pCODR EXPERT REVIEW COMMITTEE
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the CADTH pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *Procedures for the CADTH pan-Canadian Oncology Drug Review*, which are available on the CADTH website. The Final Recommendation will be posted on the CADTH website once available and will supersede this Initial Recommendation.

Drug: Atezolizumab (Tecentriq)

Submitted Reimbursement Request: Atezolizumab in combination with Avastin (bevacizumab), for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy. Maintenance atezolizumab (Tecentriq) should continue until loss of clinical benefit or unacceptable toxicity. Maintenance bevacizumab (Avastin) should continue until loss of clinical benefit or unacceptable toxicity.

Submitted by: Hoffman-La Roche Limited

Manufactured by: Hoffman-La Roche Limited

NOC date: August 7, 2020

Submission date: May 21, 2020

Initial Recommendation issued: October 29, 2020

Approximate per patient drug costs, per month (28 Days)	Atezolizumab (Tecentriq) costs $6,776.00 per 1,200 mg/20 mL Bevacizumab (Avastin) costs $519.178 per 100 mg/4 mL At the recommended dose of 1,200 mg every three weeks for atezolizumab, the 21-day cycle costs $6,776.00 and the 28-day cycle costs $9,035.00 At the recommended dose of 15 mg/kg every three weeks for bevacizumab, the 21-day cycle costs $5,711.00 and the 28-day cycle costs $7,615.00

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions***
☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of atezolizumab in combination with bevacizumab for first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy if the following condition is met:

- Cost-effectiveness improves to an acceptable level

Eligible patients should have no prior systemic treatment, have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and a Child-Pugh class status of A. Treatment with atezolizumab and bevacizumab should continue until loss of clinical benefit or unacceptable toxicity.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of atezolizumab plus bevacizumab compared with sorafenib based on a statistically significant and clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS). As well, a delay in time to deterioration of quality of life (QoL) was demonstrated. pERC noted that atezolizumab plus bevacizumab is associated with significant but manageable toxicities. pERC acknowledged that there is no direct evidence

	that compares atezolizumab plus bevacizumab to lenvatinib for outcomes important to decision-making, such as OS, PFS, and QoL. However, pERC noted that lenvatinib likely has efficacy similar to sorafenib: pERC based this on the REFLECT trial that demonstrated improved PFS, non-inferior OS and a different toxicity profile when comparing lenvatinib to sorafenib. pERC concluded that atezolizumab plus bevacizumab aligns with patient values in that it offers an additional effective treatment option, an improvement in OS, and a delay in time to deterioration of QoL, and has manageable but not insignificant toxicities compared with sorafenib. The Committee concluded that, at the submitted price, atezolizumab plus bevacizumab is not considered cost-effective when compared with sorafenib or lenvatinib. pERC also noted the results of the cost-effectiveness analysis were driven by the high cost of both atezolizumab and bevacizumab; even with a substantial price reduction for each drug, it is highly unlikely atezolizumab plus bevacizumab would become cost-effective. pERC also concluded that the submitted budget impact analysis was underestimated and that the budget impact of atezolizumab plus bevacizumab at the submitted price would be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing arrangements to improve cost-effectiveness** pERC was satisfied that there is a net clinical benefit with atezolizumab plus bevacizumab compared with sorafenib; therefore, jurisdictions may want to consider alternate pricing arrangements and/or cost structures to improve the cost-effectiveness to an acceptable level. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

In 2020, it is estimated that 3,100 new cases of HCC will be diagnosed in Canada. The treatment approach for and prognosis of patients with HCC depends on the extent of the disease, hepatic functional reserve, and performance status. Child-Pugh class (A, B, or C) is the most commonly used metric to assess hepatic reserve. The prognosis of patients with untreated and unresectable HCC is poor, with a median OS of less than one year and a five-year OS rate of 19%. Sorafenib is currently approved and reimbursed across Canada for the first-line systemic treatment of patients with Child-Pugh class A advanced HCC. Lenvatinib is also a first-line treatment option for patients with advanced HCC and Child-Pugh class A liver function that has demonstrated to be noninferior to sorafenib in OS. pERC considered that both sorafenib and lenvatinib are associated with a number of treatment-related adverse effects that have a negative impact on patients' QoL. Therefore, pERC agreed that there is a need for more treatment options that prolong survival and improve QoL for patients with unresectable or metastatic HCC.

pERC deliberated upon the results of one phase III, open-label, international, randomized controlled trial (RCT), IMbrave150, that compared atezolizumab plus bevacizumab with sorafenib monotherapy in patients with locally advanced or metastatic and/or unresectable HCC who have not received prior systemic treatment. pERC noted that treatment with atezolizumab plus bevacizumab could be continued until loss of clinical benefit, based on assessments of biochemical, radiographic data, and clinical status (e.g., symptomatic deterioration) or unacceptable toxicity. pERC further noted that if either atezolizumab or bevacizumab were withheld or discontinued, continuation of the other drug was permitted as long as the patient was deemed to be experiencing clinical benefit. pERC discussed that there was a statistically significant and clinically meaningful improvement in OS and PFS by independent review facility (IRF) assessment and according to Response Evaluation Criteria in Solid Tumors, Version 1.1(RECIST v1.1), the co-primary end point in IMbrave150, in favour of atezolizumab plus bevacizumab. However, pERC considered that the trial follow-up period was short and current OS data are immature. pERC acknowledged that the median OS was not reached at the time of the OS interim analysis for patients in the atezolizumab plus bevacizumab group, and that the magnitude of benefit over time is uncertain and will need to be confirmed with longer follow-up data. In addition, pERC noted that secondary outcomes, including objective response rate (ORR) and time to progression, favoured treatment with atezolizumab plus bevacizumab.

