CADTH

CADTH Reimbursement Review

PEMBROLIZUMAB

(Non-Sponsored Review)

Therapeutic area: Neoadjuvant treatment of adult patients with stage III or stage IV melanoma

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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.

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Abbreviations

AE	adverse event
CI	confidence interval
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention-to-treat population
OL	open label
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	standard deviation
US	United States
WDAE	withdrawal due to adverse event

Executive Summary

An overview of the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Pembrolizumab (Keytruda), 100 mg/ 4 ml solution for infusion, IV infusion.
Health Canada Indication	For the adjuvant treatment of adult patients with Stage III melanoma with lymph node involvement who have undergone complete resection.
Indication under consideration for reimbursement	For the neoadjuvant-adjuvant treatment of adult patients with stage III or stage IV melanoma.
Health Canada Approval Status	Approved for the Health Canada indication. Not approved for the indication under consideration for reimbursement.
NOC date	April 2, 2019
Requester	Provincial Advisory Group

IV = intravenous; NOC = notice of compliance.

Introduction

Malignant melanoma is a relatively uncommon but aggressive skin cancer, with an estimated 9,700 new cases projected for 2023, and approximately 1,250 melanoma-related deaths in Canada.[1] Melanoma is observed across all age groups, but remains one of the most common types of cancer diagnosed in younger individuals, as its incidence in Canada continues to rise over time.[2,3] Locally advanced melanoma poses a high risk of relapse and death.[4,5]

The goals of therapy are to extend survival, delay disease recurrences and disease progression, as well as improve quality of life. The current standard of care for resectable stage III and stage IV melanoma is initial surgical resection; when complete resection is successful, adjuvant therapy is recommended for patients who are considered at high risk for recurrence, with either immunotherapy or targeted therapy in stage III disease, and with immunotherapy in stage IV disease.[6]

There is currently no neoadjuvant therapy with Health Canada indication for adult patients with melanoma. However, the clinical experts consulted by CADTH for this review highlighted several potential benefits from neoadjuvant therapy, including downstaging the tumour prior to undergoing surgery, allowing for a better immune response against the cancer, assessing whether a tumour will be sensitive to immunotherapy, as well as initiating treatment promptly upon diagnosis.

The neoadjuvant-adjuvant treatment of adult patients with stage III or stage IV melanoma with pembrolizumab is the subject of this review. Pembrolizumab has a Health Canada-approved indication for the adjuvant treatment of adult patients with stage III melanoma with lymph node involvement who have undergone complete resection.[7] CADTH previously reviewed pembrolizumab in this indication in 2019, where the pCODR Expert Review Committee (pERC) recommended funding pembrolizumab for the adjuvant treatment of patients with stage IIIA to IIID (AJCC staging system, 8th edition) cutaneous melanoma, with conditions.[8]

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full patient group input is included in the Stakeholder Input section at the end of this report.

Two patient advocacy groups, Save Your Skin Foundation (SYSF) and Melanoma Canada, submitted the patient input for this review. Both organizations offer resources, support, prevention initiatives, and advocacy for patients with melanoma, among other cancers, and strive to ensure accessible and timely diagnosis and treatment options for all. Both submissions were based on online surveys. 17 out of the 36 respondents to SYSF's survey and 27 out of 109 respondents to Melanoma Canada's survey confirmed receiving pembrolizumab. In the SYSF survey, 6 of these patients reported receiving pembrolizumab in the neoadjuvant setting.

Patients highlighted a range of physical, emotional, and financial challenges resulting from a melanoma diagnosis, including pain, fatigue, anxiety, depression, significantly impacting their quality of life and that of their families. Patients emphasized that scarring and disfigurement post-surgery serve as constant, unpleasant reminders of their cancer journey, significantly affecting their emotional and mental well-being. The six patients who reported receiving pembrolizumab in neoadjuvant settings associated these adverse events with the drug: fatigue, cognitive impairment, skin rash, gastrointestinal issues, breathing problems, headaches, and arthritis flare-up.

Patients and caregivers advocated for incorporating neoadjuvant pembrolizumab in the survey responses, emphasizing its potential to expedite treatment initiation, mitigate metastasis risk during surgical wait times, alleviate anxiety and depression, less invasive surgery resulting in minimal scarring, and eliminate cancer or recurrence. They highlighted the overall positive impact on recovery, mental well-being of the patients and healthcare cost reduction as compelling reasons for its implementation.

Clinician input

Input from clinical experts consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of melanoma provided the input. Both clinical experts noted that there is currently no neoadjuvant therapy for adult patients with resectable Stage III or Stage IV melanoma. The treatment goals with neoadjuvant pembrolizumab, as per the clinical experts, are also to prolong life and delay disease recurrence. One clinical expert suggested that assessing immunotherapy response in the neoadjuvant setting for three cycles could inform subsequent treatment decisions, particularly in the challenging context of BRAF mutant cases where choosing between immunotherapy and targeted therapy is difficult.

Both clinical experts indicated that incorporating neoadjuvant pembrolizumab alongside surgery and adjuvant immunotherapy, signifies a notable shift in the current treatment approach. They also suggested that neoadjuvant administration of pembrolizumab would target the same patient population currently undergoing adjuvant therapy with this drug, and with the potential for those with BRAF mutation to have better outcomes. The clinical experts noted that all patients must have an R0 resection to be eligible for adjuvant immunotherapy. In the neoadjuvant-adjuvant setting, three cycles of treatment are given perioperatively, and 15 cycles post-operatively (instead of giving all 18 cycles post-operatively in the adjuvant setting). Given that the total number doses is the same as that given in the adjuvant setting, this approach (neoadjuvant-adjuvant setting) remains cost-neutral while providing crucial prognostic insights at the time of surgery.

The clinical experts suggested that patients are typically identified through physical examination, with confirmation via ultrasound and biopsy, followed by disease staging to rule out metastatic disease, and with no requirement for a companion test. The clinical experts advised that relapse or disease-free survival, distant metastasis-free survival, event-free survival and overall survival are meaningful end points. The clinical experts noted that disease progression, disease recurrence, toxicity or patient request would be the reason to discontinue treatment.

Clinician group input

Clinician input was submitted by one clinician group, Ontario Health, Cancer Care Ontario (OH-CCO) CNS Cancer Drug Advisory Committee

The clinician group noted that there are no approved or funded neoadjuvant-adjuvant treatments in the setting of clinically detected Stage IIIB/C/D or Stage IV resectable melanoma. As per the clinician group, neoadjuvant-adjuvant treatment approach has a curative intent and to prolong event-free survival as well as with a potential to reduce the occurrence of treatment failure and the development of non-resectable metastatic disease. The clinician group also highlighted that the same number of total doses would be used, and

the same patient population would be eligible for the two treatment approaches (neoadjuvant-adjuvant setting and post-surgical adjuvant setting). The clinicians noted that assessment of response would be based on lack of disease recurrence, improved relapse-free survival, improved overall survival and cure. The presence of toxicity or lack of clinical benefit would be the reasons to discontinue treatment. To allow clinicians to assess when a patient is suitable for surgery, the clinician group also suggested conducting imaging before initiating immunotherapy then repeating after completing 3 cycles of immunotherapy. The clinician group advised that a dedicated dermatopathology assessment of surgical specimens when the patient has been treated with neoadjuvant therapy would be necessary for best clinical care.

Drug program input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. The drug plans highlighted the neoadjuvant-adjuvant treatment approach to be cost neutral when compared to the adjuvant treatment approach. Referencing the Patel et al. 2023[9] trial, the drug plan provided questions on the maximum duration that can be allowed between neoadjuvant and adjuvant treatment, possibility of a dosing regimen that allows extended interval between drug cycles (6 weeks instead of 3 weeks), and suitability of the treatment approach for patients with stable CNS metastasis. Further, highlighting the inclusion and exclusion criteria of the trial, the drug plans suggested that the exclusion of patients who received previous immunotherapy from the trial, should be factored when the funding algorithm is being developed. Referring the current reimbursement policy for immunotherapies like pembrolizumab and nivolumab, the drug plans also provided questions related to total exact number of doses (17 or 18 doses), retreatment with anti-PD-1 therapy, and potential for reimbursing nivolumab in a similar setting (neoadjuvant-adjuvant).

These questions were addressed by the clinicial experts consulted for the CADTH review. Clinical experts' responses have been included in the Drug Program Input section (Appendix 4).

Clinical Evidence

Protocol Selected Studies

Description of studies

One published phase II, open-label randomized controlled trial (RCT) was included in the systematic review: the Southwest Oncology Group (SWOG) Cancer Research Network S1801 trial.[9] The SWOG S1801 study (n = 313)[9] was performed in the United States (US) and randomized patients to neoadjuvant-adjuvant pembrolizumab, or pembrolizumab given only as adjuvant treatment, for the treatment of resectable stage III or stage IV melanoma.[9] The primary outcome was event-free survival, which captured a range of efficacy and harms events, including disease progression, serious toxic effects, the incapacity to perform surgery or to initiate adjuvant treatment, and surgical complications.

The administration of pembrolizumab was in line with the Health Canada recommended dosage in oncology and what would be used in the reimbursement population, which does not currently include patients with stage IV disease. Patients presented with baseline and disease characteristics that were consistent with the population typically seen by the experts in clinical practice; however, only few patients had stage IIID and stage IV disease. This should be considered when generalizing the findings to real-life patients.

No evidence was available to inform the comparison of neoadjuvant pembrolizumab to adjuvant nivolumab.

Efficacy Results

Efficacy results are outlined in The assessment of harms outcomes suffered from limited reporting in the SWOG S1801 publication. Small proportions of patients experienced grade 3-4 drug-related AEs, which were numerically higher in patients receiving neoadjuvant-adjuvant pembrolizumab than in patients who received the drug only in the adjuvant setting. The proportions of patients experiencing SAEs and WDAEs were not reported. No mortality due to AEs was reported throughout the study. It was not possible either to assess any of the harms of special interest specified in the systematic review protocol.

The clinical experts consulted by CADTH indicated that the harms profile of pembrolizumab appeared consistent with what is currently seen in clinical practice based on the available evidence, and that it was expected to be similar whether treatment is initiated before or after surgery.

Other Considerations

The clinical experts consulted by CADTH for this review noted that there are often meaningful delays in surgical procedures across Canada, which can amount to as much as six months between the time melanoma is being diagnosed, and initiation of adjuvant therapy. Therefore, neoadjuvant pembrolizumab addresses a significant unmet need for patients, as it can be initiated promptly upon diagnosis, so that patients can access cancer treatment while waiting for initial surgical resection. The clinical experts noted that this strategy was implemented in some jurisdictions during the COVID-19 pandemic, with the aim of mitigating the impact of operating room closures and prolonged delays in access to treatment.

The clinical experts highlighted several potential additional benefits from neoadjuvant therapy, including downstaging the tumour prior to undergoing surgery, hence facilitating the surgical procedure and reducing morbidity for patients; allowing for a better immune response from the body and T-cells lymphocytes against the cancer by having the tumour present at the time of therapy; as well as assessing whether a tumour will be sensitive to immunotherapy based on pathological response to treatment after three cycles in the neoadjuvant setting, which may inform the treatment decision for some patients to either continue with immunotherapy in the adjuvant setting, or to switch to targeted adjuvant therapy.

Table 2. Improving survival in patients with cancer should remain the primary goal of therapy.[10] however, as mortality has decreased substantially with relatively new advances in the treatment of melanoma, data on overall survival may take years to accrue and may be confounded by successful salvage therapies. Based on evidence from the SWOG S1801 study, no conclusion could be drawn with regard to overall survival in patients with resectable stage III to stage IV melanoma, mainly due to the limited number of events that had accrued. No statistical comparison between treatment groups was reported in the publication, while Kaplan-Meier curves were provided with no numerical between-group result or measure of precision. This precluded any assessment of the clinical and statistical significance of potential difference between treatments. In addition, few patients were at risk at longer follow-up time, contributing to increased uncertainty. Overall, the long-term effects on overall survival are uncertain.

