CDA-AMC Drug Implementation Advice: Provisional Funding Algorithm

Proposed Scope

Indication: Melanoma

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1. Background

At the request of the drug programs that participate in the CDA-AMC drug reimbursement review processes, CDA-AMC is convening an implementation advice panel to advise the drug programs on a provisional funding algorithm for drugs used in the treatment of melanoma. This advice will be used by the drug programs and the Canadian Association of Provincial Cancer Agencies in the development of their funding criteria. For this project, CDA-AMC will be updating previously completed related work. Appendix 1 lists the past CDA-AMC algorithm implementation advice panels conducted for the indication of interest. Appendix 2 lists all past CDA-AMC recommendations for drugs in the same therapeutic space. This document outlines a draft scope for the panel discussions, including which drugs are under consideration and questions to be addressed by the panel.

2. Consultation Process and Objectives

The implementation advice panel will be comprised of Canadian clinical specialists with expertise in the diagnosis and management of patients with melanoma. The objective of the panel will be to provide advice to the participating drug programs regarding the funding algorithm and any related implementation questions. In addition to the clinical panelists and CDA-AMC staff, representatives from public drug programs, the pan-Canadian Pharmaceutical Alliance, and the Canadian Association of Provincial Cancer Agencies may participate in the discussion and provide input in advance of the meeting on the topics for discussion. For more information on the implementation advice process, please refer to *Procedures for CADTH Drug Reimbursement Reviews*.

The CDA-AMC Provincial Advisory Group raised the following questions pertaining to the development of a provisional funding algorithm. These are to be addressed by the implementation advice panel.

Implementation Questions

1. What is the available evidence to support subsequent treatment options in patients who have received neoadjuvant nivolumab-ipilimumab for melanoma?

2. What is the available evidence to support the use of nivolumab-ipilimumab in the second or subsequent line setting in advanced melanoma patients after progression on single-agent anti-PD1 therapy administered in the advanced setting?

3. Feedback Opportunities

CDA-AMC welcomes stakeholder feedback from patient and clinician groups as well as manufacturers whose product(s) may be impacted by changes in the funding algorithm. Stakeholders are invited to provide comments and/or complementary information, including published evidence on treatment sequencing, if available, in support of algorithm development. To facilitate understanding, the current draft funding algorithm is included in Section 5. The feedback will be considered in the finalization of the implementation advice scope.

When ready, a draft provisional funding algorithm report will be posted for stakeholder feedback. The final provisional funding algorithm report will be posted on the CDA-AMC website.

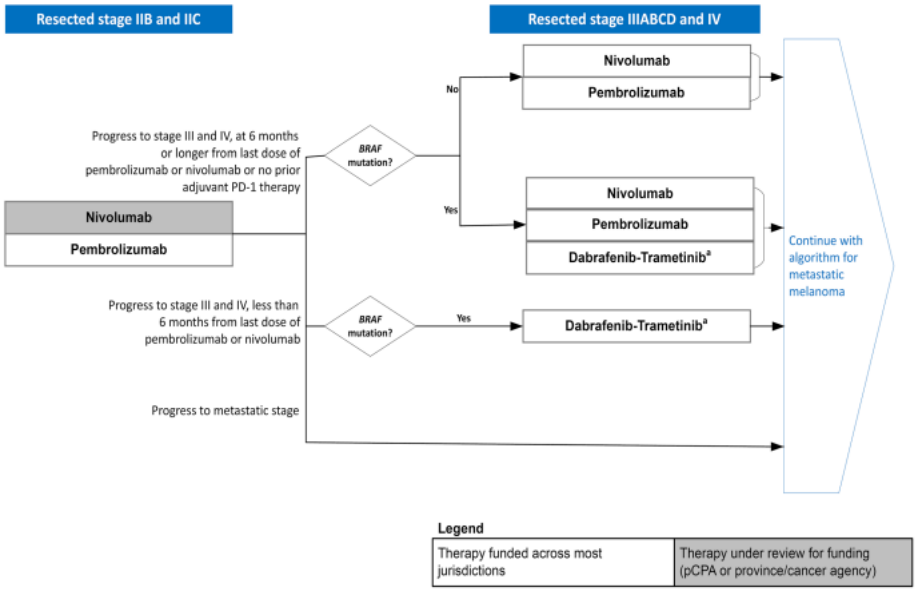
4. Drugs

Table 1: List of Drugs Under Consideration

Generic name (brand name)	Manufacturer	Indication(s)
Nivolumab Ipilimumab	n/a	For the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma when patients progress during or within 6 months of adjuvant PD-1 therapy
Nivolumab Ipilimumab	n/a	For resectable macroscopic stage III melanoma in the neoadjuvant setting

