CADTH

DCADTH Reimbursement Review

CADTH Review Report

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Nivolumab and Ipilimumab

(Non-Sponsored Review)

Therapeutic area: Anti-PD (L)-1 Resistant Advanced Melanoma

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
CI	confidence interval
CNS	central nervous system
CR	complete response
CTLA-4	cytotoxic T-lymphocyte associated protein 4
HR	hazard ratio
IQR	interquartile range
LDH	lactate dehydrogenase
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PR	partial response
RCT	randomized controlled trial
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 nivolumab /mL, 40 mg and 100 mg vials, for injection) - Ipilimumab (5 mg ipilimumab /mL, 10 mL and 40 mL vials, for injection)
Health Canada Indication	**Nivolumab** <u>Unresectable or metastatic melanoma</u> - 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 <u>Adjuvant treatment of melanoma</u> - 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 agent - 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 who progress 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-programmed death (ligand)-1 (PD (L)-1) (nivolumab, pembrolizumab, atezolizumab), and anti cytotoxic T-lymphocyte-associated protein 4 antigen (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 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 alone 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 shown a benefit of combination therapy with ipilimumab and anti-PD-1 also for patients who are resistant to anti-PD-1 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 agent ipilimumab which is associated with low response rates (10 to 15%) and a PFS of just over 2 months. Based on the Provincial Funding Algorithm for metastatic melanoma,[11] currently, patients who progress on anti-PD-1 therapy in the adjuvant setting, may only access combination ipilimumab and nivolumab if they progress more than 6 months from prior anti-PD-1 treatment; patients who progress 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 and nivolumab combination therapy in patients with metastatic melanoma who progress during or within 6 months of adjuvant anti-PD-1 therapy ('fast progressors'), to potentially remove the 6-month retreatment funding restriction that is 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 (SYSF) and Melanoma Canada, submitted the patient input for this review. The patients who reported receiving nivolumab and ipilimumab combination 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 like pneumonia, colitis, hepatitis, kidney issues, and other potentially life-threatening side effects. However, many patients in the Melanoma Canada survey expressed their willingness to tolerate the side effects of treatment and its impact on their quality of life if the treatment was effective in delaying the progression or eliminating the cancer entirely. In the overall Melanoma Canada survey, 102 of the 117 respondents indicated that they would want another alternative if they had disease progression and would consider the combination therapy.

In both surveys, patients and caregivers advocated for the funding of nivolumab and ipilimumab in the second line setting following progression on anti-PD-1 therapy. The combination therapy was noted to alleviate financial strain for patients, provide assurance of an alternative option in case of treatment failure or recurrence, and have the potential to improve patient outcomes.

Clinician Input

Input from clinical experts consulted by CADTH

The clinical experts noted that following progression on PD-1 therapy, treatment options for patients without a BRAF mutation are scarce, with the only funded option being single-agent 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 are only able to access ipilimumab and nivolumab combination treatment in the first line setting, and therefore most patients are offered combination upfront. 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 agent anti-PD-1 therapy, and only receive combination therapy if they progress.

Clinician group input

Clinician input was submitted by one clinician group, Ontario Health, Cancer Care Ontario (OH-CCO) 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 post-BRAF targeted therapy. The clinician group indicated that combination treatment with nivolumab and ipilimumab would be suitable for patients who relapse during or within 6 months of anti-PD-1 therapy regardless of if 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 combination nivolumab and ipilimumab for patients who relapse during or within 6 months of anti-PD-1 therapy is already common in the US and Australia, and that the NCCN guidelines do not exclude the use of ipilimumab and nivolumab combination in patients who have progressed on or within 6 months of anti-PD-1 therapy. The medical oncologist also suggested that as the number of this specific patient population (i.e., patients who progress during or within 6 months of anti-PD-1 therapy) is small, this may not lead to significant budget impact.

