Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Cutaneous Melanoma

This report supersedes the CADTH provisional funding algorithm report for melanoma dated February 6, 2023.

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

June 2024

Key Messages

Following nivolumab-relatlimab in the treatment of unresectable or metastatic melanoma, ipilimumab can be offered as a subsequent treatment option.

Background

The provisional funding algorithm process is used to provide advice when the drug programs have indicated that there is a need to establish an appropriate place in therapy for the drug under review relative to alternative treatments that are currently reimbursed by the drug programs, including the impact on the appropriate sequencing of treatments for the purposes of reimbursement. The creation of a new provisional funding algorithm or update of an existing provisional funding algorithm is typically initiated following the issuance of a new pERC recommendation when there are potential implications regarding the funding sequence of drugs within a therapeutic area. CADTH will only initiate work on a provisional funding algorithm at the request of its Provincial Advisory Group (PAG).

The following items are considered by the expert panels when advising the jurisdictions on the provisional algorithm for the relevant indication:

- unmet therapeutic needs for patients (particularly those in understudied populations)
- evidence supporting a particular sequence of therapies (if available)
- clinical experience and opinion that support a particular sequence of therapies
- clinical practice guidelines
- variability across jurisdictions regarding the reimbursement status of existing treatment options
- affordability and sustainability of the health care system
- implementation considerations at the jurisdictional level.

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. Most 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. Also note that as per process, implementation advice from panellists and the resulting algorithms cannot contradict prior pERC recommendations or expand target populations beyond what was recommended.

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

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.

Cancer drug programs from federal and provincial jurisdictions requested supplemental implementation advice and a CADTH provisional funding algorithm on cutaneous melanoma. Refer to Appendix 1 for a list of all past CADTH advice and recommendations relevant to this therapeutic area.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of clinical experts in Canada to provide advice for addressing the outstanding implementation issues as follows:

- downstream treatment options following nivolumab-relatlimab in the treatment of unresectable or metastatic melanoma.

Consultation Process and Objectives

The implementation advice panel comprised 5 clinician specialists in Canada with expertise in the diagnosis and management of patients with melanoma, a representative from a public drug program, and a panel chair. The panel's objective was to provide advice to the participating drug programs regarding the implementation issues noted in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders, including patient and clinician groups, pharmaceutical manufacturers, and public drug programs, were invited to provide input in advance of the meeting.

The advice presented in this report has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion; it is not necessarily based on evidence.

Panel Advice on Funding Algorithm

Summary of Implementation Advice

Table 1 summarizes implementation advice regarding the optimal sequencing of treatments. For each implementation issue, a summary of the relevant panel discussion provides additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue and population	Advice	Rationale
Downstream treatment options following nivolumab-relatlimab		
For patients without BRAF mutations	The panel advises ipilimumab should be offered as a subsequent treatment option for patients with disease progression following nivolumab-relatlimab in the setting of unresectable or metastatic melanoma.	This is based on limited retrospective data by Menzie et al.[1], in which 36 patients treated with nivolumab plus relatlimab and disease progression received ipilimumab, either as monotherapy (19 patients) or in combination with an anti-PD-1 antibody (17 patients). These results are discussed under Panel Discussion.
For patients with BRAF mutations	The panel advises that patients who have received BRAF-targeted therapy as a first-line treatment option in the metastatic setting should have the option to receive nivolumab-relatlimab in the second-line setting, followed by ipilimumab in the third-line setting.	While nivolumab-relatlimab is indicated as first-line use in metastatic melanoma, restricting access in patients with BRAF mutations may create concerns for inequity. Extending use as a second-line option following first-line BRAF-targeted agents is consistent with the previous 2019 CDIAC algorithm that allows nivolumab-ipilimumab following BRAF-targeted therapy. These patients may be treated with BRAF-targeted therapy in the first-line setting and, therefore, may benefit from nivolumab-relatlimab in the second line upon disease progression. Note that in the RELATIVITY-047 trial, about 0.3% of patients received BRAF and MEK NRAS inhibitors as prior therapies.[2]

In addition to the previously outlined advice, the panel indicated that because an improvement in cost-effectiveness was a condition for reimbursement in each of the recommendations related to the drugs in scope, implementation of any advice herein should be contingent upon ensuring that the relevant treatments are affordable to public payers.

Panel Discussion

Following first-line treatment with nivolumab-relatlimab, the panel members suggested that either nivolumab-ipilimumab or ipilimumab alone could be considered as second-line options following disease progression. However, there is very limited evidence to support either option. The panel recommended that it would be equitable to at least offer a second-line option with ipilimumab, as these patients haven't been exposed to this drug.

Downstream Option With Ipilimumab

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor. The panel has discussed the evidence in support of ipilimumab as a second-line option following nivolumab-relatlimab. In a pooled retrospective analysis from 5 centres, 36 patients who had received first-line nivolumab-relatlimab and developed disease progression were treated with ipilimumab as a monotherapy (19 patients) or in combination with an anti-PD-1 antibody (17 patients). The results were published by Menzie et al.[1] After a median follow-up of 16.8

months (95% confidence interval, 11.5 to not reached), an objective response to ipilimumab was observed in 4 patients (11%). The median progression-free survival was 2.6 months (2.1 to 3.2), and 1-year progression-free survival was 8%. The median overall survival was 9.6 months (6.2 to not reached), and the 1-year overall survival was 46%.

