 2 drugs. The clinician groups pointed out several reasons that may lead to the discontinuation of tremelimumab in combination with durvalumab, including disease progression, unacceptable drug-related toxicities, or patient preference. The clinician groups highlighted that treatment with tremelimumab in combination with durvalumab should be provided by clinicians with expertise and experience in treating HCC. The GI DAC noted that treatment with tremelimumab in combination with durvalumab should be performed in outpatient infusion clinics, including satellite clinics.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
What is the relative efficacy and safety of tremelimumab in combination with durvalumab vs. atezolizumab in combination with bevacizumab or lenvatinib?	The clinical experts noted that there are several differences between the 3 trials that assessed these therapies (HIMALAYA, IMBRAVE-150, and REFLECT) that limit cross trial comparisons such as time trial conducted, patient characteristics, and therapies before receiving systemic therapy. However, both tremelimumab in combination with durvalumab, and atezolizumab in combination with bevacizumab were superior to sorafenib. According to MAIC results, the OR for serious AEs for

Drug program implementation questions	Response
	tremelimumab in combination with durvalumab vs. atezolizumab in combination with bevacizumab was [redacted]. Given the adverse events reports in HIMALAYA, tremelimumab in combination with durvalumab does not appear to be associated with adverse events likely related to bevacizumab, such as hypertension, proteinuria, and bleeding. pERC acknowledged the input from the clinical experts and noted that there is no head-to-head clinical evidence available to inform the efficacy and safety of tremelimumab in combination with durvalumab vs. atezolizumab in combination with bevacizumab or lenvatinib. Although indirect evidence was available, pERC acknowledged the uncertainty in MAIC results and that no conclusions could be drawn from the MAICs due to methodological limitations and imprecision in the effect estimates.
Considerations for initiation of therapy	
Is histologic confirmation of HCC required to be eligible for tremelimumab in combination with durvalumab?	pERC agreed with the clinical experts that the standard of care would not require histologic tissue diagnosis, except in cases where imaging is not diagnostic.
If patients discontinue therapy for reasons other than toxicity or progressive disease and/or loss of clinical benefit, should patients be eligible for re-treatment? If yes, what re-treatment protocol and duration would be appropriate?	In the HIMALAYA trial, re-treatment was not specified unless patients had disease progression. If patients have treatment stoppage for greater than 6 months (other than toxicity), it is the opinion of the clinical experts that re-treatment would be reasonable. pERC considered continuation of treatment after a break to be reasonable. Whether the continuation of treatment after a break applies to the combination or to single drugs only is out of scope of the available evidence; rather, this choice would be at the discretion of the treating physician.
Should we allow time-limited switching from atezolizumab in combination with bevacizumab to tremelimumab in combination with durvalumab?	According to the clinical experts, switching should be event-driven for patients experiencing any serious adverse effects, such as severe proteinuria or gastrointestinal perforation, but only in the absence of disease progression. In addition to switching due to event-driven serious adverse effects, pERC also noted that it would be reasonable to offer tremelimumab in combination with durvalumab to patients who are intolerant to atezolizumab in combination with bevacizumab or lenvatinib and have not progressed.
Considerations for continuation or renewal of therapy	
What are appropriate criteria for re-treating with tremelimumab in clinical practice? Should re-treatment with tremelimumab be limited, in the setting of progression, to after cycle 5 of durvalumab (median duration of exposure was 20 weeks; range, 2 weeks to 85 weeks)?	According to the clinical experts, it would be reasonable to re-treat patients with progression with tremelimumab after cycle 4 of durvalumab. pERC noted that the study allowed for re-treatment with tremelimumab and that 30 patients were re-treated with tremelimumab. Per the study protocol, this was reasonable. Although pERC acknowledged there was some information available on the 30 patients rechallenged with tremelimumab, there is uncertainty in the derived benefit as a result of the 1-time additional treatment with tremelimumab given the small number