Drug Program Input

The drug plans suggested that inclusion of nivolumab and ipilimumab combination therapy will only require a minor modification to the current funding algorithm, as it would be added as an option to the treatment choices for patient who relapse during adjuvant anti-PD-1 therapy or within 6 months of its completion. The drug plans provided questions on eligibility of ipilimumab and nivolumab combination in a) both the first- and second-line unresectable/metastatic settings for patients who have progressed during or within 6 months of anti-PD-1 adjuvant therapy; b) for patients with BRAF mutation; and c) for patients who had received anti-PD-1 monotherapy as first line treatment for unresectable/metastatic melanoma and progressed during or within 6 months of completing treatment. The drug plans also provided question on the possibility of 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 & IV melanoma is the current standard of care in Canada. Referring to current clinical practice, they noted that anti-PD1-based regimens, including nivolumab and 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 and ipilimumab combination for the first line treatment of melanoma in the metastatic setting regardless of the timing relative to the last dose of anti-PD1 therapy received as adjuvant treatment. But in Canada, patients with unresectable/metastatic melanoma who progress on or within 6 months from their last dose of anti-PD1 therapy are ineligible for funding of retreatment with combination ipilimumab and nivolumab.

The industry input also noted that the current treatment algorithm in Canada limits the use of subsequent first-line anti-PD1 containing regimens including the nivolumab and ipilimumab combination upon progression on or within the 6 months following an anti-PD1 in the adjuvant setting; leaving ipilimumab monotherapy as the only approved treatment option for patients whose melanoma does not harbor a BRAF-mutation, as combination targeted therapy is available as an option for those with BRAF-mutated disease. The input suggested that '6-month wash-out period', as stipulated in the treatment algorithm, is not based on strong evidence, but rather 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 who progress during or within 6 months of adjuvant anti-PD-1therapy consists of two phase II randomized controlled trials (RCTs) and three observational (retrospective cohort) studies. However, the patient populations in these studies differ from the requested reimbursement population. First, all studies included patients who failed anti-PD-1 treatment in the metastatic setting only, or a mix of patients who failed anti-PD-1 treatment in the adjuvant or metastatic setting; no studies were identified that included only patients who failed anti-PD-1 therapy in the adjuvant setting. Second, none of the studies differentiated patients who progressed during or within 6 months of anti-PD-1 therapy from those who progressed more than 6 months after anti-PD-1 therapy (Table 2).

Table 2: Overview of Included Studies

Author (year)	Study Design	Patient Population	N	Treatment comparisons	Disease Setting	Timing of progression with anti-PD-1 monotherapy (<6 months or ≥ 6 months)
Friedman (2022)	RCT (phase II)	Patients who had received prior treatment with a PD-1/PD- L1 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
VanderWalde (2023)	RCT (phase II)	Patients with metastatic melanoma who had received front-line anti-PD-(L)1 therapy and whose tumors progressed	92	- Ipilimumab - Ipilimumab + nivolumab	First and second line advanced setting (mainly second line)	Unclear
Zimmer (2017)	Retrospective cohort	Patients with advanced melanoma who were treated with ipilimumab or combination ipilimumab and nivolumab after anti-PD-1 treatment failure	84	- Ipilimumab - Ipilimumab + nivolumab	Unclear	Unclear
Baron (2021)	Retrospective cohort	Patients with advanced melanoma treated with single agent anti-PD1 in the frontline setting and who subsequently received second line ipilimumab or combination ipilimumab + nivolumab	57	- Ipilimumab - Ipilimumab + nivolumab	Second line advanced setting	Unclear
Pires da Silva (2021)	Retrospective cohort	Patients with metastatic melanoma (unresectable stage III and IV), who were resistant to anti-PD-(L) 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 (56%, 95% confidence interval [CI]: 21% to 86%) in the ipilimumab arm and 2 of 10 (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), objective response rate (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, one-sided Fisher's exact test). No between-group difference with CI was reported.

