



Provisional Funding Algorithm

Indication: Melanoma

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Publication date: February 6, 2023



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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 will 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 statuses. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on melanoma. 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

CADTH has not previously published a provisional funding algorithm report on melanoma. However, previous algorithms have been developed by Cancer Drug Implementation Advisory Committee (CDIAC). The latest was a panel algorithm approved by the Canadian Association of Provincial Cancer Agencies (CAPCA) on February 6, 2020, to incorporate the [CADTH recommendation of adjuvant pembrolizumab](#) in stage III melanoma. In a previous panel algorithm approved by CAPCA on July 8, 2019, the CADTH recommendations of adjuvant [nivolumab](#) and [dabrafenib-trametinib](#) were also incorporated into the relevant section of the algorithms. The purpose of this rapid provisional funding algorithm is to incorporate the latest [CADTH recommendation of adjuvant pembrolizumab in stage IIB or IIC melanoma](#) following complete resection, as well as to incorporating other melanoma algorithms (previously developed by CDIAC) for adjuvant treatment in stage III and metastatic melanoma.

Table 1: 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	<p>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:</p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ◦ 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. <p>Guidance on sequencing:</p> <ul style="list-style-type: none"> • 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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<p>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.</p> <p>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.</p> <p>pERC agreed with the clinical experts, noting the same principles used for other recommendations should be applied.</p>
Stages IIIA, IIIB, IIIC, IIID, and IV melanoma		
Pembrolizumab (Keytruda)	August 1, 2019	<p>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:</p> <ul style="list-style-type: none"> • cost-effectiveness being improved to an acceptable level • feasibility of adoption being addressed (budget impact). <p>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.</p> <p>Guidance on optimal sequencing:</p> <p>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.</p>
Dabrafenib and trametinib in combination (Tafinlar and Mekinist in combination)	May 3, 2019	<p>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) <i>BRAF</i>-mutated (all <i>BRAD</i> 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:</p> <ul style="list-style-type: none"> • cost-effectiveness being improved to an acceptable level • feasibility of adoption being addressed (budget impact).

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<p>Treatment with dabrafenib plus trametinib should continue until disease recurrence, unacceptable toxicity, or up to a maximum of 12 months.</p> <p>Guidance on optimal sequencing:</p> <p>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 <i>BRAF</i>-mutated stage IIIA-D cutaneous melanoma. Further, the optimal sequencing of subsequent therapies for patients with <i>BRAF</i>-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.</p>
<p>Nivolumab (Opdivo)</p>	<p>March 7, 2019</p>	<p>pERC recommends to reimburse nivolumab (Opdivo) only if the following conditions are met:</p> <ul style="list-style-type: none"> • cost-effectiveness is improved to an acceptable level • feasibility of adoption is addressed (budget impact). <p>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.</p> <p>Guidance on optimal sequencing:</p> <ul style="list-style-type: none"> • 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		
<p>Encorafenib (Braftovi) in combination with binimetinib (Mektovi)</p>	<p>July 26, 2021</p>	<p>pERC recommends that encorafenib in combination with binimetinib should be reimbursed for the treatment of patients with unresectable or metastatic melanoma with a <i>BRAF</i> V600 mutation only if the following conditions are met:</p> <ul style="list-style-type: none"> • Treatment with encorafenib-binimetinib should be initiated only in adults who have the following characteristics: <ul style="list-style-type: none"> ◦ histologically confirmed locally advanced unresectable or metastatic <i>BRAF</i> V600E and/or V600K-mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC, or IV per AJCC)

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ▪ ECOG PS 0 to 1 ▪ adequate organ, bone marrow, and cardiac function, including left ventricular ejection fraction \geq 50% by cardiac imaging and laboratory parameters. ● Eligible patients should be identified through <i>BRAF</i> mutational analysis. ● Treatment with the encorafenib-binimetinib combination should not be initiated in patients with: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ encorafenib 450 mg once daily ○ binimetinib 45 mg twice daily ● Encorafenib in combination with binimetinib should not be more costly than the least costly <i>BRAF</i>i/<i>MEK</i>i combination regimen.
Nivolumab and ipilimumab (Opdivo and Yervoy in combination)	November 30, 2017	<p>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 <i>BRAF</i> status who are treatment-naive, with ECOG performance status 0-1 and with stable brain metastases, if present. Treatment should continue until unacceptable toxicity or disease progression.</p>
Cobimetinib and vemurafenib (Cotellic and Zelboraf)	June 30, 2016	<p>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 <i>BRAF</i> V600 mutation-positive unresectable stage III or stage IV melanoma who have a good performance status. Treatment should continue</p>