One panel member highlighted that in the absence of more robust evidence, a standard treatment option for patients who progress on nivolumab-relatlimab should be ipilimumab. There was consensus from other panel members as well. Note that drugs under investigation via clinical trials, best supportive care or chemotherapy are also options. One panel member also noted that patients with BRAF mutations would also have the option of BRAF/MEK inhibitors and that the option for ipilimumab following nivolumab-relatlimab should be available to these patients as well.

Downstream Option With Nivolumab-Ipilimumab

The panel discussed the role of nivolumab-ipilimumab in metastatic melanoma remains to be the gold standard treatment in the first-line setting based on the overall survival (OS) benefits as demonstrated in the CheckMate 467 trial.[3] As noted by pERC as well as the panel members, there is no direct evidence to suggest a clinical benefit of nivolumab-relatlimab when compared to nivolumab-ipilimumab combination. Some panel members have expressed the desired to use nivolumab-ipilimumab in the second-line setting based on the experience from the RELATIVITY-047 trial, where 9% of patients from the nivolumab-relatlimab were subsequently treated with a CTLA-4 inhibitor or programmed death-1 (PD-1) inhibitor.

In addition, the panel discussed the results from a multicentre, retrospective, cohort study by Pires da Silva et al. (2021)[4], which evaluated 355 patients with metastatic melanoma who are resistant to anti-PD-1 therapy. They were treated with ipilimumab (n = 162) or ipilimumab plus anti-PD-1 (n = 193). At a median follow-up of 22.1 months, the objective response rate was higher with ipilimumab plus anti-PD-1 (60[31%] of 193 patients) than the ipilimumab monotherapy (21 [13%] of 162 patients; P < 0.0001). The panel noted that this evidence is based on limited retrospective data.

One panel member has voiced that patients' tolerance of adverse events may change over time. For some patients, they may have chosen to receive nivolumab-relatlimab in the first-line setting on the basis of more favourable safety profile as compared to nivolumab-ipilimumab. However, on disease progression, they may have different threshold and would want the option to receive nivolumab-ipilimumab in the second-line setting. Another panel member also noted that in US, patients may be rechallenged with nivolumab-ipilimumab in the second-line setting.

Other Discussion

Six Months Re-Treatment Period for Metastatic Melanoma

The panel has also briefly discussed the reimbursement of ipilimumab-nivolumab in the first-line metastatic setting in patients who progress during or within 6 months of adjuvant anti-PD-1 therapy. This is out of scope for this panel algorithm and is being addressed in another reimbursement review: Nivolumab and Ipilimumab | CADTH. However, if there is a recommendation to allow re-treatment in a shorter time frame, this will have implication for the provisional funding algorithm for sequence of treatment options.

Treatment Sequences for Other Scenarios

The panel noted that the current provisional funding algorithm may benefit from further discussion. For example, if a patient with BRAF mutation has progressed on BRAF-targeted therapy in the adjuvant setting or metastatic setting, the next line of therapy in the metastatic setting would be immunotherapy. Upon further disease progression in the metastatic setting, there may be a role to be re-treated with further BRAF-targeted therapy. This was noted to be out of scope for this review.

Final Advice and Rationale on the Funding Algorithm

PAG has reviewed the implementation advice as recommended by the clinician panellists. Efforts are made to incorporate the advice while balancing the need for system affordability and sustainability. In the spirit of consistency with treatment implementations across jurisdictions, advice without or based on insufficient or evolving evidence may not be supported or may be recommended to be revisited at a later time when more high-quality evidence is available.