In the two 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* (2017). In the study by *Pires da Silva, et al* (2021), 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, 2022)		S1616 (VanderWalde et al, 2023)		Zimmer, et al (2017)		Pires da Silva, et al (2021)	
	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, n (%)	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
[a] one-sided Fisher's exact test. No threshold for statistical significance was prespecified.
[b] Pearson's χ^2 with Yate's correction.
Notes: p-values were not adjusted for multiple testing.

Neither of the RCTs were powered to detect differences in OS. In S1616 survival data were collected as a secondary endpoint; 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 alone was 0.83 (90% CI: 0.50 to 1.39, p=0.28). Of the three observational studies, in the study by *Pires da Silva, et al* (2021), 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* (2017), 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* (2021), 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 patient treated with ipilimumab plus nivolumab (p=0.99). In the study by *Pires da Silva, et al* (2021), 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).

Table 4: Overall Survival

RCTs				Observational Studies					
NCT02731729 (Friedman et al, 2022)		S1616 (VanderWalde et al, 2023)		Zimmer, et al (2017)		Baron, et al (2021)		Pires da Silva, et al (2021)	
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 (95% CI), months	
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
[a] Study S1616 was not powered to detect differences in OS and survival data were collected as a secondary endpoint.
[b] The log-rank test was used.

Notes: p-values were not adjusted for multiple testing.

One of the two RCTs reported PFS. In the S1616 trial, the HR for PFS for nivolumab plus ipilimumab versus ipilimumab alone was 0.63 (90% CI: 0.41 to 0.97, p=0.04, pre-specified one-sided alpha 0.1). Of the three observational studies, *Zimmer et al* (2017), 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* (2021) 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 5: Progression free Survival

RCT		Observational Studies					
S1616 (VanderWalde et al, 2023)		Zimmer, et al (2017)		Baron, et al (2021)		Pires da Silva, et al (2021)	
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 (95% CI), months		Time to next treatment or death (used as proxy for PFS) Median (IQR)		Median PFS (95% CI), months	
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; IQR = interquartile range; HR = hazard ratio; PFS = progression-free survival.
[a] The log-rank test was used.
Notes: p-values were not adjusted for multiple comparisons.

Harms Results

In one of the RCTs (NCT02731729), all but one patient experienced at least one 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 one 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), and 20 patients (29%) discontinued protocol therapy due to toxicity. In the ipilimumab arm, 22% of patients experienced a maximum of grade 3 AE, 9% experienced grade 4 AE, and 4% experienced a grade 5 AE. 17% discontinued therapy due to toxicity.

Of the three observational studies included, only *Pires da Silva, et al* (2021) reported AEs. In this study 32% of patients had at least one grade 3–5 AE, with similar rates in both treatment groups (33% with ipilimumab and 31% with ipilimumab plus anti-PD-1). The most common grade 3–5 AE were diarrhoea or colitis (20% with ipilimumab and 12% with ipilimumab plus anti-PD-1) followed by increased alanine aminotransferase or aspartate aminotransferase (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 as, the outcomes were objective outcomes (PFS, OS) and ORR was based on well-established consensus criteria (RECIST v 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 three observational studies were retrospective analyses and are prone to selection bias because healthier patients would be more likely to have been chosen for combination treatment with ipilimumab and anti-PD-1 therapy. Prognostic imbalances were apparent between the ipilimumab only and the combination treatment groups in all three studies.

In both RCTs, the trial inclusion and exclusion criteria were clinically relevant and included patients who had received anti-PD-1 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 where (except for reimbursement restrictions) patients who have failed anti-PD-1 therapy in the adjuvant or metastatic setting may be retreated with ipilimumab or combination ipilimumab and nivolumab. The trial treatment regimens were also consistent with common practice. In the observational studies, the study by *Pires da Silva, et al* (2021) 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 Canadian setting, but 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 progressing during or within 6 months of anti-PD-1 therapy.

