Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

Nivolumab Plus Ipilimumab

Nonsponsored Review

Therapeutic area: Anti–PD-1 resistant advanced melanoma

Clinical and Pharmacoeconomic Report

Table of Contents

Abbreviations **5**

Executive Summary **6**

Background 6

Stakeholder Perspectives 7

Clinical Evidence 9

Cost Information 15

Conclusions 15

Introduction **16**

Background 16

Standards of Therapy in Canada 17

Rationale 17

Drugs 18

Stakeholder Perspectives **19**

Patient Group Input 19

Clinician Input 20

Clinician Group Input 22

Drug Program Input 24

Industry Input 24

Clinical Evidence **25**

Methods 25

Evidence Base 26

Results of the Included RCTs 31

Results of the Included Observational Studies 40

Critical Appraisal 49

Indirect Evidence 51

Economic Evidence **51**

CADTH Analyses 51

Issues for Consideration 53

Discussion **54**
Summary of Available Evidence 54
Interpretation of Results 54
Cost Information 56
Conclusions **57**
References **59**
Appendix 1: Literature Search Strategy **61**
Appendix 2: Study Selection **71**

List of Tables

Table 1: Submitted for Review 6
Table 2: Overview of Included Studies 9
Table 3: Objective Response Rate 11
Table 4: Overall Survival 12
Table 5: Progression-Free Survival 13
Table 6: Inclusion Criteria for the Systematic Literature Review 26
Table 7: Characteristics of Included RCTs 29
Table 8: Baseline Characteristics — NCT02731729 (Friedman et al.) 31
Table 9: Baseline Characteristics — S1616 (VanderWalde et al.) 33
Table 10: Summary of Efficacy Results — RCTs 35
Table 11: Summary of Treatment-Related Adverse Events — NCT02731729 (Friedman et al.) 36
Table 12: Grade 3 or Higher Treatment-Related Toxicities in at Least 4% of Patients in Either Arm — S1616 (VanderWalde et al.) 37
Table 13: Characteristics of Included Studies — Observational Studies 39
Table 14: Baseline Characteristics — Zimmer et al. 41
Table 15: Baseline Characteristics — Baron et al. 43
Table 16: Patient Characteristics — Pires da Silva et al. 44
Table 17: Objective Response Rate 46
Table 18: Overall Survival 47
Table 19: Progression-Free Survival 48
Table 20: Subgroup Analyses by Prior Anti–PD-1 or Anti–PD-L1 Treatment in the Adjuvant Versus Metastatic Setting 48
Table 21: CADTH Cost Comparison Table for Advanced Melanoma 52
Table 22: Syntax Guide 62

List of Figures

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies 71

Abbreviations

AE	adverse event
ALT	alanine transaminase
AJCC	American Joint Committee on Cancer
AST	aspartate transaminase
CI	confidence interval
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
IQR	interquartile range
LDH	lactate dehydrogenase
ORR	objective response rate
OS	overall survival
PBAC	Pharmaceutical Benefits Scheme
PFS	progression-free survival
PR	partial response
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SYSF	Save Your Skin Foundation
TRAE	treatment-related 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	• Nivolumab (10 mg/mL, 40 mg and 100 mg vials, for injection) • Ipilimumab (5 mg/mL, 10 mL and 40 mL vials, for injection)
Health Canada indication	**Nivolumab** Unresectable or metastatic melanoma: • As monotherapy, or in combination with ipilimumab, for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma • Unresectable or metastatic melanoma and disease progression following ipilimumab and, if *BRAF* V600 mutation-positive, a *BRAF* inhibitor Adjuvant treatment of melanoma: • As monotherapy for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases • As monotherapy for the adjuvant treatment of adult patients with stage IIIB or IIC melanoma following complete resection **Ipilimumab** • Unresectable or metastatic melanoma, as a single drug • Unresectable or metastatic melanoma in adults who have not received prior systemic therapy for unresectable or metastatic melanoma, when used in combination with nivolumab
Indication under consideration for reimbursement	Ipilimumab plus nivolumab for the treatment of patients with advanced (unresectable or metastatic) melanoma that progresses during or within 6 months of adjuvant anti–PD-1 therapy
Health Canada approval status	NOC
Requester	Formulary Working Group

NOC = Notice of Compliance.

Background

Advanced melanoma is an aggressive malignancy. Immune checkpoint inhibitor immunotherapy, including anti–PD-1 (nivolumab, pembrolizumab), anti–PD-L1 (atezolizumab), and CTLA-4 (ipilimumab), given as monotherapy or in combination, are the most widely used standard of care front-line therapies for patients with melanoma in neoadjuvant, adjuvant, and advanced settings.[1] However, many patients develop resistance to immune checkpoint inhibitors and eventually experience progression.[2] Treatment with a combination of nivolumab and ipilimumab combines the actions associated with PD-1 and CTLA-4 checkpoint inhibitors and has been shown to be superior to ipilimumab only as a first-line treatment for advanced melanoma, in terms of both progression-free survival (PFS) and overall survival (OS).[3,4] Several studies have also shown a benefit of combination therapy with ipilimumab and anti–PD-1 for patients with melanoma resistant to anti–PD-1 or anti–PD-L1 therapy.[5-10]

Current treatment options for patients with advanced melanoma who fail anti–PD-1 therapy are limited, particularly for patients who do not have a *BRAF* mutation and are not suitable for *BRAF*/*MEK*-targeted therapy. The clinical experts consulted for this review noted that the only treatment option for these patients is single-drug ipilimumab, which is associated with low response rates (10% to 15%) and a PFS of just more than 2 months. According to the Provincial Funding Algorithm for metastatic melanoma,[11] currently, patients whose melanoma progresses on anti–PD-1 therapy in the adjuvant setting may access ipilimumab plus nivolumab only if their melanoma progresses more than 6 months following prior anti–PD-1 treatment; patients whose melanoma progresses during or within 6 months of anti–PD-1 treatment are not eligible for combination treatment. Following a request from jurisdictions, CADTH reviewed evidence of the efficacy and safety of ipilimumab plus nivolumab combination therapy in patients with metastatic melanoma that progresses during or within 6 months of adjuvant anti–PD-1 therapy ("fast progressors") to consider removing the 6-month restriction on re-treatment currently in place.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups, clinician group, and the industry who responded to CADTH's call for input, as well as the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Two patient advocacy groups, Save Your Skin Foundation and Melanoma Canada, submitted the patient input for this review. The patients who reported receiving nivolumab plus ipilimumab noted a number of adverse events, including fatigue, cognitive impairment, fever, nausea and vomiting, skin rash, damage to organs, and gastrointestinal issues. Respondents who did not complete the full course cited severe complications such as pneumonia, colitis, hepatitis, kidney issues, and other potentially life-threatening side effects. However, many patients in the survey conducted by Melanoma Canada expressed willingness to tolerate the side effects of treatment and its impact on their quality of life if the treatment was effective in delaying progression or eliminating cancer entirely. In the overall survey, 102 of the 117 respondents from Melanoma Canada indicated that they would want an alternative if they had disease progression and would consider the combination therapy.

In both surveys, patients and caregivers advocated for the funding of nivolumab plus ipilimumab in the second-line setting following progression on anti–PD-1 therapy. They noted that the combination therapy alleviates financial strain for patients, provides assurance of an alternative option in case of treatment failure or recurrence, and could improve patient outcomes.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts noted that, following progression on anti–PD-1 therapy, treatment options for patients without a *BRAF* mutation are scarce. The only funded option is single-drug ipilimumab, which has low response rates and a short PFS. While patients with a *BRAF* mutation have targeted therapy options, resistance is common, and toxicity often leads to treatment discontinuation or dose reductions. Based

on the current funding restrictions, patients can access ipilimumab plus nivolumab only in the first-line setting. Therefore, most patients are offered the combination up front. The experts emphasized that funding ipilimumab and nivolumab combination in second-line settings would allow patients who might not tolerate combination therapy well, or those with low-volume disease, to start with single-drug anti–PD-1 therapy and receive combination therapy if their melanoma progresses.

Clinician Group Input

Clinician input was submitted by 1 clinician group, Ontario Health, Cancer Care Ontario CNS Cancer Drug Advisory Committee, and by a consultant medical oncologist from Saskatchewan. The clinician group also noted that there are limited treatment options for patients without a *BRAF* mutation and for patients who have progressed following *BRAF*-targeted therapy. The clinician group indicated that treatment with nivolumab plus ipilimumab would be suitable for patients who experience a relapse during or within 6 months of anti–PD-1 therapy, regardless of whether prior treatment was received in an adjuvant or metastatic setting, and regardless of *BRAF* mutation status. Like the clinical experts, the clinician group and the medical oncologist emphasized that treatment with nivolumab plus ipilimumab for patients who experience a relapse during or within 6 months of anti–PD-1 therapy is already common in the US and Australia, and that the guidelines of the National Comprehensive Cancer Network in the US do not exclude the use of ipilimumab and nivolumab combination in patients whose melanoma has progressed during or within 6 months of anti–PD-1 therapy. The medical oncologist also suggested that, because the number of patients whose melanoma progresses during or within 6 months of anti–PD-1 therapy is small, this treatment option may not have a significant budget impact.

Drug Program Input

The drug plans suggested that including nivolumab plus ipilimumab will require only a minor modification to the current funding algorithm, as combination therapy would be added to the treatment choices for patients who experience a relapse during adjuvant anti–PD-1 therapy or within 6 months of its completion. The drug plans asked whether the following patients would be eligible for ipilimumab and nivolumab combination therapy: both the first- and second-line unresectable/metastatic settings for patients whose melanoma has progressed during or within 6 months of adjuvant anti–PD-1 therapy; patients with the *BRAF* mutation; and patients who have received anti–PD-1 monotherapy as first-line treatment for unresectable/metastatic melanoma and whose melanoma has progressed during or within 6 months of completing treatment. The drug plans also asked whether there should be a time-limited opportunity to add nivolumab for 4 cycles for patients currently on ipilimumab monotherapy (after progression).

Industry Input

The industry input was submitted by Bristol Myers Squibb Canada, the manufacturer of nivolumab and ipilimumab in Canada. The industry noted that adjuvant anti–PD-1 therapy following the resection of stage IIB/C, III, or IV melanoma is the current standard of care in Canada. Referring to current clinical practice, the company noted that regimens based on anti–PD-1, including nivolumab plus ipilimumab, nivolumab monotherapy, and pembrolizumab monotherapy, are used to treat patients with advanced/metastatic melanoma in a first-line setting. However, the industry input stated that physicians worldwide can prescribe

nivolumab plus ipilimumab for the first-line treatment of melanoma in the metastatic setting regardless of when the last dose of anti–PD-1 adjuvant treatment was received. However, in Canada, patients with unresectable/metastatic melanoma that progresses during or within 6 months of their last dose of anti–PD-1 therapy are ineligible for funding of re-treatment with ipilimumab plus nivolumab.

The industry input also noted that the current treatment algorithm in Canada limits the use of subsequent first-line regimens containing anti–PD-1, including nivolumab plus ipilimumab, upon progression during or within the 6 months following an anti–PD-1 in the adjuvant setting. Combination targeted therapy is available as an option for patients with a *BRAF* mutation. This leaves ipilimumab monotherapy as the only approved treatment option for patients whose melanoma does not harbour a *BRAF* mutation. The input suggested that the 6-month washout period stipulated in the treatment algorithm is based not on strong evidence but on a consultation process with local experts to help better understand appropriate use in clinical practice.

Clinical Evidence

Description of Included Studies

The evidence base for the review of the efficacy of ipilimumab plus nivolumab for patients with advanced (unresectable or metastatic) melanoma that progresses during or within 6 months of adjuvant anti–PD-1 therapy consists of 2 phase II randomized controlled trials (RCTs) and 3 observational (retrospective cohort) studies. However, the patient populations in these studies differ from the requested reimbursement population. First, all studies included patients in whom anti–PD-1 or anti–PD-L1 treatment had failed in the metastatic setting only, or a mix of patients in whom anti–PD-1 or anti–PD-L1 treatment had failed in the adjuvant or metastatic setting. No studies were identified that included only patients in whom anti–PD-1 therapy had failed in the adjuvant setting. Second, none of the studies differentiated patients whose melanoma progressed during or within 6 months of anti–PD-1 or anti–PD-L1 therapy from those whose melanoma progressed more than 6 months after anti–PD-1 or anti–PD-L1 therapy (Table 2).

Table 2: Overview of Included Studies

Author (year)	Study design	Patient population	N	Treatment comparisons	Disease setting	Timing of progression vis-à-vis anti–PD-L1 monotherapy (< 6 months or ≥ 6 months)
Friedman et al.	RCT (phase II)	Patients who had received prior treatment with a PD- 1 inhibitor in the adjuvant or metastatic setting with evidence of clinical or radiological progression	20	• Ipilimumab • Ipilimumab + nivolumab	First- and second-line advanced setting	Unclear

Author (year)	Study design	Patient population	N	Treatment comparisons	Disease setting	Timing of progression vis-à-vis anti–PD-L1 monotherapy (< 6 months or ≥ 6 months)
VanderWalde et al.	RCT (phase II)	Patients with metastatic melanoma who had received front-line anti–PD-1 or anti–PD-L1 therapy and whose tumours progressed	92	• Ipilimumab • Ipilimumab + nivolumab	First- and second-line advanced setting (mainly second-line)	Unclear
Zimmer et al.	Retrospective cohort	Patients with advanced melanoma who were treated with ipilimumab or ipilimumab + nivolumab after anti–PD-1 treatment failure	84	• Ipilimumab • Ipilimumab + nivolumab	Unclear	Unclear
Baron et al.	Retrospective cohort	Patients with advanced melanoma treated with single-drug anti–PD-1 in the front-line setting and who subsequently received second-line ipilimumab or ipilimumab + nivolumab	57	• Ipilimumab • Ipilimumab + nivolumab	Second-line advanced setting	Unclear
Pires da Silva et al.	Retrospective cohort	Patients with metastatic melanoma (unresectable stage III and IV), who were resistant to anti–PD-1 or anti–PD-L1 therapy	355	• Ipilimumab • Ipilimumab + nivolumab or pembrolizumab	First- and second-line advanced setting (mainly second-line) Subgroup analyses by setting	Unclear

RCT = randomized controlled trial.

Efficacy Results

In the first RCT (NCT02731729), objective responses were observed in 5 of 9 patients (56%; 95% confidence interval [CI], 21% to 86%) in the ipilimumab arm and 2 of 10 patients (20%; 95% CI, 3% to 56%) in the ipilimumab plus nivolumab arm at week 18. No between-group difference with CIs was reported. In the second RCT (S1616), the ORR was 28% (90% CI, 19% to 38%) in the nivolumab plus ipilimumab arm and 9% (90% CI, 2% to 25%) in the ipilimumab arm (P = 0.05, 1-sided Fisher's exact test). No between-group difference with CI was reported.

In the 2 observational studies that reported response rates, ORR was 16% for the ipilimumab group and 21% for the combination group (no CIs reported) in the study by Zimmer et al. In the study by Pires da Silva

et al., at a median follow-up of 22.1 months, ORR was 31% in the ipilimumab plus anti-PD-1 group and 13% in the ipilimumab-only group (P < 0.0001) (Table 3). Absolute between-group differences with CIs were not provided in either study.

Table 3: Objective Response Rate

	RCTs				Observational studies			
	NCT02731729 (Friedman et al.)		S1616 (VanderWalde et al.)		Zimmer et al.		Pires da Silva et al.	
Outcome	Ipilimumab (N = 9)	Nivolumab + ipilimumab (N = 10)	Ipilimumab (N = 23)	Nivolumab + ipilimumab (N = 69)	Ipilimumab + nivolumab (N = 47)	Ipilimumab (N = 37)	Ipilimumab + anti–PD-1 (N = 193)	Ipilimumab (N = 162)
ORR	56% (95% CI, 21% to 86%)	20% (95% CI, 3% to 56%)	9% (90% CI, 2% to 25%)	28% (90% CI, 19% to 38%)	7 (21%)	7 (16%)	60 (31%)	21 (13%)
			P = 0.05[a]				P < 0.0001[b]	

CI = confidence interval; ORR = objective response rate; RCT = randomized controlled trial.

Note: P values were not adjusted for multiple testing.

[a]One-sided Fisher's exact test. No threshold for statistical significance was prespecified.

[b]Pearson's x^2 with Yate's correction.

Neither of the RCTs were powered to detect differences in OS. In S1616, survival data were collected as a secondary end point; at the time of the last data lock (November 3, 2022, median follow-up = 36 months) the hazard ratio (HR) for OS for treatment with nivolumab plus ipilimumab compared with ipilimumab only was 0.83 (90% CI, 0.50 to 1.39; P = 0.28). Of the 3 observational studies, in the study by Pires da Silva et al., the median OS was 20.4 months (95% CI, 12.7 to 34.8) in the ipilimumab + anti–PD-1 group and 8.8 months (95% CI, 6.1 to 11.3) in the ipilimumab group (HR = 0.50; 95% CI, 0.38 to 0.66, P < 0.0001) (Table 4).

In the observational studies, Zimmer et al. reported a 1-year OS rate of 54% (95% CI, 35% to 70%) for the ipilimumab group and 55% (95% CI, 26% to 76%) for the combination group. Baron et al. reported a median survival from second-line therapy for patients treated with ipilimumab of 6.0 months (interquartile range [IQR], 3.1 to 11.8 months) and 5.6 months (IQR, 3.3 to 13.6 months) for patients treated with ipilimumab plus nivolumab (P = 0.99). In the study by Pires da Silva et al., median OS was 20.4 months (95% CI, 12.7 to 34.8) in the ipilimumab plus anti–PD-1 group compared with 8.8 months (95% CI, 6.1 to 11.3) in the ipilimumab group (HR = 0.50; 95% CI, 0.38 to 0.66; P < 0.0001).

One of the 2 RCTs reported PFS. In the S1616 trial, the HR for PFS for nivolumab plus ipilimumab versus ipilimumab only was 0.63 (90% CI, 0.41 to 0.97; P = 0.04; prespecified 1-sided alpha 0.1). Of the 3 observational studies, Zimmer et al. reported a median PFS of 2 months (95% CI, 1.9 to 3.0) in the ipilimumab plus nivolumab group and 3 months (95% CI, 2.8 to 3.8) in the ipilimumab-only group. Pires da Silva et al. reported a median PFS in the ipilimumab plus anti–PD-1 group of 3.0 months (95% CI, 2.6 to 3.6) compared with 2.6 months (95% CI, 2.4 to 2.9) in the ipilimumab-only group; HR 0.69 (95% CI, 0.55 to 0.87; P = 0.0019) (Table 5).