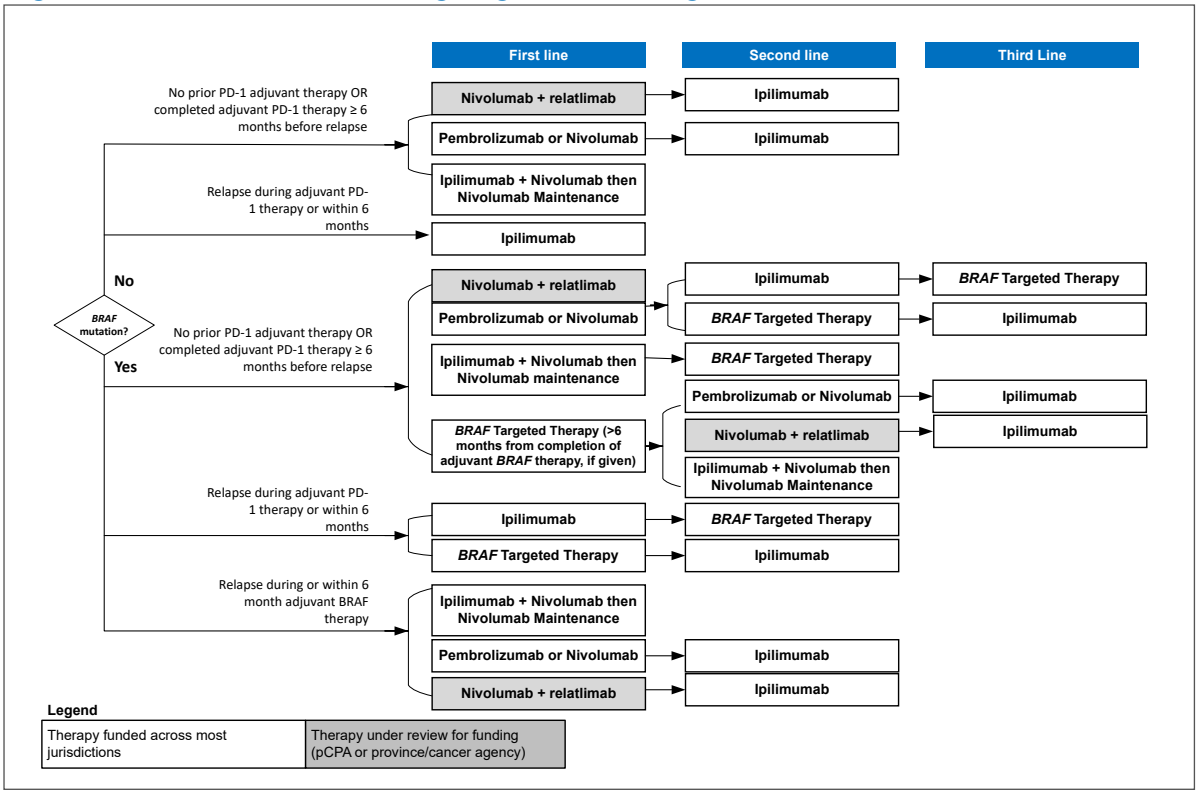
PAG has a mandate to support recommendations issued by pERC for implementation across the various jurisdictions. However, the final decisions for how these therapies are to be implemented reside with the individual jurisdictions, where they may adapt the advice locally based on regional differences and needs.

PAG endorses the panel advice as described in Table 1.

PAG would also like to highlight that extending use for nivolumab-relatlimab as a second-line option following first-line BRAF-targeted drugs is consistent with the previous 2019 CDIAC algorithm that allows nivolumab-ipilimumab as a second-line option following BRAF-targeted therapy.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Metastatic Cutaneous Melanoma



pCPA = pan-Canadian Pharmaceutical Alliance; PD-1 = programmed cell death 1 protein.

Notes: The Provisional Funding Algorithm for the adjuvant setting of melanomas can be found in the Appendix II. The discussion of this portion of the provisional funding algorithm was out of scope. For related details, refer to Melanoma | CADTH

BRAF-targeted therapy options include dabrafenib-trametinib, cobimetinib-vemurafenib and encorafenib-binimetinib. All drugs may be subject to additional funding criteria within provincial jurisdictions.

If PD-1 therapy (initiated either as nivolumab/relatlimab, a single-drug, or maintenance following combination immunotherapy) is stopped after 2 years or at time of best response without evidence of disease progression, then therapy may be restarted at relapse as the same line of therapy. Re-treatment with ipilimumab/nivolumab combination immunotherapy is not funded. All drugs may be subject to additional funding criteria within provincial jurisdictions.

Description of the Provisional Funding Algorithm

The treatment options in the metastatic setting differ depending on the status of *BRAF* mutation.

No *BRAF* Mutation

No Prior PD-1 Adjuvant Therapy or Completed Adjuvant PD-1 Therapy 6 Months or More Before Relapse

For individuals with no *BRAF* mutation and with no prior PD-1 adjuvant therapy or who completed adjuvant PD-1 therapy 6 months or more before relapse, the first-line options can be either pembrolizumab, nivolumab or nivolumab-relatlimab, followed by the second-line option of ipilimumab. Nivolumab-relatlimab is under

review for funding. Another first-line option can be ipilimumab with nivolumab followed by nivolumab maintenance therapy.

Relapse During Adjuvant PD-1 Therapy or Within 6 Months

For individuals with no *BRAF* mutation who relapse during adjuvant PD-1 therapy or within 6 months of therapy, the first-line option in the metastatic setting is ipilimumab.

With BRAF Mutation

No Prior PD-1 Adjuvant Therapy or Completed Adjuvant PD-1 Therapy 6 Months or More Before Relapse

For individuals with *BRAF* mutation and with no prior PD-1 adjuvant therapy or who completed adjuvant PD-1 therapy 6 months or more before relapse, there are 3 available first-line options, of which will determine subsequent second-line or third-line options:

- **Pembrolizumab, nivolumab or nivolumab-relatlimab:** If individuals have either pembrolizumab, nivolumab or nivolumab-relatlimab as a first-line option, the second-line option is ipilimumab or *BRAF*-targeted therapy. For those who have received ipilimumab as a second-line option, the third-line option is *BRAF*-targeted therapy. For those who have received *BRAF*-targeted therapy as a second-line option, the third-line option is ipilimumab. Nivolumab-relatlimab is under review for funding.
- **Ipilimumab-nivolumab then, followed by nivolumab maintenance:** Alternatively, individuals may begin the first-line option of ipilimumab-nivolumab, which is followed by nivolumab maintenance therapy. Following this first-line option, the second-line option is *BRAF*-targeted therapy.
- ***BRAF*-targeted therapy:** Individuals may begin with *BRAF*-targeted therapy as a first-line option. Available *BRAF*-targeted therapy options include dabrafenib-trametinib, encorafenib-binimetinib, and cobimetinib-vemurafenib. If given in this setting, these individuals must have completed prior adjuvant *BRAF* therapy more than 6 months previously. The second-line option would be a choice of pembrolizumab, nivolumab or nivolumab-relatlimab with a subsequent third-line option of ipilimumab. Another second-line option would be ipilimumab-nivolumab followed by nivolumab maintenance therapy. Nivolumab-relatlimab is under review for funding.