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<p>until unacceptable toxicity or disease progression. If brain metastases are present, patients should be asymptomatic or have stable symptoms.</p> <p>pERC does not recommend reimbursement of cobimetinib plus vemurafenib for the treatment of patients with previously treated <i>BRAF</i> V600 mutation-positive unresectable metastatic melanoma.</p> <p>Guidance on sequencing:</p> <p><i>Patients With Disease Progression After Immune Checkpoint Therapy</i></p> <p>pERC noted that there is no evidence to support or refute the use of cobimetinib plus vemurafenib in patients with <i>BRAF</i> 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.</p> <p><i>Patients With Disease Progression on First-Line Vemurafenib</i></p> <p>pERC noted that patients with <i>BRAF</i> 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, non-comparative 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 <i>BRAF</i> V600 mutation-positive unresectable or metastatic melanoma whose disease has progressed on first-line vemurafenib.</p> <p><i>Time-Limited Need for Cobimetinib Plus Vemurafenib in Patients Currently Receiving First-Line Treatment With Single-Agent Vemurafenib</i></p> <p>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 <i>BRAF</i> inhibitor or MEK inhibitor for the first-line treatment of <i>BRAF</i> V600 mutation-positive unresectable or metastatic melanoma and whose disease has not progressed.</p>
Nivolumab (Opdivo)	April 1, 2016	<p>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 <i>BRAF</i> 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 treatment of patients with <i>BRAF</i> V600 mutation-positive unresectable or metastatic melanoma.</p> <p>pERC does not recommend funding nivolumab for the treatment of patients with unresectable or metastatic melanoma who have previously received treatment with ipilimumab.</p>
Pembrolizumab (Keytruda)	November 16, 2015	<p>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 <i>BRAF</i> mutation positive, have failed <i>BRAF</i> mutation</p>

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		targeted therapies. Treatment should be in patients with an ECOG performance status of 0-1, 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 <i>BRAF</i> 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.

AJCC = American Joint Committee on Cancer; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed cell death 1 protein; PD-L1 = programmed cell death 1 ligand 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PS = performance status.

Table 2: Previous CDiac Implementation Advice Panels on Melanoma

Date of publication, advice type, drug	Implementation advice
December 17, 2019, funding recommendations, melanoma and adjuvant pembrolizumab	<p>CDIAC considered clinician input and is offering the following recommendations for consideration by the CAPCA board:</p> <ol style="list-style-type: none"> 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 <i>BRAF</i> 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 <i>BRAF</i>-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 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

Date of publication, advice type, drug	Implementation advice
	<p>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.</p> <ol style="list-style-type: none"> 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.
<p>July 8, 2019, funding recommendations, melanoma and adjuvant nivolumab</p>	<p>CDIAC considered clinician input and is offering the following recommendations for consideration by the CAPCA board:</p> <ol style="list-style-type: none"> 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 <i>BRAF</i>-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 <u>not</u> fund a switch to cobimetinib-vemurafenib in <i>BRAF</i>-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 retreatment with <i>BRAF</i>-targeted therapy if the treatment free interval is ≥ 6 months from the completion of adjuvant <i>BRAF</i> therapy. 9. That provinces fund dabrafenib + trametinib in the rare instances where a <i>BRAF</i> 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. 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). <p>Note: There does not currently exist data on retreatment 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</p>