Drug program implementation questions	Response
	of patients, the study was not powered for this comparison and no multiplicity adjustments were performed.
Considerations for discontinuation of therapy	
What are appropriate discontinuation criteria for tremelimumab in combination with durvalumab in clinical practice? Are the discontinuation criteria different if a patient has already received a tremelimumab re-treatment?	Based on the clinical expert input, discontinuation criteria include clinical deterioration or treatment-related toxicity. In practice, patients may receive several scans before progression is confirmed (and several treatments during that time), similar to confirmed progression in clinical trials. The discontinuation criteria for patients who received re-treatment with tremelimumab should not be different. pERC acknowledged the input from the clinical experts and agreed that the discontinuation criteria for patients who received re-treatment with tremelimumab should not be different.
Considerations for prescribing of therapy	
Is there any evidence for weight-based dosing of tremelimumab?	pERC acknowledged that the HIMALAYA trial excluded patients who weighed < 30 kg and that flat dose rather than weight-based dosing was given to patients who weighed ≥ 30 kg. pERC agreed with the clinical experts that most therapies have weight-based dosing for patients who weigh < 30 kg; however, this weight range is not common in clinical practice.
Administration of tremelimumab requires a 0.2 µm or 0.22 µm in-line filter.	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Can the results from the HIMALAYA trial be generalized to patients with Child-Pugh score of B7?	The clinical experts noted that although only including patients with a Child-Pugh score of A is reasonable in clinical trials, it may also be reasonable to include patients with a Child-Pugh score of B7 in clinical practice. pERC acknowledged the input from the clinical experts and noted that no clinical evidence was available to inform efficacy and safety in patients with a Child-Pugh score of B7.
Funding algorithm (oncology only)	
Tremelimumab in combination with durvalumab may change place in therapy of comparator drugs. PAG considered unresectable HCC to be a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
Tremelimumab will be available in a 25 mg and 300 mg single-use vial. Infusion will take 1 hour. Durvalumab is available as a 120 mg and 500 mg vial; infusions take 1 hour per dose.	Comment from the drug programs to inform pERC deliberations.
Preparation of durvalumab is familiar to many jurisdictions as it has funding for other indications for use. Preparation for tremelimumab would be new for many jurisdictions	Comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	Response
and is similar in preparation complexity to many other immunotherapies already in use.	
Stability of prepared tremelimumab is up to 28 days under refrigerated conditions (would be limited by NAPRA sterility maximums, thus would likely not be longer than 9 days). This extended stability is very helpful operationally to support pharmacy workflow and reduce risk of drug wastage.	Comment from the drug programs to inform pERC deliberations.
Vial sharing with tremelimumab would not be likely given the single-dose use, flat dose, and single-use vial corresponding to full dose. Vial sharing with durvalumab would be more likely given the q.4.w. interval, other indications already funded at weight-based dosing.	Comment from the drug programs to inform pERC deliberations.
Funding of durvalumab for other indications uses a weight-based dosing, up to a cap. PAG would plan to implement durvalumab dosing in a similar manner with this indication, in a funding scenario.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
Atezolizumab has confidential negotiation and bevacizumab biosimilars also have confidential prices.	—

HCC = hepatocellular carcinoma; MAIC = matching-adjusted indirect comparisons; NAPRA = National Association of Pharmacy Regulatory Authorities; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; q.4.w. = every 4 weeks.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

HIMALAYA was a randomized, open-label, sponsor-blind, multicentre, global, phase III study to assess the efficacy and safety of tremelimumab in combination with durvalumab versus sorafenib in the treatment of patients with unresectable HCC who are not eligible for locoregional therapy and who have not received prior systemic therapy for HCC in the first-line setting. The HIMALAYA study included 2 additional treatment groups who received durvalumab monotherapy and a lower dose of tremelimumab in combination with durvalumab. The HIMALAYA study was designed to compare all 3 groups (durvalumab monotherapy and both doses of tremelimumab in combination with durvalumab) to sorafenib. The 2 additional groups (durvalumab monotherapy and a lower dose of tremelimumab in combination with durvalumab) were not relevant to this review, therefore results related to the 2 additional groups were not reported.

The primary objective was to compare OS for tremelimumab in combination with durvalumab versus sorafenib in all randomized patients. Secondary objectives included comparing OS rates (at 18, 24, and 36 months), progression-free survival (PFS), time to progression, ORR, disease control rate, and duration of

response (DOR) per investigator assessment, patient-reported outcomes, and safety between both treatment groups. The study was funded by AstraZeneca Canada Inc. and included 9 study centres in Canada.

Patients were randomly assigned in a 1:1:1:1 ratio using an interactive web response system into 1 of 4 treatment groups: tremelimumab in combination with durvalumab (300 mg IV × 1 dose plus durvalumab 1,500 mg IV every 4 weeks, [n = 393]), sorafenib (400 mg orally twice daily [n = 389]), durvalumab monotherapy (not included in this review [n = 389]), and a different dosing regimen of tremelimumab in combination with durvalumab (n = 153, recruitment to group closed due to preliminary efficacy findings). Randomization was stratified according to macrovascular invasion (yes or no), etiology of liver disease (confirmed HBV vs. confirmed HCV vs. others), and ECOG performance status (0 vs 1). Tumour imaging assessments were to be performed at randomization and then every 8 weeks (± 1 week) for the first 48 weeks following randomization, and then every 12 weeks (± 1 week) thereafter until confirmed disease progression.

Patient demographic characteristics and key disease characteristics were balanced between both treatment groups. [redacted] and up to 15% of the patients in both groups were 75 years or older. Most patients were male (85%), and 15% of patients were female. [redacted]. Approximately 80% of patients had BCLC score C, and 20% had BCLC score B. Half of the patients had extrahepatic spread, and a quarter of the patients had macrovascular invasion. [redacted], and 12% in the tremelimumab in combination with durvalumab group and 10% in the sorafenib group had received prior radiotherapy.