Evidence from the SWOG S1801 study relied on event-free survival, which has however not been validated as a surrogate outcome for overall survival. Findings suggest that neoadjuvant-adjuvant pembrolizumab may result in a clinically meaningful benefit on event-free survival, compared with adjuvant-only pembrolizumab, in the treatment of patients with resectable stage III to stage IV melanoma. However, there is substantial uncertainty surrounding the findings. Results for the proportions of patients who experienced at least one of the prespecified events within the composite outcome favoured neoadjuvant-adjuvant pembrolizumab, compared to adjuvant-only pembrolizumab (24.7% versus 42.1% respectively; HR and 95% CI not reported; p = 0.004). Event-free survival probabilities at 2 years favoured neoadjuvant-adjuvant pembrolizumab, compared to adjuvant-only pembrolizumab, the magnitude of which was considered to be clinically meaningful by the clinical experts based on the point estimates; however, the confidence intervals also included the possibility that the difference between treatments might not constitute a clinically meaningful improvement for patients. As was the case for the outcome of overall survival, Kaplan-Meier curves were provided but with no between-group differences at time points other than 2 years. Additional sources of uncertainty included that few patients remained at risk at longer follow-up, such that the impact on event-free survival beyond 2 years is uncertain. Additionally, results for this outcome may have been subject to assessment and reporting bias for subjective events due to the knowledge of treatment assignment.

Findings suggest that a clinically meaningful proportion of patients may experience a complete pathological response after receiving three cycles of neoadjuvant pembrolizumab. Pathological response was assessed at the time of surgery in patients who received neoadjuvant-adjuvant pembrolizumab; therefore, results were uncontrolled, and no comparison between treatment groups was performed for this outcome. Based on natural disease history, it is however unlikely that patients who did not receive neoadjuvant treatment would show a response. Although pathological response may be considered a fairly objective outcome, a risk of assessment bias remains due to knowledge of the treatment received. Overall, these findings contribute to the evidence but should be interpreted with caution.

Finally, the evidence did not inform on HRQoL, as no data was reported in the publication for the outcome.

Harms Results

Harms results are outlined in The assessment of harms outcomes suffered from limited reporting in the SWOG S1801 publication. Small proportions of patients experienced grade 3-4 drug-related AEs, which were numerically higher in patients receiving neoadjuvant-adjuvant pembrolizumab than in patients who received the drug only in the adjuvant setting. The proportions of patients experiencing SAEs and WDAEs were not reported. No mortality due to AEs was reported throughout the study. It was not possible either to assess any of the harms of special interest specified in the systematic review protocol.

The clinical experts consulted by CADTH indicated that the harms profile of pembrolizumab appeared consistent with what is currently seen in clinical practice based on the available evidence, and that it was expected to be similar whether treatment is initiated before or after surgery.

Other Considerations

The clinical experts consulted by CADTH for this review noted that there are often meaningful delays in surgical procedures across Canada, which can amount to as much as six months between the time melanoma is being diagnosed, and initiation of adjuvant therapy. Therefore, neoadjuvant pembrolizumab addresses a significant unmet need for patients, as it can be initiated promptly upon diagnosis, so that patients can access cancer treatment while waiting for initial surgical resection. The clinical experts noted that this strategy was implemented in some jurisdictions during the COVID-19 pandemic, with the aim of mitigating the impact of operating room closures and prolonged delays in access to treatment.

The clinical experts highlighted several potential additional benefits from neoadjuvant therapy, including downstaging the tumour prior to undergoing surgery, hence facilitating the surgical procedure and reducing morbidity for patients; allowing for a better immune response from the body and T-cells lymphocytes against the cancer by having the tumour present at the time of therapy; as well as assessing whether a tumour will be sensitive to immunotherapy based on pathological response to treatment after three cycles in the neoadjuvant setting, which may inform the treatment decision for some patients to either continue with immunotherapy in the adjuvant setting, or to switch to targeted adjuvant therapy.

Table 2. The assessment of harms outcomes suffered from limited reporting in the SWOG S1801 publication. Small proportions of patients experienced grade 3-4 drug-related AEs, which were numerically higher in patients receiving neoadjuvant-adjuvant pembrolizumab than in patients who received the drug only in the adjuvant setting. The proportions of patients experiencing SAEs and WDAEs were not reported. No mortality due to AEs was reported throughout the study. It was not possible either to assess any of the harms of special interest specified in the systematic review protocol.

The clinical experts consulted by CADTH indicated that the harms profile of pembrolizumab appeared consistent with what is currently seen in clinical practice based on the available evidence, and that it was expected to be similar whether treatment is initiated before or after surgery.

Other Considerations

The clinical experts consulted by CADTH for this review noted that there are often meaningful delays in surgical procedures across Canada, which can amount to as much as six months between the time melanoma is being diagnosed, and initiation of adjuvant therapy. Therefore, neoadjuvant pembrolizumab addresses a significant unmet need for patients, as it can be initiated promptly upon diagnosis, so that patients can access cancer treatment while waiting for initial surgical resection. The clinical experts noted that this strategy was implemented in some jurisdictions during the COVID-19 pandemic, with the aim of mitigating the impact of operating room closures and prolonged delays in access to treatment.

The clinical experts highlighted several potential additional benefits from neoadjuvant therapy, including downstaging the tumour prior to undergoing surgery, hence facilitating the surgical procedure and reducing morbidity for patients; allowing for a better immune response from the body and T-cells lymphocytes against the cancer by having the tumour present at the time of therapy; as well as assessing whether a tumour will be sensitive to immunotherapy based on pathological response to treatment after three cycles in the neoadjuvant setting, which may inform the treatment decision for some patients to either continue with immunotherapy in the adjuvant setting, or to switch to targeted adjuvant therapy.

Table 2: Summary of Key Results from the Study included in the Systematic Review

Outcome	SWOG S1801[9]	
	Pembrolizumab – Neoadjuvant / adjuvant arm N = 154	Pembrolizumab – Adjuvant only arm N = 159
Event-Free Survival		
Number of events, n (%)	38 (24.7)	67 (42.1)
p-value (log-rank test)	p = 0.004	
Kaplan-Meier estimates of event-free survival at 2 years, % (95% CI)	72% (64 – 80)	49% (41 – 59)
Between-group difference (95% CI)	23% (11 – 35)	
Number of Patients with Individual Events, n (reported in >2 patients)		
Failure to receive surgery due to disease progression	12	0
Failure to receive adjuvant therapy due to…		
Neoadjuvant toxicity	3	0
Metastatic disease	9	16
Events throughout adjuvant therapy		
Disease recurrence	9	41
Death	1	4
Patients with Harms Outcomes		
Safety population	N = 152	N=141
≥1 Grade 3-4 drug-related AE	11 (7)	5 (4)
Patients with any SAEs, n (%)	nr	nr
Patients with any WDAEs, n (%)	nr	nr
Mortality, n (%)	0	0

AE = adverse event; CI = confidence interval; nr = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

Analyses were not adjusted for multiplicity.

Source: Patel et al. 2023[9]

Indirect Evidence

A focused literature search for ITCs of pembrolizumab relative to comparators in the treatment of melanoma was searched; however, no indirect evidence was considered to address important gaps in the evidence included in the systematic review.

Cost Information

The economic review included a comparison of the treatment costs of neoadjuvant-adjuvant pembrolizumab and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.
Public list prices for pembrolizumab and comparators are not available. Based on sponsor submitted prices from previous CADTH reviews, both neoadjuvant and adjuvant pembrolizumab are expected to have a 28-day cost of $11,773 per patient. Therefore, neo-adjuvant-adjuvant pembrolizumab is expected to be cost-neutral compared with adjuvant-only pembrolizumab. Adjuvant nivolumab is expected to have a 28-day cost of $9,387 per patient. As such, the incremental per patient cost of neoadjuvant-adjuvant pembrolizumab when compared to adjuvant nivolumab is $2,347 per 28-day cycle.

Conclusions

Evidence from the phase II, open-label SWOG S1801 study suggests that neoadjuvant-adjuvant pembrolizumab may result in a clinically meaningful benefit on event-free survival compared with adjuvant-only pembrolizumab at 2 years in the treatment of patients with resectable stage III or stage IV melanoma. However, there is substantial uncertainty surrounding the findings. Only limited statistical analyses were reported, precluding proper assessment of the between-group differences and the precision of the estimates. The risk of assessment and reporting bias, related to the knowledge of treatment assignment, contributed to the uncertainty of the findings. Only few patients remained at risk at longer time points, and no data contributed to understanding the long-term impact on event-free survival beyond 2 years. For similar reasons, no conclusion could be drawn with regard to overall survival; few events were recorded over the follow-up period, and no formal statistical analyses were undertaken. Longer follow-up would be needed to understand the impact on overall survival, as event-free survival has not been validated as a surrogate outcome in this population. However, as mortality has decreased substantially with relatively new advances in the treatment of melanoma, clinical experts indicated that surrogate outcomes such as event-free survival are commonly used to inform treatment decisions, as data on overall survival may take years to accrue. Findings suggest potential benefits from three cycles of neoadjuvant pembrolizumab on complete pathological response at the time of surgery; these findings should however be interpreted with caution as results were uncontrolled and assessors were aware of the treatment received. The evidence did not inform on HRQoL, as no data were reported in the publication. No evidence was identified to inform a comparison to adjuvant nivolumab. Findings were obtained in a population consisting mainly of patients with stage IIIB and IIIC disease; this should be considered when generalizing the findings to real-life patients. No indirect evidence was considered to address important gaps in the evidence included in the systematic review. The assessment of harms outcomes suffered from limited reporting in the publication. Based on the available evidence, the clinical experts consulted by CADTH indicated that the harms profile of pembrolizumab appeared consistent with what is currently seen in clinical practice. Toxicity was expected to be similar whether pembrolizumab is initiated before or after surgery, especially as neoadjuvant-adjuvant therapy would target the same patient population currently undergoing adjuvant therapy.

The clinical experts highlighted that neoadjuvant pembrolizumab addresses a significant unmet need for patients who have limited access to treatments due to the meaningful delays in surgical procedures across Canada. Neoadjuvant pembrolizumab can be initiated promptly upon diagnosis, so that patients can access cancer treatment while waiting for initial surgical resection. The clinical experts highlighted additional potential benefits from neoadjuvant therapy, including downstaging the tumour prior to undergoing surgery to facilitate the procedure and reduce morbidity for patients; allowing for a better immune response from T-cells lymphocytes against the cancer by having the tumour present at the time of therapy; and assessing whether a tumour will be sensitive to immunotherapy based on pathological response to treatment, which may inform subsequent adjuvant treatment decisions.

Results of the cost-comparison of treatment costs demonstrate that, over a 28-day cycle, neoadjuvant-adjuvant pembrolizumab is cost neutral compared with adjuvant-only pembrolizumab and $2,347 more costly per patient than adjuvant nivolumab. As such, the reimbursement of neoadjuvant-adjuvant pembrolizumab for the treatment of adult patients with resectable Stage III or IV melanoma is expected to be cost neutral compared with adjuvant-only pembrolizumab and increase overall treatment costs compared with adjuvant nivolumab.

No literature was identified comparing neoadjuvant-adjuvant pembrolizumab with nivolumab, therefore the comparative efficacy of these treatments is unknown. Based on the clinical review conclusions, neoadjuvant-adjuvant pembrolizumab may provide a clinically meaningful benefit on event-free survival and similar safety profile compared to adjuvant-only pembrolizumab, however, these findings are uncertain. Other costs such as administration costs were not considered as part of the cost comparison but neoadjuvant-adjuvant pembrolizumab administration is expected to be either cost neutral (compared with adjuvant-only pembrolizumab) or cost-saving (compared with adjuvant nivolumab). As such, neoadjuvant-adjuvant pembrolizumab is associated with a potential, though uncertain, incremental clinical benefit and equal treatment costs compared with adjuvant-only pembrolizumab – a cost effective treatment option.

Introduction

Disease Background

Malignant melanoma is a relatively uncommon but aggressive skin cancer, with an projected incidence in Canada of 9,700 new cases in 2023, and approximately 1,250 related deaths.[1] Melanoma is regarded as one of the most commonly diagnosed cancer in younger individuals, creating a disproportionate societal impact.[2,3] The incidence of melanoma in Canada continues to rise despite the efforts of patient advocacy groups and public awareness campaigns to educate the public regarding risk factor modification, specifically avoidance of ultraviolet radiation.[3]

Melanoma diagnosed in the early stage disease are cured with surgery alone; however, a proportion of patients will present with locally advanced cancers which, while also amenable to surgery, portend a high risk of relapse and death.[4] Based on the American Joint Committee on Cancer (AJCC) 8th edition classification, the ten-year melanoma survival probabilities are as follows: 88% for patients with stage IIIA disease, 77% for patients with stage IIIB disease, 60% for patients with stage IIIC disease, and 24% for patients with stage IIID disease.[5] For patients with metastatic melanoma (stage IV disease), effective systemic treatment strategies prior to the era of targeted therapy and immunotherapy did not exist. Among these are the immune checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab.