pERC discussed the available patient-reported outcomes data from the IMbrave150 trial and noted that there was a clinically meaningful delay in time to deterioration observed in three European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) subscales of QoL, including global health score (GHS)/QoL, physical functioning, and role functioning in favour of atezolizumab plus bevacizumab. pERC considered that although QoL endpoints were pre-specified, there were no adjustments made for multiplicity and thus results should be considered exploratory in nature. Furthermore, pERC discussed the toxicity profile of atezolizumab plus bevacizumab. The reported adverse events (AEs) were consistent with the known safety profile of atezolizumab and bevacizumab. The most commonly reported grade 3 or 4 treatment-related AEs in the atezolizumab plus bevacizumab group were hypertension and elevated aspartate aminotransferase (AST). Additionally, pERC noted that the reported immune-mediated AEs of atezolizumab were comparable to the known safety profile. pERC noted that treatment discontinuation due to an AE was higher in the atezolizumab plus bevacizumab group compared with the sorafenib group. pERC considered the main reasons for discontinuation of atezolizumab, which were autoimmune hepatitis, gastrointestinal (GI) hemorrhage, increased transaminases, or infusion-related reactions; bevacizumab was most frequently discontinued due to GI hemorrhage, esophageal hemorrhage, esophageal varices hemorrhage, and proteinuria. pERC also considered that bleeding or hemorrhage is a known AE of bevacizumab and that a higher proportion of patients experienced bleeding or hemorrhage in the atezolizumab plus bevacizumab group. Overall, pERC concluded that compared to sorafenib, atezolizumab plus bevacizumab is associated with significant but manageable toxicities, which can be managed by temporary dose interruptions. Furthermore, pERC agreed with the Clinical Guidance

Panel (CGP) and the registered clinicians that, prior to treatment with atezolizumab plus bevacizumab, patients with untreated or incompletely treated esophageal or gastric varices would be required to undergo an esophagogastroduodenoscopy and management of varices if found.

In addition to the IMBrave150 trial, pERC also deliberated on the results of the submitted indirect treatment comparison (ITC) in the form of a network meta-analysis (NMA) that compared atezolizumab plus bevacizumab with other available therapies, including lenvatinib. The ITC was included as part of the submission to CADTH to inform the pharmacoeconomic model supporting the reimbursement request. pERC noted that the ITC was performed by the sponsor to derive comparative efficacy estimates for OS and PFS. There were no results provided on QoL or safety outcomes. Overall, the results demonstrated that the numerical values for the hazard ratios (HRs) for OS and PFS favoured atezolizumab plus bevacizumab relative to all treatments. However, the credible intervals for the HRs did not provide evidence that atezolizumab plus bevacizumab differed from the other treatments; atezolizumab plus bevacizumab was only superior compared with sorafenib for OS. pERC discussed that the CADTH Methods Team identified a number of limitations in the analysis which led to uncertainty in the magnitude of benefit of atezolizumab plus bevacizumab relative to lenvatinib. However, pERC acknowledged that lenvatinib likely has efficacy similar to sorafenib, considering the demonstrated improved PFS and non-inferior OS.

pERC concluded that there is a net overall clinical benefit of atezolizumab plus bevacizumab compared with sorafenib based on the demonstrated improvement in OS and PFS, as well as delay in time to deterioration of QoL and an overall significant but manageable toxicity profile.

pERC deliberated upon input from two patient advocacy groups. pERC discussed that patients experience physical pain and deep mental and emotional impacts due to HCC. Patients with HCC reported poor QoL and that current treatments with sorafenib and lenvatinib result in significant adverse effects, which contributes to reduced QoL. pERC noted that patients value having access to new treatments that are associated with fewer adverse effects, improve QoL, and allow them to be active enough to attend social functions and complete daily tasks independently. pERC discussed that two patients providing input had direct experience with atezolizumab plus bevacizumab, and that the combination therapy was reported to better control symptoms and disease progression and was associated with fewer adverse effects. Overall, based on the results of the IMbrave150 trial, pERC concluded that atezolizumab plus bevacizumab aligns with the patient values in that it offers an additional effective treatment option, an improvement in PFS and OS, an observed delay in time to deterioration of QoL, and has manageable but not insignificant toxicities compared with sorafenib.