Efficacy Results

Key efficacy results of the HIMALAYA trial for all randomized patients are summarized in Table 3. As of the final primary analysis on August 27, 2021, the data cut-off date, [redacted], and median follow-up time in the tremelimumab in combination with durvalumab group was 33.2 months (95% CI, 31.7 to 34.5 months) and in the sorafenib group was 32.2 months (95% CI, 30.4 to 33.7 months). The median total treatment duration was 5.5 months (range, 0.4 to 42.7 months) in the tremelimumab in combination with durvalumab group and 4.1 months (range, 0.1 to 38.6 months) in the sorafenib group.

The efficacy analyses of OS in all randomized patients showed that patients in the tremelimumab in combination with durvalumab group had longer OS than those in the sorafenib group. The median OS was 16.4 months (95% CI, 14.2 to 19.6 months) in the tremelimumab in combination with durvalumab group compared with 13.8 months (95% CI, 12.3 to 16.1 months) in the sorafenib group, with an HR of 0.78 (96.02% CI, 0.65 to 0.93) and P value of 0.0035. The OS rate at 36 months was 30.7% (95% CI, 25.8% to 35.7%) in the tremelimumab in combination with durvalumab group and 20.2% (95% CI, 15.8% to 25.1%) in the sorafenib group. Effect estimates for all predefined subgroups were consistent with the overall OS analysis.

All secondary outcomes were based on investigator assessment according to Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) and were not adjusted for multiplicity. Median PFS in the full analysis set was 3.8 months in the tremelimumab in combination with durvalumab group and 4.1 months

in the sorafenib group, with an HR of 0.90 (95% CI, 0.77 to 1.05). ORR was 20.1% (79 patients) in the tremelimumab in combination with durvalumab group and 5.1% (20 patients) in the sorafenib group. When comparing tremelimumab in combination with durvalumab and sorafenib, the OR for ORR was 4.69 (95% CI, 2.85 to 8.04) in favour of tremelimumab in combination with durvalumab. [redacted].There were 13 patients (3.3%) in the tremelimumab in combination with durvalumab group who achieved CR, and none in the sorafenib group. Among the 79 responders in the tremelimumab in combination with durvalumab group and 20 responders in the sorafenib group, the median DOR based on investigator assessment according to RECIST 1.1 was 22.3 months (IQR, 8.5 months to not reached [NR]) and 18.4 months (IQR, 6.5 to 26 months), respectively. The percentage of patients remaining in response at 12 months based on the Kaplan-Meier technique was 65.8% in the tremelimumab in combination with durvalumab group and 63.2% in the sorafenib group. Median time to onset of response from randomization was 2.2 months (IQR, 1.8 to 4 months) in the tremelimumab in combination with durvalumab group and 3.8 months (IQR, 1.9 to 8.4 months) in the sorafenib group. The overall disease control rate (CR, PR, or stable disease) was similar between both groups with 236 patients (60.1%) in the tremelimumab in combination with durvalumab group and 236 patients (60.7%) in the sorafenib group achieving controlled disease. [redacted]. Results from the assessment of exploratory outcomes (based on BICR assessments using modified RECIST for HCC and immune-related RECIST were not provided by the sponsor).

Results for patient-reported outcomes (assessed by the European Organization for Research and Treatment of Care Core Quality of Life questionnaire [EORTC QLQ-C30 and QLQ-HCC]) suggested similar overall health status in both study groups at baseline, with no mean change scores from baseline reaching minimal important difference (MID) (i.e., mean change ≥ 10 points) at any time point. However, [redacted]. Median time to deterioration scores for patients favoured tremelimumab in combination with durvalumab over sorafenib in EORTC QLQ-C30 GHS/QoL (7.5 vs. 5.7 months; HR = 0.76; 95% CI, 0.61 to 0.96), physical functioning (12.9 vs. 7.4 months; HR = 0.68; 95% CI, 0.53 to 0.87), fatigue (7.4 vs. 5.4 months; HR = 0.71; 95% CI, 0.57 to 0.89), nausea (25.0 vs. 11.0 months; HR = 0.65; 95% CI, 0.49 to 0.87), appetite loss (12.6 vs. 6.9 months; HR = 0.59; 95% CI, 0.46 to 0.75), and EORTC QLQ-HCC18 abdominal pain (16.8 vs. 8.9 months; HR = 0.61; 95% CI, 0.47 to 0.80), and abdominal swelling (20.9 vs. 11.1 months; HR = 0.74; 95% CI, 0.56 to 0.97). The improvement rate in [redacted].