Standards of Therapy

Treatment goals

The goals of therapy for patients presenting with melanoma are to extend survival, delay disease recurrences and disease progression, as well as improve quality of life.

Current standards of therapy

Melanoma is typically detected upon physical examination, coupled with an ultrasound and biopsy to confirm the diagnosis. The current standard of care for resectable stage III and stage IV melanoma is initial surgical resection; when complete resection is successful, adjuvant therapy is recommended for patients who are considered at high risk for recurrence, with either immunotherapy or targeted therapy in stage III disease, and with immunotherapy in stage IV disease.[6]

The clinical experts consulted by CADTH indicated that neoadjuvant therapy would target the same patient population currently undergoing adjuvant therapy, including patients with clinically detectable or radiologically evident disease, as well as those with macroscopic disease that is potentially resectable at the time of initial assessment. The clinical experts noted that no companion test would be needed.

Unmet needs

The clinical experts consulted by CADTH for this review noted that there is currently no neoadjuvant therapy available for adult patients with resectable stage III or stage IV melanoma. However, the experts highlighted several potential benefits from neoadjuvant therapy, including the following:

- Neoadjuvant treatment has the potential to downstage the tumour prior to undergoing surgery, hence facilitating the surgical procedure and reducing morbidity for patients.
- The rationale behind neoadjuvant treatment acknowledges that having the tumour present at the time of therapy may allow for a better immune response from the body and T-cells against the cancer. This is compared to the immune response that is expected to be produced when treatment is administered only after the surgery, once the tumour has been already completely removed and the immune system is also being solicited to recover from the surgical procedure.
- There are currently no means to assess whether a tumour will be sensitive to immunotherapy (i.e. treatment with ipilimumab, nivolumab or pembrolizumab) once the tumour is resected. This is particularly challenging in patients whose

tumour exhibits a BRAF mutation, as these patients may receive treatment with either immunotherapy or targeted therapy. Therefore, assessing pathological response to treatment after three cycles in the neoadjuvant setting may inform the treatment decision to either continue with immunotherapy in the adjuvant setting, or to switch to targeted adjuvant therapy.

- In the context of the Canadian healthcare system, there can be meaningful delays in surgical procedures, which in turn, result in delays before patients can receive adjuvant treatment. The clinical experts noted that in some jurisdictions, it can take up to six months between a melanoma diagnosis and initiation of adjuvant therapy. As a result, patients currently remain untreated while waiting to access treatment, during which time the cancer keeps progressing. Therefore, initiating treatment promptly before surgery offers a practical and cost-neutral solution to address this inequity issue, while potentially providing meaningful prognostic insights at the time of surgery. The clinical experts noted that such a strategy was implemented in some jurisdictions during the COVID-19 pandemic, with the aim of mitigating the impact of operating room closures and prolonged delays in access to treatment.

Drug

Pembrolizumab is an antibody with high affinity against PD-1, an immune-checkpoint receptor which role is to limit the activity of T-cell lymphocytes.[7] By blocking the PD-1 pathway, pembrolizumab reactivates these T-cell lymphocytes, hence allowing them to specifically destroy the tumour cells.[7]

Pembrolizumab has a Health Canada-approved indication for the adjuvant treatment of adult patients with stage III melanoma with lymph node involvement who have undergone complete resection.[7] CADTH previously reviewed pembrolizumab in this indication in 2019, where the pCODR Expert Review Committee (pERC) recommended funding pembrolizumab for the adjuvant treatment of patients with stage IIIA to IIID (AJCC staging system, 8th edition) cutaneous melanoma, with conditions.[8] However, presence of regional lymph node with micrometastases after sentinel lymph node biopsy alone is allowed.[8]

Pembrolizumab also holds three additional Health Canada-approved indications for the treatment of melanoma, in different patient populations.[7]

Guidance on the optimal sequencing of treatments for melanoma is provided in the CADTH Provisional funding algorithm.[11]

The Provincial Advisory Group (PAG) and clinical experts consulted by CADTH for this review indicated that there is an interest in clinical practice to use pembrolizumab for the neoadjuvant-adjuvant treatment of adult patients with stage III or stage IV melanoma. The PAG requested that CADTH review pembrolizumab for this patient population and provide a reimbursement recommendation.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The input was used to inform the list of outcomes and interpretation of the findings, in order to reflect patient values and to inform on potential challenges surrounding the use of the drug under review in clinical practice.

Two patient advocacy groups, Save Your Skin Foundation and Melanoma Canada, submitted the patient input for this review. Save Your Skin Foundation (SYSF), a national patient-led not-for-profit group, focuses on educating and advocating for patients with non-melanoma skin cancers, melanoma, and ocular melanoma while providing comprehensive support for both patients and caregivers, throughout the entire continuum of care. Melanoma Canada (formerly Melanoma Network of Canada) offers resources, support, prevention initiatives, and advocacy specifically for melanoma and skin cancer patients in Canada, striving to ensure accessible and timely diagnosis and treatment options for all.

SYSF's and Melanoma Canada's submission was based on response to an online survey. SYSF's received response from 36 individuals, out of which 29 were diagnosed with Stage III (11) Stage IV (18) melanoma; and were from British Columbia, Alberta, Manitoba, Ontario, Nova Scotia, Saskatchewan, USA, and France. Melanoma Canada received 109 responses, out of which 46

were diagnosed with Stage III (19) Stage IV (27) melanoma; and majority of the responses were from British Columbia, Alberta, Manitoba, Ontario, and Quebec.

Patients identified pain, lymphedema, fatigue, disrupted sleep, blurry or poor vision, issues concentrating, as well as decline in mental health including anxiety, fear and depression, suicidal thoughts, financial strain as the common impacts of a diagnosis of melanoma that negatively affect the quality of life for patients and their families. The enduring impact of scarring and disfigurement after surgery on patients' emotional and mental well-being was highlighted, which according to them is a constant, unpleasant, and visible reminders of their cancer journey.

17 respondents to SYSF's survey, and 27 respondents to Melanoma Canda's survey confirmed receiving pembrolizumab. In the SYSF survey, 6 had received pembrolizumab in neoadjuvant settings and three out the six reported receiving it at Stage III and three out the six reported receiving when their cancer was metastatic. The six patients commonly reported the following adverse events associated with pembrolizumab in neoadjuvant therapy: fatigue, cognitive impairment, skin rash, gastrointestinal issues, breathing problems, headaches, and arthritis flare-up. Patients from both surveys noted they had experience with the one or more of the following alternate treatment options; radiation, surgery or incisions, trametinib, dabrafenib, nivolumab, ipilimumab, encorafenib, binimetinib, vemurafenib, relatlimab, aldesleukin, proleukin, aldesleukin, interferon alfa-2b, and dacarbazine.

Patients and caregivers advocated for the incorporation of neoadjuvant pembrolizumab in their response to the two surveys. The patient groups highlighted that it allows for more timely initiation of treatment, especially considering the often-extended waiting periods for surgery in Canada. Patients who responded to the survey believed that starting pembrolizumab early can provide a sense of proactive intervention, potentially mitigating the risk of metastasis during the waiting period, as well as alleviating their anxiety and depression. Further, they also noted that it could potentially eliminate recurrence or eliminate cancer altogether and may result in less extensive surgery with minimal or non-existing scarring. These prospects were associated with faster recovery, overall positive impact on mental well-being, and a positive impact on the cost to our healthcare system.

Clinician Input

Input from clinical experts consulted by CADTH

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by two clinical specialists with expertise in the diagnosis and management of melanoma.

Unmet Needs

Both clinical experts noted that there is currently no neoadjuvant therapy for adult patients with resectable Stage III or Stage IV melanoma. The current standard of care for resectable Stage III/IV melanoma is initial surgical resection, and if an R0 resection is successful then adjuvant therapy with either immunotherapy or targeted therapy (with BRAF/MEK inhibitors) for stage III disease, or immunotherapy for resection of stage IV disease. The current Cancer Care Ontario (CCO) guideline supports adjuvant therapy treatment in stage II, III and resected stage IV. Current, adjuvant treatments improve relapse free survival as well as distant metastatic free survival. The treatment goals with neoadjuvant pembrolizumab, as per the clinical experts, are also to prolong life and delay disease recurrence. The clinical experts also noted that studies investigating adjuvant therapies are not yet mature enough to assess overall survival.

One clinical expert noted that there are no means to assess whether a resected tumor is sensitive to immunotherapy. This is particularly challenging in the BRAF mutant population it is always a challenge to decide between immunotherapy versus targeted therapy. If immunotherapy was assessed in the neoadjuvant setting for 3 cycles, pathological analysis of the resected specimen could determine if there was a response to immunotherapy. If not, treatment could be switched to targeted adjuvant therapy.

Place in therapy

Both clinical experts indicated that neoadjuvant administration of pembrolizumab would target the same patient population currently undergoing adjuvant therapy. They noted that incorporating neoadjuvant pembrolizumab alongside surgery and adjuvant immunotherapy, signifies a notable shift in the current treatment approach. One clinical expert further indicated that this treatment approach acknowledges that having the tumour and the T-cells present at the time of therapy allows for a better cancer immune response.

One clinical expert noted that in the context of the Canadian healthcare system's delays in surgical procedures, initiating neo-adjuvant pembrolizumab offers a practical solution. Commencing treatment promptly allows for surgery approximately nine weeks later, with the standard post-surgery regimen comprising an additional 15 cycles of treatment. This approach remains cost-neutral while providing crucial prognostic insights at the time of surgery. The clinical expert noted that such a strategy was implemented in Alberta during the COVID-19 pandemic, mitigating the impact of operating theater closures and prolonged delays.

Patient population

Clinical experts suggested that neoadjuvant treatment would be used in patients with clinically detectable disease or evident by radiology as well as those with macroscopic disease that is potentially resectable at the time of initial assessment. As such, these would be the same patients that are currently being treated with adjuvant therapy, who would be given three cycles of treatment perioperatively, and 15 cycles post-operatively (instead of giving all 18 cycles post-operatively). The clinical experts noted that no companion test is needed.

The clinical experts note that usually a physical examination detects these patients, and an ultrasound with biopsy is used to confirm the diagnosis. These patients are then subjected to disease staging to exclude metastatic disease. The clinical experts indicated that at the present time there is no diagnostic test to determine which patient will or will not respond to treatment. The clinical experts noted that tumor necrosis, T cell infiltration, regression and melanophages indicate immune response, at the time of pathological assessment.

Assessing response to treatment

The clinical experts advised that relapse or disease-free survival, distant metastasis free survival, event free survival and overall survival are meaningful endpoints. However, they also noted that overall survival may take years to have enough events to occur and may be blunted by successful salvage therapies. The experts noted that immunotherapy is typically well tolerated with only 14% of patients having Grade III/IV toxicity, and only 5% having to discontinue therapy.

Discontinuing treatment

The clinical experts noted that disease progression, disease recurrence, toxicity or patient request would be the reason to discontinue treatment. The clinical experts suggested that most toxicities are treatable and reversible but life-threatening toxicities such as myocarditis, pneumonitis or severe neurologic toxicities are examples where patients should not be re-challenged.

Prescribing conditions

Clinical experts noted that patients with stage IIIA to stage IV resected disease, with all melanomas, except uveal melanoma would be considered as candidates for treatment with neoadjuvant pembrolizumab. The clinical experts also noted that age is not relevant as long as patient is in ECOG 0 or 1. Further, the clinical exerts also suggested that no genetics mutations are used to select patients with neoadjuvant pembrolizumab. However, they indicated that those with BRAF mutation appear to have better outcomes. The clinical experts noted that all patients must have an R0 resection to be eligible for adjuvant immunotherapy.

Additional considerations

The clinical experts mentioned the hypothesis that neoadjuvant therapy may be able to activate more antitumor T cells and improve clinical outcomes than administration of the same amount of drug delivered postoperatively due to the tumour and T cells being intact at the time of administration of immunotherapy (that is, prior to surgery). They suggested that the pathological response rates are higher than those seen in the metastatic setting, with this treatment approach. As such, citing a study ,[12] the clinical experts suggested that neoadjuvant treatment with pembrolizumab could downstage tumors, resulting in less extensive surgery, or no surgery at all; thereby causing less morbidity for patients. The experts also suggested that neoadjuvant pembrolizumab could be superior to adjuvant

pembrolizumab in patients with palpable nodal disease or on radiology. However, they have advised that the result of these studies needs to be validated with a larger study.