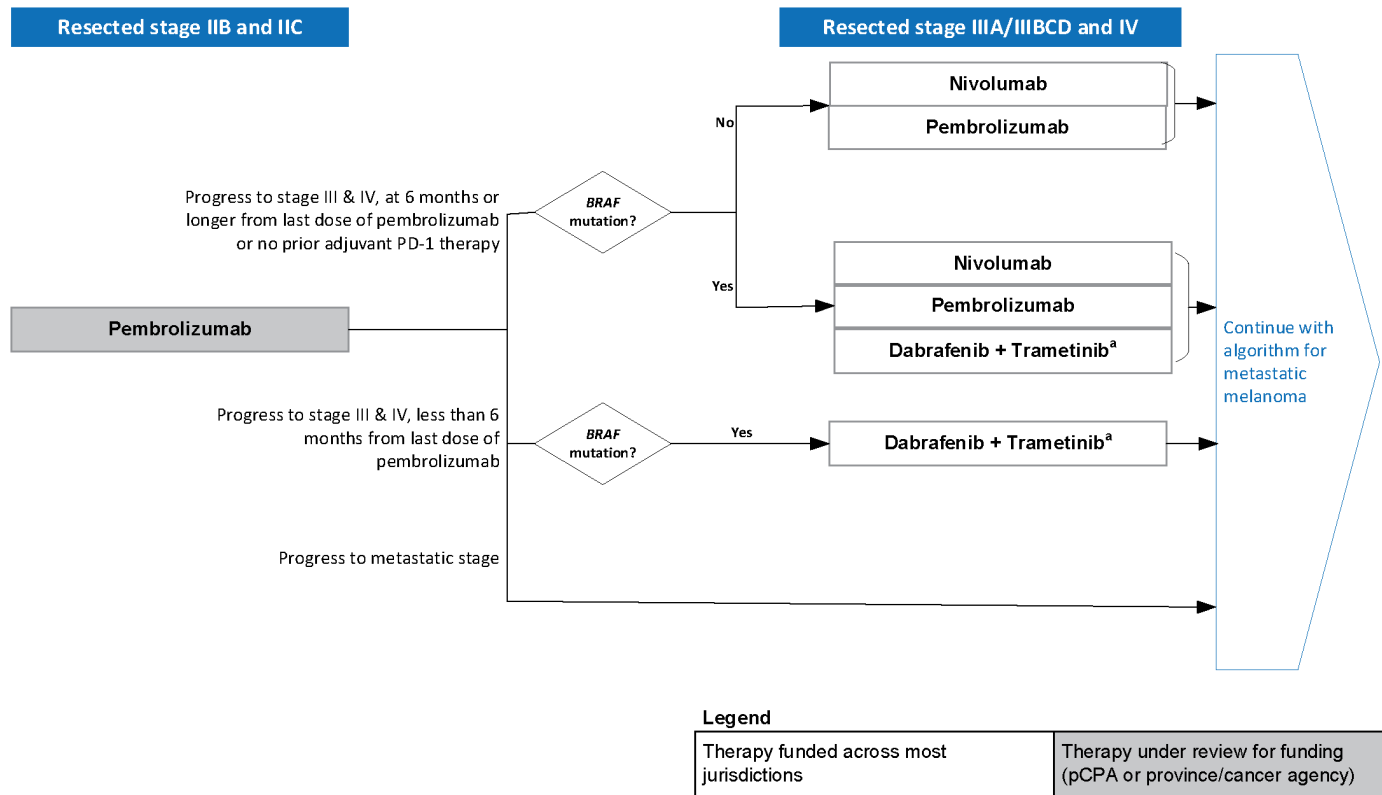
Date of publication, advice type, drug	Implementation advice
	interval for restarts on all immunotherapies and CAPCA and CADTH have proposed a process to support said standardization. Information will be used to inform these, and subsequent immunotherapy recommendations as it becomes available.

CAPCA = Canadian Association of Provincial Cancer Agencies; CDIAAC = Cancer Drug Implementation Advisory Committee; OI = osteogenesis imperfecta; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Adjuvant Therapy for Melanoma

This is not a comprehensive list of all available treatments nor a treatment algorithm. Drugs available and funded through other mechanisms (e.g., clinical trials, manufacturer’s compassionate access program, private payors) are not included.



pCPA = pan-Canadian Pharmaceutical Alliance.

Notes: Ocular melanoma is excluded.