Table 3: Summary of Key Results From the HIMALAYA Study (FAS With Final Data Cut-Off August 27, 2021)

Detail	Tremelimumab in combination with durvalumab N = 393	Sorafenib N = 389
Overall survival		
Follow-up duration in all patients (months), median (95% CI)	33.2 (31.7 to 34.5)	32.2 (30.4 to 33.7)
OS[a] (months), median (95% CI)	16.4 (14.2 to 19.6)	13.8 (12.3 to 16.1)
Hazard ratio (96.02% CI)[b]	0.78 (0.65 to 0.93)	
P value (2-sided)[b]	0.0035	
Progression-free survival		
Follow-up duration in all patients (months), median (range)	3.8 (0.0 to 41.5)	3.8 (0.0 to 33.4)
PFS[a] (months), median (95% CI)	3.78 (3.68 to 5.32)	4.07 (3.75 to 5.49)
Hazard ratio (95% CI)	0.90 (0.77 to 1.05)	
P value[c]	0.1625	
Progression-free at data cut-off, n (%)	49 (12.5)	19 (4.9)
Objective response rate in patients with confirmed responses[d]		
Objective response, n (%)	79 (20.1)	20 (5.1)
Complete response	12 (3.1)	0
Partial response	67 (17.0)	20 (5.1)
Objective response, odds ratio (95% CI)	4.69 (2.85 to 8.04)	
P value[e]	< 0.0001	
Duration of response in patients with confirmed responses[d]		
n	79	20
Duration of response (months), median (IQR)	22.34 (8.54 to NR)	18.43 (6.51 to 25.99)
Best objective response in patients with unconfirmed responses[d]		
[redacted]	[redacted]	[redacted]
Complete response, n (%)	13 (3.3)	0
Partial response, n (%)	81 (20.6)	26 (6.7)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time to progression		
[redacted]	[redacted]	[redacted]

Detail	Tremelimumab in combination with durvalumab N = 393	Sorafenib N = 389
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

CI = confidence interval; FAS = final analysis set; IQR = interquartile range; OS = overall survival; PFS = progression-free survival.

[a]Calculated using the Kaplan-Meier technique.

[b]The adjusted alpha levels for the 2-sided superiority test of tremelimumab in combination with durvalumab vs. sorafenib and CIs were derived based on the exact number of OS events for each comparison using the Lan and DeMets approach that approximates the O'Brien Fleming spending function. Analysis performed using stratified log-rank test adjusting for treatment, etiology of liver disease (hepatitis B virus vs. hepatitis C virus vs. others), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1), and macrovascular invasion (MVI) (yes vs. no). P value has been adjusted for multiple testing.

[c]Analysis performed using stratified log-rank test adjusting for treatment, etiology of liver disease (hepatitis B virus vs. hepatitis C virus vs. others), ECOG PS (0 vs. 1), and MVI (yes vs. no). P value has not been adjusted for multiple testing.

[d]A confirmed response of complete response or partial response means that a response of complete response or partial response was recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when response was first observed with no evidence of progression between the initial and confirmation visit. Unconfirmed responses were not confirmed by repeat imaging.

[e]Analysis was performed using a logistic regression model adjusted for treatment with factors for etiology of liver disease, ECOG PS, and MVI. P value has not been adjusted for multiple testing.

Source: HIMALAYA Clinical Study Report. (Note details from the table have been taken from the sponsor's Summary of Clinical Evidence.)

Harms Results

A summary of harms in the HIMALAYA trial are presented in Table 4.

A total of 378 patients (97.4%) in the tremelimumab in combination with durvalumab group and 357 patients (95.5%) in the sorafenib group experienced at least 1 adverse event (AE). The most frequently reported treatment-emergent AEs in the tremelimumab in combination with durvalumab and sorafenib groups were diarrhea (26.5% vs. 44.7%, respectively), pruritis (22.9% vs. 6.4%, respectively), rash (22.4% vs. 13.6%, respectively), fatigue (17% vs. 19%, respectively), decreased appetite (17% vs. 17.9%, respectively), and palmar-plantar erythrodysesthesia syndrome (0.8% vs. 46.5%, respectively). [redacted]. A total of 157 patients (40.5%) in the tremelimumab in combination with durvalumab group and 111 patients (29.7%) in the sorafenib group experienced at least 1 serious AE. The most frequently reported serious AEs in the tremelimumab in combination with durvalumab and sorafenib groups were diarrhea (2.3% vs. 1.6%, respectively), sepsis (2.1% vs 0, respectively), and pneumonia (1.8% vs. 2.1%, respectively). Fifty-three patients (13.7%) in the tremelimumab in combination with durvalumab group and 63 patients (16.8%) in the sorafenib group stopped treatment due to AEs.