Cost Information

The economic review included a comparison of the treatment costs of nivolumab and ipilimumab and those of comparators deemed to be 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 dosed 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 dosed at 3 mg/kg every 3 weeks for 4 cycles total (no maintenance treatment).[12] Public list prices for nivolumab and 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). As such, the incremental per patient cost of nivolumab plus ipilimumab combination therapy 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 used 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 combination 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 alone among patients with advanced melanoma who progressed during or within 6 months of adjuvant PD-1 therapy is uncertain. No evidence comparing combination ipilimumab and nivolumab to BRAF-targeted therapy in this population was identified. Although some studies showed the potential for improved objective response rate, progression free survival, or overall survival with combination therapy compared to ipilimumab alone, 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 alone specifically in patients who progress 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 PD-1 inhibitor treatment for advanced melanoma due to their prior exposure to anti-PD-1 therapy in the adjuvant setting and experiencing 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 retreatment interval of more than 6-month for patients with advanced melanoma who experience disease recurrence after anti-PD-1 therapy.

Results of the cost-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 such, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced (unresectable or metastatic) melanoma who progress during or within 6 months of adjuvant PD-1 therapy, will increase overall treatment costs compared with ipilimumab monotherapy given 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 alone in patients who progress during or within 6 months of adjuvant anti-PD-1 therapy. As such, nivolumab plus ipilimumab is associated with incremental costs and unknown clinical benefit compared with ipilimumab monotherapy alone in patients who progress during or within 6 months of adjuvant anti-PD-1 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 combination therapy to 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 sub-group 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. As such, compared with BRAF targeted therapies, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced melanoma who progress during or within 6 months of adjuvant PD-1 therapy is expected to lead to incremental costs in the first 4 cycles and result in 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 (L)-1 (nivolumab, pembrolizumab, atezolizumab), and anti-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 in the advanced settings.[1] Although initially effective, many patients develop resistance to immune checkpoint inhibitors and eventually experience progression. More than half of the patients on anti-PD-1 treatment show transient or no response at all.[2] The optimal therapeutic approach for patients who do not respond to initial single agent anti-PD-1 treatment remains unclear; patients who progress on anti-PD-1 treatments have various subsequent treatment options, including nivolumab plus ipilimumab combination therapy, ipilimumab monotherapy, and targeted therapies for patient with BRAF mutations.

The combination of nivolumab with 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 alone as a first line treatment for melanoma (with objective response rates of 58% for combination therapy versus 19% for ipilimumab alone).At an minimum 60 months follow-up, median OS among patients treated with combination ipilimumab and nivolumab was 60.0 months versus 36.9 months in patients who received ipilimumab alone.[3,4] However, it was uncertain if such benefit of combination therapy with ipilimumab and anti-PD-1 can also be expected for patients who are resistant to anti-PD-1 therapy. Given the distinct cellular mechanisms underlying anti-CTLA-4 and anti-PD-1 checkpoint blockade and the suspected mechanisms of lack of response to PD-1 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 for combined CTLA-4 and 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 and nivolumab in anti-PD-1 resistant patients with advanced melanoma.[5-10]

Standards of Therapy in Canada

The clinical experts consulted by CADTH indicated that current treatment options for patients with advanced melanoma who fail anti-PD-1 therapy are limited. Patients who fail initial therapy with anti-PD1 and have a BRAF mutation (about 40% of patients) have the option for 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 agent ipilimumab which carries low response rates (10-15%) and a PFS of just over 2 months. The clinical experts mentioned that some patients have been able to access ipilimumab and nivolumab combination therapy by private insurance coverage or by paying for their own anti-PD-1 therapy. Some provinces reimburse the ipilimumab (1 mg) and nivolumab (3 mg) for 4 cycles as it is cost effective compared to 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 this patient population.