Table 4: Overall Survival

RCTs				Observational studies					
NCT02731729 (Friedman et al.)		S1616 (VanderWalde et al.)		Zimmer et al.		Baron et al.		Pires da Silva et al.	
Ipilimumab (N = 9)	Nivolumab + ipilimumab (N = 10)	Ipilimumab (N = 23)	Nivolumab + Ipilimumab (N = 69)	Ipilimumab + nivolumab (N = 37)	Ipilimumab (N = 47)	Ipilimumab + nivolumab (N = 35)	Ipilimumab (N = 22)	Ipilimumab + anti–PD-1 (N = 193)	Ipilimumab (N = 162)
Median OS		HR (90% CI)		1-year OS, % (95% CI)		Median OS, months (IQR)		Median OS, months (95% CI)	
NE	NE	0.83[a] (0.50 to1.39) P = 0.28		55 (26 to 76)	54 (35 to 70)	5.6 (3.3 to 13.6)	6.0 (3.1 to 11.8)	20.4 (12.7 to 34.8)	8.8 (6.1 to 11.3)
								HR = 0.50 (0.38 to 0.66) P < 0.0001[b]	

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NE = not estimable; OS = overall survival; RCT = randomized controlled trial.

Note: P values were not adjusted for multiple testing.

[a]Study S1616 was not powered to detect differences in OS, and survival data were collected as a secondary end point.

[b]The log-rank test was used.

Table 5: Progression-Free Survival

RCT		Observational studies					
S1616 (VanderWalde et al.)		Zimmer et al.		Baron et al.		Pires da Silva et al.	
Ipilimumab (N = 23)	Nivolumab + ipilimumab (N = 69)	Ipilimumab + nivolumab (N = 37)	Ipilimumab (N = 47)	Ipilimumab + nivolumab (N = 35)	Ipilimumab (N = 22)	Ipilimumab + anti–PD-1 (N = 193)	Ipilimumab (N = 162)
HR (90% CI)		Median PFS, months (95% CI)		Time to next treatment or death (used as proxy for PFS) Median (IQR)		Median PFS, months (95% CI)	
0.63 (0.41 to 0.97) One-sided log-rank P value = 0.036		2 (1.9 to 3)	3 (2.8 to 3.8)	5.4 (3.0 to 21.9)	3.6 (2.5 to 5.6)	3.0 (2.6 to 3.6)	2.6 (2.4 to 2.9)
				P = 0.09		HR = 0.69 (0.55 to 0.87) P = 0.0019[a]	

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; PFS = progression-free survival; RCT = randomized controlled trial.

Note: P values were not adjusted for multiple comparisons.

[a]The log-rank test was used.

Harms Results

In 1 of the RCTs (NCT02731729), all patients except 1 experienced at least 1 adverse event (AE). AEs led to treatment withdrawal in 4 patients in the ipilimumab plus nivolumab arm, including 2 patients with diarrhea (grades 1 and 2), 1 patient with an elevated aspartate transaminase and alanine transaminase (grade 2), and 1 patient with hypophysitis (grade 2). One patient in the ipilimumab arm discontinued treatment due to adrenal insufficiency and infection (both grade 3). In S1616, in the nivolumab plus ipilimumab arm, 50% of patients experienced a maximum of grade 3 treatment-related AEs (TRAEs), 6% experienced a grade 4 AE, and 1 patient (1%) experienced a grade 5 AE (disseminated intravascular coagulation); 20 patients (29%) discontinued protocol therapy due to toxicity. In the ipilimumab arm, 22% of patients experienced a maximum of grade 3 AEs, 9% experienced a grade 4 AE, and 4% experienced a grade 5 AE; 17% discontinued therapy due to toxicity.

Of the 3 observational studies included, only Pires da Silva et al. reported AEs. In this study, 32% of patients had at least 1 grade 3 to 5 AE, with similar rates in both treatment groups (33% with ipilimumab and 31% with ipilimumab plus anti–PD-1). The most common grade 3 to 5 AEs were diarrhea or colitis (20% with ipilimumab and 12% with ipilimumab plus anti–PD-1), followed by increased alanine transaminase or aspartate transaminase (9% versus 12%).

Critical Appraisal

Both RCTs had an open-label design, but the risk of bias in the measurement of the outcome is low because the outcomes were objective (PFS, OS) and ORR was based on well-established consensus criteria (Response Evaluation Criteria in Solid Tumours Version 1.1 [RECIST 1.1]). One of the RCTs (NCT02731729) randomized only 20 patients, which may be inadequate to achieve prognostic balance between treatment arms at baseline, and lacked power to test differences in treatment effects between treatment arms. All 3 observational studies were retrospective analyses and were prone to selection bias because healthier patients were more likely to have been chosen for treatment with ipilimumab plus anti–PD-1 therapy. Prognostic imbalances were apparent between the ipilimumab-only and the combination treatment groups in all 3 studies.

In both RCTs, the trial inclusion and exclusion criteria were clinically relevant and included patients who had received anti–PD-1 or anti–PD-L1 therapy in the adjuvant or metastatic setting. While this patient population differs from the reimbursement request population for this review, it is consistent with clinical practice, in which patients in whom anti–PD-1 or anti–PD-L1 therapy in the adjuvant or metastatic setting has failed may be re-treated with ipilimumab or ipilimumab plus nivolumab (unless there are reimbursement restrictions). The trial treatment regimens were also consistent with common practice. In the observational studies, the study by Pires da Silva et al. was a multicentre study including data from different countries with different practices, regulations, and access to drugs, which may not be fully generalizable to the setting in Canada. However, given the lack of information, it is not possible to speculate on what differences, if any, may affect generalizability. There were no studies that compared ipilimumab plus nivolumab to *BRAF*-targeted therapy in patients with advanced melanoma that progressed during or within 6 months of anti–PD-1 therapy.

Cost Information

The economic review included a comparison of the treatment costs of nivolumab plus ipilimumab and those of comparators deemed appropriate based on clinical expert consultations and drug plan feedback.

When used in combination, the recommended dosage of nivolumab is 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab maintenance treatment administered at 3 mg/kg every 4 weeks until unacceptable toxicity or up to a maximum of 2 years.[3] This differs from ipilimumab monotherapy, which is administered at 3 mg/kg every 3 weeks for 4 cycles total (no maintenance treatment).[12] Public list prices for nivolumab plus ipilimumab are not available. Based on sponsor-submitted prices from previous CADTH reviews, nivolumab plus ipilimumab combination therapy is expected to cost $40,753 per patient per 28-day cycle for the first 4 cycles, followed by maintenance treatment with nivolumab alone at a cost of $9,387 per patient per 28-day cycle. Ipilimumab monotherapy is expected to cost $38,667 per patient per 28-day cycle (used for 4 cycles only). Thus, the incremental per-patient cost of nivolumab plus ipilimumab compared with ipilimumab monotherapy is $2,086 per 28-day cycle for the first 4 cycles. After 4 cycles, the per-patient incremental cost of nivolumab maintenance therapy is $9,387 per 28-day cycle because there is no maintenance treatment associated with ipilimumab monotherapy.

At publicly available list prices, costs for *BRAF*-targeted therapies range from $15,070 to $19,396 per 28-day cycle. Compared with *BRAF*-targeted therapies, nivolumab plus ipilimumab therapy is more costly in the first 4 cycles. However, after 4 cycles, when nivolumab is given alone as maintenance therapy, nivolumab maintenance is less costly compared with *BRAF*-targeted therapies.

Conclusions

The evidence regarding the efficacy of ipilimumab plus nivolumab compared with ipilimumab only among patients with advanced melanoma that progressed during or within 6 months of adjuvant anti–PD-1 therapy is uncertain. No evidence was identified comparing ipilimumab plus nivolumab with *BRAF*-targeted therapy in this population. Although some studies showed the potential for improved ORR, PFS, or OS with combination therapy compared with ipilimumab only, the results were inconsistent across studies and conclusions were limited by serious methodological limitations. However, none of the studies identified were designed to examine the comparative efficacy and safety outcomes of combination ipilimumab and nivolumab with ipilimumab only specifically in patients whose melanoma progressed during or within 6 months of adjuvant anti–PD-1 or therapy. Thus, the evidence is inconsistent with the target population of this review — that is, patients who are currently ineligible to receive anti–PD-1 treatment for advanced melanoma due to their prior exposure to anti–PD-1 or therapy in the adjuvant setting and who experience disease recurrence during or within 6 months of receiving adjuvant anti–PD-1 treatment. The lack of studies that specifically recruited this group of patients, or that reported subgroup data for these patients, may support revision of current reimbursement criteria to remove the existing restriction of the re-treatment interval of more than 6 months for patients with advanced melanoma who experience disease recurrence after anti–PD-1 therapy.

Results of the comparison of treatment costs demonstrate that, over a 28-day cycle, nivolumab plus ipilimumab is $2,086 more costly than ipilimumab monotherapy in the first 4 cycles. After 4 cycles,

maintenance treatment with nivolumab is associated with incremental costs of $9,387 per patient per 28-day cycle because there is no maintenance treatment with ipilimumab monotherapy. As a result, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced (unresectable or metastatic) melanoma that progresses during or within 6 months of adjuvant anti–PD-L1 therapy will increase overall treatment costs compared with ipilimumab monotherapy, given that nivolumab is an add-on therapy to ipilimumab.

Based on the clinical review conclusions, none of the studies identified were designed to examine the comparative efficacy and safety outcomes of combination ipilimumab and nivolumab versus ipilimumab only in patients whose melanoma progressed during or within 6 months of adjuvant anti–PD-1 therapy. Consequently, nivolumab plus ipilimumab is associated with incremental costs and unknown clinical benefit compared with ipilimumab monotherapy in patients whose melanoma progresses during or within 6 months of adjuvant anti–PD-L1 therapy. Other costs, such as administration costs, were not considered as part of the cost comparison. However, nivolumab plus ipilimumab is expected to increase administration costs compared with ipilimumab monotherapy, given that nivolumab maintenance therapy is not restricted to 4 cycles and may be used for up to 2 years. Given the absence of evidence comparing nivolumab plus ipilimumab with ipilimumab monotherapy in the target population, there is no evidence to inform comparative efficacy of these treatments. Since nivolumab is an add-on therapy, reimbursement for this clinical condition will add costs to the health system, with unknown benefit.

For a subgroup of patients with advanced melanoma with a *BRAF*-positive mutation, *BRAF*-targeted therapies were identified as relevant comparators. Compared *BRAF*-targeted therapies, nivolumab plus ipilimumab is more costly in the first 4 cycles. However, after 4 cycles, when nivolumab is given alone as maintenance therapy, nivolumab maintenance is less costly compared with *BRAF*-targeted therapies. Hence, compared with *BRAF*-targeted therapies, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced melanoma that progresses during or within 6 months of adjuvant anti–PD-1 therapy is expected to lead to incremental costs in the first 4 cycles but cost savings after 4 cycles. No literature was identified comparing nivolumab plus ipilimumab with *BRAF*-targeted therapies; therefore, the comparative efficacy of these treatments is unknown.

Introduction

Background

Advanced melanoma is one of the most aggressive malignancies of multiple origins — most commonly cutaneous, mucosal, or uveal. Immune checkpoint inhibitor immunotherapy including anti–PD-1 (nivolumab, pembrolizumab), anti–PD-L1 (atezolizumab), and CTLA-4 (ipilimumab), given as monotherapy or in combination, are the most widely used standard of care front-line therapies for patients with melanoma in neoadjuvant, adjuvant, as well as advanced settings.[1] Although these therapies are initially effective, many patients develop resistance to immune checkpoint inhibitors and eventually experience progression. More than half of the patients on anti–PD-1 or anti–PD-L1 treatment show transient or no response at all.[2] The

optimal therapeutic approach for patients who do not respond to initial single-drug anti–PD-1 or anti–PD-L1 treatment remains unclear; patients whose melanoma progresses on anti–PD-1 or anti–PD-L1 treatments have various subsequent treatment options, including nivolumab and ipilimumab combination therapy, ipilimumab monotherapy, and targeted therapies for patient with *BRAF* mutations.

The combination of nivolumab and ipilimumab combines the actions associated with PD-1 and CTLA-4 checkpoint inhibitors. Combination ipilimumab and nivolumab has been shown to be superior to ipilimumab only as a first-line treatment for melanoma (with objective response rates [ORRs] of 58% for combination therapy versus 19% for ipilimumab only). At an minimum 60 months follow-up, median OS among patients treated with ipilimumab plus nivolumab was 60.0 months versus 36.9 months in patients who received ipilimumab only.[3,4] However, it was uncertain whether such benefit of combination therapy with ipilimumab and anti–PD-1 can also be expected for patients who are resistant to anti–PD-1 or anti–PD-L1 therapy. Given the distinct cellular mechanisms underlying anti-CTLA-4 and anti–PD-1 or anti–PD-L1 checkpoint blockade and the suspected mechanisms of lack of response to anti–PD-1 or anti–PD-L1 blockade demonstrated in animal models,[13,14] several studies — including a case study, a randomized phase II clinical trial, and a retrospective cohort study — have evaluated the benefit of combined CTLA-4 and anti–PD-1 blockade therapy over CTLA-4 blockade alone, to reverse primary resistance to anti–PD-1 .[6,7,9] Findings from these studies have been inconsistent. However, larger, more recent studies have suggested the same benefit of combination therapy with ipilimumab plus nivolumab in patients with advanced melanoma that is resistant to anti–PD-1.[5-10]

Standards of Therapy in Canada

The clinical experts consulted by CADTH indicated that current treatment options for patients with advanced melanoma in whom anti–PD-1 therapy has failed are limited. Patients in whom initial therapy with anti–PD-1 has failed and who have a *BRAF* mutation (about 40% of patients) have the option of *BRAF*/*MEK*-targeted therapy. However, according to the clinical experts consulted, initial good responses on targeted therapy are often less durable than with immunotherapy. For patients who do not have a *BRAF* mutation, the only treatment option is single-drug ipilimumab, which has low response rates (10% to 15%) and a PFS of just more than 2 months. The clinical experts mentioned that some patients have been able to access ipilimumab plus nivolumab therapy through private insurance coverage or by paying for anti–PD-1 therapy themselves. Some provinces reimburse ipilimumab (1 mg) and nivolumab (3 mg) for 4 cycles, as it is cost-effective compared with full-dose ipilimumab. However, most patients in Canada do not have access to the combination therapy with ipilimumab and nivolumab. The clinical experts noted that immunotherapy has been shown to offer long-term survival in patients with stage IV disease (52% survival at 5 years, with many oncologists believing that many of these patients are cured). Therefore, the goal of treatment is long-term survival. There is currently an unmet need for access to combination therapy for this patient population.

Rationale

In 2017, CADTH issued a recommendation with conditions to reimburse nivolumab plus ipilimumab for the treatment of previously untreated adult patients with advanced melanoma, regardless of *BRAF* status.[15] This recommendation was based on CheckMate 067 and CheckMate 069 clinical trials, which showed

a net clinical benefit of nivolumab plus ipilimumab in prolonging PFS and OS compared with ipilimumab monotherapy. Pembrolizumab and nivolumab were separately reviewed by the pan-Canadian Oncology Drug Review Expert Review Committee for the adjuvant treatment of melanoma in 2019.[12,16] For both reviews, public drug plans asked about the appropriate time frame from completion of adjuvant nivolumab or pembrolizumab therapy to initiation of immunotherapy for metastatic disease. The committee indicated that there was no available clinical evidence to determine the appropriate time frame from progression on adjuvant therapy to initiation of treatment in the metastatic setting. In the absence of clinical evidence to inform an appropriate re-treatment interval, the committee used pharmacokinetic data from a CADTH optimal use 360 report entitled *Dosing and Timing of Immuno-Oncology Drugs,* which included policy questions on the use of immuno-oncology drug re-treatment after adjuvant immuno-oncology therapy; specifically, how long after the end of adjuvant therapy patients can be eligible for a second immuno-oncology treatment upon melanoma progression.[17] The pharmacokinetic data explored the time needed for an appropriate washout of immunotherapy drugs when no significant residual biological activity should be exerted on target cells. Based on a half-life of 20 days, the washout period for nivolumab was calculated to be 201 days or 6 months. The suggested washout values were to be viewed as theoretical from a policy and practice perspective. This recommendation was not considered at a CADTH expert committee meeting.

In 2019, the provisional funding algorithm for melanoma was updated, and a 6-month restriction for re-treatment was applied, such that, for patients who receive anti–PD-1 therapy (nivolumab or pembrolizumab) in the adjuvant setting, re-treatment with ipilimumab plus nivolumab is funded only if at least 6 months has elapsed from the completion of anti–PD-1 treatment in the adjuvant setting. Patients who have disease progression while receiving or within 6 months of anti–PD-1 therapy are not eligible for combination therapy in the advanced setting.[11]

Following requests from patients and clinicians, the public drug plans asked that CADTH review evidence for the efficacy and safety of ipilimumab plus nivolumab treatment in patients whose melanoma progresses during or within 6 months of adjuvant anti–PD-1 treatment. The plans noted that the Pharmaceutical Benefits Advisory Committee in Australia recently conducted a review of the evidence and recommended expanding the reimbursement of nivolumab plus ipilimumab for patients with unresectable stage III or IV malignant melanoma when disease recurs while the patient is receiving or within 6 months of completing adjuvant anti–PD-1 monotherapy.[18]

Drugs

Nivolumab is a fully human, PD-1 checkpoint inhibitor that selectively blocks the interaction of the PD-1 receptor with PD ligands 1 and 2. Nivolumab has a Health Canada indication for the treatment of patients with (1) unresectable or metastatic melanoma who have not received prior systemic therapy, as monotherapy or in combination with ipilimumab, and (2) unresectable or metastatic melanoma and disease progression following ipilimumab and, if *BRAF* V600 mutation-positive, a *BRAF* inhibitor. As monotherapy, nivolumab is also indicated for the adjuvant treatment of adult patients with stage IIBV or IIC melanoma following complete resection.[16]

Ipilimumab is a fully human monoclonal antibody to CTLA-4 antigen. As a single drug, it is indicated for the treatment of unresectable or metastatic melanoma. Ipilimumab is also indicated in combination with nivolumab for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma.[12] The recommended dosage of ipilimumab plus nivolumab is nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab 3 mg/kg every 4 weeks as continued treatment, as long as clinical benefit is observed or until the patient no longer tolerates treatment.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full patient group input is posted online.

Two patient advocacy groups, Save Your Skin Foundation (SYSF) and Melanoma Canada, submitted the patient input for this review. SYSF, a national, patient-led, not-for-profit group, focuses on educating and advocating for patients with nonmelanoma skin cancers, melanoma, and ocular melanoma and providing 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 patients with melanoma and skin cancer in Canada, striving to ensure accessible and timely diagnosis and treatment options for all.

SYSF's and Melanoma Canada's submission was based on responses to online surveys. SYSF received responses from 59 individuals, from British Columbia, Alberta, Manitoba, Ontario, Quebec, Nova Scotia, Newfoundland and Labrador, Saskatchewan, UK, and Ireland. Melanoma Canada received 117 responses, with most respondents from British Columbia, Alberta, Ontario, Quebec, and the US.