Relapse During Adjuvant PD-1 Therapy or Within 6 Months

For individuals with *BRAF* mutation who relapse during adjuvant or within 6 months of PD-1 therapy, the first-line options would be a choice between ipilimumab or *BRAF*-targeted therapy. If the first-line option is ipilimumab, then the second-line option is *BRAF*-targeted therapy. If the first-line option is *BRAF*-targeted therapy, the second-line option is ipilimumab.

Relapse During Adjuvant BRAF Therapy or Within 6 Months

For individuals with *BRAF* mutation who relapse during or within 6 months of adjuvant *BRAF*-targeted therapy, the first-line option would be a choice of pembrolizumab, nivolumab, or nivolumab-relatlimab with a subsequent second-line option of ipilimumab. Another first-line option would be ipilimumab-nivolumab, followed by nivolumab maintenance therapy. Nivolumab-relatlimab is under review for funding.

References

1. Menzies AM, Pires da Silva I, Trojaniello C, et al. CTLA-4 Blockade Resistance after Relatlimab and Nivolumab. *N Engl J Med.* 2022;386(17):1668-1669. PubMed
2. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N Engl J Med.* 2022;386(1):24-34. PubMed
3. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med.* 2019;381(16):1535-1546. PubMed
4. Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. *Lancet Oncol.* 2021;22(6):836-847. PubMed

Appendix 1: Past CADTH Advice and Recommendations

Note that this appendix has not been copy-edited.

Table 2: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Stage IIB or stage IIC melanoma		

Pembrolizumab (Keytruda)	November 22, 2022	pERC recommends that pembrolizumab be reimbursed for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB or IIC melanoma following complete resection only if the following conditions are met:
		• Patients who have stage IIB or stage IIC melanoma (as defined by the American Joint Committee on Cancer 2017 classification, eighth edition).
		• Treatment with pembrolizumab should be initiated within 12 weeks of surgery.
		• Patients must not have received prior treatment beyond complete resection.
		• Reimbursement of pembrolizumab should be discontinued in patients who exhibit any of the following:
		  ◦ clinical/radiological disease progression
		  ◦ evidence of significant toxicity or adverse events potentially related to pembrolizumab.
		• Patients should discontinue treatment following a maximum of 17 cycles of adjuvant pembrolizumab.
		• Pembrolizumab should be prescribed in an outpatient oncology clinic and should be supervised and/or delivered in institutions with expertise in delivery of immunotherapy.
		• Pembrolizumab should not be used in combination with other anticancer drugs.
		• A reduction in price.
		• The feasibility of adoption of pembrolizumab must be addressed.
		Guidance on sequencing:
		• In KEYNOTE-716, patients in the placebo arm who experienced recurrence and patients in the pembrolizumab arm who experienced recurrence greater than 6 months after completing 17 cycles of treatment were eligible to cross over or rechallenge with pembrolizumab for up to 2 years. In other solid tumours (e.g., lung, melanoma), patients are eligible for downstream PD-1 or PD-L1 inhibitor provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of an adjuvant PD-1 or PD-L1 inhibitor.
		The clinical experts indicated that the same principle used for other solid tumours could be applied to the treatment setting for patients with stage II melanoma. Overall, the experts felt that stage II melanoma should not be treated any differently from stage III.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		pERC agreed with the clinical experts, noting the same principles used for other recommendations should be applied.
Stages IIIA, IIIB, IIIC, IIID, and IV melanoma		
Pembrolizumab (Keytruda)	August 1, 2019	pERC conditionally recommends the reimbursement of pembrolizumab (Keytruda) for the adjuvant treatment of patients with stage IIIA (limited to lymph node metastases of > 1 mm) to stage IIID (8th edition of the American Joint Committee on Cancer [AJCC] staging system) cutaneous melanoma. Disease must be completely resected; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients must have good performance status. Reimbursement is only recommended if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption being addressed (budget impact). Treatment with pembrolizumab should continue up to a maximum of 18 administrations or until unacceptable toxicity or disease recurrence, at which point the intent of further therapy (adjuvant or metastatic) should be re-evaluated based on extent of recurrence. **Guidance on optimal sequencing:** No evidence for optimal sequencing. pERC acknowledged that there is no direct comparative evidence investigating the efficacy and safety or the appropriate sequence of adjuvant therapies for patients with stage IIIA-D cutaneous melanoma. Further, the optimal sequencing of subsequent therapies for patients with metastatic melanoma after disease progression with adjuvant pembrolizumab is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for pembrolizumab and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Dabrafenib and trametinib in combination (Tafinlar and Mekinist in combination)	May 3, 2019	pERC conditionally recommends to reimburse dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the adjuvant treatment of patients with stage IIIA (limited to lymph node metastases of > 1 mm) to stage IIID (8th edition of the American Joint Committee on Cancer [AJCC] staging system) *BRAF*-mutated (all BRAD V600 mutations) cutaneous melanoma. Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients must have good performance status. Reimbursement is only recommended if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption being addressed (budget impact). Treatment with dabrafenib plus trametinib should continue until disease recurrence, unacceptable toxicity, or up to a maximum of 12 months. **Guidance on optimal sequencing:** No evidence for optimal sequencing. pERC acknowledged that there is no direct comparative evidence investigating the efficacy and safety or the appropriate sequence