pERC deliberated upon the cost-effectiveness of atezolizumab in combination with bevacizumab compared with sorafenib and lenvatinib. In discussing the results of the CADTH base case, pERC noted that the change to the OS extrapolation for atezolizumab plus bevacizumab in the CADTH base case had the greatest impact on model results. pERC felt this change highlighted the uncertainty with the long-term efficacy but also noted that even with optimistic estimates of survival for atezolizumab in combination with bevacizumab, the incremental cost-effectiveness ratio (ICER) was far greater than $50,000 per quality-adjusted life-year (QALY). pERC also highlighted the analysis assessing the impact of using the price of biosimilar bevacizumab, noting atezolizumab plus bevacizumab was still not cost-effective at this lower price. pERC concluded it is highly unlikely that atezolizumab plus bevacizumab would be considered cost-effective at a willingness to pay of $50,000 per QALY even if substantial price reductions were obtained for both atezolizumab and bevacizumab.

pERC also discussed the budget impact analysis and noted that the factor most influencing the estimated budget impact was the estimated market uptake. pERC considered the estimated budget impact to be substantial, and also noted that the budget impact could be even higher because the estimated market share in the CADTH base case could have been underestimated.

pERC deliberated on the input from PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and the sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the CADTH pCODR clinical and economic review panels
- input from two patient advocacy groups: Canadian Cancer Survivor Network (CCSN) and Canadian Liver Foundation (CLF)
- input from registered clinicians: two joint inputs on behalf of two clinicians from Cancer Care Ontario (CCO) and eight clinicians from the Canadian Gastrointestinal Oncology Evidence Network (CGOEN)
- input from CADTH's PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of atezolizumab in combination with bevacizumab for the treatment of patients with unresectable HCC who have not received prior systemic therapy.

Studies included: One international, open-label, randomized phase III trial (IMbrave150)

The pCODR systematic review included one phase III, open-label RCT that compared atezolizumab in combination with bevacizumab to sorafenib monotherapy in patients with locally advanced or metastatic and/or unresectable HCC who have not received prior systemic treatment. The IMbrave150 trial enrolled a total of 501 patients who were randomized in a 2:1 ratio to receive atezolizumab plus bevacizumab (n = 336) or sorafenib (n = 165). The primary efficacy outcome was the co-primary end point of OS and PFS.

Patient populations: Adult patients with HCC who have not received prior systemic treatment, with ECOG PS 0 or 1 and Child-Pugh class A

Key eligibility criteria included adults (aged 18 years or older) who had locally advanced or metastatic and/or unresectable HCC that was not amenable to curable surgical and/or locoregional therapies or had progressed thereafter. Patients must not have received prior systemic treatment for HCC. Additional eligibility criteria included ECOG PS of 0 to 1, Child-Pugh class A, and adequate hematologic and organ function. Patients with known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC were excluded, as were patients with coinfection of both hepatitis B and C. Patients with prior solid organ transplantation were also excluded. Prior radiation therapy, locoregional therapy to the liver, and surgical procedures were permitted if they had not occurred within 28 days of initiating study treatment (60 days for abdominal or pelvic radiation therapy or abdominal surgery). Furthermore, for those who had received curative surgical and/or locoregional therapies, the lesion(s) must have subsequently progressed. Prior to study enrolment, patients with untreated or incompletely treated esophageal or gastric varices were required to undergo an esophagogastroduodenoscopy and treatment per local standard of care. Patients with untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding were excluded from the trial.

For the 501 patients enrolled, the median age was 65 years, 83% were male, 62% had an ECOG PS of 0, 72% had a Child-Pugh score of A5, 82% had Barcelona Clinic Liver Cancer Stage C (advanced) disease, and 75% had presence of macrovascular invasion and/or extrahepatic spread. The predominant etiology of HCC in the enrolled patients was hepatitis B (48%). Approximately half (49%) of patients had received at least one prior local therapy for HCC (most commonly transarterial chemoembolization or radiofrequency ablation), and 29% had prior surgical resection of the liver. Baseline demographics and characteristics were generally well balanced between the two treatment groups.

Key efficacy results: Statistically significant improvement in PFS and interim OS analyses

The key efficacy outcome deliberated on by pERC included PFS and OS, the co-primary end points.

PFS was assessed by an IRF using the RECIST v1.1 criteria. In total, 197 patients (58.6%) in the atezolizumab plus bevacizumab group and 109 patients (66.1%) in the sorafenib group experienced disease progression or died, with a median PFS of 6.8 months in patients randomized to the atezolizumab plus bevacizumab group compared with 4.3 months in patients randomized to the sorafenib group. The corresponding HR for disease progression or death was 0.59 (95% CI, 0.47 to 0.76; P < 0.001).

Final analysis of the OS data was planned to be done after 312 deaths. At the data cut-off date (interim analysis), 161 patients had died, including 96 patients (28.6%) in the atezolizumab plus bevacizumab group and 65 patients (39.4%) in the sorafenib group. Median OS was not reached for patients randomized to atezolizumab plus bevacizumab and was 13.2 months for patients randomized to the sorafenib group. The interim OS analysis data showed a HR of 0.58 (95% CI, 0.42 to 0.79; P < 0.001).