In the survey responses to SYSF, patients reported receiving nivolumab plus ipilimumab as their primary treatment (18 patients), as subsequent treatment (9 patients), or other treatment approach (4 patients). Commonly reported AEs associated with nivolumab plus ipilimumab were fatigue, cognitive impairment, fever, nausea and vomiting, skin rash, damage to organs, gastrointestinal issues, breathing problems, headaches, weight loss or weight gain, and loss or gain of appetite. Respondents who did not complete the full course cited severe complications, such as pneumonia, colitis, hepatitis, kidney issues, and potentially life-threatening side effects. In the survey responses to Melanoma Canada, 6 patients reported receiving nivolumab plus ipilimumab after experiencing disease progression with a monotherapy within 6 months of start of treatment. Many of these respondents expressed willingness to tolerate the side effects of treatment and its impact on their quality of life if it was effective in delaying progression or eliminating cancer entirely. In the overall survey responses to Melanoma Canada, the majority of respondents indicated that they would want an alternative if they had disease progression and would consider the combination therapy.

Patients from both surveys noted they had experience with the 1 or more of the following alternative treatment options: radiation, surgery or incisions/skin grafts, bevacizumab, prednisolone eye drops, trametinib, dabrafenib, nivolumab, ipilimumab, pembrolizumab, encorafenib, binimetinib, vemurafenib, cobimetinib, relatlimab, aldesleukin, proleukin, interferon alfa-2b, and dacarbazine.

In both surveys, patients and caregivers advocated for the funding of nivolumab plus ipilimumab in a second-line setting following progression on anti–PD-1 therapy. They emphasized that it would alleviate financial strain for some patients and provide assurance of an alternative option in case of treatment failure or recurrence. They noted that combination therapy is an additional line of treatment that may improve patient outcomes by reducing the spread of disease, eliminating recurrence, or eliminating cancer entirely. Such outcomes were seen as significant contributors to enhancing patients' quality of life and mental well-being.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 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 2 clinical specialists with expertise in the diagnosis and management of melanoma.

Unmet Needs

The clinical experts noted that, following progression on anti–PD-1 therapy, treatment options for the *BRAF* wild-type population (that is, patients with no *BRAF* mutation) are scarce, with single-drug ipilimumab being the only funded standard of care. The experts noted that some patients access ipilimumab plus nivolumab through private insurance or by paying for anti–PD-1 therapy themselves. In some provinces, reimbursement is available for a limited course of ipilimumab and nivolumab combination therapy because of its cost-effectiveness compared with full-dose ipilimumab. However, most patients do not have access to this combination treatment.

The clinical experts noted that, for patients with *BRAF* wild-type tumours progressing after anti–PD-1 therapy, response rates to ipilimumab only are as low as 9% and PFS is just more than 2 months. Patients with a *BRAF* mutation in whom initial therapy with anti–PD-1 has failed have the option of treatment with *BRAF*/*MEK* inhibitors. While these patients may have good responses to *BRAF*/*MEK* inhibitors, responses are not as durable as those seen with immunotherapy. As a consequence, patients with primary or secondary resistance to anti–PD-1 therapy, particularly those with *BRAF* wild-type melanoma, face a lack of effective options. While patients with a *BRAF* mutation have targeted therapy options, resistance is common, and toxicity often leads to treatment discontinuation or dose reductions.

The clinical experts noted that ipilimumab plus nivolumab results in approximately 60% of patients experiencing grade III or IV AEs, but more than half of all patients have survived at 5 years. By contrast, 20% of patients treated with single-drug anti–PD-1 therapy experience grade III or IV AEs but 5-year survival is

35% to 44%. However, given the current funding restrictions, clinicians can access the combination treatment only in the first-line setting, and therefore most patients are offered combination therapy up front. The clinical experts noted that the goals of treatment include increasing ORR, PFS, and OS, as well as maintaining quality of life and independence in activities of daily living.

Place in Therapy

Both clinical experts indicated that patients with advanced melanoma that progresses on single-drug anti–PD-1 therapy should be eligible for ipilimumab plus nivolumab, regardless of the timing of progression and of whether they progressed on anti–PD-1 monotherapy in the adjuvant or first-line metastatic setting, as these are similar populations of patients. The clinical experts emphasized that there is no scientific reason to treat these patient groups separately or to believe that they would respond to treatment differently. Patients whose melanoma progresses on single-drug anti–PD-1 therapy should be eligible for treatment with nivolumab plus ipilimumab as a second-line treatment (that is, when they fail to respond or develop resistance to single-drug anti–PD-1 therapy in first-line). This would spare some patients the toxicity of combination therapy, as they would be given single-drug anti–PD-1 therapy as first-line treatment. This shift in practice would result in some patients receiving ipilimumab plus nivolumab instead of ipilimumab only in the second-line setting.

Patient Population

The clinical experts noted that patients with central nervous system (CNS) metastases, high lactate dehydrogenase (LDH), and high-volume metastatic disease would be given nivolumab plus ipilimumab up front. This is based on the subgroup analysis of the pivotal trial that shows these patients do better with combination therapy. Patients with a normal LDH, low-volume disease, and no CNS metastases, or those more likely to develop toxicity, are generally started on single-drug anti–PD-1 therapy. The clinical experts also noted that no companion tests are required.

Assessing Response to Treatment

The clinical experts indicated that treatment response is usually assessed at the completion of cycle 4, then every 12 weeks (about 3 months) to 6 months, depending on how long the patient is on therapy. Patients with progressive disease after the first evaluation but maintaining a good performance status can continue with therapy, as progression could in fact be pseudoprogression, a well-documented phenomenon in immunotherapy. Important outcomes to consider include longer-term survival — that is, 1-, 2-, and 5-year survival and the plateaus of the survival curve. They also noted that improved duration of response and PFS are important treatment objectives.

Regarding AEs, the clinical experts noted that AEs can be related to skin, endocrine, rheumatological, cardiac, neurologic, kidney, gastrointestinal, hepatic, pancreatic, blood systems or any organ in the body. However, they noted that most AEs are reversible except for some endocrine events. Hence, immune-related AEs, such as pneumonitis, hepatitis, thyroiditis, colitis, and myocarditis, can affect any part of the body and are monitored. However, the clinical experts also indicated that AEs with nivolumab plus ipilimumab are similar to those experienced with single-drug anti–PD-1 therapy and that most patients maintain a good quality of

life and can discontinue therapy. As a consequence, many patients only receive 2 or 3 cycles of treatments and remain cancer-free for years.

Discontinuing Treatment

The clinical experts suggested that disease progression and life-threatening toxicity are the reasons to discontinue treatment. One clinical expert also noted that about 15% of patients stop treatment due to toxicity with combination immunotherapy. However, after recovery from toxicity, many patients resume maintenance therapy with single-drug anti–PD-1 therapy.

Prescribing Conditions

One clinical expert noted that the treatment is typically given in an academic setting, as it requires an experienced, knowledgeable team to recognize and treat AEs, while another noted that nivolumab plus ipilimumab should be given by a medical oncologist with expertise in melanoma and immunotherapy in a community or regional cancer centre. The experts indicated that patients also need specialists to manage rare AEs, such as cardiac or neurologic AEs, and to consult the treating oncologist.

Additional Considerations

The clinical experts noted that immune therapy has revolutionized melanoma treatment. Many potentially curative therapies are now offered, albeit with an elevated risk of toxicity. Approving this combination in the second-line setting among patients who relapse during or within 6 months of anti–PD-1 therapy would allow the use of more single-drug therapy with better tolerability in the first-line and save the combination for those patients who are resistant to upfront therapy. They emphasized that this practice is already common in the US and Europe, involving access to combination treatment as second-line therapy regardless of when progression occurs.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

Clinician input was submitted by 1 clinician group: Ontario Health, Cancer Care Ontario CNS Cancer Drug Advisory Committee, which provides timely evidence-based clinical and health system guidance on drug-related issues in support of its mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. A consultant medical oncologist from Saskatchewan also provided input.

Unmet Needs

The treatment goals for patients with advanced melanoma are delaying disease progression, improving quality of life, and improving ORR and OS. The current treatments available for patients whose melanoma progresses during or within 6 months of anti–PD-1 therapy are ipilimumab monotherapy and *BRAF*-targeted therapy (for patients with a *BRAF* mutation). However, the clinicians noted evidence of lower response rate with ipilimumab monotherapy compared with ipilimumab plus nivolumab.[9] The clinician group also noted that there are limited treatment options for patients without a *BRAF* mutation and for patients whose melanoma has progressed following *BRAF*-targeted therapy.

The medical oncologist from Saskatchewan strongly advocated for access to combination treatment in the advanced melanoma setting and noted that treatment options are especially limited for patients whose melanoma progresses within 6 months of finishing adjuvant immunotherapy and do not have a *BRAF* mutation.

Place in Therapy

The clinician group noted that nivolumab plus ipilimumab would be indicated for patients who experience a relapse during or within 6 months of anti–PD-1 therapy, regardless of whether the drug was given previously in an adjuvant or metastatic setting and regardless of *BRAF* mutation status.

Patient Population

The clinician group suggested that nivolumab plus ipilimumab is suitable for patients with metastatic or recurrent disease in whom monotherapy has failed.

Assessing Response to Treatment

Clinical stabilization, radiographic response, and improvement in quality of life would indicate response to treatment.

Discontinuing Treatment

The clinician group noted that toxicity, clinical deterioration, and disease progression would be the reasons to consider treatment discontinuation.

Prescribing Conditions

The clinician group indicated that treatment is provided in an outpatient setting under a medical oncologist's advisement.

Additional Considerations

The clinician group and the medical oncologist emphasized that there is an unmet need for this patient population and highlighted that treatment with nivolumab plus ipilimumab for patients who relapse during or within 6 months of anti–PD-1 or anti–PD-L1 therapy is considered a standard in other countries such as the US and Australia. They also added that the National Comprehensive Cancer Network guidelines in the US do not exclude the use of ipilimumab plus nivolumab in patients whose melanoma has progressed during or within 6 months of anti–PD-1 or anti–PD-L1 therapy. The medical oncologist also suggested that, since the number of patients whose melanoma progresses during or within 6 months of anti–PD-1 therapy is small, this treatment option may not have a significant budget impact.

The medical oncologist said there is an unmet need in patients who receive single-drug immunotherapy and noted that, while most patients who are fit and able to tolerate combination immunotherapy would receive it up front, certain patients, including those with low-risk disease (i.e., low burden of disease), older age groups, and those with comorbidities, are treated with single-drug immunotherapy to minimize toxicity. However, when these patients' melanoma progresses on single-drug treatment, the addition of a CTLA-4 inhibitor such as ipilimumab to existing anti–PD-1 therapy is not funded, thus limiting treatment options for these patients.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's nonsponsored reimbursement 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 and are available in a separate document.

Industry Input

This section was prepared by CADTH, based on the input provided by industry.

Industry input was provided on the research protocol by Bristol Myers Squibb Canada, the manufacturer of nivolumab and ipilimumab in Canada. The industry noted that the project scope aligns with the needs of physicians, patients, and patient advocacy groups in Canada.

Bristol Myers Squibb Canada noted that adjuvant anti–PD-1 therapy following the resection of stage IIB/C, III, and IV melanoma is the current standard of care in Canada. Referring to current clinical practice, it noted that anti–PD1-based regimens, including nivolumab plus ipilimumab, nivolumab monotherapy, and pembrolizumab monotherapy, are used by most patients with advanced or metastatic melanoma in a first-line setting.[11] However, except in Canada, physicians worldwide can prescribe nivolumab plus ipilimumab for the first-line treatment of melanoma in the metastatic setting, regardless of the timing relative to the last dose of anti–PD-1 received as adjuvant treatment, allowing patients to benefit from efficacy associated with combination immunotherapy. It indicated that, without this option, patients in Canada whose melanoma progresses to unresectable or metastatic disease during or within 6 months from their last dose of anti–PD-1therapy received in the adjuvant treatment setting (also known as "rapid progressors") are not eligible for the public funding of nivolumab plus ipilimumab, representing one of the most significant treatment gaps in melanoma treatment in Canada.

Bristol Myers Squibb Canada noted that the current treatment algorithm in Canada limits the use of subsequent first-line regimens containing anti–PD-1 , including nivolumab plus ipilimumab, upon progression during or within the 6 months following an anti–PD-1 treatment in the adjuvant setting. This leaves ipilimumab monotherapy as the only approved treatment option for patients in Canada whose melanoma does not harbour a *BRAF* mutation (*BRAF* wild-type), as combination targeted therapy is available only for patients with a *BRAF* mutation. The input suggested that a 6-month washout period, as stipulated in the treatment algorithm, is not based on strong evidence but on a consultation process with local experts to help better understand appropriate use in clinical practice.[17] It indicated that patients in Canada are faced with choosing between adjuvant therapy with an anti–PD-1 antibody (nivolumab or pembrolizumab) in a potentially curative setting at the risk of not having access to nivolumab plus ipilimumab should their melanoma progress to unresectable or metastatic disease within a certain time frame or foregoing adjuvant treatment to retain access to nivolumab plus ipilimumab should they need it for advanced disease.

Noting published studies relevant to the clinical review,[8,9,18] Bristol Myers Squibb Canada highlighted that these studies and/or datasets in the post-adjuvant anti–PD-1 setting are limited and are based on data from patients treated with anti–PD-1 in the metastatic setting. Further, it emphasized that randomized clinical trials comparing nivolumab plus ipilimumab with ipilimumab monotherapy are no longer considered ethical in the context of the data available to date (that is, a lack of clinical equipoise) and therefore cannot be expected in the future.

Bristol Myers Squibb Canada added that lack of access to nivolumab plus ipilimumab has also expanded to patients with resected stage IIB/IIC disease. Pending a positive CADTH review of pembrolizumab for the neoadjuvant treatment of adult patients with stage III or stage IV melanoma, patients in Canada whose melanoma progresses after this therapy could fall into the same treatment gap. They noted that, according to experts in Canada and evidence from phase III adjuvant anti–PD-1 trials, an estimated 25% of patients receiving an anti–PD-1 Cr in the adjuvant setting will experience disease recurrence during or within 6 months. Approximately 200 patients in Canada will fall into this category annually. Thus, the budget impact of extending funding to nivolumab plus ipilimumab is small, as these patients are mainly already receiving ipilimumab.

Clinical Evidence

The clinical evidence included in the review of nivolumab plus ipilimumab is presented in this section. The section includes studies that were selected according to an a priori protocol. A second section, including indirect evidence selected from the literature that met the selection criteria specified in the review, was not included because no indirect evidence was considered relevant to the review.

Methods

A systematic literature review was performed to identify evidence on the efficacy and harms of nivolumab plus ipilimumab for first-line treatment of advanced melanoma when patients' melanoma progresses during or within 6 months of adjuvant anti–PD-1 therapy. Details of the search and selection procedures are available in Appendix 1. Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 6. Outcomes included in the CADTH review protocol reflect outcomes considered important to patients, clinicians, and drug plans.

In total, 1,949 records were identified; 1,944 were excluded by title and abstract; and no electronic literature and no grey literature were identified. Five potentially relevant full-text reports were retrieved for scrutiny. In total, 5 reports of 5 unique studies are included in the review (Figure 1, Appendix 2).

Table 6: Inclusion Criteria for the Systematic Literature Review

Criteria	Description
Patient population	Patients with advanced (unresectable or metastatic) melanoma that progresses during or within 6 months of adjuvant anti–PD-1 or anti–PD-L1 therapy
Intervention	Nivolumab and ipilimumab *Dosage*: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab 3 mg/kg every 4 weeks

Comparators	• Ipilimumab
	• *BRAF*-targeted therapy
	  ○ dabrafenib-trametinib
	  ○ cobimetinib-vemurafenib
	  ○ encorafenib-binimetinib

Outcomes	Efficacy: • Objective response rate • Overall survival • Progression-free survival Safety: • Adverse events
Study design	Randomized controlled trials and observational studies

Evidence Base

No studies were identified that reported results specifically for patients whose melanoma progressed during or within 6 months of adjuvant anti–PD-1 therapy and who were treated with nivolumab plus ipilimumab relative to a relevant comparator in the first-line advanced setting. Due to the lack of available evidence directly relevant to the review question, studies of indirect patient populations were considered; that is, studies were included if they reported results for patients whose melanoma progressed during any time frame (i.e., during or within 6 months of adjuvant anti–PD-1 therapy, or later) and who were treated with nivolumab plus ipilimumab during any line of treatment in the advanced setting.

A total of 5 studies (2 randomized controlled trials [RCTs] and 3 observational studies) were included in the review of nivolumab plus ipilimumab. These studies included a mix of patients with advanced melanoma who had received prior anti–PD-1 or anti–PD-L1 therapy either in the adjuvant or in the advanced setting (i.e., who were now being treated in the first or second-line advanced setting). In addition, none of these studies distinguished between patients whose melanoma progressed during or within 6 months of prior anti–PD-1 or anti–PD-L1 therapy and those whose melanoma progressed more than 6 months from prior anti–PD-1 or anti–PD-L1 therapy. These studies are considered the closest evidence available on the population of interest for this reimbursement review.

Characteristics of Included RCTs

Two randomized phase II RCTs that compared combination nivolumab plus ipilimumab to single-drug ipilimumab in patients with metastatic melanoma who had progressed on prior anti–PD-1 therapy are summarized in this section.

Study Design

NCT02731729 (Friedman et al.)[6] was a randomized phase II open-label trial that evaluated ipilimumab only and in combination with nivolumab in patients with progression of disease on anti–PD-1 monotherapy in the adjuvant or metastatic setting. The trial was ended early due to poor accrual after 20 patients were enrolled out of a planned 24 in the first stage (Table 7).

The SWOG Cancer Research Network clinical trial S1616 (VanderWalde et al.)[9] was a randomized phase II study conducted at 39 academic sites across the US that aimed to address whether CTLA-4 blockade, alone or in combination with continued PD-1 blockade, could reverse resistance to prior anti–PD-1 or anti–PD-L1, sequentially or concomitantly. All patients had advanced melanoma with primary resistance to anti–PD-1 or anti–PD-L1 treatment, defined as tumours having no objective clinical response (complete response [CR] or partial response [PR]) to the prior use of anti–PD-1 or anti–PD-L1 without intervening therapy for advanced disease, or with recurrence while on adjuvant anti–PD-1 or anti–PD-L1 therapy (Table 7).

Trial Eligibility Criteria

In NCT02731729, patients were eligible if they a had histologically confirmed, American Joint Committee on Cancer (AJCC) stage IV or inoperable stage III cutaneous, acral, or mucosal melanoma; had received prior treatment with an anti–PD-1 or anti–PD-L1 in the adjuvant or metastatic setting with evidence of clinical or radiological progression. There were no restrictions placed on time elapsed from the last anti–PD-1 or anti–PD-L1 dose. To be eligible, patients needed to have measurable disease based on RECIST 1.1 criteria, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and adequate kidney, hepatic, and bone marrow function. Patients previously treated with an anti-CTLA-4 antibody, history of an autoimmune disease, systematic or untreated brain metastases or leptomeningeal disease, or a history of grade 3 or 4 immune-related reactions or grade 3 pneumonitis were excluded (Table 7).