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		of adjuvant therapies for patients with *BRAF*-mutated stage IIIA-D cutaneous melanoma. Further, the optimal sequencing of subsequent therapies for patients with *BRAF*-mutated metastatic melanoma after disease progression with adjuvant dabrafenib plus trametinib is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for dabrafenib plus trametinib, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Nivolumab (Opdivo)	March 7, 2019	pERC recommends to reimburse nivolumab (Opdivo) only if the following conditions are met: • cost-effectiveness is improved to an acceptable level • feasibility of adoption is addressed (budget impact). If the aforementioned conditions are not met, pERC does not recommend reimbursement. Reimbursement should be for the adjuvant treatment of patients with completely resected stage IIIB/C/D and stage IV disease (8th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system). Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Eligible patients should continue treatment until disease progression or a maximum of 1 year, whichever comes first. **Guidance on optimal sequencing:** pERC concluded that the optimal sequencing of therapies for patients with metastatic melanoma after adjuvant treatment with nivolumab is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for nivolumab, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Metastatic melanoma		
Nivolumab and Relatlimab (Opdualag)	February 21, 2024	pERC recommends that nivolumab and relatlimab be reimbursed for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma only if the following conditions are met: **Initiation** 1. Treatment with nivolumab and relatlimab fixed-dose combination (FDC) should be reimbursed only in patients with all of the following characteristics: 1.1. Histologically confirmed unresectable stage III or stage IV (metastatic) melanoma 1.2. Have not received prior systemic therapy for unresectable or metastatic melanoma 1.3. Aged 12 years or older

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		1.4. Good performance status 2. Treatment with nivolumab and relatlimab FDC could be reimbursed in patients who had prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy if the therapy was completed at least 6 months before the date of recurrence. 3. Treatment with the nivolumab and relatlimab FDC should not be reimbursed in patients with: 3.1. Active brain metastases 3.2. Uveal melanoma 3.3. Active autoimmune disease **Renewal** 4. Treatment with nivolumab and relatlimab FDC may continue unless any of the following occurs: 4.1. Clinical or radiographic disease progression 4.2. Intolerable side effects that cannot be managed by dose interruption 5. Patients should be assessed for a response to treatment with nivolumab and relatlimab FDC every 2 to 3 months initially and then as per standard of care. **Discontinuation** 6. Treatment with nivolumab and relatlimab FDC should be discontinued upon the occurrence of any of the following: 6.1. Clinical or radiographic disease progression 6.2. Unacceptable toxicity **Prescribing** 7. Nivolumab and relatlimab FDC should only be prescribed by clinicians who: 7.1. Have expertise in diagnosis and management of patients with melanoma 7.2. Are familiar with the toxicity profile associated with nivolumab and relatlimab FDC **Pricing** 8. A reduction in price 9. The feasibility of adoption of nivolumab and relatlimab must be addressed **Guidance on sequencing:** • pERC discussed the possible place in therapy of nivolumab and relatlimab, and concluded that nivolumab and relatlimab would be another alternative treatment option for patients who are not fit enough to receive nivolumab and ipilimumab combination or for patients who are ipilimumab ineligible and could have otherwise received nivolumab monotherapy, pembrolizumab monotherapy, or targeted BRAF therapy. • Based on the direct evidence, while pERC was confident in the PFS benefit of nivolumab and relatlimab compared to nivolumab