Rationale

In 2017, CADTH issued a recommendation with conditions to list 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 that showed a net clinical benefit with the combination of nivolumab plus ipilimumab on prolonging PFS and OS compared to ipilimumab monotherapy. Pembrolizumab and nivolumab were separately reviewed by the pCODR (pan Canadian Oncology Drug Review) Expert Review Committee (pERC) 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/pembrolizumab therapy to initiation of immunotherapy for metastatic disease. pERC 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 on an appropriate retreatment interval, pharmacokinetic data from a CADTH optimal use 360 report titled 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 were used.[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. Of note, the suggested washout values were to be viewed as theoretical from a policy and practice perspective. This recommendation was not deliberated on at a CADTH expert committee meeting.

In 2019, the provisional funding algorithm for melanoma was updated and a 6 month restriction for retreatment was applied such for patients who receive anti-PD-1 therapy (nivolumab or pembrolizumab) in the adjuvant setting, retreatment with combination 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 a review of evidence for the efficacy and safety of combination ipilimumab and nivolumab treatment in patients who progress during or within 6 months of adjuvant anti-PD-1 treatment be conducted. Of note, they cited that Pharmaceutical Benefits Advisory Committee (PBAC) in Australia recently conducted a review of the evidence and recommended an expansion of the listing of nivolumab and ipilimumab for patients with unresectable stage III or IV malignant melanoma when disease recurrence occurs while receiving or within 6 months of completing adjuvant PD-1 monotherapy.[18]

Drugs

Nivolumab is a fully human, anti-programmed death-1 (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 unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma, as monotherapy or in combination with ipilimumab, and for 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 cytotoxic T-lymphocyte-associated protein 4 antigen. Ipilimumab as a single agent 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 combination ipilimumab and nivolumab is nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 cycles then nivolumab 3 mg/kg every 4 weeks as continued treatment as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

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

SYSF's and Melanoma Canada's submission was based on responses to an online survey. SYSF's received response 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 SYSF's survey, patients reported receiving nivolumab and ipilimumab as their primary treatment (18 patients), as subsequent treatment (9 patients) or other treatment approach (4 patients). Commonly reported adverse events associated with nivolumab and ipilimumab combination 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 like pneumonia, colitis, hepatitis, kidney issues, and potentially life-threatening side effects. In the Melanoma Canada survey, 6 patients reported receiving nivolumab and ipilimumab combination, after experiencing disease progression with a monotherapy within six months of start of treatment; many of whom expressed their willingness to tolerate the side effects of treatment and its impact on their quality of life if treatment was effective in delaying the progression or eliminating the cancer entirely. In the overall Melanoma Canada survey, 102 of the 117 respondents indicated that they would want another alternative if they had disease progression and would consider taking the combination therapy.

Patients from both surveys noted they had experience with the one or more of the following alternate 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 and ipilimumab in 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. The combination therapy was noted as an option of an additional line of treatment that may improve patient outcomes by reducing the spread of disease, or potentially 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 one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by two clinical specialists with expertise in the diagnosis and management of melanoma.

Unmet Needs

The clinical experts noted that following progression on anti-PD-1 therapy, treatment options for the BRAF wild-type population (that is, no BRAF mutation) are scarce, with single-agent ipilimumab being the only funded standard of care. The experts noted that some patients access the ipilimumab and nivolumab combination therapy through private insurance or self-payment for anti-PD-1 therapy, and in some provinces, reimbursement is available for a limited course of ipilimumab and nivolumab combination therapy due to its cost-effectiveness compared to 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-PD1 therapy, response rates to ipilimumab alone are as low as 9% and a short PFS of just over 2 months. Patients with a BRAF mutation who fail initial therapy with anti-PD1, have the option for treatment with BRAF/MEK inhibitors. While these patients may get good responses to BRAF/MEK inhibitors, responses are not as durable as those seen with immunotherapy. As such, patients with primary or secondary resistance to anti-PD-1 therapy face a lack of effective options, particularly those with BRAF wild-type melanoma; and while BRAF-mutated patients have targeted therapy options, resistance is common, and toxicity often leads to treatment discontinuation or dose reductions.

