CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Unresectable hepatocellular carcinoma

This report supersedes the CADTH Provisional Funding Algorithm report for unresectable hepatocellular carcinoma dated April 2021.

Please always check CADTH Provisional Funding Algorithms | CADTH to ensure you are reading the most recent algorithm report.

January 2024

Background

Following a request from jurisdictions, CADTH may design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of Provisional Funding Algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information referenced in Table 1 and Table 2 as well as related reports on the CADTH website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH Provisional Funding Algorithm on unresectable hepatocellular carcinoma. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

Relevant CADTH Recommendations

In the 2021 panel algorithm, CADTH developed the first Provisional Funding Algorithm for drugs that can be used to treat adults with unresectable hepatocellular carcinoma (HCC), which incorporated recommendations for the following:

- atezolizumab (Tecentriq) in combination with bevacizumab (Avastin)

- lenvatinib (Lenvima)
- regorafenib (Stivarga)
- cabozantinib (Cabometyx).

These are outlined in Table 1. For this rapid algorithm, the purpose is to incorporate the latest pERC recommendation on durvalumab-tremelimumab for the first-line treatment of patients with unresectable HCC.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
First-line setting		
Tremelimumab (Imjudo) in combination with durvalumab (Imfinzi)	November 20, 2023	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 following conditions are met: 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. 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. 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. 4. Tremelimumab in combination with durvalumab should be prescribed by clinicians with expertise and experience in treating unresectable HCC. 5. Tremelimumab in combination with durvalumab should not be reimbursed if given in combination with other systemic anti-cancer drugs. 6. A reduction in price. 7. The feasibility of adoption of tremelimumab in combination with durvalumab must be addressed. **Guidance on sequencing:** 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 who had not undergone prior systemic therapy. As well, at the time the study was conducted, sorafenib was considered standard-of-care therapy. pERC noted that sorafenib as the active comparator is

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		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.
Atezolizumab (Tecentriq) in combination with bevacizumab (Avastin)	November 17, 2020	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, noninferior OS, and a different toxicity profile when comparing lenvatinib to sorafenib. pERC concluded that atezolizumab plus bevacizumab aligns with patient values because 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 that atezolizumab plus bevacizumab would become cost-effective. pERC also concluded that the submitted budget impact analysis may be underestimated and that the budget

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		impact of atezolizumab plus bevacizumab at the submitted price would be substantial. **Guidance on sequencing:** 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 the 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.
Lenvatinib (Lenvima)	July 24, 2019	pERC recommends reimbursement of lenvatinib (Lenvima) for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC) only if the following condition is met: • the public drug plan cost of treatment with lenvatinib should not exceed the public drug plan cost of treatment with sorafenib. Reimbursement should be for patients with Child-Pugh class A liver function who have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 and who would otherwise meet the inclusion criteria for the REFLECT trial. Treatment with lenvatinib should continue until confirmed disease progression or unacceptable toxicity. pERC made this recommendation because it was satisfied that there may be a net clinical benefit of lenvatinib in this setting. This was based on the noninferiority on overall survival for lenvatinib compared with sorafenib, a different toxicity profile compared with sorafenib, and no detriment to quality of life. pERC was also satisfied that lenvatinib aligns with patient values of having a treatment option that offers different and potentially more manageable toxicities compared to sorafenib and provides ease of administration for patients. Given the likelihood of similarity in efficacy between lenvatinib and sorafenib, pERC concluded that the public drug plan cost of treatment with lenvatinib should not exceed the public drug plan cost of treatment with sorafenib. Considerations for switching between sorafenib and lenvatinib should be based on tolerability not progression. pERC noted that there is currently no evidence to help determine which patients may be better suited for lenvatinib or sorafenib treatment. pERC acknowledged that tolerability may be used to select patients (e.g., patients with uncontrolled hypertension may be better suited for soratinib). For patients who have not