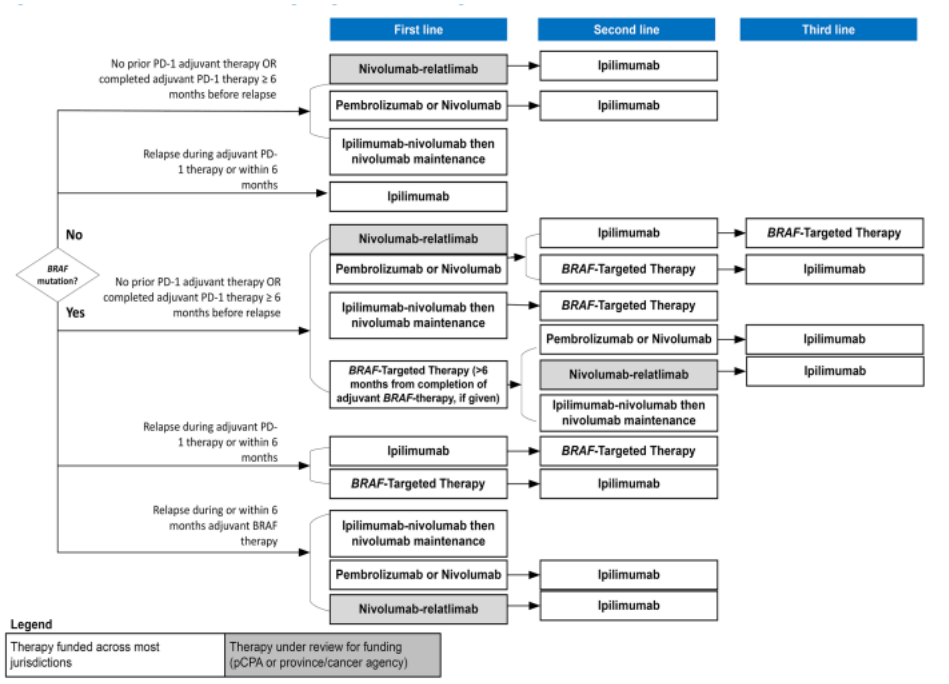
5. Funding Algorithms

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



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.
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.
[a] For cutaneous melanoma only. Also excludes resected stage IV melanoma.

Figure 2: Current Funding Algorithm Diagram for Metastatic Melanoma



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. 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.

Note: These diagrams are summary representations of the drug funding options for the condition of interest. They are not treatment algorithms and are not 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 provinces. Drugs are subject to explicit funding criteria. Please refer to the individual drug entries on the CDA-AMC website for more details.

Appendix 1: History of CDA-AMC Algorithm Panels on Melanoma

Table 2: Previous CDA-AMC Implementation Advice With Funding Algorithms

Date	Main revisions
June 4, 2024	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. 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.
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 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. 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 retreatment 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. 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 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 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; CDIAC = Cancer Drug Implementation Advisory Committee; OI = osteogenesis imperfecta; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Appendix 2: CDA-AMC Recommendations on Drugs for Melanoma