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		monotherapy, pERC was less confident in the OS benefit since these results were not statistically significant and longer length of follow up is needed to confirm an OS benefit. • pERC acknowledged an established clinical benefit with nivolumab and ipilimumab combination for patients who are fit enough to endure the toxicities associated with this combination compared with nivolumab. While the RELATIVITY-047 study compared nivolumab and relatlimab to nivolumab monotherapy, there is no direct evidence to suggest a clinical benefit compared to nivolumab and ipilimumab combination. There remains uncertainty in the comparative efficacy of nivolumab and relatlimab compared to relevant comparators, including nivolumab and ipilimumab combination. pERC, however, acknowledged that according to clinical expert opinion, nivolumab and relatlimab has less toxicity than nivolumab and ipilimumab combination. • pERC recognized that nivolumab and relatlimab would be an alternative therapy in patients who progress on BRAF/MEK therapies used in the adjuvant setting. While pERC noted that the enrolment criteria permitted neoadjuvant or adjuvant IFN therapy with the last dose at least 6 weeks before randomization, pERC noted the infrequent and rare use of IFN therapy in neoadjuvant or adjuvant in Canada. Prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy should be followed as per RELATIVITY-047. • Eligibility to-re-treatment: ◦ pERC agreed with the clinical experts that re-initiation of treatment would be permitted for those who chose to take a treatment break but did not experience progression or unacceptable toxicity while on treatment on a case-by-case basis based on the discretion of the treating clinician. ◦ pERC agreed with the clinical experts that re-initiation would be considered in the case of progression while off therapy, and acknowledged that commonly, progression after a 6-month break is accepted as a guideline to reinstitute treatment.
Encorafenib (Braftovi) in combination with binimetinib (Mektovi)	July 26, 2021	pERC recommends that encorafenib in combination with binimetinib should be reimbursed for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation only if the following conditions are met: • Treatment with encorafenib-binimetinib should be initiated only in adults who have the following characteristics: ◦ histologically confirmed locally advanced unresectable or metastatic *BRAF* V600E and/or V600K-mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC, or IV per AJCC) ◦ no previous treatment received (treatment naive) or must have progressed on or after prior first-line immunotherapy for advanced or metastatic disease ◦ performance status defined as: ▪ ECOG PS 0 to 1

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		▪ adequate organ, bone marrow, and cardiac function, including left ventricular ejection fraction ≥ 50% by cardiac imaging and laboratory parameters. • Eligible patients should be identified through BRAF mutational analysis. • Treatment with the encorafenib-binimetinib combination should not be initiated in patients with: ◦ untreated CNS lesions ◦ uveal or mucosal melanoma ◦ known positive serology for HIV, or an active hepatitis B or hepatitis C infection, or both ◦ history of leptomeningeal metastases • Treatment with encorafenib-binimetinib may be continued unless any of the following occurs: ◦ clinical or radiographic disease progression ◦ intolerable side effects that are not responsive to dose reductions or dose delays. • Patients should be assessed for a response (as per RECIST 1.1) to treatment with encorafenib and binimetinib combination every 2 to 3 months. • Treatment with the encorafenib and binimetinib combination should be discontinued upon the occurrence of any of the following: ◦ clinical or radiographic disease progression ◦ unacceptable toxicity ◦ development of adverse reactions that do not resolve despite dose delays or dose reductions. • If 1 component of the combination therapy is discontinued for toxicity or intolerance, the other drug in the combination should also be discontinued. • Encorafenib in combination with binimetinib should only be prescribed by clinicians who: ◦ have expertise in diagnosis and management of patients with melanoma ◦ are familiar with the toxicity profile associated with the encorafenib and binimetinib regimen. • Dosing of the encorafenib and binimetinib combination should be as follows: ◦ encorafenib 450 mg once daily ◦ binimetinib 45 mg twice daily • Encorafenib in combination with binimetinib should not be more costly than the least costly *BRAFi/MEKi* combination regimen.
Nivolumab and ipilimumab (Opdivo and Yervoy in combination)	November 30, 2017	pERC recommends reimbursement of the combination of nivolumab plus ipilimumab conditional on the feasibility of adoption being addressed (budget impact). Reimbursement should be for patients with unresectable or metastatic melanoma regardless of *BRAF* status who are treatment naive, with ECOG performance status 0 to 1 and with

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		stable brain metastases, if present. Treatment should continue until unacceptable toxicity or disease progression.
Cobimetinib and vemurafenib (Cotellic and Zelboraf)	June 30, 2016	pERC recommends reimbursement of cobimetinib conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be in combination with vemurafenib, for the treatment of patients with previously treated *BRAF* V600 mutation-positive unresectable stage III or stage IV melanoma who have a good performance status. Treatment should continue until unacceptable toxicity or disease progression. If brain metastases are present, patients should be asymptomatic or have stable symptoms. pERC does not recommend reimbursement of cobimetinib plus vemurafenib for the treatment of patients with previously treated *BRAF* V600 mutation-positive unresectable metastatic melanoma. **Guidance on sequencing:** • *Patients With Disease Progression After Immune Checkpoint Therapy:* pERC noted that there is no evidence to support or refute the use of cobimetinib plus vemurafenib in patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma with disease progression after treatment with an immune checkpoint inhibitor. Therefore, pERC does not recommend reimbursement for cobimetinib plus vemurafenib in this group of patients. • *Patients With Disease Progression on First-Line Vemurafenib:* pERC noted that patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma with disease progression on first-line vemurafenib were excluded from the pivotal trial for this submission (coBRIM). The committee also considered evidence from a small phase I, noncomparative trial (BRIM7) that demonstrated poor response rates with cobimetinib plus vemurafenib in the cohort of patients whose disease had progressed while receiving vemurafenib. Therefore, pERC does not recommend reimbursement for cobimetinib plus vemurafenib for the treatment of patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma whose disease has progressed on first-line vemurafenib. • *Time-Limited Need for Cobimetinib Plus Vemurafenib in Patients Currently Receiving First-Line Treatment With Single-Agent Vemurafenib:* At the time of implementing a reimbursement recommendation for cobimetinib plus vemurafenib, jurisdictions may consider addressing the short-term, time-limited need to offer cobimetinib plus vemurafenib to patients currently receiving a single-agent *BRAF* inhibitor or MEK inhibitor for the first-line treatment of *BRAF* V600 mutation-positive unresectable or metastatic melanoma and whose disease has not progressed.
Nivolumab (Opdivo)	April 1, 2016	pERC recommends funding nivolumab (Opdivo) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with unresectable or metastatic *BRAF* wild-type melanoma who are previously treated, with good performance status and who have stable brain metastases (if present). Treatment should continue until unacceptable toxicity or disease progression. However, pERC does not recommend funding nivolumab for the