In S1616, eligible patients were aged 18 years or older with pathologically confirmed stage IV or unresectable stage III mucosal or cutaneous melanoma with melanoma that had progressed on prior treatment with anti–PD-1 or anti–PD-L1 without intervening therapy. To be eligible, patients had to have measurable disease based on RECIST 1.1, a Zubrod performance status of 0 to 2, and adequate hepatic, kidney, and hematologic function. Patients must not have had a confirmed PR or CR before progression. Patients with uveal melanoma, with active CNS metastases (unless adequately treated and free from symptoms), with a history of immune-related pneumonitis or colitis requiring steroid treatment, or who had prior treatment with ipilimumab or other CTLA-4 antibodies were excluded (Table 7).

Interventions

In NCT02731729, patients were randomly assigned 1: 1 via centralized randomization software to receive either nivolumab 1 mg/kg of body weight plus ipilimumab 3 mg/kg every 3 weeks for up to 4 doses, or

ipilimumab 3 mg/kg every 3 weeks for up to 4 doses. Randomization was stratified based on melanoma histological subtype, as well as prior response to anti–PD-1 therapy. Patients with primary refractory disease were those who had anti–PD-1 therapy within 2 months of study enrolment, and patients with progressive disease were those who received their last dose of PD-1 blocking antibody at least 2 months before enrolment. Nivolumab and ipilimumab were administered by IV infusion. Treatment was continued until disease progression or unacceptable toxicity. Patients could receive up to 4 cycles of treatment and were then observed for up to 2 years. There was no nivolumab maintenance therapy mandated in the protocol.

In S1616, patients were randomly assigned 3:1 to receive combination therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab 480 mg every 4 weeks for up to 2 years, or to ipilimumab 3 mg/kg every 3 weeks for 4 cycles. In the combination arm, nivolumab was administered intravenously over 30 minutes on day 1 of each cycle, and ipilimumab was administered intravenously over 90 minutes starting 30 minutes after the end of the nivolumab infusion on day 1 of the first 4 cycles. In the ipilimumab arm, ipilimumab was administered intravenously over 90 minutes on day 1 of the first 4 cycles only. In the ipilimumab arm, treatment continued until disease progression (per RECIST 1.1), development of unacceptable toxicities, or until the completion of 4 cycles of treatment, whichever was first. In the nivolumab plus ipilimumab arm, treatment continued until disease progression, development of unacceptable toxic AEs, or until 2 years of treatment with nivolumab, whichever was first. Treatment beyond initial progression was allowed if the investigators determined that the patient was clinically benefiting from the treatment. Dose reductions were not permitted, and dose delays due to toxicity were allowed up to 12 weeks.

End Points and Assessments

The efficacy end points identified in the CADTH review protocol that were assessed in the 2 RCTs are summarized in this section.

In NCT02731729, the primary end point was ORR, which was defined as either PR or CR defined by RECIST 1.1 criteria by week 18. Secondary end points included disease control rate, time to treatment failure, OS, and safety. OS was defined as the time from treatment initiation to death from any cause. Disease was assessed by CT or MRI of the chest, abdomen, and pelvis within 28 days before study treatment, and then at weeks 12 and 18 according to RECIST 1.1. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 during each cycle.

In S1616, the primary end point was PFS assessed according to RECIST 1.1 by the investigator and defined as the time between the date of randomization until the earliest date of documented disease progression or the date of death from any cause, whichever occurred first. Secondary end points included ORR and OS. Tumour response, according to RECIST 1.1, was assessed by the treating investigator every 12 weeks until disease progression. ORR was defined as a CR or PR to therapy according to RECIST 1.1. Tissue and blood biopsies were collected on or before day 1 of protocol treatment and on day 28 to 35 of protocol treatment. AEs were assessed continuously throughout the trial and for up to 30 days after completion of the trial using the National Cancer Institute CTCAE 5.0.

Statistical Analyses

NCT02731729 was not designed for hypothesis testing between treatment arms. An optimal Simon 2-stage design was used for each arm. The study initially planned to enrol 12 patients per arm, with a plan to enrol up to 35 patients per arm if at least 2 patients per arm responded in the first stage. Assuming 10% and 30% ORRs for the null and alternative hypotheses, the design would yield type I (false-positive) and type II (false-negative) errors of 0.10. Ultimately, the trial was closed early due to slow accrual, following the randomization of 20 patients. Confidence intervals for ORR were calculated using the Clopper-Pearson method, and OS was estimated using the Kaplan-Meier method. For OS, patients who were alive and had not started another therapy at the time of database lock were censored at the date of the last follow-up. There were no reported adjustments for multiple testing.

In S1616, the primary end point analysis was performed once the protocol-specified anticipated number of 78 PFS events had occurred, with data lock date of March 9, 2022, at a time when the median follow-up among patients last known to be alive and progression-free was 28 months (range, 4 to 40 months). Per the investigators, a total of 84 patients with 78 events would provide 89% power for a 1-sided alpha of 10% using a log-rank test. This data lock date was used for the PFS analysis, as it was event-driven and conducted at the specified event timing based on the protocol. All other analyses used the final data lock date of November 3, 2022, when the median follow-up among patients last known to be alive was 36 months (range, 4 to 55 months). The Kaplan-Meier method was used to estimate survival outcomes, and log-rank tests were used to evaluate associations with the outcomes. Fisher's exact test and the Wilcoxon rank sum test were used to assess differences in categorical and continuous variables, respectively, across treatment arms. There were no reported adjustments for multiple testing.

Table 7: Characteristics of Included RCTs

Detail	NCT02731729 (Friedman et al.)	S1616 (VanderWalde et al.)
Study design	Randomized multicentre open-label phase II trial	Randomized multicentre open-label phase II trial
Locations	US (4 centres)	US (39 centres)
Enrolment dates	June 2016 to May 2018	July 2017 to July 2020
Randomization	Ratio 1:1 Stratified by melanoma histological subtype and prior response to anti–PD-L1 therapy	Ratio 3:1 No stratification
Number randomized	20 (1 patient withdrew consent before treatment in the ipilimumab arm) Nivolumab + ipilimumab (n = 10) Ipilimumab (n = 10)	94 Nivolumab + ipilimumab (n = 70) Ipilimumab (n = 24)
Inclusion criteria	• Histologically confirmed, AJCC stage IV or inoperable stage III cutaneous, acral, or mucosal melanoma • Prior treatment with a PD-1 inhibitor in the adjuvant or metastatic setting with evidence	• At least 18 years old • Pathologically confirmed melanoma that was either stage IV or unresectable stage III • Measurable disease using RECIST 1.1. However, if the only measurable disease was cutaneous or

Detail	NCT02731729 (Friedman et al.)	S1616 (VanderWalde et al.)
	of clinical or radiological progression • Measurable disease based on RECIST 1.1 • ECOG performance status score of 0 to 1 • Adequate kidney, hepatic, and bone marrow function	subcutaneous, lesions must have been at least 10 mm in greatest dimension and could be serially recorded using calipers and photographs • Prior treatment with anti–PD-1 or anti–PD-L1 drugs • Documented disease progression either while on anti–PD-1 or anti–PD-L1 drugs or after stopping therapy without intervening therapy • No confirmed PR or CR to anti–PD-1 or anti–PD-L1 drugs before progression • No active central nervous system metastases unless they were adequately treated and patient was symptom-free without requiring steroids for 14 days before registration. • Zubrod performance status of 0 to 2, and adequate hepatic, kidney, and hematologic function
Exclusion criteria	• Prior treatment with a CTLA-4 antibody • History of autoimmune disease • Symptomatic or untreated brain metastases or leptomeningeal disease • History of a grade 4 immune-related toxicity or grade 3 pneumonitis	• Uveal melanoma • Prior treatment with ipilimumab or other CTLA-4 antibodies • History of immune-related pneumonitis or colitis requiring steroid treatment
Intervention (daily dose)	Nivolumab + ipilimumab (nivolumab 1 mg/kg of body weight plus ipilimumab 3 mg/kg every 3 weeks for up to 4 doses)	Nivolumab + ipilimumab (nivolumab 1 mg/kg of body weight and ipilimumab 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab 480 mg every 4 weeks for up to 2 years)
Comparators	Ipilimumab (3 mg/kg every 3 weeks for 4 doses)	Ipilimumab (3 mg/kg every 3 weeks for 4 cycles)
Discontinuation	Until disease progression or unacceptable toxicity	Until disease progression or unacceptable toxicity
Follow-up	2 years	Median 28 months
Primary end point	ORR (per RECIST 1.1)	PFS (per RECIST 1.1)
Secondary end points	• Disease control rate • Time to treatment failure • OS • Safety	• Change in CD8 T-cell infiltrate between responding and nonresponding tumours • ORR • OS • Toxicity
Publications	Friedman et al.	VanderWalde et al.
Sources of support	Parker Institute for Cancer Immunotherapy, Bristol Myers Squibb, and MSK Cancer Center	Government (NIH and NCI)

CR = complete response; MSK = Memorial Sloan Kettering; NCI = National Cancer Institute; NIH = US National institutes of Health; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria for Solid Tumours.

Source: Friedman et al.,[6] and VanderWalde et al.[9]

Results of the Included RCTs

Trial Population and Baseline Characteristics

NCT02731729 randomized 20 patients from 4 centres in the US between June 2016 and May 2018. One patient was randomized to the ipilimumab monotherapy arm but withdrew consent before starting treatment. This patient was excluded from the efficacy analyses. The trial was ended early due to slow accrual. In the efficacy-evaluable population, 12 patients (63%) discontinued study treatment prematurely, most frequently due to disease progression (n = 5, 26%) or AEs (n = 5, 26%). The median number of treatment cycles was 4 (range 2 to 4) in the ipilimumab arm and 3 (range 1 to 4) in the ipilimumab plus nivolumab arm. All patients were followed up for a minimum of 7.6 months (median 12.2 months). There were some imbalances across the treatment arms, likely due to the small sample size. Patient characteristics are shown in Table 8.

The S1616 trial registered 94 patients between July 17, 2017, and July 15, 2020. Of these, 92 met eligibility criteria (2 patients were found to be ineligible after randomization and were excluded from analyses); 91 received study therapy. There were some notable imbalances in patient characteristics across the treatment arms. In the nivolumab plus ipilimumab arm compared with the ipilimumab arm, there were more patients aged less than 65 years (51% versus 39%); fewer patients had elevated LDH at baseline (13% versus 26%); more patients had stage IV disease (83% versus 74%); more patients had not received prior adjuvant therapy (84% versus 74%); and fewer patients had received priori anti–PD-1 or anti–PD-L1 metastatic therapy (78% versus 87%), whereas more had received other anti–PD-1 or anti–PD-L1 combination metastatic therapy (12% versus 4%). All eligible patients had received prior anti–PD-1 or anti–PD-L1 therapy without intervening therapy, with 10% in the nivolumab plus ipilimumab arm and 13% in the ipilimumab arm having received anti–PD-1 therapy in the adjuvant setting; 65% of patients in the ipilimumab arm and 64% of patients in the ipilimumab plus nivolumab arm had received prior anti–PD-1 or anti–PD-L1 therapy for less than 6 months. Most (> 90%) patients in both arms were white; approximately two-thirds were male; approximately two-thirds had a Zubrod performance status of 0; and most (> 90%) had brain or CNS involvement at baseline (Table 9).

Table 8: Baseline Characteristics — NCT02731729 (Friedman et al.)

Characteristic	Ipilimumab (N = 9)	Nivolumab + ipilimumab (N = 10)
Age (years), median (range)	66 (35 to 83)	56 (39 to 66)
Sex, n (%)		
Male	6 (67)	9 (90)
Female	3 (33)	1 (10)
Race, n (%)		
Asian	0	1 (10)
White	9 (100)	7 (70)
Other	0	2 (20)

Characteristic	Ipilimumab (N = 9)	Nivolumab + ipilimumab (N = 10)
ECOG performance status score, n (%)		
0	6 (67)	7 (70)
1	3 (33)	3 (30)
M stage, n (%)		
M0	3 (33)	1 (10)
M1a	1 (11)	2 (20)
M1b	2 (22)	3 (30)
M1c without brain metastases	3 (33)	4 (40)
Type of melanoma, n (%)		
Acral	1 (11)	1 (10)
Cutaneous	7 (89)	8 (90)
Mucosal	1 (11)	1 (10)
Lactate dehydrogenase (unit/L), median (range)	208 (152 to 1,800)	214 (157 to 310)
Genomic driver, n (%)		
BRAF	2 (22)	3 (30)
NRAS	4 (44)	2 (20)
Other/unknown	3 (33)	5 (50)
Prior treatment, n (%)		
Anti–PD-1	9 (100)	10 (100)
Other[a]	1 (11)	3 (30)
Time since last anti–PD-1 treatment (weeks), median (range)	6.0 (3 to 55)	4.3 (2 to 36)
Best response to prior anti–PD-1 or treatment, n (%)		
Stable disease	1 (11)	0
Progressive disease	6 (67)	9 (90)
Unknown	2 (22)	1 (10)

ECOG = Eastern Cooperative Oncology Group.

[a]Other prior treatments include talimogene laherparepvec (patient randomized to ipilimumab), high-dose interferon, dabrafenib plus trametinib, and vemurafenib plus cobimetinib.

Source: Friedman et al.[6]

Table 9: Baseline Characteristics — S1616 (VanderWalde et al.)

Characteristic	Ipilimumab (N = 23)	Nivolumab + ipilimumab (N = 69)
Age (years), median (range)	69 (40 to 91)	64 (34 to 90)
Age, n (%)		
< 65 years	9 (39)	35 (51)
≥ 65 years	14 (61)	34 (49)
Sex, n (%)		
Male	15 (65)	46 (67)
Female	8 (35)	23 (33)
Race, n (%)		
White	22 (96)	63 (91)
Black	0 (0)	1 (1)
Asian	1 (4)	3 (4)
Unknown	0 (0)	2 (3)
Performance status, n (%)		
0	15 (65)	45 (65)
1	6 (26)	20 (29)
2	2 (9)	4 (6)
LDH at baseline, n (%)		
Elevated LDH	6 (26)	9 (13)
Normal LDH	5 (22)	28 (41)
LDH not done	12 (52)	32 (46)
AJCC melanoma classification, n (%)		
Stage III	6 (26)	12 (17)
Stage IV	17 (74)	57 (83)
Adjuvant therapy, n (%)		
No prior adjuvant therapy	17 (74)	58 (84)
Adjuvant anti–PD-1 or anti–PD-L1	3 (13)	7 (10)
Adjuvant *BRAF*/*MEK*	0 (0)	2 (3)
Other adjuvant therapy	3 (13)	2 (3)
Prior metastatic therapy, n (%)		
Adjuvant therapy only	1 (4)	6 (9)
Anti–PD-1 or anti–PD-L1 only	20 (87)	54 (78)

Characteristic	Ipilimumab (N = 23)	Nivolumab + ipilimumab (N = 69)
BRAF/*MEK* followed by anti–PD-1 or anti–PD-L1	1 (4)	1 (1)
Other anti–PD-1 or anti–PD-L1 combination	1 (4)	8 (12)
Duration of prior anti–PD-1 or anti–PD-L1 therapy, n (%)		
< 6 months	15 (65)	44 (64)
≥ 6 months	8 (35)	25 (36)
Brain/CNS involvement at baseline, n (%)		
Yes	2 (9)	5 (7)
No	21 (91)	64 (93)

CNS = central nervous system; LDH = lactate dehydrogenase.

Note: Patient characteristics among randomized patients. Two-sided P values from Wilcoxon(quantitative covariates) and Fisher's exact (categorical covariates) reported.

Source: VanderWalde et al.[9]

VanderWalde A, Bellasea SL, Kendra KL, et al., Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma: a randomized phase 2 trial, Nat Med., 29(9):2278 to 2285, 2023, reproduced with permission from Springer Nature. https://www.nature.com/nm/

Efficacy

Only those efficacy outcomes identified as relevant in the review protocol are reported in this section (Table 10).

Overall Response Rate

In NCT02731729, objective responses were observed in 5 of 9 (56%; 95% CI, 21% to 86%) evaluable patients in the ipilimumab arm and 2 of 10 (20%; 95% CI, 3% to 56%) in the ipilimumab plus nivolumab arm at week 18. One patient in the ipilimumab arm achieved a best response of CR; 4 patients in the ipilimumab arm and 2 patients in the ipilimumab plus nivolumab arm achieved a PR. No between-group difference was reported.

In S1616, ORR was 28% (90% CI, 19% to 38%) in the nivolumab plus ipilimumab arm and 9% (90% CI, 2% to 25%) in the ipilimumab arm (P = 0.05, 1-sided Fisher's exact test). Eight patients (12%) in the nivolumab plus ipilimumab arm had a CR, and 11 (16%) had a PR. No patients in the ipilimumab arm achieved a CR, and 2 (9%) achieved a PR. No between-group difference in ORR was reported. Among patients with a response, the 2 patients receiving ipilimumab only had ongoing responses of more than 16 and more than 33 months, respectively, while 9 of 19 (47%) patients in the nivolumab plus ipilimumab arm had responses over a range of 6 to more than 37 months. The median duration of response in the nivolumab plus ipilimumab arm was 40.9 months (90% CI, 8 to not reached [NR]), while the median response duration could not be estimated for the patients in the ipilimumab only arm due to the small sample size.

Overall Survival

In NCT02731729, the median OS was not reached in either arm; 2 deaths (22%) were observed in the ipilimumab arm and 2 deaths (20%) in the ipilimumab plus nivolumab arm; none were attributed to the study drug.

S1616 was not powered to detect differences in OS, and survival data were collected as a secondary end point. At the time of the last data lock (November 3, 2022) the HR for OS was 0.83 (90% CI, 0.50 to 1.39; P = 0.28).

Progression-Free Survival

PFS was not an outcome in the NCT02731729 trial.

In S1616, the HR for PFS for nivolumab plus ipilimumab versus ipilimumab only was 0.63 (90% CI, 0.41 to 0.97; P = 0.04; prespecified 1-sided alpha 0.1). The 6-month KM-estimated probabilities of PFS were 34% (90% CI, 25% to 43%) and 13% (95% CI, 4% to 27%) for nivolumab plus ipilimumab versus ipilimumab, respectively.

Table 10: Summary of Efficacy Results — RCTs

Outcome	NCT02731729 (Friedman et al.)		S1616 (VanderWalde et al.)	
	Ipilimumab (N = 9)	Nivolumab + ipilimumab (N = 10)	Ipilimumab (N = 23)	Nivolumab + ipilimumab (N = 69)
ORR	5 (56%) (95% CI, 21% to 86%)	2 (20%) (95% CI, 3% to 56%)	9% (90% CI, 2% to 25%)	28% (90% CI, 19% to 38%)
			P = 0.05[a]	
CR, n (%)	1 (11)	0	0	8 (12)
PR, n (%)	4 (44)	2 (20)	2 (9)	11 (16)
OS	Median NE (95% CI, 11.5 to NE)	Median NE (95% CI, 1.6 to NE)	HR = 0.83[b] (90% CI, 0.50 to1.39) P = 0.28	
PFS	Not an outcome		HR = 0.63 (90% CI, 0.41 to 0.97) One-sided log-rank P value = 0.036	
KM estimated probability of PFS at 6 months	NA		34% (90% CI, 25% to 43%)	13% (90% CI, 4% to 27%)

CI = confidence interval; CR = complete response; HR = hazard ratio; KM = Kaplan-Meier; NA = not applicable; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

Note: P values were not adjusted for multiple comparisons.