At the final data cut-off date of August 21, 2021, in the FAS, there were 262 deaths (66.7%) in the tremelimumab in combination with durvalumab group and 293 deaths (75.3%) in the sorafenib group, [redacted]. In the safety analysis set, 30 patients (7.7%) and 27 patients (7.2%) died in the tremelimumab in combination with durvalumab group and sorafenib group, respectively.

[redacted]. All AEs of special interest were more frequently reported in the tremelimumab in combination with durvalumab group, except for

diarrhea or colitis which was more frequently reported in the sorafenib group (45% vs. 28%, respectively). Immune-mediated AEs were also more frequently reported in patients in the tremelimumab in combination with durvalumab group than the sorafenib group (36% vs. 8%, respectively). There were 6 patients in the tremelimumab in combination with durvalumab group that died due to immune-mediated AEs (pneumonitis, 3 hepatic events, myocarditis, and myasthenia gravis) and no deaths in the sorafenib group. [redacted].

There were 144 patients (37.1%) in the tremelimumab in combination with durvalumab group with any Hepatic Standardized MedDRA Query (SMQ) AE compared with 121 patients (32.4%) in the sorafenib group. [redacted]. There were 44 patients (11.3%) in the tremelimumab in combination with durvalumab group with any Hemorrhage SMQ AE compared with 56 patients (15%) in the sorafenib group. [redacted]. In the HIMALAYA trial, tremelimumab in combination with durvalumab showed no increase in liver toxicity or risk of bleeding.

Table 4: Summary of Key Harms Results From the HIMALAYA Study (SAS With Final Data Cut-Off August 27, 2021)

Harms, n (%)	Tremelimumab in combination with durvalumab (N = 388)	Sorafenib (N = 374)
Patients with ≥ 1 adverse event	378 (97.4)	357 (95.5)
[redacted]	[redacted]	[redacted]
Patients with ≥ 1 SAE	157 (40.5)	111 (29.7)
Patients who stopped treatment due to AEs	53 (13.7)	63 (16.8)
Deaths[a]	30 (7.7)	27 (7.2)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
imAE	139 (35.8)	30 (8.0)
[redacted]	[redacted]	[redacted]
imAE grade 3 or 4	49 (12.6)	9 (2.4)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Harms, n (%)	Tremelimumab in combination with durvalumab (N = 388)	Sorafenib (N = 374)
Hepatic SMQ[c]	144 (37.1)	121 (32.4)
Hemorrhage SMQ[d]	44 (11.3)	56 (15)

AESI = AE of special interest (list); imAE = immune-mediated adverse event; SAE = serious adverse event; SAS = safety analysis set; SMQ = Standardized MedDRA Query.

[a]Adverse event with outcome of death.

[b]AESIs for tremelimumab in combination with durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions, such as steroids, immunosuppressants, and/or hormone replacement therapy.

[c]The following hepatic SMQs were considered of relevance to the HCC patient population: cholestasis and jaundice of hepatic origin, hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions, hepatitis noninfectious, liver infections, liver malignant tumours, liver-related investigations, signs and symptoms, and liver-related coagulation and bleeding disturbances.

[d]Hemorrhage SMQs included hemorrhage terms and hemorrhage laboratory terms.

Source: HIMALAYA Clinical Study Report. (Note details from the table have been taken from the sponsor's Summary of Clinical Evidence.)

Critical Appraisal

Internal Validity

HIMALAYA was an open-label, sponsor-blind, randomized phase III study comparing tremelimumab in combination with durvalumab and sorafenib in adult patients with unresectable HCC who required systemic therapy. The sponsor stated that an open-label, sponsor-blind design was used due to the nature of the treatment administration (IV versus oral) and the different administration schedules (every 4 weeks versus twice daily). The study used an appropriate central randomization method sufficient for concealing allocation until assignment to the intervention. Randomization appeared adequate in balancing baseline demographic and disease characteristics between the tremelimumab in combination with durvalumab group and the sorafenib group. The open-label design can result in a risk of bias in the study conduct, including the measurement of the outcomes, particularly for subjective outcomes assessed by unblinded assessor such as PFS and ORR, or self-reported such as HRQoL, and subjective harms. With the exception of subjective harms, the bias will likely favour the experimental intervention, although the extent and direction of bias are uncertain. This bias would not be introduced into the measurement of objective outcomes, such as OS, which is the primary outcome of the trial. At the first interim analysis after at least 32 weeks of follow-up, tumour response assessments were performed by BICR (which would minimize bias in the measurement of these outcomes) but, in the final analysis, tumour response assessments were performed only by investigator assessment. Results from the interim analysis were similar to results from the final analysis. In the final analysis, exploratory end points included assessment of the PFS, time to progression, ORR, disease control rate, and DOR by BICR to mitigate this bias; however, the results of these assessments were not available. The study was powered to detect a treatment difference in the primary end point of OS between treatment group, and the enrolled sample size was adequate. However, the study was not powered for individual subgroup comparisons and no multiplicity adjustments were made, rendering any conclusion uncertain. There was no multiplicity control for other outcomes which may have increased the risk of false-positive conclusions. Maintaining and improving quality of life overall was rated as an important outcome by patients, yet the interpretation of results for the HRQoL instruments (i.e., the ability to assess trends over

time and to make comparisons across treatment groups) is limited by the significant decline in the number of patients available to provide an assessment over time.