Clinician group input

This section was prepared by CADTH staff based on the input provided by patient groups. The full clinician group input is included in the Stakeholder Input section at the end of this report.

Clinician input was submitted by one clinician group: Ontario Health, Cancer Care Ontario (OH-CCO) Drug Advisory Committee. The committee provides timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Unmet Needs

The clinician group noted that there are no approved or funded neoadjuvant-adjuvant treatments in the setting of clinically detected Stage IIIB/C/D or Stage IV resectable melanoma. They specified that the only treatment options for stage III melanoma patients are anti-PD1 medications such as pembrolizumab or nivolumab, and targeted therapy for BRAF mutated melanoma, after surgical treatment. If recommended, this would be the first neoadjuvant drug used in this setting.

Place in therapy

The clinician group noted that neoadjuvant-adjuvant pembrolizumab will be used for curative intent, and with the intent to prolong event-free survival. The clinician group suggested that implementing neoadjuvant to adjuvant pembrolizumab has the potential to reduce the occurrence of treatment failure and the development of non-resectable metastatic disease.

The clinician group advised that the same number of total doses would be used in the neoadjuvant-adjuvant setting and in the post-surgical adjuvant setting, that is, the total number of pembrolizumab cycles (18 cycles) remains consistent in both scenarios. However, 3 cycles are given prior to surgery and the remaining cycles are administered post-surgery in the neoadjuvant-adjuvant protocol, as opposed to all 18 cycles being post-surgery in the adjuvant setting.

Patient population

As per the clinician, patients with resectable stage IIIB, IIIC and IIID, and resectable stage IV disease would be best suited for this treatment approach. They also specified that eligible patients should have clinical or radiologic detection of lymph node involvement or resectable Stage IV disease.

Assessing response to treatment

The clinician noted that lack of disease recurrence, improved relapse-free survival, improved overall survival and cure would be the outcomes to determine response. The clinician group advised that treatment response should be assessed as per the OH-CCO guideline "Surveillance of patients with Stage I, II, III or resectable IV melanoma who were treated with curative intent."[13] In addition to this, the clinician group also suggested conducting imaging before initiating immunotherapy then repeating after completing 3 cycles of immunotherapy. As per the clinician group, this approach allows clinicians to assess when a patient is suitable for surgery.

Discontinuing treatment

The presence of toxicity or lack of clinical benefit were noted as reasons to discontinue treatment, by the clinician group.

Prescribing conditions

The clinician group suggested that treatment should be provided in an outpatient setting with multidisciplinary care including a medical oncologist and surgical oncologist.

The clinician group also advised that a dedicated dermatopathology assessment of surgical specimens when the patient has been treated with neoadjuvant therapy would be necessary for best clinical care.

Additional considerations

The clinician group stated that the use of neoadjuvant pembrolizumab for resectable stage 3B to stage 4 melanoma is recommended in the updated August 2023 ASCO guidelines[4] and NCCN guidelines.[14] They also advised that in May 2023, the Pharmaceutical Benefits Advisory Committee Australia recommended to fund neoadjuvant pembrolizumab in resectable stage IIIB-D melanoma.[15]

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's non-sponsored review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in **Error! Reference source not found.**.

The drug plans noted that the total number of doses is 18 (3 doses neo-adjuvant, followed by surgery, and then 15 doses as adujvant therapy), up to 1 year or until disease progression or unacceptable toxicity. Given that pembrolizumab in adjuvant setting is also reimbursed for 18 doses, the neoadjuvant-adjuvant treatment approach is cost -neutral. The drug plan also noted that pembrolizumab is publicly funded for adjuvant therapy with successful price negotiation.

With respect to comparators, the drug plans noted that nivolumab which is publicly funded for adjuvant melanoma, and BRAF targeted therapies such as dabrafenib/trametinib were not comparators in the adjuvant therapy arm of the pivotal phase II trial.[9] Further, they noted that the trial was conducted in Stage IIIB to IIID melanoma or oligometastatic resectable stage IV (M1a, M1b and M1c) melanoma. Highlighting the inclusion and exclusion criteria of the trial, the drug plans suggested that the exclusion of patients who received previous immunotherapy from the trial, should be factored when the funding algorithm is being developed.

Industry Input

No industry input was received by CADTH.

Clinical Evidence

The clinical evidence included in the review of pembrolizumab is presented in three sections. The first section, the Systematic Review, includes studies that were selected according to an a priori protocol. The second section includes indirect evidence selected from the literature that met the selection criteria specified in the review, and the third section includes long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review; however, no indirect evidence, long-term extension studies, or additional relevant studies were considered relevant for inclusion in the review.

Systematic Review

Objectives

To perform a systematic review of the beneficial and harmful effects of pembrolizumab for the neoadjuvant plus adjuvant treatment of adult patients with resectable Stage III or Stage IV melanoma.

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 33. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 33: Inclusion criteria for the systematic review

Patient Population	Adult patients with resectable Stage III or IV melanoma Subgroups: • Stage (III or IV)
Intervention	**Neoadjuvant plus adjuvant pembrolizumab, as follows:** **Neoadjuvant pembrolizumab** 200 mg every 3 weeks, or 400 mg every 6 weeks, administered as IV infusion, until complete resection (i.e., approximately 3 doses of pembrolizumab before surgery); **followed by** **Adjuvant pembrolizumab** 200 mg every 3 weeks, or 400 mg every 6 weeks, administered as IV infusion, until disease progression or unacceptable toxicity, for up to 1 year following complete resection (i.e., approximately 15 doses of pembrolizumab after surgery).
Comparators	**Adjuvant pembrolizumab** 200 mg every 3 weeks, or 400 mg every 6 weeks, administered as IV infusion, until disease progression or unacceptable toxicity, for up to 1 year, following complete resection (i.e., approximately 18 doses of pembrolizumab after surgery). **Adjuvant nivolumab** 3 mg/kg or 240 mg every 2 weeks, or 480 mg every 4 weeks, administered as IV infusion, as long as clinical benefit is observed and treatment is tolerated, for up to 1 year following complete resection.
Outcomes	***Efficacy outcomes:*** Overall survival Relapse-free survival Event-free survival Distant metastasis-free survival Pathological response HRQoL ***Harms outcomes:*** AEs, SAEs, WDAEs, Mortality Harms of special interest: • Immune-mediated adverse reactions (e.g., immune-mediated pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, severe skin reactions, endocrinopathies [i.e., adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, and thyroid disorders] and infusion-related reactions).
Study Design	Published and unpublished Phase II, III and IV RCTs

AE=adverse events; HRQoL=quality of life; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawal due to adverse events.

Note: Pembrolizumab has a Health Canada indication for the adjuvant treatment of adult patients with Stage III melanoma with lymph node involvement who have undergone complete resection.[7]

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[1]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in Endnote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were Keytruda (pembrolizumab) and melanoma. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

CADTH-developed search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on December 14, 2023. Regular alerts updated the search until the meeting of the CADTH Formulary Management Expert Committee (FMEC) on May 10, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included, and differences were resolved through discussion.

Protocol Selected Studies

Characteristics of Included Studies

The flow diagram is presented in Appendix 2, **Error! Reference source not found.**. A list of excluded studies is presented in Appendix 3.

Of 674 records identified by the search, one published phase II, open-label RCT was identified from the literature for inclusion in the systematic review: the Southwest Oncology Group (SWOG) Cancer Research Network S1801 trial.[9] The included study is summarized in Table 4.

Table 4: Details of Included Study

Detail	SWOG S1801[9]
Design	
Study Design	Phase II, open-label RCT
Locations	Multicentre, 90 study sites in the US
Patient enrolment dates	February 2019 to May 2022
Randomized (N)	N = 313; randomized in a 1:1 ratio.
Population	
Inclusion Criteria	• Patients aged ≥ 18 years. • Histologically confirmed melanoma (cutaneous, acral or mucosal). • Clinically detectable and measurable disease according to RECIST 1.1. • Stage IIIB-D melanoma, or oligometastatic resectable Stage IV melanoma, according to the Cancer Staging Manual of the American Joint committee on Cancer, 8th edition. • Initial presentation or first detected nodal, satellite, in-transit or distant metastases.
Exclusion Criteria	• Prior immunotherapy for melanoma. • Active autoimmune disease despite systemic treatment within the prior 2 years. • Uveal melanoma. • Local recurrences in the scar or surgical bed of primary melanoma as sole site of disease.

Detail	SWOG S1801[9]
	• History of brain metastasis.
Drugs	
Intervention	Pembrolizumab, 200 mg every 3 weeks, administered as an IV infusion, as follows: 3 doses before surgery, followed by an additional 15 doses after the surgery.
Comparator(s)	Pembrolizumab, 200 mg every 3 weeks, administered as an IV infusion, for 18 doses after surgery.
Concomitant treatment	Radiotherapy was allowed after the surgery, but before pembrolizumab was started or re-started.
Follow-up	Median duration of follow-up of 14.7 months in both groups.
Outcomes	
Primary end point	Event-free survival in the ITT population. Events were defined as: - disease progression or toxic effects precluding surgery; - inability to resect all gross disease; - disease progression, surgical complications, or toxic effects of treatment precluding the initiation of adjuvant therapy within 84 days after surgery; - recurrence of melanoma after surgery; - death from any cause.
Secondary and exploratory end points	Overall survival Length of disease control Length of locoregional control in the surgical site(s) Pathologic response rate per RECIST 1.1 Proportion of patients receiving planned surgery Safety
Notes	
Publications	• Patel et al. 2023[9]
Funding sources	Funded by: National Cancer Institute (NCI) and Merck. Conducted by: The SWOG Cancer Research Network.

AEs = adverse events; CI = confidence interval; ITT = intention-to-treat; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; SWOG = Southwest Oncology Group; US = United States.

Source: Patel et al. 2023[9]

Study Design

The SWOG S1801 study (n = 313)[9] was performed in the US with funding from the National Cancer Institute and Merck. Patients were randomized in a 1:1 ratio to receive neoadjuvant-adjuvant pembrolizumab, or pembrolizumab given only as adjuvant treatment, in patients with resectable stage III or stage IV melanoma.[9] Treatment allocation was performed centrally using a dynamic balancing method for stratification according to the following allocation factors:

- stage (IIIB, IIIC, or IIID or IV); and
- lactate dehydrogenase level (assessed as within the normal range, or above).

Patients and investigators were not blinded to treatment assignment; the rationale was not discussed in the published article.

Inclusion and Exclusion Criteria

Patients were eligible for the SWOG S1801 study if they were at least 18 years of age and had histologically confirmed, stage IIIB-D or oligometastatic resectable stage IV melanoma, with clinically detectable and measurable disease according to RECIST 1.1. In order to be considered clinically detectable in the study, the disease had to be apparent and measurable either upon physical exam, radiographic imaging, or magnetic resonance imaging.[9]

Patients could enter the study upon initial disease presentation, or upon first detected nodal, satellite, in-transit or distant metastases, even if these were in multiple regional nodal basins.[9] However, patients were not eligible for the study if a local recurrence at the primary site was identified as the sole disease location. In the case of metastatic disease, nodal metastases had to be resectable, with a minimal short-axis diameter of 1.5 cm; for other types of metastases, the minimal size was 1 cm.[9] The type and extent of the prespecified surgery needed to be documented and was intended to be carried out in all patients, even if a response to neoadjuvant therapy was observed. Patients with stable human immunodeficiency virus (HIV) infection, regardless of antiviral treatment status, were allowed to participate in the study.

Patients were not eligible for the study if they had uveal melanoma, or if they received prior immunotherapy for the treatment of melanoma (receipt of other prior adjuvant treatments was allowed). Additional exclusion criteria included autoimmune disease that remained active despite systemic treatment within the prior 2 years, as well as history of brain metastasis.

Interventions

The intervention evaluated in the SWOG S1801 study was neoadjuvant-adjuvant pembrolizumab, 200 mg every 3 weeks, administered as a 30-minute IV infusion, as follows: 3 doses before surgery, followed by an additional 15 doses after the surgery. The comparator was pembrolizumab, given only as adjuvant treatment, i.e., 200 mg every 3 weeks, administered as an IV infusion, for 18 doses after the surgery.