[a]One-sided Fisher's exact test. No threshold for significance was prespecified.

[b]Study S1616 was not powered to detect differences in OS, and survival data were collected as a secondary end point.

Source: Friedman et al.[6] and VanderWalde et al.[9]

Harms

Of the 19 patients in NCT02731729 who received at least 1 dose of study drug and were evaluable for safety, all but 1 experienced at least 1 treatment-related AE (TRAE), as assessed by the investigator. More patients in the nivolumab plus ipilimumab arm experienced treatment-related diarrhea (60% versus 33%), aspartate aminotransferase (AST) increase (50% versus 22%), alanine aminotransferase (ALT) increase (40%

versus 11%), hypophysitis (30% versus 11%), and hypotension (20% versus 0%), whereas fewer experienced treatment-related colitis (10% versus 22%) and hypokalemia (10% versus 22%). Forty percent of patients in the nivolumab plus ipilimumab arm and 56% in the ipilimumab arm experienced grade 3 or 4 TRAEs; no single grade 3 or 4 AE occurred in more than 2 patients in either treatment arm. TRAEs led to treatment withdrawal in 4 patients in the ipilimumab plus nivolumab arm, including 2 patients with diarrhea (grades 1 and 2), 1 patient with an elevated AST and ALT (grade 2), and 1 patient with hypophysitis (grade 2). One patient in the ipilimumab arm discontinued treatment due to adrenal insufficiency and infection (both grade 3) (Table 11).

In S1616, in the nivolumab plus ipilimumab arm, 34 patients (50%) experienced a maximum of grade 3 TRAEs (as assessed by the investigator), 4 patients (6%) experienced a grade 4 TRAE, and 1 patient (1%) experienced a grade 5 TRAE (disseminated intravascular coagulation); 20 patients (29%) discontinued protocol therapy due to toxicity. In the ipilimumab arm, 5 patients (22%) experienced a maximum of grade 3 TRAE, 2 patients (9%) experienced grade 4 TRAEs, and 1 patient (4%) experienced a grade 5 TRAE (colonic perforation); 4 patients (17%) discontinued therapy due to toxicity. In both treatment arms, the most frequent grade 3 or higher AE was diarrhea (13% in both arms) (Table 12). Treatment-related grade 3 or higher AST and ALT increase occurred in 7% of patients in each arm, whereas other grade 3 or higher TRAEs occurred less frequently.

Table 11: Summary of Treatment-Related Adverse Events — NCT02731729 (Friedman et al.)

Event	Ipilimumab (N = 9)		Nivolumab + ipilimumab (N = 10)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any TRAE, n (%)	9 (100)	5 (56)	9 (90)	4 (40)
Pruritus	5 (56)	0	5 (50)	0
Maculopapular rash	3 (33)	0	4 (40)	0
Diarrhea	3 (33)	1 (11)	6 (60)	2 (20)
Colitis	2 (22)	2 (22)	1 (10)	0
Alanine aminotransferase increased	2 (22)	0	5 (50)	1 (10)
Aspartate aminotransferase increased	1 (11)	0	4 (40)	1 (10)
Hyponatremia	2 (22)	1 (11)	2 (20)	0
Hypokalemia	2 (22)	1 (11)	1 (10)	1 (10)
Arthralgia	2 (22)	0	1 (10)	0
Hypophysitis	1 (11)	0	3 (30)	0
Adrenal insufficiency	1 (11)	1 (11)	0	0
White blood cell count decreased	2 (22)	1 (11)	1 (10)	0
Neutrophil count decreased	1 (11)	1 (11)	1 (10)	0

Event	Ipilimumab (N = 9)		Nivolumab + ipilimumab (N = 10)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Urinary tract infection	1 (11)	1 (11)	0	0
Hypotension	0	0	2 (20)	1 (10)
TRAE leading to discontinuation, n (%)	1 (11)	1 (11)	4 (40)	0

TRAE = treatment-related adverse event.

Source: Friedman et al.[6]

Table 12: Grade 3 or Higher Treatment-Related Toxicities in at Least 4% of Patients in Either Arm — S1616 (VanderWalde et al.)

Event, n (%)	Ipilimumab (N = 23)	Nivolumab + ipilimumab (N = 68)
Diarrhea	3 (13)	9 (13)
Aspartate aminotransferase increased	2 (7)[a]	5 (7)
Alanine aminotransferase increased	2 (7)[a]	5 (7)
Rash	1 (4)	4 (6)
Fatigue	1 (4)	4 (6)
Anemia	0 (0)	4 (6)
Hypotension	0 (0)	4 (6)
Hyponatremia	1 (4)	4 (6)[a]
Pruritus	0 (0)	3 (4)
Vomiting	0 (0)	3 (4)
Endocrine disorders (other)	0 (0)	3 (4)
Increased alkaline phosphatase	1 (4)	2 (3)
Colitis	0 (0)	3 (4)[a]
Hypokalemia	0 (0)	3 (4)[a]
Adrenal insufficiency	1 (4)	3 (4)[a]
Atrial fibrillation	1 (4)	1 (1)
Bilirubin increased	1 (4)	0 (0)
Hypophosphatemia	1 (4)	0 (0)
Hyperglycemia	1 (4)[a]	0 (0)
Colonic perforation	1 (4)	0 (0)

AE = adverse event.

[a]One each of these events was grade 4.
Source: VanderWalde et al.[9]

Characteristics of Included Observational Studies

Study Design and Patient Population

The earliest study identified that evaluated the efficacy of ipilimumab only or in combination with nivolumab after treatment failure to anti–PD-1 therapy was a retrospective study of patients with advanced melanoma from 12 centres in the US and Europe by Zimmer et al. Patients with stage III or IV melanoma (per AJCC seventh edition criteria) who had received at least 1 dose of ipilimumab or ipilimumab and nivolumab, either on or off a trial, and had documented disease progression on prior anti–PD-1 therapy per RECIST 1.1 were identified via electronic medical records and pharmacy databases at the participating centres.

The second study by Baron et al. was a retrospective cohort study using real-world data from the Flatiron Health database, including de-identified electronic health record data from more than 265 cancer clinics across the US. This study compared the OS of patients with unresectable or metastatic melanoma treated in the front-line setting with anti–PD-1 antibodies who subsequently received either second-line ipilimumab or ipilimumab plus nivolumab. Patients with incomplete records or less than 1 month of follow-up were excluded.

The third study, conducted by Pires da Silva et al., was a multicentre retrospective cohort study at 15 melanoma centres in Australia, Europe, and the US that evaluated the safety and efficacy of ipilimumab plus anti–PD-1 (nivolumab or pembrolizumab) compared with ipilimumab monotherapy in patients with metastatic melanoma (unresectable stage III and IV) whose melanoma progressed or recurred during or after anti–PD-1 or anti–PD-L1 therapy (nivolumab, pembrolizumab, atezolizumab) in the adjuvant or metastatic setting.

Treatments

Two of the retrospective studies compared single-drug ipilimumab to ipilimumab plus nivolumab (Zimmer et al. and Baron et al.) after anti–PD-1 treatment failure. One of the retrospective studies (Pires da Silva et al.) compared ipilimumab to combination ipilimumab and anti–PD-1 therapy with either nivolumab or pembrolizumab after anti–PD-1 or anti–PD-L1 treatment failure (Table 13).

End Points and Statistical Analyses

ORR, defined as the proportion of patients with a PR or CR to treatment, was reported in 2 of the studies (Zimmer et al. and Pires da Silva et al.). All 3 studies reported OS and PFS. PFS was defined as time from the first dose of ipilimumab or ipilimumab plus nivolumab to the first date of documented progression as per RECIST 1.1, or date of death, whichever came first. Baron et al. used time to next therapy or death as a surrogate for PFS. OS was defined as time from the first administration of ipilimumab or ipilimumab and nivolumab to death from any cause.

Zimmer et al. estimated PFS and OS using the Kaplan-Meier method. Between-group differences were not tested.

Baron et al. compared OS from the initiation of second-line therapy between the 2 treatment groups using Kaplan-Meier curves and log-rank analyses. Time to next therapy or death was used as a proxy for PFS and was estimated in a hierarchical fashion: for patients who received treatment with a third line of therapy, time to next therapy or death was measured as the difference between the initiation of second-line therapy and third-line therapy. For patients who died without receiving a third line of therapy, time to next therapy or death was measured as the difference between the date of initiation of second-line therapy and the date of death. Patients who did not receive third-line therapy and were alive at the time of analysis were censored at the date of last follow-up.

Pires da Silva et al. assessed tumour response per standard of care (CT or PET–CT scans every 3 months) based on RECIST 1.1, according to the physicians' best estimate, but no confirmatory scans were done. The study end points were ORR, PFS, OS, and safety of ipilimumab compared with ipilimumab plus anti–PD-1. AEs were monitored from initiation of anti–PD-1 monotherapy, and the severity of treatment-related AEs was graded according to the CTCAE version 4.03. ORR and AEs were reported as proportions in each treatment group, and the between-group differences were tested using Pearson's x^2 test or Fisher's exact text. Survival curves were estimated using the Kaplan-Meier method, stratified by treatment. The log-rank test was used to compare PFS and OS between the treatment groups. The proportional hazards assumption was evaluated graphically and using the Schoenfeld residuals test.

Table 13: Characteristics of Included Studies — Observational Studies

Characteristic	Zimmer et al.	Baron et al.	Pires da Silva et al.
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort
Country and data source(s)	US, Europe (12 tertiary referral centres)	US real-world data: Flatiron Health (electronic health records data from more than 265 cancer clinics)	Australia, Europe, US (15 centres)
Study year	January 2010 to June 2016	Not reported	February 2011 to February 2020
Number of patients	84 Ipilimumab (n = 47) Ipilimumab + nivolumab (n = 37)	57 Ipilimumab (n = 22) Ipilimumab + nivolumab (n = 35)	355 Ipilimumab (n = 162) Ipilimumab + nivolumab (n = 193)
Patient population	Patients with advanced melanoma who were treated with nivolumab + ipilimumab or ipilimumab only after anti–PD-1 treatment failure. • histologically proven unresectable stage III or IV melanoma (AJCC seventh edition) • received at least 1 dose of ipilimumab or ipilimumab and nivolumab, either on or off a trial • documented disease progression	Patients with unresectable/ metastatic melanoma who were treated with single-drug anti–PD-1 in the front-line setting and who subsequently received second-line ipilimumab or ipilimumab + nivolumab.	Patients with metastatic melanoma who were resistant to anti–PD-1 or anti–PD-L1 in the adjuvant or metastatic setting, and who received ipilimumab only or ipilimumab + anti–PD-1. • age 18 years and older • metastatic melanoma (unresectable stage III and IV) • received anti–PD-1 or anti–PD-L1 (nivolumab, pembrolizumab,

Characteristic	Zimmer et al.	Baron et al.	Pires da Silva et al.
	on prior anti–PD-1 therapy as per RECIST1.1		atezolizumab) in the adjuvant or metastatic setting • progression (per RECIST 1.1 on prior anti–PD-1 or anti–PD-L1 monotherapy; no confirmatory scans) • no prior use of ipilimumab (previous systemic treatments, including *BRAF* inhibitors + *MEK* inhibitors, other immune checkpoint inhibitors, and chemotherapy, were allowed)
Treatments (dosage)	• Ipilimumab (3 mg/kg every 3 weeks for 4 IV infusions) • Ipilimumab + nivolumab (3 or 1 mg/kg) given in combination with nivolumab (1 or 3 mg/kg); the combination was typically administered for up to 4 infusions followed by nivolumab maintenance therapy at 3 mg/kg every 2 weeks)	• Ipilimumab (dose not reported) • Ipilimumab + nivolumab (dose not reported)	• Ipilimumab (3 mg/kg every 3 weeks) • Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg) or pembrolizumab (2 mg/kg)
Disease setting	Unclear	Second-line advanced	First- and second-line advanced
Follow-up, median	Ipilimumab group: 6 months (range, 1 to 63 months) Ipilimumab + nivolumab group: 4 months (range, 1 to 12 months)	14.7 months	22.1 months
End points	• ORR • Duration of disease control • PFS • OS	• OS • Time to next therapy or death (used as a surrogate for PFS)	• ORR • PFS • OS • Safety
Publications	Zimmer et al.	Baron et al.	Pires da Silva et al.
Funding	None	None	None

AJCC = American Joint Committee on Cancer; ORR = overall response rate; OS = overall survival; PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours.

Source: Zimmer et al.,[10] Baron et al.,[5] Pires da Silva et al.[8]

Results of the Included Observational Studies

Patient Characteristics and Disposition

Zimmer et al. included 47 patients who were treated with at least 1 dose of ipilimumab and 37 patients who were treated with at least 1 dose of ipilimumab plus nivolumab after treatment failure to prior anti–PD-1 therapy. Patients in the combination group were younger (56 versus 65 years), were more likely to have a *BRAF* V600 mutation (43% versus 15%), and were more likely to have received systemic treatment between

termination of anti–PD-1 therapy and initiation of ipilimumab plus nivolumab (41% versus 11%) compared with patients in the ipilimumab group. More patients in the combination group were female (46% versus 36%), more had the uvea as primary melanoma site (13.5% versus 6%) (whereas fewer had the skin as the primary site; 68% versus 77%), fewer had brain metastases (32% versus 45%), more had an ECOG performance status score of 2 (13% versus 2%), more had prior therapy with a *BRAF* and/or *MEK* inhibitor (43% versus 19%), ipilimumab (43% versus 26%), or pembrolizumab (65% versus 53%) (whereas fewer had prior therapy with nivolumab; 35% versus 47%), more had received 3 or more prior therapies (52% versus 30%), and fewer received sequential treatment (59% versus 89%). More patients in the combination group had received prior therapy with ipilimumab and were subsequently re-treated (26% versus 43%). All patients had undergone interval treatment with anti–PD-1 therapy with subsequent progression. Disease control rate (PR, CR, stable disease) to prior anti–PD-1 therapy was 40% in the ipilimumab group and 30% in the combination group. The ORR to prior anti–PD-1 therapy in the ipilimumab and the combination group were 19% and 16%, respectively. The median time to progression on prior anti–PD-1 therapy was 3 months (range, 0.8 to 20.2 months) (Table 14).

Four patients in each group died before the assessment of change in tumour burden and were not evaluable for efficacy assessment. Twenty-five patients (53%) in the ipilimumab group received all 4 doses of ipilimumab and 21 patients (45%) stopped treatment early due to side effects and/or clinical deterioration. In the combination group, 15 patients (41%) received fewer than 4 doses of ipilimumab and nivolumab, due to disease progression (67%) or toxicity (33%). The median interval between the last dose of anti–PD-1 therapy and the first dose of ipilimumab or ipilimumab plus nivolumab was 28 days (range, 7 to 660 days) and 42 days (range, 1 to 588 days), respectively.

Table 14: Baseline Characteristics — Zimmer et al.

Characteristic	Ipilimumab (N = 47)	Ipilimumab + nivolumab (N = 37)
Age in years, median (range)	65 (29 to 80)	56 (27 to 81)
Sex, n (%)		
Female	17 (36)	17 (46)
Male	30 (64)	20 (54)
Primary site, n (%)		
Skin	36 (77)	25 (68)
Unknown primary site	4 (8.5)	5 (13.5)
Mucosal	4 (8.5)	2 (5)
Uveal	3 (6)	5 (13.5)
Mutation status, n (%)		
Wild-type	38 (81)	18 (49)
BRAF V600	7 (15)	16 (43)

Characteristic	Ipilimumab (N = 47)	Ipilimumab + nivolumab (N = 37)
Unknown	2 (4)	3 (8)
AJCC stage, n (%)		
Stage III, N3	0	1 (3)
Stage IV, M1b	0	1 (3)
Stage IV, M1c	47 (100)	35 (94)
Brain metastases, n (%)		
No	26 (55)	25 (68)
Yes	21 (45)	12 (32)
LDH, n (%)		
Normal	11 (23)	11 (30)
Elevated	31 (66)	24 (65)
< 2 × ULN	28 (59)	27 (73)
≥ 2 × ULN	14 (30)	8 (22)
Unknown	5 (11)	2 (5)
ECOG performance status, n (%)		
0	23 (49)	22 (59)
1	23 (49)	10 (27)
2	1 (2)	5 (14)
0 + 1	46 (98)	32 (87)
2	1 (2)	5 (13)
Prior systemic therapy, n (%)		
BRAF ± *MEK* inhibitor	9 (19)	16 (43)
Ipilimumab	12 (26)	16 (43)
Nivolumab	22 (47)	13 (35)
Pembrolizumab	25 (53)	24 (65)
Number of prior therapies, n (%)		
1	26 (55)	9 (24)
2	7 (15)	9 (24)
≥ 3	14 (30)	22 (52)
1 + 2	33 (70)	18 (49)
≥ 3	14 (30)	19 (51)
Sequential treatment, n (%)[a]		
Yes	42 (89)	22 (59)

Characteristic	Ipilimumab (N = 47)	Ipilimumab + nivolumab (N = 37)
No	5 (11)	15 (41)

AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ULN = upper limit of normal.

[a]Ipilimumab or ipilimumab plus nivolumab directly after progression of prior anti–PD-1 therapy.

Source: Zimmer et al.[10]

Baron et al. included 57 patients with metastatic or unresectable melanoma who had received treatment with front-line anti–PD-1 treatment and who were subsequently treated with either ipilimumab (n = 22) or ipilimumab plus nivolumab (n = 35) in the second-line setting. The median duration of treatment with front-line anti–PD-1 therapy was 3.9 months (interquartile range [IQR] = 3.0 to 6.7 months). Few baseline demographic and disease characteristics were reported, and information about some baseline characteristics was limited due to missing data. Fewer patients who received ipilimumab plus nivolumab compared with ipilimumab only had an ECOG performance status greater than 1 (4% versus 21% based on data from 39 patients), fewer had a pathogenic somatic *NRAS* mutation (35% versus 85% based on data from 24 patients), fewer had the site of origin at the head and neck (3% versus 29%) or upper extremity (3% versus 15%) (whereas more had an unknown site of origin; 77% versus 59%), and fewer had received third-line or more therapy (9% versus 32%) (Table 15).

Table 15: Baseline Characteristics — Baron et al.