Key secondary end points were ORR, which included complete response or partial response by IRF assessment (ORR-IRF), according to RECIST v1.1 and hepatocellular carcinoma-specific modified RECIST (HCC mRECIST). The ORR-IRF per RECIST v1.1 was 27.3% (95% CI, 22.5% to 32.5%) in the atezolizumab plus bevacizumab group and 11.9% (95% CI, 7.4% to 18.0%) in the sorafenib group. The ORR-IRF per HCC mRECIST was 33.2% (95% CI, 28.1% to 38.6%) in the atezolizumab plus bevacizumab group and 13.3% (95% CI, 8.4% to 19.6%) in the sorafenib group. Time to progression by IRF assessment (according to RECIST v1.1) was another secondary end point explored in the trial; the results showed a median time to progression of [redacted] in the atezolizumab plus bevacizumab group and [redacted] in the sorafenib group.
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Patient-reported outcomes: Clinically meaningful delay in time to deterioration of QoL

QoL was measured using the EORTC QLQ-C30 and HCC disease-specific treatment questionnaire (EORTC QLQ-HCC18). Health status utility scores used in health economic analyses were obtained through the EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L). The questionnaires were completed by patients on day 1 of each treatment cycle, at treatment discontinuation, and every three months for one year during post-treatment follow-up.

Time to deterioration in three EORTC QLQ-C30 subscales (i.e., GHS/QoL, physical functioning, and role functioning) was a secondary end point in the trial. A clinically significant deterioration was deemed as a decrease in score of 10 points or greater from baseline, which had to be maintained for two consecutive assessments or for one assessment if followed by death from any cause within three weeks. A clinically meaningful delay in deterioration for all three subscales was observed in patients in the atezolizumab plus bevacizumab group compared with patients who were treated with sorafenib. Specifically, the median times to deterioration for atezolizumab plus bevacizumab compared with sorafenib were 11.2 months versus 3.6 months for the GHS/QoL subscale, 13.1 months versus 4.9 months for the physical functioning subscale, and 9.1 months versus 3.6 months for the role functioning subscale, respectively.

Safety: Different and acceptable safety and tolerability profile

Adverse events were evaluated in a safety population consisting of 329 patients in the atezolizumab plus bevacizumab group and 156 patients in the sorafenib group. The median duration of treatment was 2.8 months for sorafenib, 7.4 months for atezolizumab, and 6.9 months for bevacizumab. Broadly, a similar number of patients in each treatment group experienced an AE due to any cause (all grades; atezolizumab plus bevacizumab: 98.2%, n = 323; sorafenib: 98.7%, n = 154). Grade 3 or 4 AEs due to any cause were also comparable (atezolizumab plus bevacizumab: 56.5%, n = 186; sorafenib: 55.1%, n = 86). A higher proportion of patients treated with atezolizumab plus bevacizumab (38.0%, n = 125) experienced a serious AE compared with patients treated with sorafenib (30.8%, n = 48), although no specific cause was identified; the difference in the incidence of identified serious AEs was less than 2% between treatment groups. Reported AEs were generally consistent with the known safety profile of atezolizumab and bevacizumab. Immune-mediated AEs of atezolizumab were comparable to the known safety profile, except for the following which occurred at a higher incidence than anticipated: immune-related hepatitis (43.2%, including diagnosis and abnormal liver function tests or 13.1% for diagnosis only), immune-related hyperthyroidism (4.6%), and immune-mediated diabetes mellitus (2.4%). Grade 3 or 4 immune-related AEs, specifically colitis and nephritis, occurred at an incidence of less than 1% in each treatment group.

Upper GI bleed occurred in 7% of patients treated with atezolizumab plus bevacizumab and 4.5% of those treated with sorafenib.

A higher proportion of patients in the sorafenib group experienced a treatment-related AE of any grade compared with patients in the atezolizumab plus bevacizumab group (94.2%, n = 147 versus 83.9%, n = 276) and grade 3 or 4 treatment-related AEs (45.5%, n = 71 versus 35.6%, n = 117).

The most commonly reported (10% or greater) any-grade treatment-related AEs in the atezolizumab plus bevacizumab group were hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%), elevated AST (14.0%), pruritis (13.1%), infusion-related reaction (10.9%), diarrhea (10.3%), elevated alanine aminotransferase (10.3%), and reduced appetite (10.3%). In patients who received sorafenib, the most common (10% or greater) treatment-related AEs were palmar-plantar erythrodysesthesia syndrome (48.1%), diarrhea (42.9%), hypertension (19.9%), reduced appetite (19.9%), rash (16.7%), fatigue (15.4%), alopecia (13.5%), nausea (12.8%), and asthenia (10.3%).

In the atezolizumab plus bevacizumab group, AEs led to discontinuation of one component of the combination in 15.5% of patients; both components were stopped in 7.0% of patients. In patients who received sorafenib treatment, 10.3% discontinued the study drug due to an AE. Deaths due to an AE occurred in 4.6% (n = 15) and 5.8% (n = 9) of patients in the atezolizumab plus bevacizumab and sorafenib groups, respectively.