For patients in the neoadjuvant-adjuvant arm, 3 doses of pre-operative pembrolizumab were intended. Administration of fewer than 3 doses were allowed for reason of progressive disease requiring surgery or toxicity. It was expected that surgery be performed within 5 weeks from the last neoadjuvant pembrolizumab administration. For patients in the adjuvant arm, surgery was intended to occur within 17 days after randomization. Regardless of treatment allocation, surgical resection consisted of a lymphadenectomy or resection of in-transit or distant metastasis with or without wide local excision. Radiotherapy was allowed after the surgery, but before adjuvant pembrolizumab was started. The timing of initiation or re-initiation of pembrolizumab treatment after surgery was at the discretion of the investigator, but was intended to not exceed 84 days.

Pembrolizumab dosing interruptions were allowed in the case of AEs or logistical reasons. Patients were intended to resume study therapy within 3 weeks of the interruption. Discontinuation criteria included the following:

- disease progression per RECIST 1.1 that precludes the planned surgery;
- disease relapse post-surgery;
- treatment delay longer than 84 days post-surgery;
- unacceptable toxicity;
- pregnancy;
- patient or investigator decision.

Prohibited or cautionary concomitant medications included any non-study anti-cancer agent (investigational or non-investigational), live vaccines, and glucocorticoids for any purpose other than to modulate immune-related AEs. Physiologic doses of corticosteroids (i.e., 10 mg prednisone) were allowed; higher doses required approval of the Study Chair. Appropriate supportive care measures for immune-related AEs that were deemed by the investigator to be medically necessary were allowed.

There were no specific recommendations for subsequent-line treatments in SWOG S1801.

Outcomes

A list of efficacy endpoints identified in the CADTH review protocol that were assessed in SWOG S1801 are provided in Table 5.

Table 5: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome Measure	SWOG S1801[9]
Overall survival	Secondary
Relapse-free survival	NR
Event-free survival	Primary
Distant metastasis free survival	NR
Pathological response	Secondary*
HRQoL	NR
AEs	Secondary
SAEs	NR
WDAEs	NR
Mortality due to AEs	Secondary

AE = adverse event; HRQoL = health-related quality of life; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

* Assessed only in the neoadjuvant-adjuvant group.

Source: Patel et al. 2023[9]

Event-free survival was the primary efficacy outcome in the SWOG S1801 study. Event-free survival was defined in the trial as time from randomization to the first event, which included any of the following:

- disease progression or toxic effects precluding surgery;
- inability to resect all gross disease;
- disease progression, surgical complications, or toxic effects of treatment precluding the initiation of adjuvant therapy within 84 days after surgery;
- recurrence of melanoma after surgery;
- death from any cause.

Although event-free survival has not been validated as a surrogate outcome for overall survival in patients with melanoma, the clinical experts consulted by CADTH emphasized that event-free survival may be considered a relevant outcome, and it is recommended as a key survival outcome by the International Neoadjuvant Melanoma Consortium[16]; it is akin to relapse-free survival but incorporates progression and toxic events occurring before the planned surgery (i.e., in the neoadjuvant phase).[16]

In patients receiving neoadjuvant pembrolizumab, response to treatment prior to surgery was assessed using RECIST, version 1.1.[9] Declining surgery due to complete response was not counted as an event. Disease progression or recurrence after surgery was to be confirmed with biopsy when possible, but could also be assessed by the investigator using imaging or upon physical examination, which occurred every 3 months for 2 years, and every 6 months afterwards until year 5.[9] Although there was no prespecified assessment afterwards, patients were followed-up for event-free survival and overall survival status for up to 10 years.[9]

Relevant secondary efficacy outcomes measured in the study included overall survival and pathological response rates; however, no statistical comparison for these outcomes was reported in the publication. Overall survival was defined as time from randomization to death from any cause. Response was assessed via imaging among the neoadjuvant-adjuvant group after completion of neoadjuvant therapy. Responses were classified as complete or partial according to RECIST 1.1.

Safety outcomes included adverse events (AEs) and mortality due to AEs, which were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[9]

Statistical analysis

The protocol-specified sample size calculation estimated that having 104 events would enable the study to achieve 81% power, at a one-sided significance level of 15%, to detect a hazard ratio (HR) of 0.64 using a stratified log-rank test, in order to assess the difference between neoadjuvant–adjuvant pembrolizumab and adjuvant-only pembrolizumab in event-free survival.[9]

The study was designed to test for superiority of neoadjuvant–adjuvant pembrolizumab relative to adjuvant-only pembrolizumab. Efficacy analyses were performed in the intention-to-treat (ITT) population and included all randomized patients. For safety analyses, the safety population consisted of all patients who received at least one dose of study treatment.

The primary outcome was event-free survival, which was estimated with the use of a stratified log-rank test, adjusted for stratification factors used at randomization, at a one-sided significance level of 15%. Results were expressed using a hazard ratio (HR) with confidence interval using a Cox regression modelThe Kaplan–Meier technique was used to generate survival curves. Patients who did not experience an event were censored at the time of their latest study follow-up.[9] There was a difference between groups in terms of when adjuvant pembrolizumab was initiated after enrollment into the study. In order to account for this, events occurring prior to initiation of adjuvant treatment were assigned the event time of day 84.[9]

Secondary outcomes such as overall survival were intended to be analyzed using methods similar to the primary analysis of event-free survival. Specifically, a stratified log-rank test was planned and a Cox regression model was intended to be used to calculate between-group HRs. However, no statistical comparisons were reported in the publication, owing to few events at the time of the analysis. Kaplan-Meier curves of overall survival were generated for each treatment group.

No analyses were performed for response rates; instead, these were reported descriptively as frequencies. Similarly, the number and proportion of patients experiencing grade 3 and grade 4 AEs were reported.

Analyses were not adjusted for multiplicity. No information was reported in the publications as to how missing data were handled.

Critical Appraisal

Internal validity

Study Design, Intervention, and Comparators

SWOG S1801 was a phase II trial designed to evaluate the superiority of neoadjuvant–adjuvant pembrolizumab over adjuvant-only pembrolizumab for the treatment of resectable stage III or stage IV melanoma. Phase II trials typically include fewer patients and aim to provide preliminary evidence about the efficacy and harms of a drug, later to be confirmed in a larger phase III trial.[10,17]

The trial was randomized but was not blinded. By having an OL design, there is a potential for bias due to deviations from the intended interventions; in addition, the study was susceptible to assessment and reporting biases, as knowledge of treatment assignment could influence investigators' assessment of efficacy (which included subjective components), such as tumour response outcomes, and patient-reported outcomes, such as subjective AEs. Ideally, anticancer drug trials should be blinded, when possible, with centralized review of tumour-based outcomes;[27] in SWOG S1801, no central assessment was reported. It is not possible to determine the impact or direction of a potential bias that knowledge of treatment assignment may have had on the outcomes assessed.

There was no recommendation for subsequent-line treatments upon disease progression; therefore, it is unknown whether these subsequent treatments were balanced between groups, and whether they were representative of Canadian clinical practice. This could confound the assessment of overall survival, as the estimated effect of neoadjuvant–adjuvant pembrolizumab relative to adjuvant-only pembrolizumab on overall survival is reflective of the effect of the intervention drugs, followed by subsequent treatments.

Selection, Allocation, and Disposition of Patients

Patients were centrally randomized at a ratio of 1:1 using appropriate methods to achieve prognostic balance and conceal allocation until group assignment. The randomization process was stratified by disease stage and lactate dehydrogenase level. Reported

baseline demographic and disease characteristics were equally balanced between treatment groups, suggesting that known confounding factors are not likely to have a significant impact on the results.

The open-label design introduces the potential for bias due to deviations from the intended interventions. It is notable that 2 (1.3%) of patients in the neoadjuvant-adjuvant group and 7 (4.4%) of patients in the adjuvant group withdrew consent prior to receiving treatment. In addition, high and imbalanced proportions of patients discontinued treatment (59 / 154 [38%] patients in the neoadjuvant–adjuvant group and 73 / 159 [46%] patients in the adjuvant-only group, respectively); however, reasons for discontinuations were not reported. There were differences between groups in terms of treatment discontinuations, especially when timing is being considered. Several patients receiving neoadjuvant-adjuvant pembrolizumab discontinued before receiving surgery; according to the clinical experts, this may be representative of the fact that in clinical practice, it has been observed that a small proportion of patients do not respond to treatment. Numerically less patients who received neoadjuvant–adjuvant pembrolizumab discontinued during the adjuvant treatment phase compared with patients who received adjuvant-only pembrolizumab. According to the clinical experts, these may be correlated with the results of individual events contributing to the primary outcome analysis of event-free survival, where numerically fewer patients experienced treatment recurrence with neoadjuvant–adjuvant pembrolizumab than with adjuvant-only pembrolizumab. There is however a concern as to the potential impact on the results of these high treatment discontinuation rates, given that reasons were not described in the trial. The magnitude and direction of bias remain uncertain.

Outcome Measures

The primary efficacy outcome in SWOG S1801 was event-free survival, which has not been validated as a surrogate outcome for overall survival, the preferred and most reliable endpoint in oncology trials,[10] in patients with melanoma. However, the clinical experts consulted by CADTH emphasized that event-free survival may be considered a relevant outcome, especially for the comparison at hand. When considering moving initiation of pembrolizumab before surgery, the clinical experts noted that it is particularly important to assess any potential negative impact of this change. In addition to disease progression, event-free survival also included serious toxic effects, the incapacity to perform surgery or to initiate adjuvant treatment, and surgical complications, which allows for an exhaustive assessment according to the clinical experts. As mortality has decreased substantially with relatively new advances in the treatment of melanoma, most clinical trials do not have sufficient power to show a difference between groups in overall survival, the data for which may take years to accrue, and may be confounded by successful salvage therapies.

Patients were intended to be followed for event-free survival and overall survival status for up to 10 years, however the follow-up reported in the trial was much shorter.[9] There were no specific recommendations in SWOG S1801 for use of subsequent-line treatments. Therapies received by patients upon disease progression were not reported in the publication, precluding assessment of whether these were balanced between treatment groups. As the study was performed in the United States, the clinical experts consulted by CADTH indicated that patients may have had access to subsequent treatments which are considered effective but are unavailable in Canada at the time of this review.

Statistical Analysis

In SWOG S1801 the total number of events was aligned with the initial power calculations, indicating sufficient power for the analysis of the primary outcome if the assumptions underlying the sample size calculation were met. Though analyses were not adjusted for multiplicity, only event-free survival was formally tested; therefore, the possibility of an increased risk of type 1 error (false positive conclusions) for statistically significant results is of little relevance in this particular context. The alpha was set at 30%, which may be considered high compared to the usual value of 5% set in most studies; however, the result obtained for statistical testing ($p = 0.004$) would still have met a more stringent alpha.

The methods used for the analyses were appropriate for the event-free survival time-to-event outcome (i.e., stratified log-rank test and Cox regression model). Based on visual inspection of the Kaplan-Meier plots for event-free survival, there did not appear to be a crossing of the curves, suggesting no violation of the underlying assumption of proportional hazards for the primary outcome assessment.

Data reported for the statistical analyses were limited, including for analysis of the primary outcome. Measures of precision were missing in order to adequately interpret the absolute results, and between-group differences with confidence intervals were not reported for several of the analyses. No data were reported for many of the outcomes specified in the study protocol, such as length

of disease control, length of locoregional control in the surgical site, and various harms outcomes. As such, interpretation of the study results is limited.

External validity

Patient Selection

The inclusion and exclusion criteria in SWOG S1801 were deemed clinically relevant and reasonable by CADTH's clinical experts. Patients in the study presented with baseline and disease characteristics that were consistent with the population typically seen by the experts in clinical practice. However, only few patients had stage IIID and stage IV disease; this should be considered when generalizing the findings from the study to real-life patients.

Treatment Regimen and Length of Follow-Up

The administration of pembrolizumab was in line with the Health Canada recommended dosage in oncology and what would be used in the reimbursement population. Treatment duration was considered adequate in the context of the disease; however, the follow-up was considered too short to show the impact of treatment on overall survival. In addition, due to limited follow-up, it is uncertain whether results for event-free survival would be similar over longer periods of time.

There was no recommendation in SWOG S1801 for subsequent-line treatments and therapies received by patients upon disease progression were not reported in the publication, precluding assessment of whether these were representative of Canadian clinical practice. It should be noted that the estimated effect of neoadjuvant–adjuvant pembrolizumab relative to adjuvant-only pembrolizumab on outcomes such as overall survival will be reflective of the effect of the intervention drugs, followed by subsequent treatments.

Radiotherapy was allowed after the surgery, but before pembrolizumab was started or re-started. Overall, only a small number of patients (n = 3 patients) received radiotherapy during the study. The clinical experts consulted by CADTH noted that in Canadian clinical practice, radiotherapy may be given to patients who are considered at high risk.

