CADTH

CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Adult classical Hodgkin lymphoma

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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.

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 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 pCODR 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 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 for adult patients with classical Hodgkin lymphoma (cHL). 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.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Pembrolizumab (Keytruda)	January 18, 2018	pERC recommends reimbursement of pembrolizumab (Keytruda) as monotherapy in adult patients with refractory or relapsed classical Hodgkin lymphoma (cHL) who • have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or • are not candidates for ASCT and have failed BV, conditional on the cost-effectiveness being improved to an acceptable level.
	November 1, 2021	The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab should be reimbursed, as monotherapy, for the treatment of adult and pediatric patients with refractory or relapsed classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT, only if the conditions listed in Table 1 are met. Treatment with pembrolizumab should be initiated in adult and pediatric patients with relapsed or refractory cHL with either of the following: 1. have failed to achieve a response or progressed after ASCT, or 2. are not eligible to receive ASCT due to chemotherapy-resistant disease, advanced age, or any significant coexisting medical condition that may have a negative impact on tolerability of ASCT. **Implementation guidance** • **Patients whose disease has progressed on a prior PD-1 or PD-L1 inhibitor:** The clinical experts consulted did not support the use of pembrolizumab in these patients as the mechanism of action of checkpoint inhibitors is too similar. pERC also noted that patients who had received prior PD-1 or PD-L1 inhibitors were excluded from the Keynote 204 trial and that there are no data available to support the use of pembrolizumab in these patients. • **Patients who have completed the 35 cycles of treatment:** pERC noted that Keynote 204 did not allow for re-treatment with pembrolizumab. The clinical experts consulted by CADTH noted that there is evidence available from case reports and case series that supports re-treatment with pembrolizumab in patients who stopped treatment upon achieving a complete response after receiving 35 cycles, and patients who stopped achieving a good response after 35 cycles and discontinued treatment without signs of progression. pERC agreed with the clinical experts that these patients may be eligible for re-treatment with an additional 17 cycles of pembrolizumab upon experiencing disease progression. • **Patients who proceed to transplant after responding to pembrolizumab and relapse after ASCT**: The clinical experts

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		indicated that there is currently insufficient evidence to support re-treatment in these patients. The committee was not able to make an informed recommendation about re-treatment with pembrolizumab in these patients. However, pERC recognized that this a very small group of cHL patients with unmet need. • pERC was unable to make an informed recommendation on the sequencing options after pembrolizumab, as the committee did not review evidence to inform optimal sequencing of treatments after disease progression with pembrolizumab. • pERC discussed the optimal sequencing of pembrolizumab and BV in patients with relapsed or refractory cHL who are transplant-ineligible and noted that it did not review sufficient evidence to inform the clinical scenario where BV is used in patients who experience disease progression after pembrolizumab. pERC acknowledged that, in general, there is potential benefit in the sequencing of drugs that have different mechanisms of action. However, the committee was unable to make an informed conclusion regarding the sequence of these treatments for the indication under review.
Brentuximab vedotin (Adcetris)	August 29, 2013	The pCODR Expert Review Committee (pERC) recommends funding brentuximab vedotin (Adcetris) in patients with Hodgkin lymphoma, conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients with Hodgkin lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status of 0 or 1 pERC did not recommend funding brentuximab in patients with Hodgkin lymphoma who are not candidates for ASCT and who have relapsed disease following at least 2 prior multi-agent chemotherapies. This patient population was not included in the non-randomized non-comparative phase 2 study, therefore, pERC considered there was insufficient evidence to determine if there was a clinical benefit in this patient population.
	February 21, 2018	pERC recommends reimbursement of brentuximab vedotin (BV) for the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with Hodgkin lymphoma (HL) at increased risk (see Definition of Increased Risk on page 2) of relapse or progression, conditional on cost-effectiveness being improved to an acceptable level. There is currently insufficient evidence to make an informed recommendation on re-treatment with BV. pERC noted that re-treatment of patients with BV who (1) have received and responded to BV pre-ASCT, or (2) have relapsed after receiving BV consolidation therapy post-ASCT, is out of scope of this review. pERC agreed with the CGP's speculation that, rather than re-treatment with BV, clinicians might move to other options, such as PD-1 inhibitors.