Limitations: Open-label study with change in subsequent interim and final OS analysis schedule

Overall, the IMbrave150 trial was a well-designed RCT, although there are some limitations that should be considered when interpreting the results. A key limitation involves the pre-specified interim and final analysis plan. Final analysis of OS for the IMbrave150 trial was originally scheduled for after 312 deaths, which had yet to occur at the data cut-off date; however, as the co-primary OS end point was met at the first interim analysis, this analysis was considered as definitive by the study sponsor. According to the sponsor, although the study is still ongoing, the event-driven second interim analysis of OS will no longer be performed. Instead, a time-driven descriptive OS analysis is planned with a data cut-off date in August 2020, approximately 12 months after the first interim analysis. A final descriptive analysis is also under discussion. Because the median OS had not been reached in the atezolizumab plus bevacizumab group with the current duration of follow-up (median 8.6 months; first interim analysis), the absolute difference between the two treatment groups in this end point is unknown. The magnitude of benefit over time will need to be confirmed with longer follow-up data; this change in the pre-specified analysis plan contributes to uncertainty in the degree of sustained effect of atezolizumab plus bevacizumab.

There are also other limitations and potential sources of bias affecting external or internal validity that should be considered when interpreting the results of the trial. Due to the open-label study design, the investigators and patients were aware of the treatment allocation. This could potentially favour the new treatment, although treatment response and disease progression were measured by a central, blinded IRF to reduce investigator bias. The lack of blinding may also have affected the reporting of subjective outcomes (e.g., AEs, patient-reported outcomes). Furthermore, although measures of health-related QoL were pre-specified in the protocol, results should be considered exploratory in nature because health-related QoL analysis was not considered in the adjustment for multiplicity. Specific to sorafenib treatment, Canadian prescribers often opt to use a lower starting dose of 200 mg twice a day to improve tolerability. Thus, starting patients in the clinical trial at 400 mg twice a day may have contributed to reduced tolerability and more AEs than would normally be anticipated.

Comparator information: ITC of atezolizumab plus bevacizumab compared with lenvatinib

The available clinical trial did not capture all relevant comparators identified during the review; thus, the sponsor supplied an ITC to relevant comparators based on a systematic review of treatments for locally advanced metastatic HCC. Three levels of NMA were initially attempted for two outcomes: OS and PFS. The level 1 analysis, which included systemic therapies considered standard of care in HCC (sorafenib, nivolumab, lenvatinib), was deemed most relevant to this review.

Three trials were included in the level 1 network, including four interventions (atezolizumab plus bevacizumab, lenvatinib, nivolumab, and sorafenib). The OS results from the level 1 analysis found that atezolizumab plus bevacizumab was favoured compared with sorafenib. There was insufficient evidence of difference between atezolizumab plus bevacizumab and lenvatinib or nivolumab. The PFS results did not provide evidence that atezolizumab plus bevacizumab differed from other treatments. No results for

any other effectiveness outcomes were provided. There were no results reported on any of the harms outcomes.

A number of limitations were identified in the NMA: the analyses were overly restricted, resulting in few trials being eligible for inclusion in the NMA; the dataset was relatively sparse, leading to broad credible intervals and potential failure to detect real differences; not all outcome results could be analyzed and there was no data reported on harms; and not all sensitivity analyses were possible due to a dearth of data. Thus, these limitations must be considered when drawing conclusions based on the results of the NMA.

Need and burden of illness: Poor prognosis and need for superior treatment options

In 2020, it is estimated that 3,100 new cases of HCC will be diagnosed in Canada. In addition, 1,450 Canadians are predicted to die from this disease, which has a five-year OS rate of 19%. HCC is a challenging disease to treat because it commonly occurs in the setting of underlying hepatic cirrhosis, which can lead to underlying hepatic impairment. Systemic therapy is often not well tolerated in patients with underlying hepatic dysfunction. Thus, the treatment approach and consequent prognosis of patients with HCC depends upon the extent of disease, hepatic functional reserve, and performance status. Per the Barcelona Clinic Liver Cancer algorithm, the prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve is poor, with a median OS of less than one year. HCC is considered to be a chemotherapy-refractory tumour.

Sorafenib is currently approved and reimbursed across Canada for the first-line systemic treatment of patients with Child-Pugh class A advanced HCC. Lenvatinib is also a first-line systemic treatment option for patients with advanced HCC and Child-Pugh class A liver function; it has demonstrated to be noninferior to sorafenib in OS. In August 2019, lenvatinib was recommended for reimbursement by pERC and is now available for reimbursement in some provinces. Over the past 15 years, numerous phase III trials involving various therapeutic agents (e.g., sunitinib, nivolumab, brivanib, linifanib, erlotinib) have been conducted in the first-line setting in HCC but have not demonstrated superiority over sorafenib.

Registered clinician input: Limited treatment options and unmet need

Two registered clinician inputs were provided on behalf of two clinicians from CCO and eight clinicians from CGOEN. Both inputs indicated that there is an unmet need for more effective first-line systemic therapies because sorafenib and lenvatinib provide modest improvements in survival. The CGOEN clinicians added that lenvatinib and sorafenib may result in treatment-related adverse effects and may potentially elicit a negative impact on patients' QoL. The clinicians noted that in current clinical practice, lenvatinib may be preferred in patients who are symptomatic or have rapidly progressive disease; however, the different adverse effect profiles of lenvatinib and sorafenib may also inform treatment selection.