Characteristic	Ipilimumab (N = 22)	Ipilimumab plus nivolumab (N = 35)
Age, mean	73	67
ECOG > 1, % (n/N)	21 (31/14)	4 (1/25)
LDH > ULN, % (n/N)	50 (3/6)	43 (3/7)
Presence of *BRAF* mutation, % (n/N)	15 (3/20)	17 (6/35)
Presence of *KIT* mutation, % (n/N)	0 (0/5)	0 (0/16)
Presence of *NRAS* mutation, % (n/N)	85 (6/7)	35 (6/17)
PD-L1 > 0, % (n/N)	0 (0)	14 (1/7)
Site of origin, % (n/N)		
Head and neck	29 (2/22)	3 (1/35)
Trunk	14 (3/22)	14 (5/35)
Upper extremity	14 (3/22)	3 (1/35)
Lower extremity	5 (1/22)	3 (1/35)
Unknown	59 (13/22)	77 (27/35)
Front-line treatment, % (n/N)		
Nivolumab	72 (16/22)	65 (23/35)

Characteristic	Ipilimumab (N = 22)	Ipilimumab plus nivolumab (N = 35)
Pembrolizumab	27 (6/22)	34 (12/35)
Third-line therapy or greater	32 (7/22)	9 (3/35)

ECOG = Eastern Cooperative Cancer Group; LDH = lactate dehydrogenase; ULN = upper limit of normal.

Source: Baron et al.[5]

Pires da Silva et al. included 355 patients with metastatic melanoma resistant to anti–PD-1 or anti–PD-L1 monotherapy (29.5% nivolumab, 69.5% pembrolizumab, 1% atezolizumab), who had been treated with ipilimumab only (n = 162 [46%]) or ipilimumab plus nivolumab or pembrolizumab (n = 193 [54%]). Most patients (n = 311 of 355) were receiving anti–PD-1 or anti–PD-L1 in the metastatic setting; most of these patients (72% in both treatment groups) had innate resistance to anti–PD-1 or anti–PD-L1. There were some differences in patient characteristics between the 2 treatment groups. Compared with patients in the ipilimumab group, patients in the ipilimumab plus anti–PD-1 group were younger (median age 67 versus 61 years) and had a better ECOG performance status (ECOG 0, 40% versus 69%). The median time to recurrence or progression after anti–PD-1 or anti–PD-L1 treatment was similar between ipilimumab and ipilimumab plus anti–PD-1 treatment groups (3.0 months, IQR = 2.5 to 5.7 versus 2.9 months, IQR = 2.1 to 6.7). However, more patients received anti–PD-1 or anti–PD-L1 in the adjuvant setting in the ipilimumab plus anti–PD-1 group than in the ipilimumab-only group (19% versus 5%). Fewer patients in the ipilimumab plus anti–PD-1 group compared with the ipilimumab group were treated in Europe (48% versus 14%), whereas more were treated in Australia (48% versus 14%), more were treated in the adjuvant setting (19% versus 5%), and more had brain metastases (37% versus 27%) (Table 16).

Table 16: Patient Characteristics — Pires da Silva et al.

Characteristic	Ipilimumab plus anti–PD-1 (n = 193)	Ipilimumab (n = 162)
Age, years		
Median (IQR)	61.0 (51.5 to 70.0)	67.0 (58.0 to 74.0)
Range	22.0 to 91.0	21.0 to 85.0
Sex, n (%)		
Male	124 (64)	103 (64)
Female	69 (36)	59 (36)
Geographic location, n (%)		
Australia	93 (48)	22 (14)
Europe	55 (28)	113 (70)
US	45 (23)	27 (17)

Characteristic	Ipilimumab plus anti–PD-1 (n = 193)	Ipilimumab (n = 162)
Mutational status, n (%)		
BRAF mutant	70 (36)	34 (21)
NRAS mutant	43 (22)	26 (16)
Wild-type *BRAF* and *NRAS*	80 (41)	102 (63)
Anti–PD-(L)1 treatment setting, n (%)		
Adjuvant	36 (19)	8 (5)
Metastatic	157 (81)	154 (95)
Type of resistance to anti–PD-(L)1, n (%)		
Innate	113 (72)	111 (72)
Acquired	44 (28)	43 (28)
Not applicable[a]	36	8
Median time to progression with anti–PD-(L)1, months, n (%)		
Median, IQR	2.9 (2.1 to 6.7)	3.0 (2.5 to 5.7)
Range	0.5 to 42.3	1.0 to 24.4
ECOG performance status, n (%)		
0	130 (69)	64 (40)
≥ 1[b]	58 (31)	95 (60)
Missing values	5	3
Staging, n (%)		
Stage III/M1a/M1b	60 (31)	44 (27)
M1c/M1d	133 (69)	118 (73)
Presence of liver metastases, n (%)		
No	137 (71)	107 (66)
Yes	56 (29)	55 (34)
Presence of brain metastases, n (%)		
No	122 (63)	119 (73)
Yes	71 (37)	43 (27)
Lactate dehydrogenase, n (%)		
Normal	93 (58)	95 (63)
Higher than upper limit of normal	67 (42)	57 (38)
Missing values	33	10

ECOG = Eastern Cooperative Cancer Group; IQR = interquartile range.

Note: Percentages do not add up to 100% due to rounding.

[a]Patients treated in the adjuvant setting (n = 36 in the ipilimumab plus anti–PD-1 group and n = 8 in the ipilimumab group); therefore, best response to anti–PD-1 was not available for this subgroup.

[b]Included 8 patients with ECOG performance status of 2:1 patient in the ipilimumab plus anti–PD-1 group and 7 in the ipilimumab group; no patients had an ECOG performance status greater than 2.

Source: Pires da Silva et al.[8]

Efficacy

Only those efficacy outcomes identified as relevant in the review protocol are reported in this section.

Objective Response Rate

In the study by Zimmer et al., the ORR was 16% for the ipilimumab group and 21% for the combination group.

In the study by Pires da Silva et al., ORR was 31% in the ipilimumab plus anti–PD-1 group and 13% in the ipilimumab group (P < 0.0001) at a median follow-up of 22.1 months (95% CIs were not reported). Twenty-one patients (11%) in the ipilimumab plus anti–PD-1 group and 3 patients (2%) in the ipilimumab group had a CR (Table 17). Between-group differences were not reported. In the multivariate regression model, which controlled for geographical location, ECOG performance status, lung metastasis, liver metastasis, AJCC v8 staging, platelet count, and neutrophil-lymphocyte ratio, the adjusted OR for treatment with ipilimumab plus anti–PD-1 compared with ipilimumab was 2.11 (95% CI, 1.06 to 4.21; P = 0.033).

Table 17: Objective Response Rate

Outcome	Zimmer et al.		Pires da Silva et al.	
	Ipilimumab + nivolumab (n = 47)	Ipilimumab (n = 37)	Ipilimumab + anti–PD-1 (n = 193)	Ipilimumab (n = 162)
Complete response, n (%)	1 (3)	0	21 (11)	3 (2)
Partial response, n (%)	6 (16)	7 (15)	39 (20)	18 (11)
Overall response rate, n (%)	7 (21)	7 (16)	60 (31)	21 (13)
P value	P value not reported		P < 0.0001[a]	

[a]Estimated using Pearson χ^2 test with Yate's correction.

Source: Zimmer et al.,[10] Pires da Silva et al.[8]

Overall Survival

In the study by Zimmer et al., the 1-year OS rate after initiation of ipilimumab or ipilimumab plus nivolumab was 54% (95% CI, 35 to 70) for the ipilimumab group and 55% (95% CI, 26 to 76) for the combination group. The between-group difference was not reported.

In the study by Baron et al., with a median follow-up of 14.7 months from the initiation of second-line therapy, median survival from second-line therapy for patients treated with ipilimumab was 6.0 months (IQR, 3.1 to 11.8 months), and 5.6 months (IQR, 3.3 to 13.6 months) for patients treated with ipilimumab plus nivolumab (P = 0.99).

In the study by Pires da Silva et al., median OS was 20.4 months (95% CI, 12.7 to 34.8) in the ipilimumab plus anti–PD-1 group, compared with 8.8 months (95% CI, 6.1 to 11.3) in the ipilimumab-only group (HR = 0.50; 95% CI, 0.38 to 0.66; P < 0.0001). In the multivariate regression model, which adjusted for sex, geographical location, mutation status, anti–PD-1 or anti–PD-L1 treatment setting, length of time on anti–PD-1 or anti–PD-L1 treatment, time to progression with anti–PD-1 or anti–PD-L1 treatment, ECOG performance status, lung metastasis, liver metastasis, bone metastasis, number of metastases, AJCC staging, lymphocyte count, neutrophil count, platelet count, LDH, and neutrophil-lymphocyte ratio, the adjusted HR for treatment with ipilimumab plus anti–PD-1 compared with ipilimumab only was 0.67 (95% CI, 0.45 to 0.99; P = 0.042).

Table 18: Overall Survival

Zimmer et al.		Baron et al.		Pires da Silva et al.	
Ipilimumab + nivolumab (N = 37)	Ipilimumab (N = 47)	Ipilimumab + nivolumab (N = 35)	Ipilimumab (N = 22)	Ipilimumab + anti–PD-1 (N = 193)	Ipilimumab (N = 162)
1-year OS, % (95% CI)		Median OS, months (IQR)		Median OS, months (95% CI)	
55 (26 to 76)	54 (35 to 70)	5.6 (3.3 to 13.6)	6.0 (3.1 to 11.8)	20.4 (12.7 to 34.8)	8.8 (6.1 to 11.3)
Not reported		P = 0.99		HR = 0.50 (0.38 to 0.66) P < 0.0001[a]	

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; OS = overall survival.

[a]Estimated using the log-rank test.

Source: Zimmer et al.,[10] Baron et al.,[5] Pires da Silva et al.[8]

Progression-Free Survival

In the study by Zimmer et al., median PFS was 3 months (95% CI, 2.8 to 3.8 months) for the ipilimumab group and 2 months (95% CI, 1.9 to 3 months) for the combination group.

In the study by Baron et al., median time to next therapy or death (used as a surrogate for PFS) for patients treated with second-line ipilimumab plus nivolumab was 5.4 months (IQR, 3.0 to 21.97) compared with 3.67 months (IQR, 2.5 to 5.6) for patients treated with ipilimumab (P = 0.092).

In the study by Pires da Silva et al., median PFS was 3.0 months (95% CI, 2.6 to 3.6) in the ipilimumab plus anti–PD-1 group and 2.6 months (95% CI, 2.4 to 2.9) in the ipilimumab group (HR = 0.69; 95% CI, 0.55 to 0.87; P = 0.0019). The authors reported that the proportional hazards assumption was violated for this outcome.

Table 19: Progression-Free Survival

Zimmer et al.		Baron et al.		Pires da Silva et al.	
Ipilimumab + nivolumab (N = 37)	Ipilimumab (N = 47)	Ipilimumab + nivolumab (N = 35)	Ipilimumab (N = 22)	Ipilimumab + anti–PD-1 (N = 193)	Ipilimumab (N = 162)
Median PFS, months (95% CI)		Time to next treatment or death (used as proxy for PFS) Median (IQR)		Median PFS, months (95% CI)	
2 (1.9 to 3)	3 (2.8 to 3.8)	5.4 (3.0 to 21.9)	3.6 (2.5 to 5.6)	3.0 (2.6 to 3.6)	2.6 (2.4 to 2.9)
Not reported		P = 0.09		HR = 0.69 (0.55 to 0.87) P = 0.0019	

CI = confidence interval; IQR = interquartile range; HR = hazard ratio; PFS = progression-free survival.
Source: Zimmer et al.,[10] Baron et al.,[5] Pires da Silva et al.[8]

Subgroup Analyses by Prior Anti–PD-1 or Anti–PD-L1 Treatment

Pires da Silva reported subgroup analyses by prior anti–PD-1 or anti–PD-L1 treatment comparing ORR, PFS, and OS between patients who received prior anti–PD-1 or anti–PD-L1 treatment in the adjuvant setting (n = 44) versus the metastatic setting (n = 311). However, the subgroup analysis is underpowered, as the study was not designed to detect differences in efficacy between the 2 treatment groups in this subpopulation (Table 20).

Table 20: Subgroup Analyses by Prior Anti–PD-1 or Anti–PD-L1 Treatment in the Adjuvant Versus Metastatic Setting

	Ipilimumab + anti–PD-1			Ipilimumab		
Outcome	Full cohort (N = 193)	Prior anti–PD-1 or anti–PD-L1 in the adjuvant setting (N = 36)	Prior anti–PD-1 or anti–PD-L1 in metastatic setting (N = 157)	Full cohort (N = 162)	Prior anti–PD-1 or anti–PD-L1 in the adjuvant setting (N = 8)	Prior anti–PD-1 or anti–PD-L1 in metastatic setting (N = 154)
ORR, N (%)	63 (31)	13 (36)	47 (30)	21 (13)	1 (13)	20 (13)
Median PFS, months (95% CI)	3.0 (2.6 to 3.6)	3.3 (2.5 to NR)	3.0 (2.3 to 3.5)	2.6 (2.4 to 2.9)	2.5 (1.8 to NR)	2.6 (2.4 to 2.9)
12-month PFS, %	24	47	22	12	25	13
Median OS, months (95% CI)	20.4 (12.7 to 34.8)	NR	16.7 (10.7 to 32.8)	8.8 (6.1 to 11.3)	11.2 (9.2 to NR)	8.5 (5.6 to 10.6)
12-month OS, %	58	75	55	38	38	38

CI = confidence interval; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
Source: Pires da Silva et al.[8]

Harms

Of the 3 observational studies included, only Pires da Silva et al. reported AEs. In this study, 32% of patients had at least 1 grade 3 to 5 AE, with similar rates in both treatment groups (33% with ipilimumab and 31% with ipilimumab plus anti–PD-1). The most common grade 3 to 5 AEs were diarrhea or colitis (20% with ipilimumab and 12% with ipilimumab plus anti–PD-1), followed by increased ALT or AST (9% versus 12%). Grade 1 to 2 AEs were reported for 43% of patients in the ipilimumab group and 53% of patients in the combination group. Grade 3 and grade 4 AEs were reported in 31% and 2% of patients in the ipilimumab group, respectively, and 22% and 10% of patients in the combination group, respectively. One death occurred in the ipilimumab group 26 days after the last treatment: a colon perforation due to immune-related pancolitis.

Critical Appraisal

Internal Validity

Randomized Controlled Trials

In the 2 randomized multicentre open-label phase II trials, the methods for randomization appeared appropriate. However, due to the small sample sizes, there is an increased risk that prognostic balance was not achieved, as evidenced by imbalances in patients' baseline disease and demographic characteristics. As a result, the observed effects may have been over- or underestimated and may have been driven by prognostic differences between the 2 treatment arms.[19] Phase II trials typically include fewer patients and aim to provide preliminary evidence about the efficacy and harms of a drug, to be confirmed later in a larger phase III trial. In S1616, a randomization ratio of 3:1 was used. The authors explained that this unbalanced randomization ratio was to power the study for the main translational objective, which was to assess differences in CD8 T-cell infiltration between biopsies of patients with and without response to therapy in the ipilimumab plus nivolumab arm. This was to test the hypothesis that primary anti–PD-1 resistance could be reversed by adding anti-CTLA-4 therapy to continued anti–PD-1 therapy, as evidenced by increases in infiltrating CD8 T-cells. This necessitated an adequate number of patients in the combination therapy group whose tumours both responded or did not respond to therapy. Unbalanced randomization ratios require a larger sample size to maintain adequate statistical power.

Both studies had an open-label design, so there is a risk of bias in the measurement of outcomes that require assessments with some degree of subjectivity, including ORR, which was measured by the investigators using RECIST 1.1 in both trials. Both reported outcomes (ORR, PFS, OS) were appropriate for this setting. NCT02731729 was not designed for hypothesis testing between arms. Hence, there was no statistical testing and no between-group differences with their measure of precision provided for relevant outcomes, precluding conclusions about the clinical importance of observed results. In S1616, the study was powered to detect a change in median PFS to 6 months in the combination therapy group, and analyses of the primary end points were appropriate. S1616 was not powered to detect differences in OS, and survival data were collected as a secondary end point because such OS results are affected by imprecision (wide CI that spans the null). No between-group differences along with their measures of precision were provided for ORR and PFS, precluding conclusions about whether the between-group differences were clinically important. In

addition, no adjustments for multiple testing were performed, so there is an increased risk of type I error. Neither study conducted a true intention-to-treat analysis, as patients found to be ineligible or nonevaluable after randomization were excluded from some analyses.

Observational Studies

All 3 observational studies were retrospective analyses and are prone to selection bias, because healthier patients were more likely to have been chosen for combination treatment with ipilimumab and anti–PD-1 therapy. Prognostic imbalances were apparent between the ipilimumab-only groups and the combination groups in all 3 studies. Important prognostic factors, including age and ECOG performance status (among others), may influence ORR, PFS, and survival in the context of metastatic melanoma. In the study by Pires da Silva et al., patients who received combination therapy had a more favourable profile in terms of age, ECOG performance status, and mutational status. There was an attempt in this study to account for important prognostic factors, but the method for selecting variables to include in the multivariate regression model was not appropriate, since it was based on statistical significance in the univariate model. (Ideally, prognostic variables should be included in the model on the basis of being prognostic, regardless of whether the result of the univariate model is statistically significant.) In the studies by Zimmer et al. and Baron et al., there was no adjustment for confounding variables; as a result, there is a risk of bias due to confounding. All patients had unresectable or metastatic melanoma; their melanoma had progressed on prior anti–PD-1 therapy; and they were re-treated with either ipilimumab monotherapy or ipilimumab plus anti–PD-1 therapy. In the study by Zimmer et al., patients did not consistently receive these regimens directly after anti–PD-1 therapy, and patients could have received and lost response to single-drug anti–PD-1 treatment on any line of therapy.

All 3 studies reported OS and PFS, but Baron et al. used time to next therapy or death as a surrogate for PFS. ORR was based on RECIST 1.1 in the 2 studies that reported this outcome. Zimmer et al. did not report whether confirmatory scans were performed. In the study by Pires da Silva et al., response was according to physicians' best estimate but no confirmatory scans were conducted to exclude potential pseudoprogression. In addition, while the authors appropriately tested the proportional hazard assumption for the Cox models of PFS and OS, these tests may not be well powered to detect nonproportional hazards. The authors noted that, for the PFS analysis, the proportional hazards assumption was violated (Schoenfeld P = 0.019); as a result, the HR may be unreliable. In addition, this study reported AEs, but this reporting may be prone to recall bias if the AEs were not recorded and graded when they occurred.

External Validity

Randomized Controlled Trials

In both RCTs, the trial inclusion and exclusion criteria were clinically relevant and included patients who had received anti–PD-1 or anti–PD-L1 therapy in the adjuvant or metastatic setting. The trials restricted combination treatment to patients without active CNS metastases and with good performance status. This is consistent with clinical practice, in which combination therapy may be reserved for patients who are considered as more likely to tolerate combination therapy that carries a higher risk of toxicity.

While this patient population differs from the reimbursement request population for this review, it is consistent with clinical practice, in which patients who have failed anti–PD-1 therapy in the adjuvant or

metastatic setting may be re-treated with ipilimumab or ipilimumab plus nivolumab (unless there are reimbursement restrictions). The trial treatment regimens were also consistent with common practice. However, neither trial reported results specific to the population under review (i.e., patients with advanced melanoma that progressed during or within 6 months of adjuvant anti–PD-1 therapy, now being treated in the first-line advanced setting). It is unclear whether the results are generalizable to this subgroup of patients.