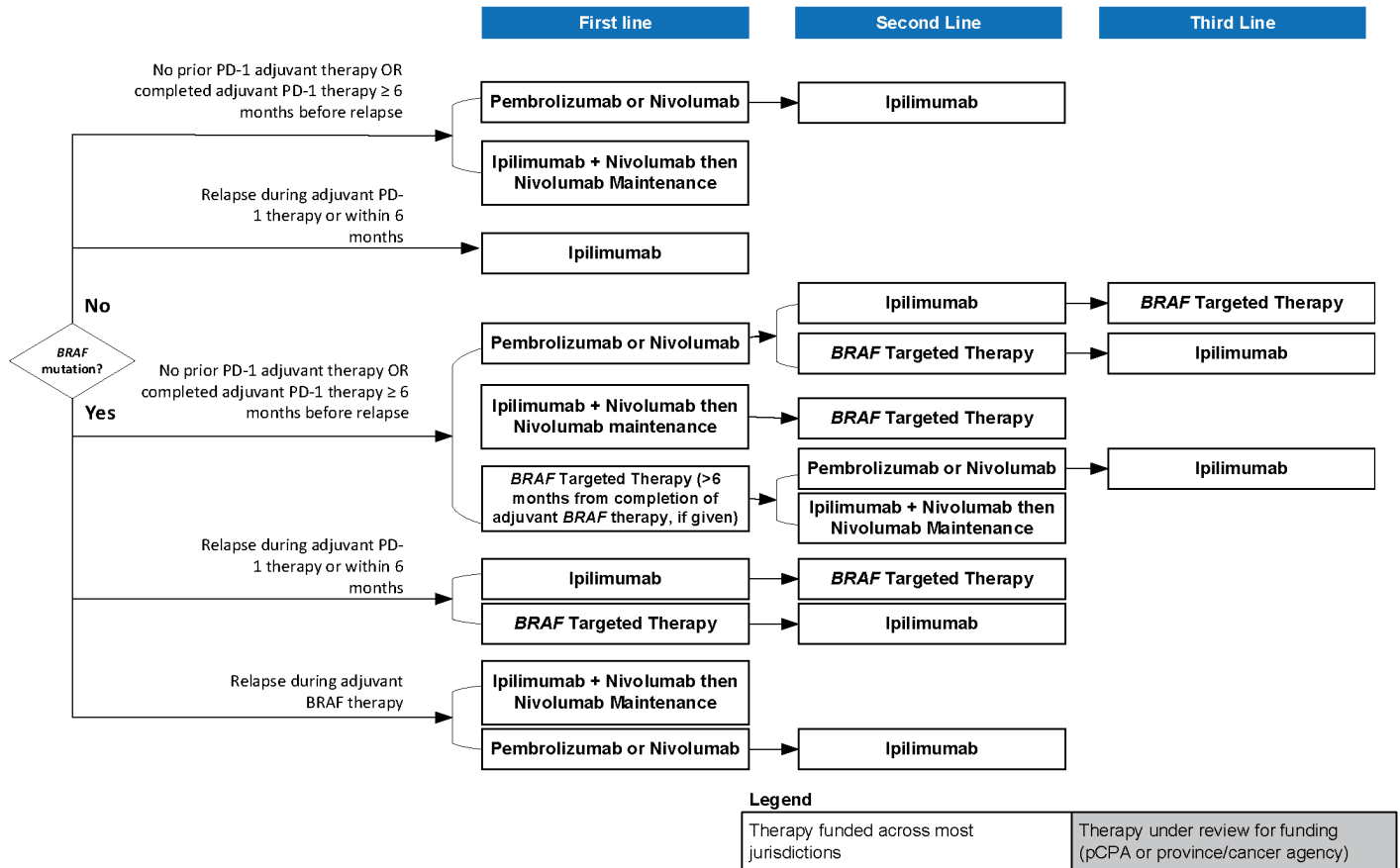
High-dose interferon is a historical treatment that is no longer used in the Canadian treatment landscape for adjuvant therapy of patients with high-risk melanoma.

All drugs may be subject to additional funding criteria within provincial jurisdictions.