Both the CCO and CGOEN clinicians indicated that the inclusion and exclusion criteria of the pivotal trial (IMbrave150) can be generally applied in clinical practice. However, the CCO clinicians noted that patients in the pivotal trial were required to undergo an assessment of varices by upper endoscopy, which is a common practice but not mandated in clinical practice.

The CGOEN clinicians stated that the majority of patients with advanced HCC and Child-Pugh class A cirrhosis should receive atezolizumab plus bevacizumab as first-line treatment in the absence of contraindications to bevacizumab or to anti-PD-L1 antibodies, such as active autoimmune diseases, recent stroke or myocardial infarction, recent bleeding, and arterial thrombotic events. Both inputs noted that patients unable to undergo endoscopic surveillance for esophageal or gastric varices, patients with untreated or incompletely treated esophageal or gastric varices, or patients who do not meet standard criteria for atezolizumab plus bevacizumab should be treated with sorafenib or lenvatinib. The CGOEN clinicians stated that atezolizumab plus bevacizumab addresses the need for more effective and tolerable first-line therapies for HCC, and both inputs reported that atezolizumab plus bevacizumab would replace existing treatments (sorafenib and lenvatinib) except in patients with contraindications to the treatment combination.

The CCO clinicians noted that the role of sorafenib and lenvatinib in the second-line setting is unknown, and the CGOEN clinicians specified that no direct evidence exists. However, in the absence of direct evidence, the CGOEN clinicians recommend that lenvatinib and sorafenib should be administered in the second-line setting if a patient progresses on first-line treatment of atezolizumab plus bevacizumab, and cabozantinib, regorafenib, and ramucirumab should be administered in the third-line setting.

PATIENT-BASED VALUES

Experience of patients with HCC: Poor prognosis and limited treatment options

Patient input was provided by CCSN and CLF. CCSN collected input from 15 respondents; CLF provided input from two respondents (one patient and one caregiver) from a 2020 online survey, as well as information from a 2016 global survey of 256 respondents. To further supplement the input, CLF included insights from 45 Canadian liver cancer patients.

According to CLF, patients experience a deep mental and emotional impact in addition to the physical symptoms of HCC. All Canadian patients (n = 8) from the Global Survey-2016 described their experience using the words *fear*, *worry*, *shock*, *scared*, and *sad*. According to the Global Survey-2016, approximately 80% of respondents reported their current QoL as poor. Pain and confusion were commonly reported among patient accounts of their experience with HCC.

The CLF highlighted that HCC is often difficult to treat because it is usually a result of a pre-existing and progressive underlying liver disease. Sorafenib and lenvatinib were reported to result in significant adverse effects that greatly reduce patient QoL.

CCSN caregiver respondents most commonly reported fatigue and emotional drain as issues associated with caring for someone with HCC; however, anxiety/worrying, management of medications, hours spent in medical appointments, inability to plan ahead, anger, and feelings of helplessness were also mentioned.

Patient values, experience on or expectations for treatment: Improved QoL, tolerable adverse effects

Overall, patients and caregivers value having access to new treatments for unresectable HCC that are associated with fewer adverse effects, improved QoL, and allow patients to be active enough to attend social functions and complete daily tasks independently. Two patients providing input had experience with atezolizumab plus bevacizumab. Both patients experienced adverse effects related to atezolizumab plus bevacizumab, including diarrhea. Overall, the patients noted that adverse effects were tolerable.

The patient groups highlighted the rarity of HCC and the poor survival prognosis of the disease, particularly in the advanced stages; thus, the possibility of a new first-line treatment option offers hope to patients and their families who would otherwise have very limited options. CLF believes that patients and their physicians should have access to a broad range of treatment options regardless of geographic location, financial status, treatment status, or disease severity to ensure the best possible outcomes.

ECONOMIC EVALUATION

Atezolizumab is supplied as 1,200 mg vials for intravenous infusion. The recommended dosage regimen is 1,200 mg of atezolizumab in combination with 15 mg/kg of bevacizumab administered intravenously every three weeks until loss of clinical benefit or unacceptable toxicity. At the sponsor-submitted price of $6,776 per vial, the drug acquisition cost of atezolizumab is $6,776 per treatment cycle and $117,773 annually. In combination with bevacizumab, the total regimen cost is $11,021 per cycle and $191,555 annually.