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		treatment of patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma. pERC does not recommend funding nivolumab for the treatment of patients with unresectable or metastatic melanoma who have previously received treatment with ipilimumab.
Pembrolizumab (Keytruda)	November 16, 2015	pERC recommends funding pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be in patients with unresectable or metastatic melanoma (stage III or IV) who are naive to ipilimumab treatment and funding should also be in patients who have failed ipilimumab and, if *BRAF* mutation positive, have failed *BRAF* mutation targeted therapies. Treatment should be in patients with an ECOG performance status of 0 to 1, who have stable brain metastases (if present), using the 2 mg/kg dose every 3 weeks for 24 months or until disease progression, whichever occurs first.
Dabrafenib (Tafinlar) in combination with trametinib (Mekinist)	July 21, 2015	pERC recommends funding dabrafenib (Tafinlar) plus trametinib (Mekinist), conditional on cost-effectiveness being improved to an acceptable level. Funding should be for patients with *BRAF* V600 mutation-positive, unresectable, or metastatic melanoma in the first-line setting and who have an ECOG performance status of 0 or 1. Treatment is until disease progression. If brain metastases are present, patients should be asymptomatic or have stable symptoms.

[a]Refer to published recommendation reports for full details including conditions and criteria.

Table 3: CADTH Implementation Advice Panels on Melanoma

Date of publication, advice type, drug	Implementation advice (from prior CDIAC)
December 17, 2019, funding recommendations, melanoma and adjuvant pembrolizumab	CDIAC considered clinician input and is offering the following recommendations for consideration by the CAPCA board: 1. That provinces expand the eligible population for adjuvant pembrolizumab to include resected stage IV, mucosal melanoma, and patients resected with in transit and satellite mets, which aligns with the eligible population for nivolumab. Clinicians consider these drugs to have similar enough efficacy in melanoma to want to be able to use either pembrolizumab or nivolumab. 2. That provinces not fund any immunotherapy (pembrolizumab or nivolumab) or *BRAF*-targeted therapy for adjuvant treatment in ocular melanoma at this time, pending further evidence of benefit. Ocular melanoma has a different genetic profile than cutaneous melanoma; this recommendation aligns with a pERC recommendation suggesting that evidence of benefit in this patient population is lacking. 3. That provinces allow a one-time switch for *BRAF*-mutated patients between adjuvant therapies, within a time limit of 3 months after the initiation of therapy, but funded adjuvant therapy will be limited to 12 months total. This recommendation aligns with that previously approved for adjuvant nivolumab. 4. That provinces fund, on a time-limited basis, a switch from adjuvant interferon to adjuvant immunotherapy, for patients who are otherwise eligible for these regimens, at any time and to complete a year of therapy. This recommendation