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		progressed radiographically on sorafenib but are sorafenib intolerant, pERC agreed that it would be reasonable to consider switching to lenvatinib. Likewise, it would be reasonable to consider switching to sorafenib for patients who have not progressed radiographically on lenvatinib but are lenvatinib intolerant. pERC noted that these considerations were also supported by input from registered clinicians. **Guidance on sequencing:** pERC agreed that there currently is no evidence to suggest that the efficacy of second-line HCC treatments would be influenced by the first-line therapy for these drugs with a fairly similar mechanism of action. While acknowledging the lack of evidence in this specific setting, pERC agreed that oncologists often extrapolate the efficacy of second-line therapies after a new standard first-line therapy is established across multiple tumour sites, pERC therefore supports the use of regorafenib after lenvatinib if clinically warranted. Furthermore, the CGP does not anticipate there will be a preference to use sorafenib upfront to ensure that patients can qualify for regorafenib or other second-line therapies.
Second-line setting		
Cabozantinib (Cabometyx)	April 22, 2020	pERC conditionally recommends reimbursement of cabozantinib (Cabometyx) in adult patients with unresectable hepatocellular carcinoma (HCC) in the second-line setting after progression on sorafenib or lenvatinib if the following condition is met: • cost-effectiveness being improved to an acceptable level. Eligible patients should have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 and a Child-Pugh class status of A. Treatment with cabozantinib should continue until the patient no longer experiences clinical benefit or experiences unacceptable toxicity. pERC made this recommendation because it was satisfied that there is a net clinical benefit of cabozantinib compared with best supportive care (BSC) based on a clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS) with no detriment to quality of life (QoL). pERC noted that cabozantinib is associated with increased but manageable toxicities. However, pERC was uncertain on how cabozantinib compared with regorafenib with regard to outcomes important to decision-making, such as OS, PFS, and QoL, due to a lack of robust direct or indirect comparative efficacy data. pERC also concluded that cabozantinib aligns with patient values in that it offers an improvement in OS, no detriment to QoL, and has manageable but not insignificant toxicities compared with BSC. pERC concluded that at the submitted price, cabozantinib could not be considered cost-effective compared with BSC. Additionally, pERC noted that there was considerable uncertainty in the cost-effectiveness estimates of cabozantinib compared with regorafenib due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation. **Guidance on sequencing:** pERC agreed that there is minimal evidence to support the use of cabozantinib after treatment with regorafenib in the third-line setting. pERC also noted that there is currently no evidence to support the use of regorafenib in the third-line setting after treatment with cabozantinib. The optimal sequencing of tyrosine kinase inhibitors for HCC is unknown because the landscape is evolving.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Regorafenib (Stivarga)	April 18, 2018	pERC conditionally recommends the reimbursement of regorafenib (Stivarga) for patients with unresectable HCC who have been previously treated with sorafenib only if the following condition is met: • cost-effectiveness being improved to an acceptable level. If the aforementioned condition cannot be met, pERC does not recommend reimbursement of regorafenib. Eligible patients should have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1, a Child-Pugh class status of A, be able to tolerate sorafenib as defined in the RESORCE trial, and otherwise meet the RESORCE trial criteria. Treatment with regorafenib should continue until disease progression. pERC made this recommendation because it was satisfied that there is a net clinical benefit of regorafenib based on a clinically meaningful improvement in overall survival (OS) and an acceptable toxicity profile. pERC also concluded that the therapy aligns with patient values in that it offers an improvement in OS and no detriment in quality of life in a disease for which there is considerable unmet need. However, pERC noted that, at the submitted price, regorafenib could not be considered cost-effective compared with best supportive care. **Guidance on sequencing:** pERC agreed that there is no evidence for the use of regorafenib in the first-line setting.

CGP = Clinical Guidance Panel; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; OS = overall survival; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; QoL = quality of life.

Table 2: CADTH Implementation Advice Panels on Unresectable Hepatocellular Carcinoma

Date of publication	Implementation advice
April 2021	The panel advises that the best available therapy for which the patient is eligible and can tolerate should be used in the first line. Atezolizumab-bevacizumab would be the first-line treatment of choice for eligible patients because it has demonstrated superior overall and progression-free survival outcomes. For patients not eligible for first-line immunotherapy with atezolizumab-bevacizumab, lenvatinib would be available as an alternative first-line treatment, with sorafenib as an option in case of lenvatinib intolerance or contraindication. For patients experiencing disease progression following first-line therapy with atezolizumab-bevacizumab, the panel advises that lenvatinib or sorafenib would offer appropriate second-line options. Emerging evidence suggests that lenvatinib and sorafenib offer efficacy and manageable toxicities for these patients. The panel did not identify any evidence regarding the use of TKIs in subsequent lines (third line and beyond, after atezolizumab-bevacizumab) and thus cannot advise on the use of drugs in this setting.