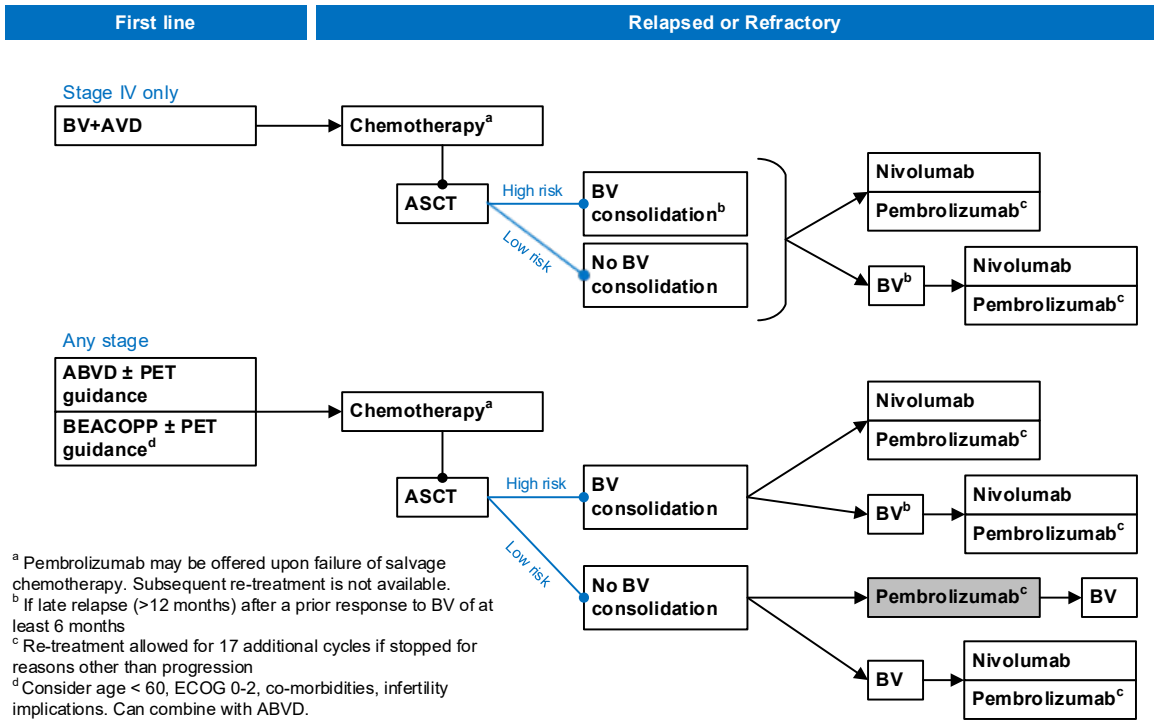
Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
	March 7, 2019	pERC does not recommend reimbursement of brentuximab vedotin for the treatment of adult patients (≥ 18 years) with Hodgkin lymphoma (HL) after failure of at least 2 multi-agent chemotherapy regimens in patients who are not candidates for autologous stem cell transplant (ASCT).
	December 3, 2020	pERC conditionally recommends reimbursement of brentuximab vedotin (BV) in combination with doxorubicin, vinblastine, and dacarbazine (AVD) for the treatment of previously untreated patients with stage IV Hodgkin lymphoma (HL), if the following condition is met: • cost-effectiveness being improved to an acceptable level pERC was unable to make an informed recommendation on the optimal sequencing of treatments for patients with stage IV HL who progress after treatment with BV in combination with AVD. pERC noted that it did not review evidence to inform sequencing of treatments after progression with BV. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of BV in combination with AVD and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
Nivolumab (Opdivo)	May 3, 2018	pERC conditionally recommends reimbursement of nivolumab (Opdivo) for patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) only if the following condition is met: • cost-effectiveness being improved to an acceptable level. pERC does not recommend funding nivolumab for patients with cHL that has relapsed or progressed after 3 or more lines of systemic therapy, one of which was ASCT, and who are eligible for BV.