Table 3: Related CDA-AMC Recommendations

Generic name (brand name)	Date of recommendation	Recommendation
Neoadjuvant melanoma		
Nivolumab and ipilimumab	January 29, 2025	FMEC recommends that nivolumab and ipilimumab be reimbursed for the neoadjuvant treatment of resectable stage III melanoma, if the following conditions are met: · Patients are aged at least 16 years · Patients have cytologically or histologically confirmed resectable stage III melanoma of cutaneous or unknown primary origin with 1 or more macroscopic lymph node metastases that can be biopsied, or any number of resectable in-transit metastases · Patients have good performance status · Treatment should be discontinued if there is disease recurrence during treatment or intolerable adverse events · Nivolumab plus ipilimumab should be discontinued after 2 cycles of neoadjuvant ipilimumab plus nivolumab every 3 weeks · Prescribing should be limited to clinicians with expertise in the diagnosis and management of melanoma · A reduction in price may be required
Pembrolizumab	August 1, 2024	FMEC recommends that pembrolizumab be reimbursed for the neoadjuvant-adjuvant treatment of adult patients with stage III or stage IV melanoma, if the following conditions are met: · Treatment should be reimbursed in patients with clinically detectable and measurable stage IIIB-D or resectable stage IV melanoma · Pembrolizumab should be discontinued until a maximum of 18 doses. · Pembrolizumab must be initiated by a clinician with expertise in the treatment of melanoma.
Stage IIB or stage IIC melanoma		
Nivolumab (Opdivo)	June 14, 2024	pERC recommends that nivolumab be reimbursed as monotherapy for the adjuvant treatment of adult patients with stage IIB or IIC melanoma following complete resection, only if the following conditions are met: · Treatment with nivolumab should be reimbursed in adult patients with completely resected stage IIB or IIC cutaneous melanoma (as defined by the AJCC classification, eighth edition) · Treatment with nivolumab should be initiated within 12 weeks of surgery · Patient must not have received prior treatment beyond complete resection. · Reimbursement of nivolumab should be discontinued in patients who exhibit any of the following: o clinical or radiological disease recurrence

		o evidence of significant toxicity or adverse events potentially related to nivolumab · Patients should discontinue treatment following a maximum of 12 months of adjuvant nivolumab · Nivolumab should be prescribed in an outpatient oncology clinic and should be supervised and/or delivered in institutions with expertise in the delivery of immunotherapy · Nivolumab should not be combined with other anticancer drugs for melanoma. · The price of nivolumab should be negotiated so that the total cost of treatment does not exceed the drug program cost of treatment, with the least costly adjuvant therapy reimbursed for the treatment of adult patients with stage IIB or IIC melanoma following complete resection Guidance on sequencing: · In Checkmate-76K placebo-treated patients who experienced disease recurrence within 3 years after the last dose of placebo and nivolumab treated patients who experienced recurrence greater than 6 months and within 3 years after completing treatment, were eligible to cross over or rechallenge with nivolumab. Patients with recurrent, resectable disease were offered nivolumab for a maximum duration of 12 months. Patients in other solid tumours (e.g., lung, melanoma) are eligible for downstream PD-1/PD-L1 inhibitor provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of adjuvant PD-1/ PD-L1 inhibitor. pERC agreed with the clinical experts that the same principle used for other solid tumours could be applied in this case, according to the common standard clinical practice.
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:

		o clinical/radiological disease progression o 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. 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		
Nivolumab and ipilimumab	August 1, 2024	FMEC recommends the reimbursement of nivolumab and ipilimumab for the first-line treatment of advanced melanoma in patients who progress during or within 6 months of adjuvant PD-1 therapy.
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 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 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 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 enrollment criteria permitted neoadjuvant or adjuvant IFN therapy with the last dose at least 6 weeks prior to 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-retreatment: o 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: o 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) o no previous treatment received (treatment naive) or must have progressed on or after prior first-line immunotherapy for advanced or metastatic disease o performance status defined as: § ECOG PS 0 to 1 § 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: o untreated CNS lesions o uveal or mucosal melanoma o known positive serology for HIV, or an active hepatitis B or hepatitis C infection, or both o history of leptomeningeal metastases · Treatment with encorafenib-binimetinib may be continued unless any of the following occurs: o clinical or radiographic disease progression o 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: o clinical or radiographic disease progression o unacceptable toxicity o 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: o have expertise in diagnosis and management of patients with melanoma o are familiar with the toxicity profile associated with the encorafenib and binimetinib regimen.

		· Dosing of the encorafenib and binimetinib combination should be as follows: o encorafenib 450 mg once daily o 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 0-1 and with 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, 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 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 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 0-1, 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	July 21, 2015	pERC recommends funding dabrafenib (Tafinlar) plus trametinib (Mekinist), conditional on cost-effectiveness

trametinib (Mekinist)		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 perf brain metastases are present, patients should be asymptomatic or have stable symptoms.