TKI = tyrosine kinase inhibitor.

Provisional Funding Algorithm

Description of the Provisional Funding Algorithm

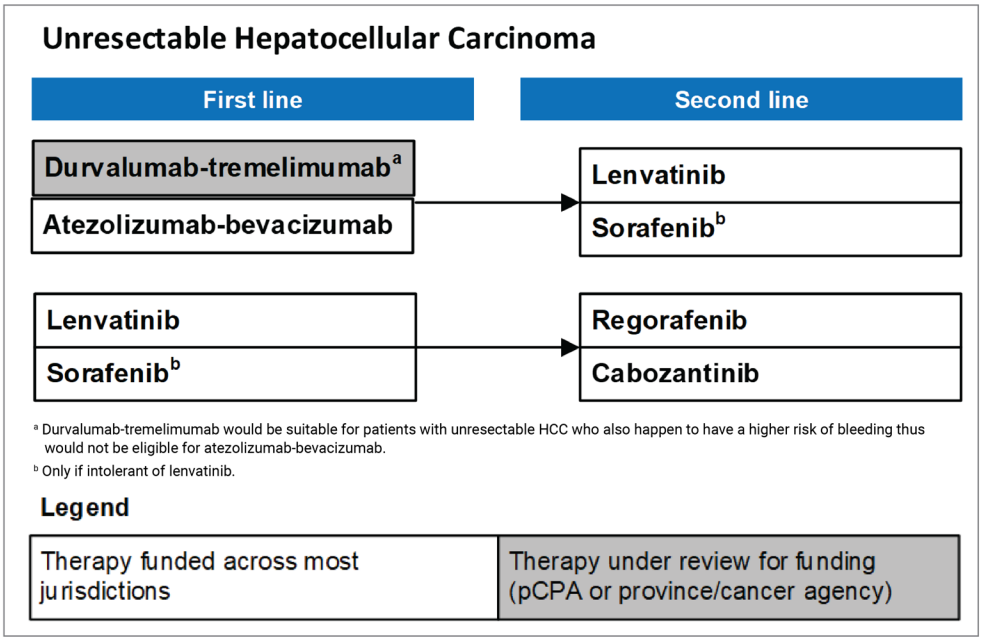
First-Line Setting

For adult patients with previously untreated, unresectable HCC, a choice between atezolizumab-bevacizumab, durvalumab-tremelimumab, and tyrosine kinase inhibitors (TKIs) is available, with durvalumab-tremelimumab under review for funding. Durvalumab-tremelimumab would be suitable for patients with unresectable HCC who also have a higher risk of bleeding, thus they would not be eligible for atezolizumab-bevacizumab. If immunotherapy is unavailable or not indicated for the patient, lenvatinib would be an alternative first-line treatment. In cases of lenvatinib intolerance or contraindication, sorafenib treatment can be offered.

Relapsed or Refractory

Patients who experience disease progression following first-line atezolizumab-bevacizumab therapy may be able to access lenvatinib or sorafenib as second-line therapy; sorafenib would be restricted to those with lenvatinib intolerance or a contraindication. Patients who progress following first-line TKI therapy are eligible to access second-line TKIs (i.e., regorafenib or cabozantinib) where funding is available. Third-line therapies are not funded.

Figure 1: Provisional Funding Algorithm Diagram for Unresectable Hepatocellular Carcinoma



pCPA = pan-Canadian Pharmaceutical Alliance.

Additional Remarks

CADTH would like to acknowledge stakeholder feedback to consider funding therapies in the third-line options in HCC. Although stakeholder feedback is out of scope for consideration in this algorithm project (the purpose of this project is to incorporate the latest pERC recommendation on durvalumab-tremelimumab in the first-line setting), other opportunities for feedback can be explored. For example, a tumour group application can be submitted for consideration of third-line options in HCC. For more information, refer to Submit a Request | CADTH.

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