CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Melanoma

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CADTH

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 status. 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 one was a panel algorithm approved by 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. In this rapid provisional funding algorithm, the purpose 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	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 six 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.
Stage IIIA/B/C/D 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, atwhich 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 &Trametinib in Combo (Tafinlar & Melkinist in Combo)	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 one 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-Ipilimumab (Opdivo and Yervoy in Combo)	November 30, 2017	pERC recommends reimbursement of the combination of nivolumab plus ipilumumab 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-naïve, 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 cobimetrinib 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 1, 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 ont 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 naïve 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 2mg/kg dose every three weeks for 24 months or until disease progression, whichever occurs first.

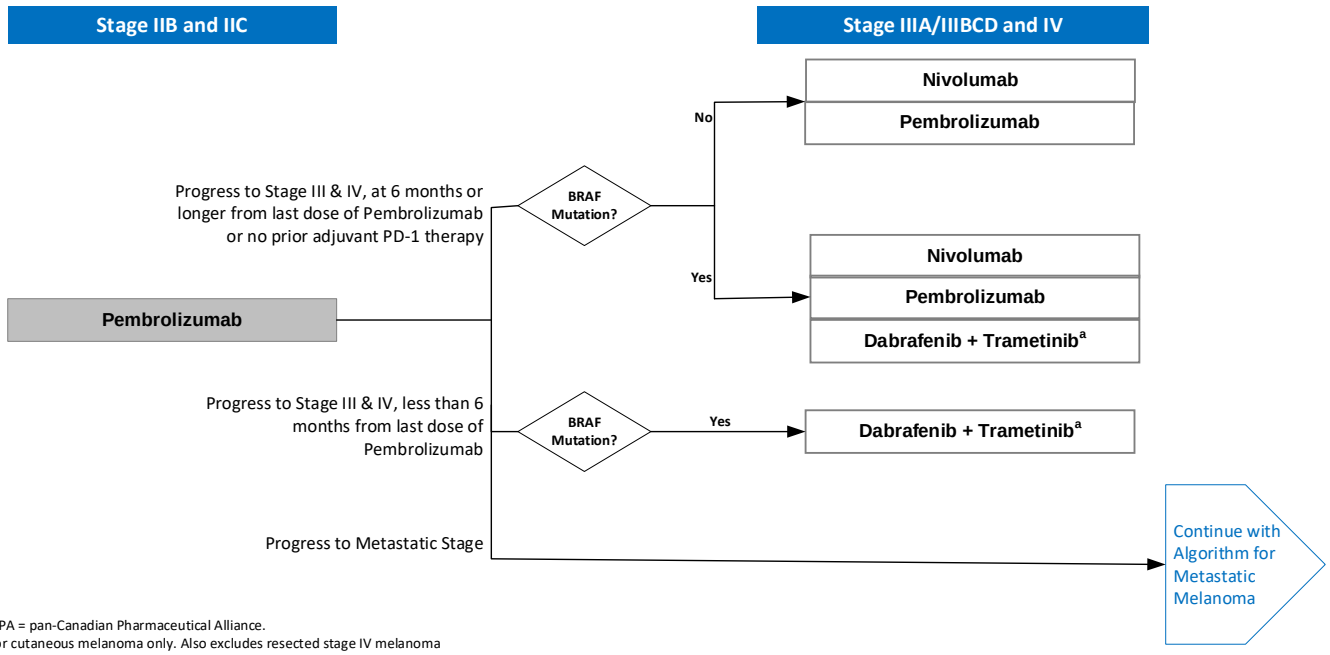
Table 2: Previous CDIAC Implementation Advice Panels on Melanoma

Date of publication	Implementation Advice
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 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 ipilmumab 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 OI retreatment 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 238trial 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 population] 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.

Provisional Funding Algorithm

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



pCPA = pan-Canadian Pharmaceutical Alliance.
[a]For cutaneous melanoma only. Also excludes resected stage IV melanoma
Notes:
1. Ocular Melanoma is excluded
2. High-dose interferon is a historical treatment no longer used in the Canadian treatment landscape for adjuvant therapy of patients with high-risk melanoma.
3. 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.
4. All drugs may be subject to additional funding criteria within provincial jurisdictions.