External Validity

According to the clinical experts consulted by CADTH for this review, the demographic and disease characteristics of the HIMALAYA study population were reflective of the Canadian population with unresectable HCC. There were a large number of screening failures in the study in which almost a third of screened patients were not randomized, most commonly due to eligibility criteria not being fulfilled. However, the eligibility criteria that were most commonly not fulfilled were clear contraindications to treatment with tremelimumab in combination with durvalumab, such as lack of adequate organ and marrow function. The clinical experts noted that, although including only patients with a Child-Pugh score of A is reasonable in clinical trials, it would be reasonable to include other patients (e.g., Child-Pugh score of B7) in clinical practice. They also noted that, although the trial excluded patients with prior systemic therapy, a large number of patients in clinical practice would have already received prior systemic therapy. It is unclear if findings from this study can be generalized to patients beyond the first-line of therapy. All patients in the trial had ECOG PS 0 or 1 as per the eligibility criteria, but the experts indicated this would not be reflective of clinical practice and that clinicians would require some flexibility in restricting treatment by performance status. The clinical experts consulted by CADTH indicated that at the time of the HIMALAYA study design, sorafenib was the only approved treatment for unresectable HCC patients who were ineligible for locoregional therapy and who had not undergone prior systemic therapy. Hence, in this study, sorafenib was considered standard of care treatment for these patients and was selected as the active comparator. According to the clinical experts and recent clinical guidelines, sorafenib is no longer the most common standard of care therapy and has been replaced by current therapies that include atezolizumab in combination with bevacizumab, and lenvatinib.

Long-Term Extension Studies

No long-term extension studies were identified by the sponsor.

Indirect Comparisons

Description of Studies

Two MAICs and a published indirect treatment comparison (ITC) submitted by the sponsor were summarized and appraised for this CADTH review.

In the absence of direct comparative evidence from trials, the aim of the MAICs conducted by the sponsor was to compare the efficacy and safety of tremelimumab in combination with durvalumab against atezolizumab in combination with bevacizumab (from the IMbrave150 trial), and lenvatinib (from the REFLECT trial) in patients with unresectable HCC. MAIC was identified as the preferred option to adjust for suspected heterogeneity between trials with individual patient data for the HIMALAYA and aggregate data available from the comparator trials. Individual patient data from the HIMALAYA trial were used to match and adjust patients to those included in the comparator trials (IMbrave150 and REFLECT). All 3 trials (HIMALAYA, IMbrave150, and REFLECT) were phase III, open-label, multicentre studies. The mean duration

of study follow-up was 33.2 months in HIMALAYA, 27.5 months in REFLECT, and 8.5 months in IMbrave150. The efficacy end points included OS and PFS in both MAICs, and ORR and DOR were only assessed in the MAIC comparing tremelimumab in combination with durvalumab versus atezolizumab in combination with bevacizumab. For parameters related to disease progression, the HIMALAYA and IMbrave150 trials used the RECIST 1.1, whereas the REFLECT trial used the modified RECIST. Harms related to the use of tremelimumab in combination with durvalumab were also evaluated in both MAICs, including AEs, serious AEs, and AEs leading to treatment discontinuation. Patient-reported outcomes were only reported in the MAIC comparing tremelimumab in combination with durvalumab versus atezolizumab in combination with bevacizumab.

Efficacy Results

This section will focus on the findings of the sponsor-submitted MAICs.

Tremelimumab in Combination With Durvalumab Versus Atezolizumab in Combination With Bevacizumab

After restriction and reweighting, the HR was 1.09 (95% CI, 0.80 to 1.48) for OS, and [redacted]. The OR was 1.18 (95% CI, 0.44 to 3.21) for ORR, and [redacted]. The HR for [redacted]), while the HR for [redacted].

Tremelimumab in Combination With Durvalumab Versus Lenvatinib

[redacted].

Harms Results

Tremelimumab in Combination With Durvalumab Versus Atezolizumab in Combination With Bevacizumab

After restriction and reweighting, the OR was 0.73 (95% CI, 0.44 to 1.19) for AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4, [redacted].

Tremelimumab in Combination With Durvalumab Versus Lenvatinib

[redacted].