Observational Studies

As in the RCTs, the populations of the 3 observational studies differ from those in the reimbursement request (i.e., patients with advanced melanoma that progressed during or within 6 months of adjuvant anti–PD-1 therapy, now being treated in the first-line advanced setting). Hence, it is unclear whether the results are generalizable to this subgroup of patients. The treatments compared and dosages (where reported) were consistent with clinical practice in Canada. The study by Pires da Silva et al. was a multicentre study including data from different countries with different practices, regulations, and access to drugs, which may not be fully generalizable to the setting in Canada. However, given the lack of information, it is impossible to speculate on what differences if any may affect generalizability. There were no studies that compared ipilimumab plus nivolumab with *BRAF*-targeted therapy in patients with advanced melanoma that progressed during or within 6 months of anti–PD-1 therapy.

Indirect Evidence

A total of 184 references were identified from the indirect treatment comparison search. After title and abstract screening, none met the selection criteria and included for full-text review. No indirect treatment comparisons were included in this review.

Economic Evidence

The economic review consisted of a cost comparison for nivolumab plus ipilimumab compared with ipilimumab monotherapy and *BRAF*-targeted therapy (dabrafenib plus trametinib, cobimetinib plus vemurafenib, encorafenib plus binimetinib) for patients with advanced (unresectable or metastatic) melanoma that progresses during or within 6 months of adjuvant anti–PD-1 therapy.

CADTH Analyses

The comparators presented in Table 3 have been deemed appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs, unless otherwise indicated and validated by clinical experts. The price of nivolumab plus ipilimumab was obtained from a previous CADTH review of nivolumab, which priced nivolumab 40 mg and 100 mg vials at $782 and $1,956, respectively, and ipilimumab 50 mg vial at $5,8000.[20] Pricing for comparator products was based on publicly available list prices.[21]

The recommended dosage of nivolumab is 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab maintenance treatment administered at 3 mg/kg every 4 weeks until unacceptable toxicity or up to a maximum of 2 years.[16] When used as recommended in the nivolumab

product monograph, the per-patient cost of nivolumab plus ipilimumab combination therapy for the treatment of patients with advanced melanoma is $40,753 per standardized 28-day cycle for the first 4 cycles. After 4 cycles of combination treatment, the cost of nivolumab maintenance therapy is $9,387 per patient per 28-day cycle. The per-patient cost of ipilimumab monotherapy per 28-day cycle is $38,667 for 4 cycles. Thus, the cost comparison demonstrates that, over a 28-day cycle, nivolumab plus ipilimumab is associated with an incremental cost of $2,086 per patient compared with ipilimumab monotherapy for the first 4 cycles. After 4 cycles, maintenance treatment with nivolumab is associated with incremental costs of $9,387 per patient per 28-day cycle compared with ipilimumab monotherapy, because there is no maintenance ipilimumab monotherapy.

For a subgroup of *BRAF*-positive patients with advanced melanoma, current therapies include dabrafenib plus trametinib, cobimetinib plus vemurafenib, and encorafeni plus binimetinib. Compared with *BRAF*-targeted therapy regimens, nivolumab plus ipilimumab is between $21,356 to $25,683 more costly in the first 4 cycles and $5,683 to $9,387 less costly for the remainder of treatment. Hence, compared with *BRAF*-targeted therapies, the reimbursement of nivolumab plus ipilimumab combination therapy is expected to increase the upfront overall treatment costs, and potentially be cost-saving after 4 cycles. Note that results may differ by jurisdiction if prices differ from those presented in Table 3.

Table 21: CADTH Cost Comparison Table for Advanced Melanoma

Treatment	Strength or concentration	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average cost per 28 days ($)
Nivolumab	10 mg/mL	Sterile solution for injection 40 mg vial 100 mg vial	782.2200[a] 1,955.5600[a]	Initial dose: 1 mg/kg every 3 weeks for 4 cycles Maintenance dose: 3 mg/kg of nivolumab every 2 weeks or 6 mg/kg of nivolumab every 4 weeks	Initial dose: 74.50[b] Maintenance dose: 335.24	Initial dose: 2,086 Maintenance dose: 9,387
Ipilimumab	5 mg/mL	IV infusion Solution 50 mg vial[b]	5,800.0000[a]	3 mg/kg every 3 weeks for 4 cycles	1,380.95	38,667
Nivolumab plus ipilimumab (first 4 cycles)	—	—	—	—	1,455.45	40,753
Nivolumab (maintenance)	—	—	—	—	335.24	9,387
Immunotherapy						
Ipilimumab (monotherapy)	5 mg/mL	IV infusion Solution 50 mg vial[b]	5,800.0000[a]	3 mg/kg every 3 weeks for 4 cycles	1,380.95	38,667

Treatment	Strength or concentration	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average cost per 28 days ($)
***BRAF*-targeted therapies**						
Dabrafenib (Tafinlar)	50 mg 75 mg	Capsule	47.5667 71.2168	150 mg twice daily	284.87	7,976
Trametinib (Mekinist)	0.5 mg 2 mg	Tablet	81.7520 325.6493	2 mg daily	325.65	9,118
Cobimetinib (Cotellic)	20 mg	Tablet	131.3576	60 mg daily for 21 days every 4 weeks	394.07	11,034
Vemurafenib (Zelboraf)	240 mg	Tablet	37.3316	960 mg twice daily	298.65	8,362
Encorafeni (Braftovi)	75 mg	Capsule	51.9585	450 mg daily	311.75	8,729
Binimetinib (Mektovi)	15 mg	Tablet	37.7410	45 mg twice daily	226.45	6,340
Dabrafenib plus trametinib	—	—	—	—	610.52	17,094
Cobimetinib plus vemurafenib[c]	—	—	—	—	692.73	19,396
Encorafenib plus binimetinib[c]	—	—	—	—	538.20	15,070

Notes: All prices are from the Ontario Exceptional Access Program Formulary (accessed April 2, 2024),[21] unless otherwise indicated, and do not include dispensing fees. For treatments using weight-based dosing, CADTH assumed a weight of 75 kg. All costs include wastage of unused medication in vials. If vial sharing is assumed, the average cost per 28-day cycle is $40,622 for nivolumab plus ipilimumab and $8,800 for nivolumab maintenance treatment.

Dosages are based on treatment product monographs,[12,16,22] unless otherwise specified, and validated by clinical experts.

[a]CADTH review of nivolumab.[20]

[b]Ipilimumab is available in 200 mg strength (40 mL vial) in the product monograph, but there is no cost available for this strength.[12]

[c]Cancer Care Ontario Drug Formulary, accessed April 2, 2024.[23]

Issues for Consideration

- No Canadian cost-effectiveness studies were identified, based on a literature search conducted on March 18, 2024.
- Nivolumab-relatlimab (Opdualag) is undergoing a concurrent reimbursement review by CADTH for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma.[24]
- Nivolumab plus ipilimumab combination therapy has been previously reviewed and received a conditional recommendation by CADTH for metastatic melanoma at $1,956.00 per 100 mg/10 mL vial.[25]
- Nivolumab plus ipilimumab combination therapy may increase administration costs compared with ipilimumab monotherapy because nivolumab maintenance therapy is not restricted to 4 cycles, while ipilimumab monotherapy treatment duration is a maximum of 4 cycles. Nivolumab plus ipilimumab

administration is also expected to be associated with additional costs of IV infusion compared with orally administered *BRAF*-targeted therapies.

Discussion

Summary of Available Evidence

The objective of this CADTH nonsponsored review was to evaluate evidence regarding the efficacy of ipilimumab plus nivolumab in patients with advanced (unresectable or metastatic) melanoma that progresses during or within 6 months of adjuvant anti–PD-1 therapy (i.e., treatment in the first-line advanced setting). CADTH identified 2 phase II RCTs and 3 retrospective cohort studies. However, the patient populations in these studies differ from the requested reimbursement population. First, all studies included patients in whom anti–PD-1 treatment failed in the metastatic setting only or a mix of patients in whom anti–PD-1 failed in the adjuvant or metastatic setting; no study included only patients who received anti–PD-1 therapy in the adjuvant setting. Second, none of the studies differentiated patients whose melanoma progressed during or within 6 months of adjuvant anti–PD-1treatment from those whose melanoma progressed more than 6 months after such therapy. All of the available studies compared nivolumab plus ipilimumab (or pembrolizumab plus ipilimumab) to ipilimumab monotherapy; no evidence was identified that compared nivolumab plus ipilimumab with *BRAF*-targeted therapies.

Interpretation of Results

Efficacy

In 1 of the RCTs (NCT 0231729) evaluating ipilimumab only and in combination with nivolumab in patients with progression of disease on anti–PD-1 monotherapy, objective responses were observed in 5 of 9 patients in the ipilimumab group and 2 of 10 patients in the combination group (56% and 20%, respectively). Median OS could not be estimated, and PFS was not assessed. This trial had many limitations, including a small sample size and imbalances in baseline prognostic characteristics. The trial ended early due to poor accrual after 20 patients were recruited and was not designed to test treatment effects between arms. The between-arm difference with CIs for ORR was not reported. Thus, the precision of the between-arm difference could not be assessed. The larger RCT (S1616) showed that combination therapy with ipilimumab plus nivolumab may be associated with better ORR and PFS than ipilimumab monotherapy after failure on prior anti–PD-1 therapy in patients with advanced melanoma. However, no absolute between-arm differences with CIs were reported for ORR or PFS, so the precision of the between-group differences could not be assessed. S1616 was a phase II trial with a relatively small sample size (n = 92) compared with most phase III trials in melanoma and lacked power to test between-group differences in OS. The HR for OS in this trial was affected by serious imprecision (i.e., wide confidence intervals that spanned the null), precluding any conclusion as to which treatment may be favoured. Based on visual inspection of the Kaplan-Meier plot, it appears that the HR may not be reliable. In addition, although a benefit for PFS was observed despite the small sample size, the confidence intervals around the HR are wide, so the magnitude of the effect is uncertain.

Of the 3 observational studies included in this review, 2 studies (Zimmer et al. and Baron et al.) were limited by relatively small sample sizes (n < 100) and lack of power and statistical testing to detect differences in treatment effects between groups. In addition, Zimmer et al. did not specify the setting in which prior anti–PD-1 treatment resistance occurred, and Baron et al. evaluated anti–PD-1 re-treatment in the second-line metastatic setting only. The study by Pires da Silva et al. benefits from a larger sample size and more extensive statistical analyses, but it is affected by a critical risk of bias due to confounding, as some baseline characteristics and prognostic factors differed between the 2 treatment groups. Younger patients, those with better ECOG performance status, and those with a *BRAF* mutation were more likely to receive ipilimumab plus anti–PD-1 than ipilimumab only. These patients are known to be more responsive to combination ipilimumab and anti–PD-1 therapy in first-line immunotherapy studies.[3,26]

ORR appeared higher with combination ipilimumab in both studies that reported this outcome, although Zimmer et al. did not report between-group differences and did not undertake statistical testing. Absolute between-group differences with CIs were not reported in either study, precluding judgments about the precision of any differences. One of the observational studies (Pires da Silva et al.) reported an improved median OS and PFS with combination ipilimumab and nivolumab compared with ipilimumab monotherapy. However, no absolute between-group differences in event probabilities with CIs were reported, precluding a comprehensive appraisal of the clinical importance of the differences and their precision. Although no absolute between-group differences were reported for OS, the 95% CI for the adjusted HR was wide and included effects that may be trivial. The authors noted that the proportional hazards assumption was violated for PFS; as a result, the reported HR may not be reliable. Although results need to be interpreted with caution, given that the study was retrospective and nonrandomized, with baseline prognostic imbalances between treatment groups, it does provide more reliable evidence of the efficacy of ipilimumab with or without nivolumab in anti–PD-1 resistant metastatic melanoma.

The results of the S1616 RCT and the retrospective study by Pires da Silva et al. may suggest better outcomes with combination ipilimumab and anti–PD-1 therapy compared with ipilimumab only in patients with advanced melanoma resistant to prior anti–PD-1 treatment. Combination ipilimumab and anti–PD-1 resulted in response rates of 31%, which is similar to the 28% response rate in the S1616 trial. In the retrospective study, ipilimumab monotherapy showed an ORR of 13% among 162 patients, which was similar to the ORR of 9% among the 23 patients treated with ipilimumab only in S1616 trial. The 2 studies also reported similar HRs for PFS (HR = 0.63; 90% CI, 0.41 to 0.97 in the RCT and HR = 0.69; 95% CI,0.55 to 0.87 in the retrospective study). However, these results should be interpreted in the context of the potential for important biases in these studies. In addition, ORR is unlikely to be a valid surrogate for OS, which is an important clinical outcome.

International melanoma guidelines (National Comprehensive Cancer Network in the US)[1] recognize that anti anti–PD-1 therapy plays an important role in combination with ipilimumab; with combination CTLA-4 and anti–PD-1 treatment as the standard second-line immunotherapy in this setting. The clinical experts consulted and the clinician group that provided input on this review emphasized that there is an unmet need for this patient population and highlighted that treatment with nivolumab plus ipilimumab for patients who relapse during or within 6 months of anti–PD-1 therapy is considered a standard in other countries. In

addition, the National Comprehensive Cancer Network guidelines do not exclude the use of ipilimumab plus nivolumab in patients whose melanoma has progressed during or within 6 months of anti–PD-1 therapy. Therefore, the 6-month recurrence-free interval for re-treatment does not seem to be supported by currently available clinical evidence, as no study was identified that specifically recruited this group of patients or that reported subgroup data for these patients. The Pharmaceutical Benefits Scheme (PBAC) in Australia recently re-reviewed the evidence (based on the study by Pires da Silva et al. and other supportive evidence) and expanded the listing for ipilimumab plus nivolumab to patients who had previously received adjuvant anti–PD-1 monotherapy and had a recurrence on treatment or within 6 months of treatment. The PBAC considered that, although available evidence was uncertain and that the included studies were not designed to examine the comparative efficacy and safety outcomes of ipilimumab plus nivolumab against ipilimumab monotherapy or *BRAF*-targeted therapy in the target population of the submission, the cost-effectiveness of combination therapy with ipilimumab and nivolumab as previously determined for patients with unresectable stage III or IV malignant melanoma was unlikely to be substantially altered by inclusion of the expanded population. The PBAC considered these uncertainties acceptable in the context of the modest financial impact and strong clinician support for the expansion.[18]

Harms

In NCT 0231729, the rate of TRAEs was similar in the 2 treatment arms. However, in S1616, nivolumab plus ipilimumab was associated with a higher rate of AEs compared with ipilimumab monotherapy. In S1616, 50% of the patients in the combination group experienced grade 3 or lower AEs, compared with 22% in the ipilimumab-only group. In NCT02731729, all patients in the ipilimumab arm and all but 1 patient in the combination arm experienced at least 1 AE. These AE rates are consistent with previously published RCT data for ipilimumab and ipilimumab plus nivolumab.[3]

The proportions of patients with AEs in the only observational study that reported safety results were lower than those observed in the 2 RCTs. In the study by Pires da Silva et al., a similar proportion of patients in the 2 treatment groups (33% in the ipilimumab group and 31% in the combination group) had grade 3 to 5 AEs. While this may suggest that ipilimumab plus nivolumab is not associated with worse toxicity than ipilimumab only, limitations due to selection and recall bias preclude such conclusions. It is possible that patients with severe AEs after anti–PD-1 monotherapy may not have been offered or selected for further immunotherapy because they had a higher risk of recurrence of AEs.

Cost Information

Based on sponsor-submitted prices from previous CADTH reviews, nivolumab plus ipilimumab therapy is expected to cost $40,753 per patient per 28-day cycle for the first 4 cycles, followed by maintenance treatment with nivolumab alone at a cost of $9,387 per patient per 28-day cycle. Ipilimumab monotherapy is expected to cost $38,667 per patient per 28-day cycle (used for 4 cycles only). Thus, the incremental per-patient cost of nivolumab plus ipilimumab compared with ipilimumab monotherapy is $2,086 per 28-day cycle for the first 4 cycles. After 4 cycles, the per-patient incremental cost of nivolumab maintenance therapy is $9,387 per 28-day cycle because there is no maintenance treatment with ipilimumab monotherapy. These

incremental costs are based on sponsor-submitted prices from previous CADTH reviews and may not reflect actual prices paid by Canadian public drug plans.

At publicly available list prices, costs for *BRAF*-targeted therapies range from $15,070 to $19,396 per 28-day cycle. Compared with *BRAF*-targeted therapies, nivolumab plus ipilimumab is more costly in the first 4 cycles. However, after 4 cycles, when nivolumab is given alone as maintenance therapy, nivolumab maintenance is less costly compared with *BRAF*-targeted therapies.

Conclusions

The evidence regarding the efficacy of ipilimumab plus nivolumab compared with ipilimumab only among patients with advanced melanoma that progressed during or within 6 months of adjuvant anti–PD-1 therapy is uncertain. No evidence was identified comparing ipilimumab plus nivolumab with *BRAF*-targeted therapy in this population. Although some studies showed the potential for improved ORR, PFS, or OS with combination therapy compared with ipilimumab only, the studies had serious methodological limitations, and the results were inconsistent across studies. However, none of the studies identified were designed to examine the comparative efficacy and safety outcomes of combination ipilimumab and nivolumab with ipilimumab only specifically in patients whose melanoma progressed during or within 6 months of adjuvant anti–PD-1 therapy. Thus, the evidence is inconsistent with the target population of this review — that is, patients who are currently ineligible to receive anti–PD-1treatment for advanced melanoma due to their prior exposure to anti–PD-1 therapy in the adjuvant setting and who experience disease recurrence during or within 6 months of receiving anti–PD-1 treatment in the adjuvant setting. The lack of studies that specifically recruited this group of patients, or that reported subgroup data for these patients may support revision of current reimbursement criteria to remove the existing restriction of the re-treatment interval of more than 6 months for patients with advanced melanoma who experience disease recurrence after anti–PD-1 therapy.

Results of the comparison of treatment costs demonstrate that, over a 28-day cycle, nivolumab plus ipilimumab is $2,086 more costly than ipilimumab monotherapy in the first 4 cycles. After 4 cycles, maintenance treatment with nivolumab is associated with incremental costs of $9,387 per patient per 28-day cycle because there is no maintenance treatment with ipilimumab monotherapy. As a result, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced (unresectable or metastatic) melanoma that progresses during or within 6 months of adjuvant anti–PD-1therapy will increase overall treatment costs compared with ipilimumab monotherapy, given that nivolumab is an add-on therapy to ipilimumab.