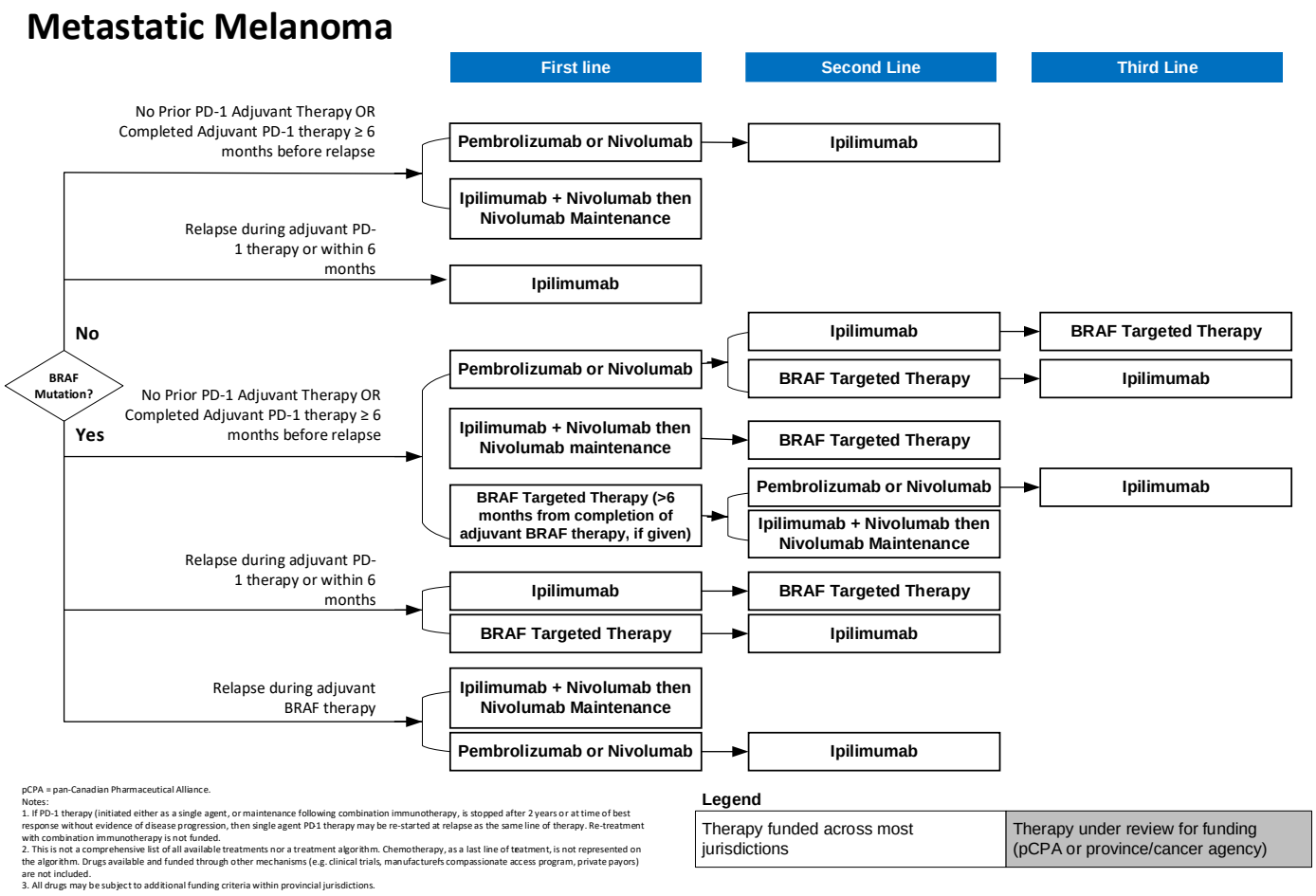
Legend

Therapy funded across most jurisdictions	Therapy under review for funding (pCPA or province/cancer agency)

pCPA = pan-Canadian Pharmaceutical Alliance; BRAF = B-rapidly accelerated fibrosarcoma

Alt text: This figure depicts the adjuvant treatment options in Stage II, Stage III and Stage IV melanoma.

Figure 2: Provisional Funding Algorithm Diagram for Metastatic Melanoma



pCPA = pan-Canadian Pharmaceutical Alliance; BRAF = B-rapidly accelerated fibrosarcoma

Alt text: This figure depicts the adjuvant treatment options in metastatic melanoma.

Description of the Provisional Funding Algorithm

Adjuvant Therapy for Melanoma (depicted in Figure 1)

Stage IIB and IIC

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

Stage IIIA/IIIBCD and IV

In the adjuvant setting of Stage IIIA/IIIBCD 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, no additional PD1-inhibitor or PD-L1 inhibitor would be funded in Stage III/IV of the adjuvant setting. However if the individual has confirmed BRAF mutation, dabrafenib-trametinib is an option for cutaneous melanoma, excluding individuals 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 PD1-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 adjuvant PD-1 or PD-L1 inhibitor would be eligible for treatment options funded in the stage IIIA/IIIBCD and IV adjuvant setting.

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 before relapse

For individuals with no BRAF mutation and with no prior PD-1 adjuvant therapy or completed adjuvant PD-1 therapy 6 months or longer, the first line options can be either pembrolizumab or nivolumab, followed by a 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, 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 before relapse

For individuals with BRAF mutation and with no prior PD-1 adjuvant therapy or completed adjuvant PD-1 therapy 6 months or longer, there are three 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 first-line option as ipilmumab-nivolumab which is followed by nivolumab maintenance therapy.
3. BRAF targeted therapy: Individuals may begin with BRAF targeted therapy as a first-line option. These individuals must have at least completed prior adjuvant BRAF therapy more than 6 months ago, if given in this setting. 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, 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 mutation, 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 ipilmumab-nivolumab followed by nivolumab maintenance therapy.