The sponsor submitted a cost-utility analysis based on a partitioned survival model that compared atezolizumab in combination with bevacizumab with the current standards of care, sorafenib and lenvatinib, for patients with unresectable HCC who had not received prior systemic therapy. The model consisted of three primary health states (PFS, progressed disease, and death). All patients entered the model in the PFS health state and remained in this health state until they progressed or died. Progressive disease was defined as patients who were alive but had experienced disease progression according to the RECIST v1.1 criteria. Costs and QALYs were modelled over a 10-year time horizon based on patients' progression status from a public health care payer perspective. Clinical efficacy was based on data from the IMbrave150 trial for atezolizumab plus bevacizumab and sorafenib monotherapy. These curves were extrapolated using parametric survival analysis to determine the proportion of patients in each health state over the model time horizon. The HRs for lenvatinib were obtained from a sponsor-commissioned NMA and applied to the extrapolated OS and PFS curves for atezolizumab plus bevacizumab. In the sponsor's base case, atezolizumab plus bevacizumab was associated with an ICER of $332,281 per QALY gained.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- There was uncertainty regarding the long-term extrapolation of the OS and PFS data beyond the observed trial period for atezolizumab plus bevacizumab, and of the OS data for sorafenib. The sponsor's chosen extrapolated curves for atezolizumab plus bevacizumab predicted highly optimistic long-term survival gains despite there being no clinical evidence to substantiate the plausibility of these projections.

- The CADTH clinical review concluded that the NMA informing the relative treatment efficacy of atezolizumab plus bevacizumab with lenvatinib was subject to limitations and the magnitude of clinical benefit of atezolizumab plus bevacizumab is associated with uncertainty as a result.

- There was uncertainty with the utility values used in the model and whether they captured key changes in patient QoL. The sponsor used utility values based on patient progression status, whereas patient QoL is likely to be most impacted by whether they are on or off treatment according to CADTH clinical experts. Additionally, the sponsor's utility value elicitation methods were poorly described, they used treatment-specific utility values when the values should have been based solely on health states, and the values identified by the sponsor likely did not capture the impacts of acute AEs related to treatment.

- The proportion of patients receiving subsequent therapy was not representative of Canadian clinical practice, with more patients on sorafenib and lenvatinib receiving subsequent therapy than was expected.

- Total drug acquisition costs of sorafenib may have been overestimated due to the sponsor's choice of extrapolation for time to off treatment with sorafenib.

CADTH addressed some of the noted limitations by undertaking the following reanalyses: selecting alternative parametric survival distributions for OS and PFS with atezolizumab plus bevacizumab and for OS with sorafenib; applying health state utilities based on patients being on or off treatment and applying utility values for atezolizumab plus bevacizumab to all comparators; assuming an equal proportion of patients receive subsequent therapy regardless of first-line therapy; and selecting an alternative parametric survival distribution for the extrapolation of time to off treatment with sorafenib. Based on these revisions, the results of the CADTH reanalyses were consistent with the overall findings of the sponsor's base case: atezolizumab plus bevacizumab is not cost-effective at a willingness to pay threshold of $50,000 per QALY. Specifically, atezolizumab plus bevacizumab was associated with a sequential ICER of $771,970 per QALY gained compared with sorafenib.

The results are primarily driven by the combined cost of treatment for atezolizumab plus bevacizumab. With a 99% price reduction for atezolizumab, the ICER is $309,306 per QALY; with a 99% price reduction for atezolizumab and a 71% price reduction for bevacizumab, the ICER falls below $50,000 per QALY.

Overall, it is highly unlikely that atezolizumab plus bevacizumab would be considered cost-effective at a willingness to pay of $50,000 per QALY, even if substantial price reductions were obtained for both atezolizumab and bevacizumab.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Submitted budget impact analysis is overestimated

CADTH identified the following key limitations with the sponsor's analysis: the market share of sorafenib was overestimated when compared with lenvatinib and certain parameters used to derive the market size were unable to be validated. CADTH corrected the market shares of sorafenib and lenvatinib as part of the base case, which resulted in an estimated budget impact of $199,200,041 over three years. Uncertainty still remains with the potential market uptake of atezolizumab plus bevacizumab. Should the market uptake be greater than anticipated, the budget impact of atezolizumab plus bevacizumab may be substantially underestimated.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. W. Dominika Wranik, who was not present for the meeting
- Dr. Maureen Trudeau, who did not vote due to their role as the pERC Chair.

Avoidance of conflicts of interest

All members of the CADTH pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of atezolizumab plus bevacizumab for HCC through their declarations, no members had a real, potential, or perceived conflict; therefore, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical efficacy information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *pCODR Disclosure of Information 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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