Critical Appraisal

Although the methodology for matching and adjustment was in line with the technical guidance, the sponsor-submitted MAICs had a number of limitations that challenge the interpretation of the internal and external validity of the findings. Overall, based on the methods detailed in the report, the systematic literature review had a comprehensive search, and the screening strategies were sufficient to minimize error and selection bias. The risk of bias of included studies was assessed per individual study; however, it may be different depending on the study outcomes (i.e., OS versus patient-reported outcomes). The clinical experts consulted by CADTH for this review mentioned several studies published over the past year providing updated efficacy and safety data from IMbrave150 and REFLECT, which were not identified in this search and therefore were not included in the ITC. As a result, MAIC analyses did not select some efficacy outcomes (i.e., PFS,

ORR, DOR, patient-reported outcomes) based on the longer follow-up data, which may have influenced the results. Although the sponsor inadvertently missed including the reference of longer follow-up data for the IMbrave150 trial in the MAIC report and the clinical evidence document, OS results from the IMbrave150 trial used in the MAIC analysis (HR = 0.66; 95% CI, 0.52 to 0.85) were as reported in the Cheng et al. (2022) publication. The matching criteria were based on the inclusion and exclusion criteria for the IMbrave150 and REFLECT trials and availability of comparable data from the HIMALAYA trial; therefore, matching was not possible for all criteria that may remove an important portion of the patient population from the HIMALAYA trial. The effective sample size was reduced after matching and adjustment in both MAICs (65.7% to 78% of the original sample size in HIMALAYA). This implies that the weighted estimates are influenced by a subset of the patients from the HIMALAYA trial that may not be representative of the entire study population, which may limit the generalizability of the results. In addition, the MAIC analysis could not account for some sources of heterogeneity in trials, such as differences in observation times or definition of end points. The clinical experts noted that given the time gap, there is a possibility of systemic differences between patients in the HIMALAYA trial (from 2017 to 2019) and the REFLECT trial (from 2013 to 2016), such as treatments received before systemic therapy (i.e., locoregional treatment). Furthermore, not all trials included the same subjective and objective measurements, so the comparative efficacy and safety of relevant treatments included remain unknown. Although OS and PFS were available in all 3 trials, ORR and DOR were not assessed in the REFLECT trial. In addition, disease control rate, considered by clinical experts consulted for this review as an important outcome, was assessed only in the HIMALAYA trial. Results on patient-reported outcomes (quality of life, abdominal swelling), which was considered as an important outcome for this review, were only reported in the MAIC comparing tremelimumab in combination with durvalumab versus atezolizumab in combination with bevacizumab in patients with unresectable HCC. In both MAICs, results for some efficacy and harm estimates were imprecise (i.e., wide confidence intervals favouring either tremelimumab in combination with durvalumab or the comparators), which precluded conclusions from being drawn.

Fulgenzi et al. (2022)

In addition to the MAICs conducted by the sponsor, a published network meta-analysis (NMA) conducted by Fulgenzi et al. (2022) was also identified. A frequentist NMA using fixed-effects models was performed to compare the efficacy and safety of first-line treatments for unresectable HCC from 2007 to 2022. Two analyses were performed: the first comparing the efficacy of atezolizumab in combination with bevacizumab versus all other first-line treatments and the second comparing all first-line treatments with placebo. Because tremelimumab in combination with durvalumab is of interest to this report, only a comparison of atezolizumab in combination with bevacizumab versus tremelimumab in combination with durvalumab was presented in this report. The results of the NMA showed that the HR for OS for atezolizumab in combination with bevacizumab compared with tremelimumab in combination with durvalumab was 0.74 (95% CI, 0.52 to 1.06). The HR for PFS for atezolizumab in combination with bevacizumab compared with tremelimumab in combination with durvalumab was 0.66 (95% CI, 0.49 to 0.87). The OR for ORR for atezolizumab in combination with bevacizumab compared with tremelimumab in combination with durvalumab was 0.60 (95% CI, 0.28 to 1.25).

The results of the published NMA are highly uncertain given the heterogeneity in the baseline characteristics of patients within the included trials, data sparseness, network structure, and differences in the duration of follow-up for efficacy outcomes. The use of fixed-effect models seems appropriate given the sparsity of data; however, no rationale was provided for the selection of the model in the published NMA. Furthermore, the evidence is imprecise in the effect estimates from the NMA due to the sparseness of data, with wide confidence intervals which, for many outcomes, included the possibility of benefit, lack of benefit, or harm for atezolizumab in combination with bevacizumab compared with tremelimumab in combination with durvalumab. Model fit was not evaluated, so it is not clear how well the model estimates treatment differences. No results on patient-reported quality of life were evaluated, which was considered an important end point for this review. In addition, there were no comparative effect estimates for the harms. Thus, these limitations must be considered when drawing conclusions on the results of the published NMA.