Outcome Measures

Outcome measures of efficacy were considered relevant to clinical practice by the experts consulted by CADTH for this review. Focus was placed on event-free survival for interpretation of the results, which captures a range of efficacy and harms events, although overall survival remains the primary goal of therapy. Other efficacy outcomes reported were not as clinically meaningful to inform treatment decisions according to the clinical experts. However, HRQoL was not assessed in the study; therefore, there is currently no information regarding the impact of neoadjuvant–adjuvant pembrolizumab relative to adjuvant-only pembrolizumab on this outcome, which was identified as important to patients based on the input received. Similarly, no information was reported in the publication on various important harms outcomes such as SAEs and WDAEs.

Results of the Included Study

Baseline Characteristics

Baseline characteristics were balanced between treatment groups in the SWOG S1801 study. Full details regarding baseline characteristics are provided in Patel et al.[9]

Patients had a median age of 64 years (range 19 to 90 years) in the neoadjuvant-adjuvant group and of 62 years (range 22 to 88 years) in the adjuvant-only group. Overall, 35% of patients in the study were female and 65% were male. The proportions of patients within each of the Zubrod's performance status scores, in the neoadjuvant-adjuvant and adjuvant-only treatment arms, were as follows: 73% and 79% of patients, respectively, had a performance status of 0 (fully active); 25% and 21%, respectively, had a performance status of 1 (restricted in strenuous activities but ambulatory); and 1 patient only in the neoadjuvant-adjuvant group had a performance status of 2 (unable to work but ambulatory and capable of self-care). A total of 87% of patients had low or normal LDH levels.

The majority of patients had stage IIIB or IIIC disease. More specifically, the proportions of patients within each disease stage, in the neoadjuvant-adjuvant and adjuvant-only treatment arms, were as follows: 40% in each group had stage IIIB disease; 45% and 47%, respectively, had stage IIIC disease; 6% in each group had stage IIID disease; and 9% and 7%, respectively, had stage IV disease. A total of 93% of patients in the neoadjuvant-adjuvant arm and 96% of patients in the adjuvant-only arm had cutaneous primary melanoma subtype; only few patients had acral or mucosal melanoma. A total of 99% of patients received no prior BRAF and MEK adjuvant therapy or radiotherapy.

Patient Disposition

In SWOG S1801, 345 patients were assessed for eligibility, 32 were deemed ineligible and 313 were randomized. Among these, 154 patients were randomly assigned to receive neoadjuvant-adjuvant pembrolizumab, while 159 patients were randomized to adjuvant-only pembrolizumab. Two (1.3%) patients in the neoadjuvant-adjuvant pembrolizumab arm and 7 (4.4%) patients in the adjuvant-only pembrolizumab arm received no treatment due to withdrawal of consent. At the time of the analysis, 43 (27.9%) patients in the neoadjuvant-adjuvant arm and 41 (25.8%) in the adjuvant-only arm continued to be on therapy. A total of 50 (32.5%) patients in the neoadjuvant-adjuvant arm, and 38 (23.9%) patients in the adjuvant-only arm, completed the protocol-specified treatment. High discontinuation rates were reported (59 / 154 [38.3%] patients and 73 / 159 [45.9%] patients, respectively); details are provided in Patel et al.[9] However, reasons for discontinuations were not reported.

There were differences between groups in terms of treatment discontinuations, especially when timing is being considered. A total of 15 patients receiving neoadjuvant-adjuvant pembrolizumab discontinued before receiving surgery, compared to 1 patient randomized to adjuvant-only pembrolizumab. The number of patients who discontinued during adjuvant therapy was 26 in the neoadjuvant-adjuvant pembrolizumab group and 51 in the adjuvant-only pembrolizumab group.

Exposure to Study Treatments

The length of exposure to study treatments was not reported. Two patients in the neoadjuvant-adjuvant group and 7 in the adjuvant-only group withdrew consent and did not receive any doses of assigned treatment.

Concomitant and Subsequent Treatments

The use of postsurgical radiotherapy, although allowed based on investigators' decision, was infrequent in the SWOG S1801 trial and did not differ between treatment groups, with 2 patients receiving radiotherapy in neoadjuvant-adjuvant pembrolizumab arm and 1 patient in the adjuvant-only pembrolizumab arm.

There were no specific recommendations in SWOG S1801 for use of subsequent-line treatments. Therapies received by patients upon disease progression were not reported in the publication.

Efficacy Results

Only those efficacy outcomes identified in the review protocol are reported subsequently. Results are summarized in

Table 6. In SWOG S1801, the median follow-up at the time of data cut-off was 14.7 months in both groups (no measures of variation were reported).

Overall Survival

Overall survival was assessed as a secondary outcome in the SWOG S1801 study. At the time of the data cut-off, 14 (9.1%) patients in the neoadjuvant-adjuvant group and 22 (13.8%) in the adjuvant-only group had died. The publication reported that no analysis was performed due to the small number of events that had accrued.

In the Kaplan-Meier plot, provided in Patel et al.[9] the curves initially followed a similar pattern, but appeared to separate slightly at approximately 18 months. The curves did not appear to cross afterwards; however, no between-group estimates or measures of precision were reported, precluding assessment of the uncertainty, and whether any difference between groups was actually significant. In addition, the number of patients remaining at risk was low at 24 months and beyond.

Relapse-Free Survival

No data were reported in the SWOG S1801 publication for relapse-free survival; however, disease recurrence throughout the adjuvant treatment period was part of the composite outcome of event-free survival, and narrative results were available for this individual outcome. The number of patients experiencing disease recurrence at the time of data cut-off was 9 patients in the neoadjuvant-adjuvant pembrolizumab group and 41 patients in the adjuvant-only pembrolizumab group; no measures of precision, or statistical comparison between groups, was reported.

Event-Free Survival

Event-free survival was the primary outcome in SWOG S1801. At the time of the data cut-off, 38 (24.7%) patients in the neoadjuvant-adjuvant group and 67 (42.1%) patients in the adjuvant-only group experienced a protocol-specified event (p = 0.004). Event-free survival probabilities at 2 years were 72% (95% confidence interval [CI] 64 – 80) in patients receiving neoadjuvant-adjuvant pembrolizumab and 49% (95% CI 41 – 59) in patients receiving adjuvant-only pembrolizumab, yielding a between-group difference of 23% (95% CI 11 – 35). Between-group differences at other potentially relevant time points were not reported. The hazard ratios and associated confidence intervals were not reported.

In the Kaplan-Meier plot, provided in Patel et al.,[9] the curves appeared to separate at approximately 3 months, favouring neoadjuvant-adjuvant treatment, and remained separate afterwards. The number of patients remaining at risk was low at 24 months and beyond.

Patel et al.[9] also reported the breakdown of individual events forming the composite outcome, which are described in Table 6. No statistical analysis was performed for individual events and no measures of precision were reported, precluding proper assessment of the difference between groups. Among the individual events reported, 12 patients in the neoadjuvant-adjuvant group (none in the adjuvant-only group) failed to receive planned surgery due to disease progression. Failure to receive planned adjuvant therapy was reported in 3 patients in the neoadjuvant-adjuvant group (none in the adjuvant-only group) due to neoadjuvant toxicity, and in 9 patients in the neoadjuvant-adjuvant group and 16 patients in the adjuvant-only group due to metastatic disease. Throughout adjuvant therapy, 9 patients in the neoadjuvant-adjuvant group and 41 patients in the adjuvant-only group had disease recurrence, while 1 patient in the neoadjuvant-adjuvant group and 4 patients in the adjuvant-only group died.

Subgroup Analyses:

The Forest Plot according to subgroup, provided in Patel et al.[9] reports data according to disease stage, which was identified in the systematic review protocol as a subgroup of interest.

In patients with stage IIIB disease, 19 / 62 (30.6%) patients in the neoadjuvant-adjuvant group and 24 / 64 (37.5%) patients in the adjuvant-only group experienced an event. The difference between groups in event-free survival probabilities at 2 years was 11% (95% CI -8, 30). In patients with stage IIIC disease, the number of patients who experienced an event was 14 / 69 (20.3%) patients in the neoadjuvant-adjuvant group and 34 / 74 (45.9%) patients in the adjuvant-only group, yielding a difference between groups in event-free survival probabilities at 2 years of 32 (95% CI 16, 49). Few patients in the study had stage IIID and stage IV disease. Although results are trending in a similar direction as for the overall population, they are associated with a wide confidence interval

that also includes the possibility of no difference between treatments, limiting the conclusions that can be drawn in these subgroups of patients.

Pathological Response

Pathological and imaging response was assessed in the SWOG S1801 trial at the end of neoadjuvant therapy in the group who received such treatment. A complete pathological response, defined as the absence of viable tumour, was reported in 28 (21%) patients out of the 132 evaluable patients who received neoadjuvant pembrolizumab.[9] Of 142 patients considered evaluable, 9 (6%) patients were assessed as having a complete imaging response, and 58 (41%) patients as having a partial imaging response.

Health-Related Quality of Life

No data were reported in the publication for the outcome of HRQoL.

Table 6: Summary of Efficacy Outcomes for the Study Included in the Systematic Review

Outcome	SWOG S1801[9]	
	Pembrolizumab – Neoadjuvant / adjuvant arm N = 154	Pembrolizumab – Adjuvant only arm N = 159
Event-Free Survival		
Number of events, n (%)	38 (24.7)	67 (42.1)
p-value (log-rank test)	p = 0.004	
Kaplan-Meier estimates of event-free survival at 2 years, %	72%	49%
(95% CI)	(64 – 80)	(41 – 59)
Between-group difference (95% CI)	23 (11, 35)	
Individual Events Contributing		
Failure to receive surgery, n		
Toxicity	1	0
Progression	12	0
Co-morbidities	1	0
Scheduling issue	0	1
Failure to receive adjuvant therapy, n		
Patient refusal	1	2
Neoadjuvant toxicity	3	0
Metastatic disease	9	16
Residual disease	1	2
Extended radiation	0	1
Throughout adjuvant therapy, n		
Recurrence	9	41
Death	1	4
Subgroup Analyses by Disease Stage		
Stage IIIB		
Number of events, n / N	19 / 62	24 / 64
Between-group difference, Kaplan-Meier estimates of event-free survival at 2 years, % (95% CI)	11 (−8, 30)	
Stage IIIC		
Number of events, n / N	14 / 69	34 / 74
Between-group difference, Kaplan-Meier estimates of event-free survival at 2 years, % (95% CI)	32 (16, 49)	
Stage IIID		
Number of events, n / N	4 / 9	6 / 10
Between-group difference, Kaplan-Meier estimates of event-free survival at 2 years, % (95% CI)	9 (−40, 58)	

Stage IV		
Number of events, n / N	1 / 14	3 / 11
Between-group difference, Kaplan-Meier estimates of event-free survival at 2 years, % (95% CI)	42 (−6, 89)	
Overall survival		
Number of deaths, n (%)	14 (9.1)	22 (13.8)

CI = confidence interval.

Analyses were not adjusted for multiplicity. A formal hypothesis test was reported for event-free survival only.

Source: Patel et al. 2023[9]

Harms Results

Only those harms identified in the review protocol are reported below. See Table 7 for detailed harms data.

Adverse events

In the SWOG S1801 study, the proportions of patients who experienced grade 3-4 drug-related AEs were 7% in the neoadjuvant-adjuvant group and 4% in the adjuvant-only group. The most frequently reported events are provided in Patel et al.[9]; however, as these events are grade 3-4 drug-related AEs, numerically few events are reported for each individual AEs, precluding comparison between treatment groups.

Serious adverse events

No data were reported in the publication for the outcome of SAEs.

Withdrawals due to adverse events

No data were reported in the publication for the outcome of WDAEs.

Mortality

No deaths were reported as harms outcomes throughout the trial duration.

Harms of Special Interest

The data reported in the publication was insufficient to assess the harms of special interest specified in the systematic review protocol.

Table 7: Summary of Key Harms Outcomes in Study Included in the Systematic Review

Outcome	SWOG S1801[9]	
	Pembrolizumab – Neoadjuvant / adjuvant arm N = 152	Pembrolizumab – Adjuvant only arm N = 141
AEs, n (%)		
≥1 Grade 3-4 drug-related AE	11 (7)	5 (4)
Deaths as Harms Outcomes, n (%)		
Number of deaths	0	0

AE = adverse event; N/A = not applicable; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

Source: Patel et al. 2023[9]

Indirect Evidence

A focused literature search for indirect treatment comparisons (ITCs) dealing with Keytruda (pembrolizumab) and melanoma was run in MEDLINE All (1946-) on December 13, 2023. No limits were applied. However, no indirect evidence was considered to address important gaps in the evidence included in the systematic review.