APPENDIX 1: CADTH pCODR EXPERT REVIEW COMMITTEE RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation questions	pERC Recommendation
Currently funded treatments	
The first-line standard of care for patients with unresectable HCC is treatment with sorafenib, which is funded in all jurisdictions. Lenvatinib is another option that is under consideration for funding by the provinces. The IMbrave150 trial compared atezolizumab plus bevacizumab to sorafenib. PAG is also seeking comparative information with lenvatinib.	The IMbrave150 trial compared atezolizumab plus bevacizumab to sorafenib. The sponsor commissioned an NMA to derive the comparative efficacy of atezolizumab plus bevacizumab versus lenvatinib for PFS and OS outcomes. Based on the submitted NMA, pERC noted that there is uncertainty about the magnitude of the benefit of atezolizumab plus bevacizumab relative to lenvatinib due to several limitations in the NMA. However, pERC acknowledged that lenvatinib likely has efficacy similar to sorafenib based on the REFLECT trial that demonstrated improved PFS and non-inferior OS.
PAG is seeking clarity on whether the following patients would be eligible for treatment with atezolizumab plus bevacizumab: • patients with ECOG performance score ≥ 2	pERC agreed with the CGP that only patients with ECOG PS 0-1 should be eligible for treatment with atezolizumab plus bevacizumab because there is no clinical trial evidence to support the use of atezolizumab plus bevacizumab in patients with an ECOG PS ≥ 2.
• patients with CNS metastases	pERC agreed with the CGP that patients with treated CNS metastases who are stable and not on steroids could be eligible for treatment with atezolizumab plus bevacizumab.
• patients with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC	pERC agreed with the CGP that patients with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC would not eligible for atezolizumab plus bevacizumab.
• patients with Child-Pugh score B liver function	pERC agreed with the CGP that patients with Child-Pugh class B liver function would not be eligible for atezolizumab plus bevacizumab.
• patients with intermediate stage HCC unable to receive TACE.	pERC agreed with the CGP that patients with intermediate stage HCC who are unable to receive TACE would be eligible for atezolizumab plus bevacizumab, as long as other eligibility criteria are met for the combination treatment (e.g., Child-Pugh class A, no risk of bleeding).
PAG noted that the trial excluded patients who had local therapy in the 28 days prior to initiation and seeks confirmation that these patients (including those who had TACE) would not be candidates for atezolizumab plus bevacizumab.	pERC noted that patients who had local therapy in the 28 days prior to initiation (including those who had TACE) would not be candidates for atezolizumab plus bevacizumab.
Implementation factors	
PAG is seeking clarity on treatment duration and treatment until "loss of clinical benefit" with a definition of disease progression and treatment duration to assist in the development of stopping rules for atezolizumab plus bevacizumab.	pERC noted that patients should continue treatment with atezolizumab plus bevacizumab according to the IMbrave150 study protocol. Treatment should be continued until unacceptable toxicity or loss of clinical benefit. In the trial, loss of clinical benefit was determined by the investigator after an assessment of biochemical and radiographic data and of clinical status (e.g., symptomatic deterioration such as pain due to disease). Patients who met the

	criteria for radiographic disease progression per RECIST v1.1 were permitted to continue the assigned study treatment if the following requirements were met: the investigator determines that available data indicate there is evidence of clinical benefit, there are no signs or symptoms indicating unequivocal disease progression, there is no decline in ECOG PS attributed to disease progression, and there is no tumour progression at critical sites that cannot be managed by medical interventions allowed in the protocol (e.g., leptomeningeal disease).
PAG seeks guidance on the management of instances wherein one of the biologic drugs needs to be discontinued (e.g., if atezolizumab has to be stopped, should bevacizumab be discontinued and vice versa).	pERC agreed with the CGP that for patients who stop either atezolizumab or bevacizumab due to intolerance, it would be reasonable to continue treatment with the remaining agent in the absence of progression if the clinician determines there would be clinical benefit. Monotherapy with the remaining agent should stop if the patient develops intolerance or has progression. This strategy was permitted in the IMbrave150 trial.
Sequencing and priority of treatment	
PAG is seeking guidance on the appropriate place in therapy and sequencing with other drug regimens for HCC. In particular, the circumstances justifying the preferential use of atezolizumab plus bevacizumab or sorafenib or lenvatinib. • switching from atezolizumab plus bevacizumab to other first-line drugs due to intolerance • the place in therapy of current first-line kinase inhibitors (sorafenib and lenvatinib) relative to atezolizumab plus bevacizumab, including evidence on their use after failure of atezolizumab plus bevacizumab • appropriateness of re-treatment with atezolizumab plus bevacizumab if the disease progresses after the regimen is discontinued.	There is limited evidence and uncertainty on the optimal sequencing of available agents following first-line treatment with atezolizumab plus bevacizumab. pERC concluded that the optimal sequencing of therapies is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on the sequencing of treatments. pERC recognized that provinces will need to address this issue upon implementation of a reimbursement recommendation for atezolizumab plus bevacizumab and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value. pERC agreed with the CGP that if a patient had intolerance to, but did not progress on, atezolizumab plus bevacizumab, it would be reasonable to switch to lenvatinib. pERC noted that there is a time-limited need to switch patients who have been initiated on first-line sorafenib or lenvatinib treatment and have not experienced disease progression to atezolizumab plus bevacizumab. pERC acknowledged that the IMbrave150 trial did not have specific guidelines regarding re-treatment with atezolizumab plus bevacizumab upon disease progression. pERC agrees with the CGP that re-treatment would be reasonable if the treatment was discontinued for reasons other than progression (e.g., treatment break, intolerance). Re-treatment would be reasonable if progression occurs more than 6 months after stopping treatment with atezolizumab plus bevacizumab.
Companion diagnostic testing	
PAG would like confirmation that PD-L1 testing is not required.	PD-L1 testing was not required for trial enrolment. There are currently no biomarkers that identify patients who are most likely to benefit from atezolizumab plus bevacizumab.

CGP = Clinical Guidance Panel; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HCC = hepatocellular carcinoma; NMA = network meta-analysis; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; TACE = transarterial chemoembolization.