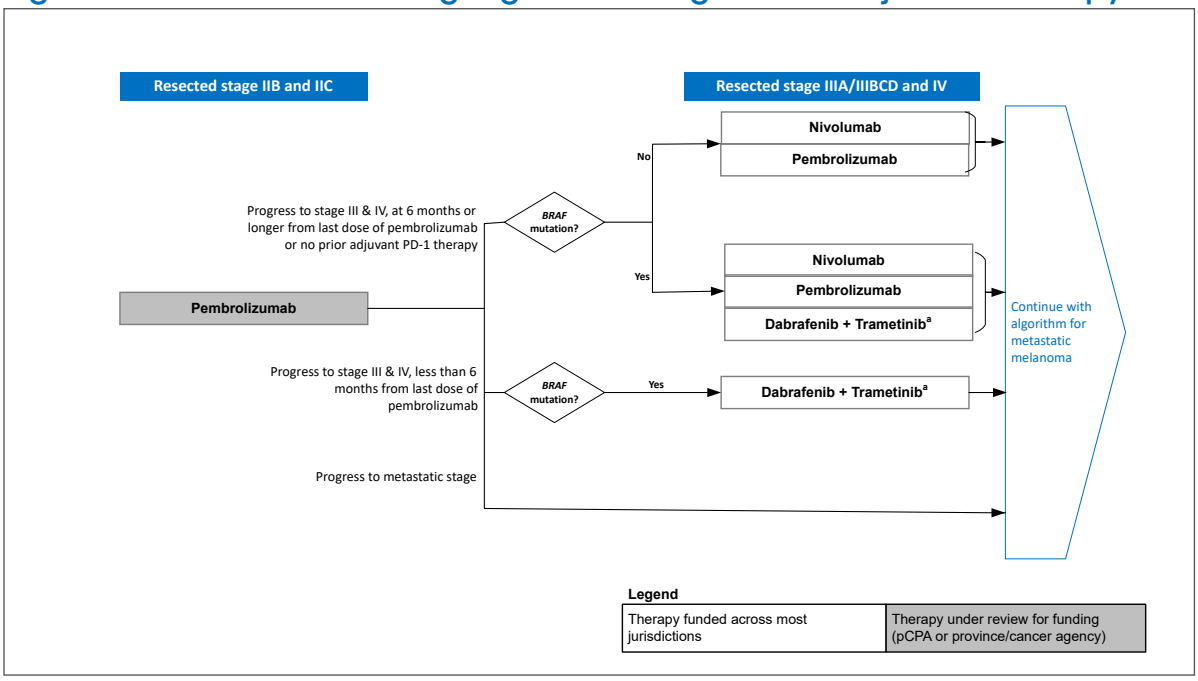
Date of publication, advice type, drug	Implementation advice (from prior CDIAC)
	aligns with that previously approved for adjuvant nivolumab. 5. That high-dose interferon be removed from the funding algorithm and noted as a historical treatment as it is no longer a Canadian standard of care for adjuvant therapy. This recommendation aligns with that previously approved for adjuvant nivolumab. 6. That provinces fund ipilimumab single agent therapy in the metastatic setting for patients who progress on adjuvant immunotherapy or progress within 6 month of last dose of pembrolizumab in the adjuvant setting. 7. That patients who receive pembrolizumab as potentially curative therapy and then relapse be eligible for downstream immunotherapy with nivolumab or pembrolizumab if equal or greater than 6 months have elapsed from the completion of adjuvant therapy. The provinces should continue to monitor the evolving evidence for IO re-treatment when IO is used in this potentially curative setting. 8. That provinces fund combination immunotherapy (nivolumab + ipilimumab) for patients relapsing at ≥ 6 months after completing adjuvant immunotherapy. 9. For patients relapsing ≥ 6 months after completing adjuvant immunotherapy and who are unfit for combination nivolumab + ipilimumab, that provinces fund single agent nivolumab or pembrolizumab immunotherapy as a treatment choice in the metastatic setting.
July 8, 2019, funding recommendations, melanoma and adjuvant nivolumab	CDIAC considered clinician input and is offering the following recommendations for consideration by the CAPCA board: 1. That provinces align with CheckMate 238 trial data and adhere to biweekly dosing of adjuvant nivolumab. 2. That provinces allow weight-based dosing of nivolumab with no dose cap as per the CheckMate 238 trial. 3. That provinces allow a one-time switch for *BRAF*-mutated patients between adjuvant therapies, within a time limit of 3 months after the initiation of therapy, but funded adjuvant therapy will be limited to 12 months total. 4. That provinces fund, on a time-limited basis, a switch from adjuvant interferon to adjuvant immunotherapy or dabrafenib-trametinib, for patients who are otherwise eligible for these regimens, at any time and allow a full year of therapy. 5. #That provinces not fund a switch to cobimetinib-vemurafenib in *BRAF*-positive patients. 6. That provinces fund ipilimumab single agent therapy in the metastatic setting for patients who progress on adjuvant immunotherapy. 7. That provinces fund combination immunotherapy (nivolumab + ipilimumab) for patients relapsing on or any time after dabrafenib + trametinib therapy. 8. That provinces allow re-treatment with *BRAF*-targeted therapy if the treatment free interval is ≥ 6 months from the completion of adjuvant *BRAF* therapy. 9. That provinces fund dabrafenib + trametinib in the rare instances where a BRAF-positive patient relapses, and would otherwise be eligible for this therapy, after adjuvant immunotherapy. 10. That high-dose interferon be removed from the funding algorithm and noted as a historical treatment as it is no longer a Canadian standard of care for adjuvant therapy.

Date of publication, advice type, drug	Implementation advice (from prior CDIAC)
	11. Provinces should expand the eligible population for adjuvant nivolumab to include stage IIIA (with node metastases > 1 mm) — this will correspond to the population included in the pembrolizumab study (clinicians consider these drugs therapeutically equivalent — so makes no sense to have them available in different populations). NOTE: There does not currently exist data on re-treatment with immunotherapy after adjuvant therapy, nor the timing of such. There is data that suggests that metastatic patients progressing off immunotherapy can respond by restarting the same immunotherapy. Provinces will likely benefit from having a standard time interval for restarts on all immunotherapies and CAPCA and CADTH have proposed a process to support said standardization. Information will be used to inform these, and subsequent immunotherapy recommendations as it becomes available.

Appendix 2: Other Provisional Funding Algorithm in Cutaneous Melanoma

Note that this appendix has not been copy-edited.

Figure 2: Provisional Funding Algorithm Diagram for Adjuvant Therapy for Melanoma



pCPA = pan-Canadian Pharmaceutical Alliance.
Note ocular melanoma is excluded.
High-dose interferon is a historical treatment that is no longer used in the treatment landscape for adjuvant therapy of patients with high risk of melanoma.
All drugs may be subject to additional funding criteria within provincial jurisdictions.
[a] For cutaneous melanoma only. Also excludes resected stage IV melanoma

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