Other Relevant Evidence

No long-term extension study, or additional relevant study was considered to address important gaps in the evidence included in the systematic review.

Economic Evidence

The economic review consisted of only a cost comparison for neoadjuvant-adjuvant pembrolizumab compared with adjuvant-only pembrolizumab or adjuvant nivolumab for adult patients with resectable Stage III or IV melanoma.

CADTH Analyses

The comparators presented in **Error! Reference source not found.** have been deemed to be appropriate based on feedback from clinical experts and drug plans. The recommended dose for neoadjuvant-adjuvant pembrolizumab was based on Patel et al., 2023.[18] Recommended doses for comparators were based on each product's respective product monograph and validated by clinical experts. If discrepancies in dosing between the product monograph and Canadian clinical practice, the dose specified by clinical experts was used. Based on sponsor submitted prices from previous CADTH reviews, 100 mg vials of pembrolizumab are priced at $4,400.[19]

The recommended dosage of pembrolizumab (both neoadjuvant and adjuvant) is 200 mg every 3 weeks or 400 mg every 6 weeks. For neoadjuvant-adjuvant pembrolizumab, 3 doses are administered prior to surgical resection followed by 15 doses post resection.[18] Adjuvant pembrolizumab is received for up to 1 year (i.e., 18 doses) or until disease recurrence or unacceptable toxicity.[20] Similarly, adjuvant nivolumab is received for up to 1 year as long as clinical benefit is observed or until the treatment is no longer tolerated.[21]

When used as recommended, the standardized 28-day cycle per patient cost for both neoadjuvant and adjuvant pembrolizumab for the treatment of adults with resectable Stage III or IV melanoma is $11,733 per patient. The per patient standardized 28-day cycle cost is $9,387 for adjuvant nivolumab. As such, results of the cost-comparison demonstrate that, over a 28-day cycle, neoadjuvant-adjuvant pembrolizumab is expected to be cost neutral compared with adjuvant-only pembrolizumab. Compared with adjuvant nivolumab, over a 28-day cycle, neoadjuvant-adjuvant pembrolizumab is associated with incremental costs of $2,347 per patient. Note that results may differ by jurisdiction should prices differ from those presented in Table 8.

Table 8: CADTH Cost Comparison Table for Advanced Melanoma

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average cost per 28-days ($)
Pembrolizumab	25 mg/mL	4 mL vial Solution for IV infusion	4,400.0000[a]	200 mg every 3 weeks or 400 mg every 6 weeks	419.05	11,733
Neoadjuvant pembrolizumab (neoadjuvant – 3 doses; adjuvant – 15 doses)					419.05	11,733
Pembrolizumab only (adjuvant – 18 doses)					419.05	11,733
Nivolumumab	10 mg/mL	Sterile solution for injection 40 mg vial 100 mg vial	782.2200[b] 1,955.5600[b]	3 mg/kg or 240 mg every 2 weeks, or 480 mg every 4 weeks	335.24	9,387

Note: Dosing for neoadjuvant-adjuvant pembrolizumab is based on Patel et al., 2023,[18] and validated by clinical experts. Dosing for other treatments are obtained from respective product monographs.[20,21] For treatments using weight-based dosing, CADTH assumed a weight of 75 kg. All costs include wastage of unused medication in vials and do not include dispensing fees. For nivolumab, if vial sharing is assumed, the average cost per 28-day cycle would be $8,800.

Clinical experts indicated that weight based dosing may be used for pembrolizumab.[22] If using weight-based dosing (i.e., 2 mg/kg every 3 weeks or 4 mg/kg every 6 weeks) and assuming vial sharing, the average cost per 28-day cycle for pembrolizumab would be $8,800.

[a] CADTH review of pembrolizumab (Keytruda).[19]

[b] CADTH review of nivolumab.[23]

Issues for Consideration

- No Canadian cost-effectiveness studies were identified based on a literature search conducted on April 2, 2024.
- The clinical experts consulted for this review noted that the use of pembrolizumab in neoadjuvant setting would allow an assessment of whether a tumour will be sensitive to immunotherapy based on pathological response to treatment after three cycles in the neoadjuvant setting, which may inform the treatment decision for some patients to either continue with immunotherapy in the adjuvant setting, or to switch to targeted adjuvant therapy. The impact of neoadjuvant pembrolizumab on healthcare systems costs has not been assessed in this review.
- The clinical experts consulted for this review noted that neoadjuvant pembrolizumab may improve access to patient care by providing cancer treatment while awaiting surgical resection, which is especially important in settings with long waiting periods for surgery.

- Pembrolizumab has been previously reviewed by CADTH for melanoma adjuvant treatment and received a recommendation to reimburse conditional on improved cost-effectiveness. The submitted price for pembrolizumab in this review was $2,200 and $4,400 per 50 mg and 100 mg vial, respectively.[24,25]

Discussion

Summary of Available Evidence

One published phase II, open-label RCT was included in the systematic review: the SWOG S1801 trial.[9] The study (n = 313)[9] was performed in the US and randomized patients to neoadjuvant-adjuvant pembrolizumab, or pembrolizumab given only as adjuvant treatment, for the treatment of resectable stage III or stage IV melanoma.[9] The primary outcome was event-free survival, which captured a range of efficacy and harms events, including disease progression, serious toxic effects, the incapacity to perform surgery or to initiate adjuvant treatment, and surgical complications. Phase II trials typically include fewer patients and aim to provide preliminary evidence about the efficacy and harms of a drug, which typically would later be confirmed in a larger phase III trial.

The administration of pembrolizumab was in line with the Health Canada recommended dosage in oncology and what would be used in the reimbursement population, which does not currently include patients with stage IV disease. Findings from SWOG S1801 were obtained in a population that was consistent with patients typically seen by the experts in clinical practice; however, only few had stage IIID or stage IV disease. This should be considered when generalizing the findings to real-life patients. By having an open-label design, the study was susceptible to assessment and reporting biases for subjective efficacy and harms outcomes. High treatment discontinuation rates, which differed between treatment groups, would be expected given the context of the disease and likelihood of recurrence; however, they remain a concern as the reasons were not clarified. The impact and direction of these sources of bias are uncertain.

No evidence was available to inform the comparison of neoadjuvant pembrolizumab to adjuvant nivolumab. A focused literature search for ITCs of pembrolizumab relative to comparators in the treatment of melanoma was searched; however, no indirect evidence was considered to address important gaps in the evidence included in the systematic review.

Interpretation of Results

Efficacy

Improving survival in patients with cancer should remain the primary goal of therapy.[10] In the SWOG S1801 study, no conclusion could be drawn with regard to this outcome mainly due to the limited reporting. No statistical comparison between treatment groups was reported in the publication, while Kaplan-Meier curves were provided with no numerical between-group result or measure of precision. This precluded any assessment of the clinical and statistical significance of potential difference between treatments, as well as any assessment of the uncertainty surrounding the findings. In addition, few patients were at risk at later follow-up time points, contributing to the increased uncertainty about the long-term impact on mortality. According to the clinical experts consulted by CADTH, mortality has decreased substantially with relatively new advances in the treatment of melanoma; therefore, the data needed to inform a valid analysis may take many years to accrue. The clinical experts indicated that the absence of information on overall survival is common, and that treatment decisions may thus be informed by surrogate outcomes, such as event-free survival.

Evidence from the SWOG S1801 study relied on event-free survival as a surrogate for overall survival. Results for the between-group difference in the hazard of experiencing at least one of the prespecified events within the composite outcome favoured neoadjuvant-adjuvant pembrolizumab, compared to adjuvant-only pembrolizumab (24.7% versus 42.1% respectively; HR and 95% CI not reported; p = 0.004). The between-group difference in the probability of event-free survival was of 23% (95% CI 11 – 35) at 2 years, favouring neoadjuvant-adjuvant pembrolizumab, compared to adjuvant-only pembrolizumab. The magnitude of these results was considered to be clinically meaningful by the clinical experts based on the point estimates; however, the confidence intervals also included the possibility that the difference between treatments might not constitute a clinically meaningful improvement for patients. As was the case for the outcome of overall survival, Kaplan-Meier curves were provided, but between-group differences in survival probabilities at other potentially relevant timepoints (aside from 2 years) were not reported. Between-group differences were informed by relatively few events which introduces some uncertainty in the results. Additionally, results for this outcome may have been subject to assessment and reporting bias for subjective events related to disease progression or toxic effects, due to the knowledge of treatment assignment. There were few patients at risk at longer follow-up timepoints, and no data presented to support results for event-free survival beyond 2 years. Therefore, the evidence suggests that neoadjuvant-adjuvant pembrolizumab may

result in a clinically meaningful benefit on event-free survival at 2 years compared with adjuvant-only pembrolizumab in the treatment of patients with resectable stage III or stage IV melanoma; however, there is substantial uncertainty surrounding the findings. The longer-term benefit is unclear.

Findings suggest that a clinically meaningful proportion of patients may experience a complete pathological response after receiving three cycles of neoadjuvant pembrolizumab. Pathological response was assessed at the time of surgery in patients who received neoadjuvant-adjuvant pembrolizumab; therefore, results were uncontrolled, and no comparison between treatment groups was performed for this outcome. Based on natural disease history, it is however unlikely that patients who did not receive neoadjuvant treatment would show a response. Although pathological response may be considered a fairly objective outcome, a risk of assessment bias remains due to knowledge of the treatment received. Overall, these findings contribute to the evidence but should be interpreted with caution.

The evidence did not inform on HRQoL, as no data was reported in the publication for the outcome.

Harms

The assessment of harms outcomes suffered from limited reporting in the SWOG S1801 publication. Small proportions of patients experienced grade 3-4 drug-related AEs, which were numerically higher in patients receiving neoadjuvant-adjuvant pembrolizumab than in patients who received the drug only in the adjuvant setting. The proportions of patients experiencing SAEs and WDAEs were not reported. No mortality due to AEs was reported throughout the study. It was not possible either to assess any of the harms of special interest specified in the systematic review protocol, as these were not reported in the study.

The clinical experts consulted by CADTH indicated that the harms profile of pembrolizumab appeared consistent with what is currently seen in clinical practice based on the available evidence, and that it was expected to be similar whether treatment is initiated before or after surgery.

Other Considerations

The goals of therapy for patients presenting with aggressive cancer such as melanoma are to extend survival, delay disease recurrences and progression, as well as improve quality of life. In patients at high risk for recurrence, this is achieved through initial surgical resection, coupled with systemic therapy.[6] In the context of the Canadian healthcare system however, there can be meaningful delays in surgical procedures, which in turn, result in delays before patients can receive adjuvant treatment. The clinical experts noted that in some jurisdictions, it can take up to six months between a melanoma diagnosis and initiation of adjuvant therapy. As a result, patients currently remain untreated while waiting to access treatment, during which time the cancer keeps progressing. Initiating treatment promptly before surgery addresses this inequity issue. The clinical experts noted that this strategy was implemented in some jurisdictions during the COVID-19 pandemic, with the aim of mitigating the impact of operating room closures and prolonged delays in access to treatment.

In addition, the clinical experts consulted by CADTH for this review highlighted several potential benefits from neoadjuvant therapy, including downstaging the tumour prior to undergoing surgery, hence facilitating the surgical procedure and reducing morbidity for patients. Another clinically plausible benefit from neoadjuvant therapy includes allowing for a better immune response from the body and T-cells lymphocytes against the cancer by having the tumour present at the time of therapy; this is based on these hypothesized benefits that the trial was designed to evaluate. In addition, the clinical experts noted that use of pembrolizumab in the neoadjuvant phase would allow an assessment of whether a tumour will be sensitive to immunotherapy based on pathological response to treatment after three cycles in the neoadjuvant setting, which may inform the treatment decision for some patients to either continue with immunotherapy in the adjuvant setting, or to switch to targeted adjuvant therapy.

Neoadjuvant therapy would target the same patient population currently undergoing adjuvant therapy.