ASCT = autologous stem cell transplant; AVD = doxorubicin, vinblastine, and dacarbazine; BV = brentuximab vedotin; cHL = classical Hodgkin lymphoma; pERC = CADTH pCODR Expert Review Committee.

Provisional Funding Algorithm

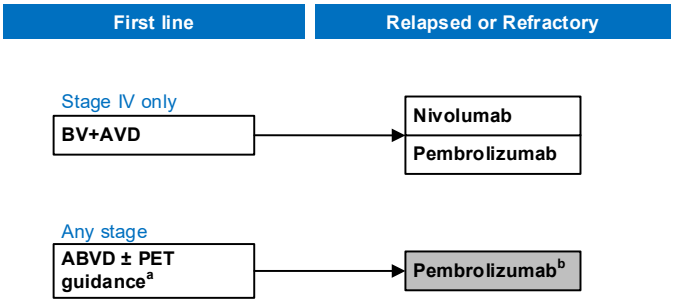
Figure 1: Provisional Funding Algorithm Diagram for Adult cHL

Transplant Eligible



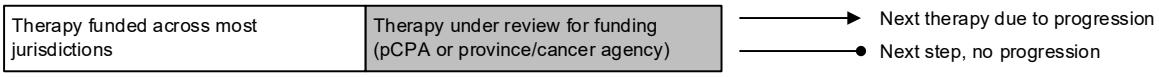
[a] Pembrolizumab may be offered upon failure of salvage chemotherapy. Subsequent re-treatment is not available.
[b] If late relapse (>12 months) after a prior response to BV of at least 6 months
[c] Re-treatment allowed for 17 additional cycles if stopped for reasons other than progression
[d] Consider age < 60, ECOG 0-2, co-morbidities, infertility implications. Can combine with ABVD.

Transplant Ineligible



[a] Other chemotherapy options may be considered
[b] Re-treatment allowed for 17 additional cycles if stopped for reasons other than progression

Legend



ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT = autologous stem cell transplant; AVD = doxorubicin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BV = brentuximab vedotin; cHL = class Hodgkin lymphoma; PET = positron emission tomography.

Description of the Provisional Funding Algorithm

Transplant-Eligible Patients

Primary therapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is available for cHL patients. A regimen comprising bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) is available as an alternative. Both treatments may be combined in eligible patients and may be guided by positron emission tomography. Brentuximab vedotin (BV) combined with doxorubicin, vinblastine, and dacarbazine (AVD) is available for stage IV patients only.

Upon progression, salvage chemotherapy followed by autologous stem cell transplant can be offered. For patients with high-risk factors, consolidation with BV is funded. Following further progression, BV may be considered. Either pembrolizumab or nivolumab are reimbursed for patients previously treated with BV. Reimbursement of pembrolizumab without prior use of BV is currently under consideration by jurisdictions. Should this be implemented, subsequent treatment with BV would be reimbursed if it was not received previously. BV re-treatment may be offered to patients who relapse more than 12 months after completion of prior BV therapy with at least 6 months of response. Pembrolizumab re-treatment is allowed for an additional 17 cycles if the prior treatment was stopped for reasons other than progression.

In some instances, pembrolizumab may become a second salvage option if the patient does not respond to the initial salvage chemotherapy. If these patients end up responding to pembrolizumab to move on to transplant, they would not be eligible for subsequent anti-PD-1 therapy.

Transplant-Ineligible Patients

The previously mentioned primary therapies are also available for transplant-ineligible patients, although other chemotherapies may be preferred over BEACOPP. Either nivolumab or pembrolizumab are reimbursed following BV plus AVD. Pembrolizumab is currently under consideration for patients who progress following other primary therapies.

Additional Remarks

The following implementation decisions were made by jurisdictions independent of the CADTH Reimbursement Review process:

- reimbursement of nivolumab in transplant-ineligible cHL patients
- re-treatment with BV and associated parameters.

Since such funding decisions were made at the pan-Canadian level, CADTH reflects them in the provisional funding algorithm for transparency. However, CADTH will not consider stakeholder feedback on these legacy decisions.