Based on the clinical review conclusions, none of the studies identified were designed to examine the comparative efficacy and safety outcomes of combination ipilimumab and nivolumab versus ipilimumab only in patients whose melanoma progressed during or within 6 months of adjuvant anti–PD-1 therapy. Consequently, nivolumab plus ipilimumab is associated with incremental costs and unknown clinical benefit compared with ipilimumab monotherapy in these patients. Other costs, such as administration costs, were not considered as part of the cost comparison. However, nivolumab plus ipilimumab is expected to increase

administration costs compared with ipilimumab monotherapy, given that nivolumab maintenance therapy is not restricted to 4 cycles and may be used for up to 2 years. Given the absence of evidence comparing nivolumab plus ipilimumab with ipilimumab monotherapy in the target population, there is no evidence to inform comparative efficacy of these treatments. Since nivolumab is an add-on therapy, reimbursement for this clinical condition will add costs to the health system, with unknown benefit.

For a subgroup of patients with advanced melanoma with a *BRAF*-positive mutation, *BRAF*-targeted therapies were identified as relevant comparators. Compared to *BRAF*-targeted therapies, nivolumab plus ipilimumab is more costly in the first 4 cycles. However, after 4 cycles, when nivolumab is given alone as maintenance therapy, nivolumab maintenance is less costly compared with *BRAF*-targeted therapies. Hence, compared with *BRAF*-targeted therapies, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced melanoma that progresses during or within 6 months of adjuvant anti–PD-1 therapy is expected to lead to incremental costs in the first 4 cycles but cost savings after 4 cycles. No literature was identified comparing nivolumab plus ipilimumab with *BRAF*-targeted therapies; therefore, the comparative efficacy of these treatments is unknown.

References

1. NCCN Guidelines. Melanoma: cutaneous, version 1.2021. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2021: https://www.nccn.org/. Accessed 2024 Mar 27.
2. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet.* 2017;390(10105):1853-1862. PubMed
3. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373(1):23-34. PubMed
4. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* 2019;381(16):1535-1546. PubMed
5. Baron K, Moser JC, Patel S, Grossmann KF, Colonna SV, Hyngstrom JR. Comparative effectiveness of second-line ipilimumab vs. nivolumab in combination with ipilimumab in patients with advanced melanoma who received frontline anti-PD-1 antibodies. *J Oncol Pharm Pract.* 2021;27(3):555-559. PubMed
6. Friedman CF, Spencer C, Cabanski CR, et al. Ipilimumab alone or in combination with nivolumab in patients with advanced melanoma who have progressed or relapsed on PD-1 blockade: clinical outcomes and translational biomarker analyses. *J Immunother Cancer.* 2022;10(1):e003853. PubMed
7. Olson DJ, Rajagopal P, Tjota MY, Venkataraman G, Luke JJ, Gajewski TF. A case of dual-mechanism immune-related anaemia in a patient with metastatic melanoma treated with nivolumab and ipilimumab. *J Immunother Cancer.* 2020;8(1):e000380. PubMed
8. Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. *Lancet Oncol.* 2021;22(6):836-847. PubMed
9. VanderWalde A, Bellasea SL, Kendra KL, et al. Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma: a randomized phase 2 trial. *Nat Med.* 2023;29(9):2278-2285. PubMed
10. Zimmer L, Apuri S, Eroglu Z, et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. *Eur J Cancer.* 2017;75:47-55. PubMed
11. Provisional Funding Algorithm: melanoma. *(CADTH reimbursement review)*. Ottawa (ON): CADTH; 2023: https://www.cadth.ca/sites/default/files/DRR/2023/PH0022%20Rapid%20Algorithm%20Report%20for%20Melanoma_with%20CAPCA%20Endorsement_FINAL.pdf. Accessed 2024 Mar 10.
12. Yervoy (ipilimumab for injection): 10 mL and 40 mL vials, 5 mg ipilimumab/mL, for intravenous infusion [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada; 2023 Dec 07: https://www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf. Accessed 2024 Mar 28.
13. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell.* 2015;161(2):205-214. PubMed
14. Wei SC, Levine JH, Cogdill AP, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. *Cell.* 2017;170(6):1120-1133.e1117. PubMed
15. Drug Reimbursement Review clinical guidance report: nivolumab (Opdivo) with ipilimumab (Yervoy) for metastatic melanoma. 2017 Nov 30. https://www.cadth.ca/sites/default/files/pcodr/pcodr_opdivo_yervoy_metmela_fn_cgr.pdf. Accessed 2024 Mar 10.
16. Opdivo (nivolumab for injection): 40 mg and 100 mg single-use vials, 10mg/mL nivolumab, for intravenous infusion [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada; 2023 Dec 29: https://www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf. Accessed 2024 Apr 04.
17. Dosing and timing of immuno-oncology drugs. *(CADTH technology review: Optimal Use 360 report; no. 25)*. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/sites/default/files/ou-tr/ho0008-dosing-timing-immuno-oncology-drugs.pdf. Accessed 2024 Mar 21.
18. Pharmaceutical Benefit Advisory Committee. Public summary document: nivolumab plus ipilimumab: nivolumab: injection concentrate for I.V. infusion 100 mg in 10 mL, injection concentrate for I.V. infusion 40 mg in 4 mL, Opdivo; ipilimumab: injection

concentrate for I.V. infusion 200 mg in 40 mL, injection concentrate. Canberra (AU): Pharmaceutical Benefits Scheme; 2022: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-11/nivolumab-%20Opdivo-PSD-November-2022. Accessed 2024 Mar 10.

19. Chu R, Walter SD, Guyatt G, et al. Assessment and implication of prognostic imbalance in randomized controlled trials with a binary outcome--a simulation study. *PLoS One.* 2012;7(5):e36677. PubMed
20. Drug Reimbursement Review clinical guidance and pharmacoeconomic reports: nivolumab (Opdivo) in combination with ipilimumab (Yervoy) for malignant pleural mesothelioma. *Can J Health Technol.* 2021;1(9). https://www.canjhealthtechnol.ca/index.php/cjht/article/view/pc0229r/pc0229r. Accessed 2024 Apr 02.
21. Exceptional Access Program (EAP). Toronto (ON): Ontario Ministry of Health; Ontario Ministry of Long-Term Care; 2023: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx. Accessed 2024 Apr 02.
22. Mekinist (tramerinib): 0.5 mg and 2 mg, oral tablets; Mekinist (tramerinib): 4.7 mg/bottle powder for oral solution [product monograph]. Montreal (QC): Novartis Pharmaceuticals Canada Inc.; 2024 Jan 16: https://pdf.hres.ca/dpd_pm/00074274.PDF. Accessed 2024 Apr 04.
23. Cancer Care Ontario: funded evidence-informed regimens. 2023; https://www.cancercareontario.ca/en/drugformulary/regimens. Accessed 2024 Apr 02.
24. Drug Reimbursement Expert Review Committee final recommendation: nivolumab and relatlimab (Opdualag - Bristol Myers Squibb Canada). *Can J Health Technol.* 2024;4(2). https://www.canjhealthtechnol.ca/index.php/cjht/article/view/PC0329/PC0329. Accessed 2024 Apr 04.
25. Drug Reimbursement Review: nivolumab (Opdivo) in combo with ipilimumab (Yervoy) for metastatic melanoma. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/opdivo-combo-yervoy-metastatic-melanoma-details. Accessed 2024 Apr 04.
26. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* 2018;19(5):672-681. PubMed

Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

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.

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were manually removed in EndNote. The search strategy comprised 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 nivolumab and ipilimumab and melanoma. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO'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 any types of clinical trials or observational studies. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to 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 CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials.

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.

A focused literature search for indirect treatment comparisons dealing with melanoma was run in MEDLINE on December 13, 2023. No limits were applied to the search.

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 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

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: Biweekly alerts

Search filters applied: randomized controlled trials; controlled clinical trials; observational studies.

Limits:

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

Table 22: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
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
?	Truncation symbol for one or no characters only
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)

Syntax	Description
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
freq = #	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MEDLINE Strategy

1. Nivolumab/
2. (opdivo* or nivolumab* or nivo or bms 936558 or bms936558 or cmab 819 or cmab819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or HSDB 8256 or HSDB8256 or GTPL 7335 or GTPL7335 or xdivane* or ba 1104 or ba1104 or "ly 01015" or ly01015 or pbp 2101 or pbp2101 or bms 986213 or bms986213 or bms 986298 or bms986298 or 31YO63LBSN).ti,ab,kf,ot,hw,rn,nm.
3. or/1-2
4. Ipilimumab/
5. (yervoy* or ipilimumab* or IPI or strentarga* or anti ctla 4* or anti ctla4* or antictla4* or mdx ctla 4 or mdx ctla4 or mdxctla 4 or mdxctla4 or "mdx 010" or mdx010 or mdx 101 or mdx101 or bms 734016 or bms734016 or moab ctla 4 or moabctla 4 or moab ctla4 or moabctla4 or cs 1002 or cs1002 or ibi 310 or ibi310 or 6T8C155666).ti,ab,kf,ot,hw,rn,nm.
6. or/4-5
7. exp melanoma/ or exp skin neoplasms/
8. (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*).ti,ab,kf.
9. ((skin or cutaneous or dermal or dermis or epidermal or epidermis) adj3 (cancer* or neoplas* or tumor* or tumour*)).ti,ab,kf.
10. or/7-9
11. 3 and 6 and 10
12. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.

13. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
14. Multicenter Study.pt.
15. Clinical Studies as Topic/
16. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/
17. Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
18. Randomization/
19. Random Allocation/
20. Double-Blind Method/
21. Double Blind Procedure/
22. Double-Blind Studies/
23. Single-Blind Method/
24. Single Blind Procedure/
25. Single-Blind Studies/
26. Placebos/
27. Placebo/
28. Control Groups/
29. Control Group/
30. Cross-Over Studies/ or Crossover Procedure/
31. (random* or sham or placebo*).ti,ab,hw,kf.
32. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
33. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
34. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
35. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
36. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
37. (phase adj3 (study or studies or trial*)).ti,ab,hw,kf.
38. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
39. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
40. allocated.ti,ab,hw.
41. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
42. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
43. (pragmatic study or pragmatic studies).ti,ab,hw,kf.

44. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
45. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
46. trial.ti,kf.
47. or/12-46
48. exp animals/
49. exp animal experimentation/
50. exp models animal/
51. exp animal experiment/
52. nonhuman/
53. exp vertebrate/
54. or/48-53
55. exp humans/
56. exp human experiment/
57. or/55-56
58. 54 not 57
59. 47 not 58
60. 11 and 59
61. Epidemiologic Methods/
62. exp Epidemiologic Studies/
63. Observational Studies as Topic/
64. Clinical Studies as Topic/
65. single-case studies as topic/
66. case reports as topic/
67. (Observational Study or Validation Studies or Clinical Study).pt.
68. (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
69. cohort*.ti,ab,kf.
70. (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
71. ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
72. ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.
73. (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.
74. ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.
75. (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
76. (population adj3 (study or studies or analysis or analyses)).ti,ab,kf.

77. (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
78. ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
79. (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.
80. ((natural adj experiment) or (natural adj experiments)).ti,ab,kf.
81. (quasi adj (experiment or experiments or experimental)).ti,ab,kf.
82. ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
83. (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.
84. case series.ti,ab,kf.
85. case reports.pt.
86. (case adj3 (report or reports or study or studies or histories)).ti,ab,kf.
87. organizational case studies/
88. or/61-87
89. 11 and 88
90. 60 or 89

Embase Strategy

1. *nivolumab/
2. (opdivo* or nivolumab* or nivo or bms 936558 or bms936558 or cmab 819 or cmab819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or HSDB 8256 or HSDB8256 or GTPL 7335 or GTPL7335 or xdivane* or ba 1104 or ba1104 or “ly 01015” or ly01015 or pbp 2101 or pbp2101 or bms 986213 or bms986213 or bms 986298 or bms986298).ti,ab,kf,dq.
3. or/1-2
4. *ipilimumab/
5. (yervoy* or ipilimumab* or IPI or strentarga* or anti ctla 4* or anti ctla4* or antictla4* or mdx ctla 4 or mdx ctla4 or mdxctla 4 or mdxctla4 or “mdx 010” or mdx010 or mdx 101 or mdx101 or bms 734016 or bms734016 or moab ctla 4 or moabctla 4 or moab ctla4 or moabctla4 or cs 1002 or cs1002 or ibi 310 or ibi310).ti,ab,kf,dq.
6. or/4-5
7. exp melanoma/ or exp skin tumor/
8. (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*).ti,ab,kf,dq.

9. ((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/7-9
11. 3 and 6 and 10
12. 11 not (conference abstract or conference review).pt.
13. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
14. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
15. Multicenter Study.pt.
16. Clinical Studies as Topic/
17. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp “Clinical Trial (topic)”/
18. Multicenter Study/ or Multicenter Studies as Topic/ or “Multicenter Study (topic)”/
19. Randomization/
20. Random Allocation/
21. Double-Blind Method/
22. Double Blind Procedure/
23. Double-Blind Studies/
24. Single-Blind Method/
25. Single Blind Procedure/
26. Single-Blind Studies/
27. Placebos/
28. Placebo/
29. Control Groups/
30. Control Group/
31. Cross-Over Studies/ or Crossover Procedure/
32. (random* or sham or placebo*).ti,ab,hw,kf.
33. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
34. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
35. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
36. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
37. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
38. (phase adj3 (study or studies or trial*)).ti,ab,hw,kf.

39. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
40. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
41. allocated.ti,ab,hw.
42. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
43. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
44. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
45. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
46. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
47. trial.ti,kf.
48. or/13-47
49. exp animals/
50. exp animal experimentation/
51. exp models animal/
52. exp animal experiment/
53. nonhuman/
54. exp vertebrate/
55. or/49-54
56. exp humans/
57. exp human experiment/
58. or/56-57
59. 55 not 58
60. 48 not 59
61. 12 and 60
62. observational study/
63. cohort analysis/
64. longitudinal study/
65. follow up/
66. retrospective study/
67. exp case control study/
68. cross-sectional study/
69. quasi experimental study/
70. prospective study/
71. (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.

72. cohort*.ti,ab,kf.
73. (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
74. ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
75. ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.
76. (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.
77. ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.
78. (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
79. (population adj3 (study or studies or analysis or analyses)).ti,ab,kf.
80. (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
81. ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
82. (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.
83. ((natural adj experiment) or (natural adj experiments)).ti,ab,kf.
84. (quasi adj (experiment or experiments or experimental)).ti,ab,kf.
85. ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
86. (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.
87. case series.ti,ab,kf.
88. case study/
89. case report/
90. (case adj3 (report or reports or study or studies or histories)).ti,ab,kf.
91. or/62-90
92. 12 and 91
93. 61 or 92

Clinical Trials Registries

ClinicalTrials.gov

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

Search -- (ipilimumab OR yervoy) AND (nivolumab OR opdivo) AND melanoma

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

Search terms -- (ipilimumab OR yervoy) AND (nivolumab OR opdivo) AND melanoma

Health Canada's Clinical Trials Database

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

Search terms -- nivolumab AND melanoma; ipilimumab AND melanoma

EU Clinical Trials Register

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

Search terms -- (ipilimumab OR yervoy) AND (nivolumab OR opdivo) AND melanoma

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 -- (ipilimumab OR yervoy) AND (nivolumab OR opdivo) AND melanoma

Grey Literature

Search dates: December 6 – December 13, 2023

Keywords: ipilimumab, yervoy, nivolumab, opdiv, melanoma

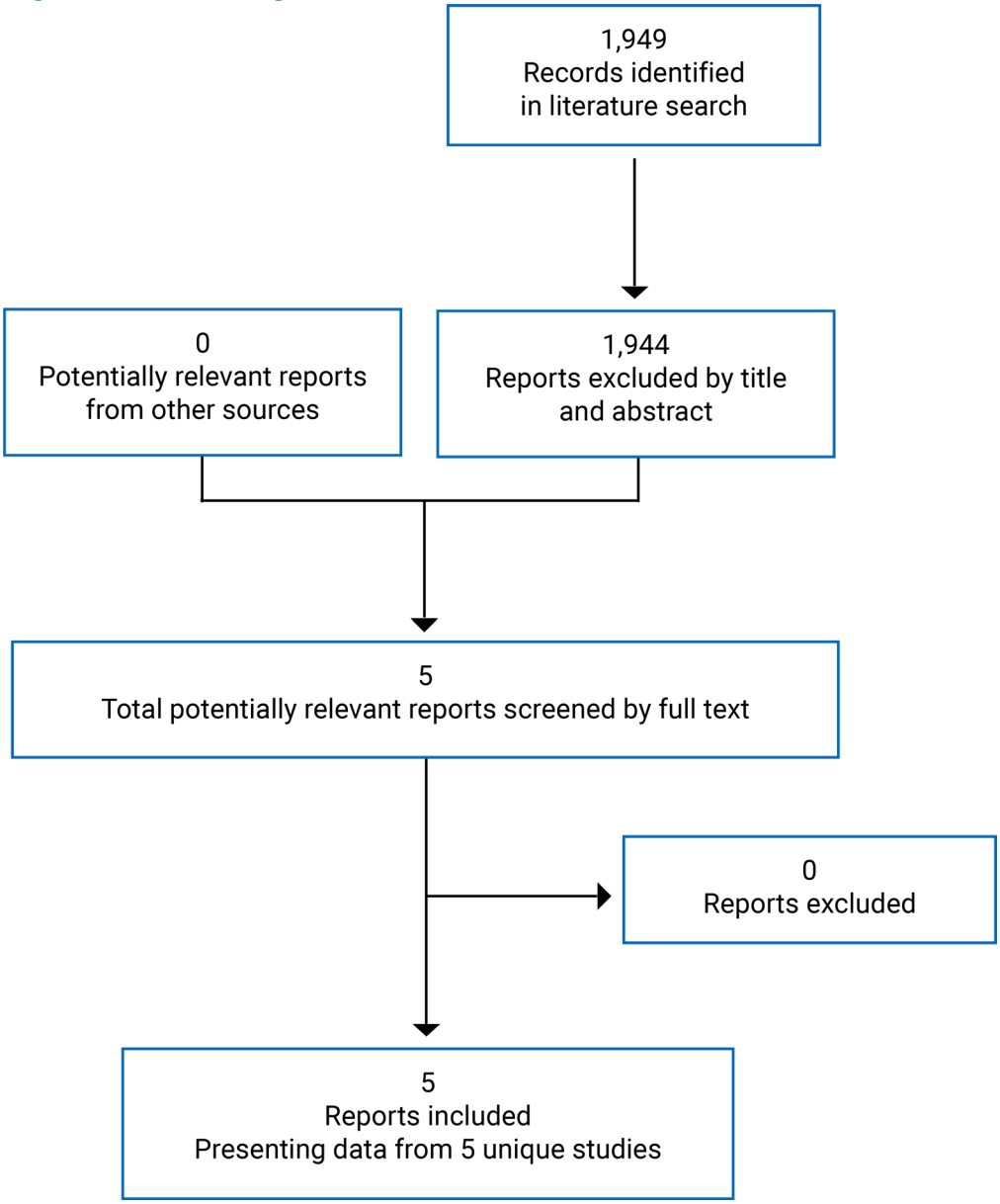
Limits: none

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature 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)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Study Selection

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.