Cost Information

Public list prices for pembrolizumab and comparators are not available. Based on sponsor submitted prices from previous CADTH reviews, neoadjuvant-adjuvant pembrolizumab is expected to have a 28-day per patient cost of $11,733, which is equal to the 28-day per patient costs associated with adjuvant-only pembrolizumab. As such, neoadjuvant-adjuvant pembrolizumab is cost neutral compared with adjuvant-only pembrolizumab. Adjuvant nivolumab is expected to have a 28-day per patient cost of $9,387, meaning that neoadjuvant-adjuvant pembrolizumab is more costly, associated with $2,347 in incremental costs, compared with adjuvant nivolumab. These incremental costs are based on prices submitted by sponsors from previous CADTH reviews and may not reflect actual prices paid by Canadian public drug plans.

Conclusions

Evidence from the phase II, open-label SWOG S1801 study suggests that neoadjuvant-adjuvant pembrolizumab may result in a clinically meaningful benefit on event-free survival compared with adjuvant-only pembrolizumab at 2 years in the treatment of patients with resectable stage III or stage IV melanoma. However, there is substantial uncertainty surrounding the findings. Only limited statistical analyses were reported, precluding proper assessment of the between-group differences and the precision of the estimates. The risk of assessment and reporting bias, related to the knowledge of treatment assignment, contributed to the uncertainty of the findings. Only few patients remained at risk at longer time points, and no data contributed to understanding the long-term impact on event-free survival beyond 2 years. For similar reasons, no conclusion could be drawn with regard to overall survival; few events were recorded over the follow-up period, and no formal statistical analyses were undertaken. Longer follow-up would be needed to understand the impact on overall survival, as event-free survival has not been validated as a surrogate outcome in this population. However, as mortality has decreased substantially with relatively new advances in the treatment of melanoma, clinical experts indicated that surrogate outcomes such as event-free survival are commonly used to inform treatment decisions, as data on overall survival may take years to accrue. Findings suggest potential benefits from three cycles of neoadjuvant pembrolizumab on complete pathological response at the time of surgery; these findings should however be interpreted with caution as results were uncontrolled and assessors were aware of the treatment received. The evidence did not inform on HRQoL, as no data were reported in the publication. No evidence was identified to inform a comparison to adjuvant nivolumab. Findings were obtained in a population consisting mainly of patients with stage IIIB and IIIC disease; this should be considered when generalizing the findings to real-life patients. No indirect evidence was considered to address important gaps in the evidence included in the systematic review. The assessment of harms outcomes suffered from limited reporting in the publication. Based on the available evidence, the clinical experts consulted by CADTH indicated that the harms profile of pembrolizumab appeared consistent with what is currently seen in clinical practice. Toxicity was expected to be similar whether pembrolizumab is initiated before or after surgery, especially as neoadjuvant-adjuvant therapy would target the same patient population currently undergoing adjuvant therapy.

The clinical experts highlighted that neoadjuvant pembrolizumab addresses a significant unmet need for patients who have limited access to treatments due to the meaningful delays in surgical procedures across Canada. Neoadjuvant pembrolizumab can be initiated promptly upon diagnosis, so that patients can access cancer treatment while waiting for initial surgical resection. The clinical experts highlighted additional potential benefits from neoadjuvant therapy, including downstaging the tumour prior to undergoing surgery to facilitate the procedure and reduce morbidity for patients; allowing for a better immune response from T-cells lymphocytes against the cancer by having the tumour present at the time of therapy; and assessing whether a tumour will be sensitive to immunotherapy based on pathological response to treatment, which may inform subsequent adjuvant treatment decisions.

Results of the cost-comparison of treatment costs demonstrate that, over a 28-day cycle, neoadjuvant-adjuvant pembrolizumab is cost neutral compared with adjuvant-only pembrolizumab and $2,347 more costly per patient than adjuvant nivolumab. As such, the reimbursement of neoadjuvant-adjuvant pembrolizumab for the treatment of adult patients with resectable Stage III or IV melanoma is expected to be cost neutral compared with adjuvant-only pembrolizumab and increase overall treatment costs compared with adjuvant nivolumab.

No literature was identified comparing neoadjuvant-adjuvant pembrolizumab with nivolumab, therefore the comparative efficacy of these treatments is unknown. Based on the clinical review conclusions, neoadjuvant-adjuvant pembrolizumab may provide a clinically meaningful benefit on event-free survival and similar safety profile compared to adjuvant-only pembrolizumab, however, these findings are uncertain. Other costs such as administration costs were not considered as part of the cost comparison but neoadjuvant-adjuvant pembrolizumab administration is expected to be either cost neutral (compared with adjuvant-only pembrolizumab) or cost-saving (compared with adjuvant nivolumab). As such, neoadjuvant-adjuvant pembrolizumab is associated with a potential, though uncertain, incremental clinical benefit and equal treatment costs compared with adjuvant-only pembrolizumab – a cost effective treatment option.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid
Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: December 14, 2023
Alerts: Weekly search updates until project completion
Search filters applied: randomized controlled trials; controlled clinical trials.
Limits

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Table 9: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

#	Searches
1	(Keytruda* or pembrolizumab* or lambrolizumab* or xtrudane* or bcd 201 or bcd201 or MK 3475 or MK3475 or Merck 3475 or mk 7684a or mk7684a or pbp 2102 or pbp2102 or HSDB 8257 or HSDB8257 or Sch 900475 or Sch900475 or DPT0O3T46P).ti,ab,kf,ot,hw,rn,nm.
2	exp melanoma/ or exp skin neoplasms/
3	(melanoma* or melanocarcinoma* or melano-carcinoma* or melanoblastoma* or melano-blastoma* or melanomalignoma* or melano-malignoma* or melanosarcoma* or melano-sarcoma* or naevocarcinoma* or naevo-carcinoma*or nevocarcinoma* or nevo-carcinoma* or pigmentary cancer* or dermatoma or melanocytic maligan* or melanotic carcinoma* or ((skin or cutaneous or dermal or dermis or epidermal or epidermis) adj3 (cancer* or neoplas* or tumor* or tumour*))).ti,ab,kf.
4	or/2-3
5	1 and 4
6	5 use medall
7	*pembrolizumab/ or (Keytruda* or pembrolizumab* or lambrolizumab* or xtrudane* or bcd 201 or bcd201 or MK 3475 or MK3475 or Merck 3475 or mk 7684a or mk7684a or pbp 2102 or pbp2102 or HSDB 8257 or HSDB8257 or Sch 900475 or Sch900475).ti,ab,kf,dq.
8	exp melanoma/ or exp skin tumor/
9	(melanoma* or melanocarcinoma* or melano-carcinoma* or melanoblastoma* or melano-blastoma* or melanomalignoma* or melano-malignoma* or melanosarcoma* or melano-sarcoma* or naevocarcinoma* or naevo-carcinoma*or nevocarcinoma* or nevo-carcinoma* or pigmentary cancer* or dermatoma or melanocytic maligan* or melanotic carcinoma* or ((skin or cutaneous or dermal or dermis or epidermal or epidermis) adj3 (cancer* or neoplas* or tumor* or tumour*))).ti,ab,kf,dq.
10	or/8-9
11	7 and 10
12	11 use oemezd
13	12 not (conference review or conference abstract).pt.
14	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
15	Randomized Controlled Trial/
16	exp Randomized Controlled Trials as Topic/
17	"Randomized Controlled Trial (topic)"/
18	Controlled Clinical Trial/
19	exp Controlled Clinical Trials as Topic/
20	"Controlled Clinical Trial (topic)"/
21	Randomization/
22	Random Allocation/

23 Double-Blind Method/

24 Double Blind Procedure/

25 Double-Blind Studies/

26 Single-Blind Method/

27 Single Blind Procedure/

28 Single-Blind Studies/

29 Placebos/

30 Placebo/

31 Control Groups/

32 Control Group/

33 (random* or sham or placebo*).ti,ab,hw,kf.

34 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.

35 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.

36 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.

37 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.

38 allocated.ti,ab,hw.

39 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.

40 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.

41 (pragmatic study or pragmatic studies).ti,ab,hw,kf.

42 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.

43 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.

44 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.

45 or/14-44

46 6 and 45

47 13 and 45

48 46 or 47

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

Search terms – Keytruda (pembrolizumab), melanoma, neoadjuvant/surgery

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

Search terms – Keytruda (pembrolizumab), melanoma, neoadjuvant/surgery

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

Search terms – Keytruda (pembrolizumab), melanoma, neoadjuvant/surgery

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

Search terms – Keytruda (pembrolizumab), melanoma, neoadjuvant/surgery

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

Search terms – Keytruda (pembrolizumab), melanoma, neoadjuvant/surgery

Grey Literature

Search dates: December 6-12, 2023

Keywords: Keytruda (pembrolizumab) and melanoma

Limits: none

Updated: Search updated prior to the completion of stakeholder feedback period

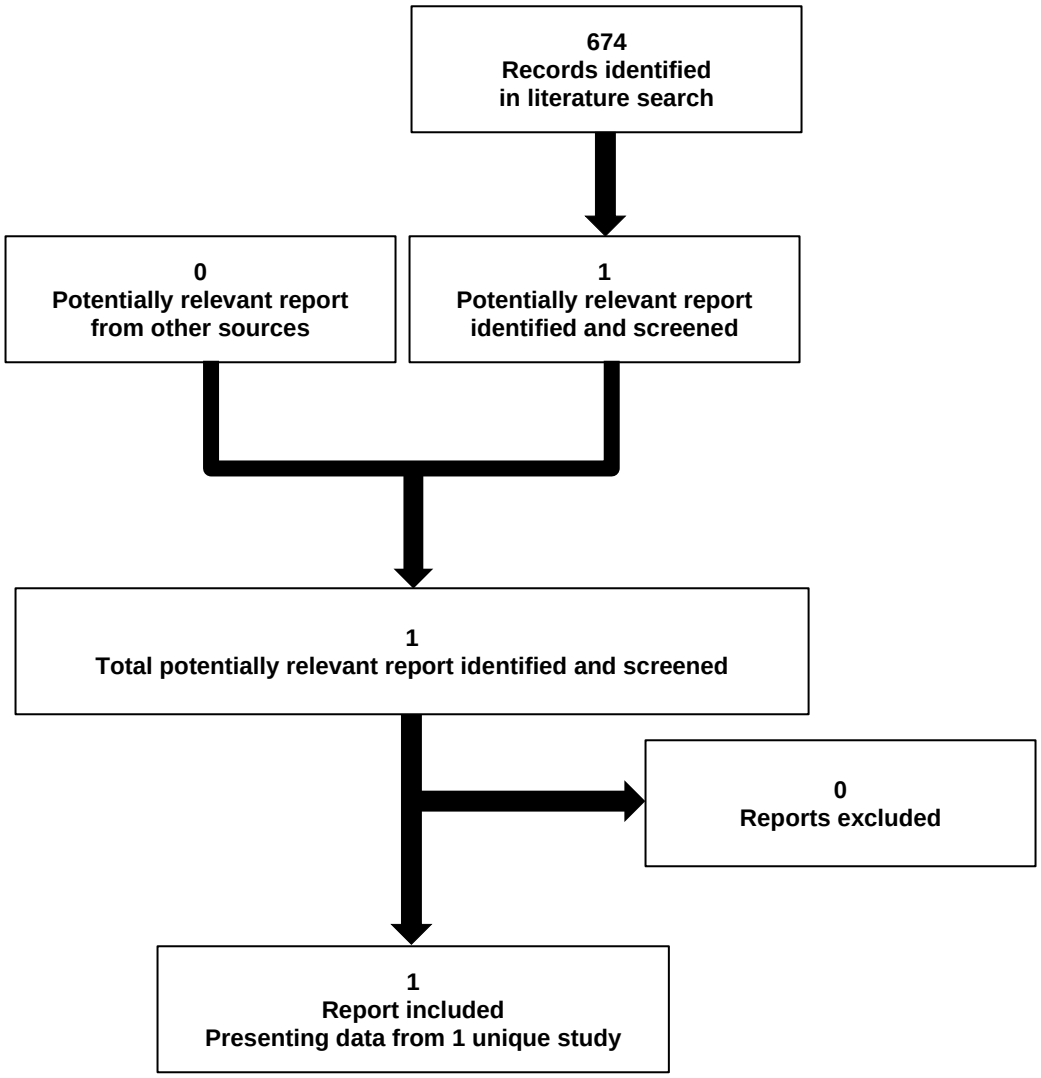
Relevant websites from the following sections of the CADTH grey literature checklist https://greymatters.cadth.ca/ were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

Appendix 2: Flow Diagram

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

Alt text: 674 citations were identified, 673 were excluded, while no electronic literature and no grey literature potentially relevant full text reports were retrieved for scrutiny. In total 1 report is included in the review.



Appendix 3: Excluded Studies

There was no excluded study from the systematic review process.