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy (i.e., first-line treatment)
Treatment	Single-dose tremelimumab in combination with regular-interval durvalumab (STRIDE)
Dose regimen	300 mg IV single-dose tremelimumab in combination with durvalumab on cycle 1, day 1 1,500 mg IV dose of durvalumab every 4 weeks for as long as clinical benefit is observed or until unacceptable toxicity
Submitted price	Tremelimumab, 15 mL vial (300 mg): $34,319.58 per single-use vial Durvalumab, 2.4 mL vial (120 mg): $938.67 per single-use vial Durvalumab, 10 mL vial (500 mg): $3,911.11 per single-use vial
Treatment cost	Assuming a patient weight of more than 30 kg and no vial sharing, the 28-day cost of treatment is expected to be $46,053 per patient for the first cycle and $11,733 per patient for subsequent cycles.
Comparators	• Sorafenib • Lenvatinib • Atezolizumab plus bevacizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (15 years)

Component	Description
Key data source	• OS, PFS, and treatment discontinuation for STRIDE were derived from the phase III HIMALAYA trial. • Comparative efficacy for sorafenib and lenvatinib were derived from a MAIC conducted of lenvatinib vs. STRIDE (reweighted HIMALAYA population used for sorafenib). • Comparative efficacy for atezolizumab plus bevacizumab was derived from a separate MAIC compared to STRIDE.
Key limitations	• The use of sorafenib efficacy data from the lenvatinib MAIC was inappropriate, given that direct comparative evidence from the HIMALAYA trial is available. • There is no direct comparative evidence to inform the comparative efficacy of lenvatinib or atezolizumab plus bevacizumab vs. STRIDE. CADTH's clinical review reported that the sponsor-submitted MAICs for these comparators had methodological limitations and imprecise effect estimates, which introduced substantial uncertainty into the results of the pharmacoeconomic evaluation. Moreover, sequential analysis was deemed inappropriate. • The use of treatment-specific utility values that were applied by treatment status (i.e., on/off treatment regardless of progression) is contradictory to CADTH's guidelines and best practices that utilities should reflect the health states of the economic model. • Regarding treatment discontinuation, the sponsor assumed that STRIDE and sorafenib would continue to be taken after disease progression, and lenvatinib and atezolizumab plus bevacizumab were discontinued at the time of progression. Clinical experts consulted by CADTH indicated that at the time of disease progression, patients would move to second-line therapy for all treatment options. • The long-term extrapolation of the clinical efficacy of STRIDE was not considered plausible by clinical experts consulted by CADTH. Further, because a proportional hazards approach relative to STRIDE was used to extrapolate OS and PFS for the comparators, the uncertainty in the extrapolation period existed for all modelled comparators.
CADTH reanalysis results	• To account for the key limitations, several changes were made to derive the CADTH base case: the comparative clinical efficacy for sorafenib was informed by the HIMALAYA trial results, health state utilities were applied consistently for all treatments, and treatment was assumed to be discontinued at the time of disease progression for all treatments. • In the CADTH base case, the ICER for STRIDE vs. sorafenib was $265,036 per QALY gained (incremental costs: $95,359; incremental QALYs: 0.36). A price reduction of approximately 50% would be required for STRIDE to be cost-effective at a $50,000 per QALY gained threshold. • A scenario analysis assuming that the clinical efficacy of STRIDE and atezolizumab plus bevacizumab was equivalent found that STRIDE was more costly and equally effective. A comparison of costs found that the total treatment costs for both comparators are equal at approximately 60 weeks of continuous treatment.

ICER = incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; STRIDE = single-dose tremelimumab in combination with regular-interval durvalumab; vs. = versus.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the health care payer perspective was inappropriate; the sponsor's estimates of the NIHB population did not consider provincial coverage of oncology treatments; BCLC staging at diagnosis was inappropriately derived; some patients with BCLC stage A were inappropriately excluded; the efficacy of sorafenib was inappropriately modelled, as was the time to discontinuation of single-dose tremelimumab in combination with regular-interval durvalumab (STRIDE) and sorafenib; the proportion of patients receiving systemic therapy may have been underestimated; and the market displacement caused by STRIDE is uncertain. CADTH estimated a revised base case by assuming a drug payer perspective, adjusting the NIHB population, revising the BCLC staging distribution of HCC

patients at diagnosis, incorporating patients diagnosed at BCLC stage A who initially received treatments other than liver transplant or resection, and adjusting the median OS of patients treated with sorafenib and the median time-to-treatment discontinuation of STRIDE and patients treated with sorafenib to match those of the CADTH pharmacoeconomic reanalysis. The CADTH reanalysis suggests that reimbursing the STRIDE regimen for the treatment of unresectable HCC would be associated with an incremental cost of $5,816,972 in year 1, $6,532,047 in year 2, and $6,053,880 in year 3, for a 3-year budgetary impact of $18,402,899.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: August 9, 2023

Regrets: 3 expert committee members did not attend.

Conflicts of interest: None

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the CADTH Drug Reimbursement Review Confidentiality Guidelines.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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