^aFor cutaneous melanoma only. Also excludes resected stage IV melanoma.

Figure 2: Provisional Funding Algorithm Diagram for Metastatic Melanoma

This is not a comprehensive list of all available treatments nor a treatment algorithm. Chemotherapy, as a last line of treatment, is not represented on the algorithm. Drugs available and funded through other mechanisms (e.g., clinical trials, manufacturer’s compassionate access program, private payors) are not included.



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

Notes: BRAF-targeted therapy options include dabrafenib-trametinib, cobimetinib-vemurafenib, and encorafenib-binimetinib.

If PD-1 therapy (initiated either as a single agent, or maintenance following combination immunotherapy) is stopped after 2 years or at time of best response without evidence of disease progression, then single-agent PD-1 therapy may be restarted at relapse as the same line of therapy. Re-treatment with combination immunotherapy is not funded.

All drugs may be subject to additional funding criteria within provincial jurisdictions.

Description of the Provisional Funding Algorithm

Adjuvant Therapy for Melanoma (Depicted in Figure 1)

Resected Stage IIB and IIC

At this time, pembrolizumab is the only option indicated as an adjuvant treatment for patients with stage IIb and IIc melanoma after complete resection. Pembrolizumab is currently under review for funding.

Resected Stage IIIA, III, IIIB, IIIC, IIID, and IV

In the adjuvant setting of stage IIIA, IIIB, IIIC, IIID, and IV, the treatment options depend on if there has been prior use of pembrolizumab in stage IIB and IIC, as well as if there is *BRAF* mutation.

- If the progression or relapse has occurred within 6 months of pembrolizumab treatment, no additional programmed cell death 1 protein (PD-1) inhibitor or programmed cell death 1 ligand 1 (PD-L1) inhibitor would be funded in stage III or IV of the adjuvant setting. However, if the individual has a confirmed *BRAF* mutation, dabrafenib-trametinib is an option for cutaneous melanoma, excluding for those with resected stage IV melanoma.
- If the progression or relapse has occurred at 6 months or longer (or in cases with no prior use of PD-1 inhibitor or PD-L1 inhibitor), then treatment options also depend on *BRAF* mutation. If there is no *BRAF* mutation, the available options are nivolumab and pembrolizumab. If *BRAF* mutation is present, the available options are nivolumab, pembrolizumab, and dabrafenib-trametinib. However, dabrafenib-trametinib is only for cutaneous melanoma and excludes individuals with resected stage IV melanoma.

Note that ocular melanoma is excluded in this funding algorithm. Also, it would be rare that individuals would progress from stage II to stage III for additional treatment options. If this does occur, only individuals who have had a disease-free period of at least 6 months or longer since the last dose of an adjuvant PD-1 or PD-L1 inhibitor would be eligible for treatment options funded in the stage IIIA, IIIB, IIIC, IIID, and IV adjuvant setting.

For individuals whose disease progresses to advanced or metastatic melanoma after receiving adjuvant treatments in resected stage II, III, or IV, please refer to the algorithm for metastatic melanoma for funding options.

Metastatic Melanoma (Depicted in Figure 2)

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 or nivolumab, followed by the second-line option of ipilimumab. 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:

1. **Pembrolizumab or nivolumab:** If individuals have either pembrolizumab or nivolumab as a first-line option, the second-line option can be 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.
2. **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.
3. ***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 or nivolumab with a subsequent third-line option of ipilimumab. Another second-line option would be ipilimumab-nivolumab followed by nivolumab maintenance therapy.

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

For individuals with *BRAF* mutation who relapse during adjuvant *BRAF*-targeted therapy, the first-line option would be a choice of pembrolizumab or nivolumab with a subsequent second-line option of ipilimumab. Another second-line option would be ipilimumab-nivolumab followed by nivolumab maintenance therapy.

Additional Remarks

Six-Month Retreatment Interval

These algorithms have adopted guidance from pERC and recommendations from previous panel algorithm projects conducted by CDIA in July 2019 and December 2019 on a cut-off re-treatment interval of 6 months. Individuals are generally not eligible for re-treatment with drugs from the same drug categories if they have disease progression within 6 months of treatment completion.