The clinical experts noted that combination of ipilimumab and nivolumab results in approximately 60% of patients experiencing Grade III/IV toxicities, but with over half of all patients surviving at 5 years. By contrast, 20% of patients treated with single agent anti-PD-1 therapy experience Grade III/IV toxicities with 5-year survival of 35% to 44%. However, given the current funding restrictions clinicians are only able to access the combination treatment in the first line setting, and therefore most patients are offered combination upfront. The clinical experts noted that the goals of treatment include increasing ORR, PFS and OS, and maintaining quality of life and independence in activities of daily living (ADLs).

Place in therapy

Both clinical experts indicated that patients with advanced melanoma who progress on single agent anti-PD-1 therapy should be eligible for combination ipilimumab and nivolumab regardless of the timing of progression and regardless of if 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 who progress on single agent anti-PD-1 therapy should be eligible for treatment with nivolumab and ipilimumab combination, as a second line treatment (that is, when they fail to respond or develop resistance to single agent anti-PD-1 therapy in first line). This would spare some patients the toxicity of combination therapy, as they would be given single agent anti-PD-1 therapy as first line treatment. This shift in practice would result in some patients receiving the combination of ipilimumab plus nivolumab instead of ipilimumab alone 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 and ipilimumab combination upfront, and 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 agent 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 the length of time the patients 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 pseudo progression, which is a well documented phenomenon in immunotherapy. Important outcomes to consider include longer-term survival, that is 1-, 2- and 5-year survivals and the plateaus of the survival curve. They also noted that 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, neurological, kidney, gastrointestinal, hepatic, pancreatic, blood or any organ in the body. However, they noted that most toxicities are reversible except for some endocrine toxicities. As such, 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 and ipilimumab combination therapy are similar to those experienced with single agent anti-PD-1 therapy and that most patients maintain a good quality of life and can discontinue therapy. As such, 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 agent 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 toxicities, while another noted that nivolumab and ipilimumab combination should be given by a medical oncologist with expertise in melanoma and immunotherapy either in the community or regional cancer centre. The experts indicated that patients also need specialists to manage rare toxicities such as cardiac or neurological toxicities and to consult the treating oncologist.

Additional considerations

The clinical experts noted that immune therapy has revolutionized melanoma treatment, and 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 agent 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 with 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 patient groups.

Clinician input was submitted by one clinician group: Ontario Health, Cancer Care Ontario (OH-CCO) Drug Advisory Committee which provides timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program. 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 response rate and overall survival. The current treatments available for patients who progress during or within 6 months of PD-1 therapy are ipilimumab monotherapy and BRAF targeted therapy for patients with a BRAF mutation. However, they noted evidence of lower response rate with ipilimumab monotherapy compared to combination of ipilimumab and nivolumab.[9] The clinician group also noted that there are limited treatment options for patients without a BRAF mutation and for patients that have progressed post-BRAF targeted therapy.

The medical oncologist from Saskatchewan strongly advocated for access to combination treatment in the advanced melanoma setting and noted that patients who progress within 6 months of finishing adjuvant immunotherapy and are BRAF mutation negative have especially limited treatment options.

Place in therapy

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

Patient population

The clinician group suggested that nivolumab and ipilimumab combination is suitable for patients with metastatic or recurrent disease that have failed monotherapy.

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 and ipilimumab combination for patients who relapse during or within 6 months of anti-PD-1 therapy is considered a standard in other countries such as the US and Australia. They also added that the NCCN guidelines do not exclude the use of ipilimumab and nivolumab combination in patients who have progressed on or within 6 months of ati-PD-1 therapy. The medical oncologist also suggested that as the number of patients in this specific population (that is, patients who progress during or within 6 months of anti-PD-1 therapy) is small, this may not lead to significant budget impact.

Identifying the unmet need in patients who receive single agent immunotherapy, the medical oncologist noted that while most patients who are fit and able to tolerate doublet immunotherapy would receive it upfront, certain patients, including those with low-risk disease (i.e. low burden of disease), older age groups, and with comorbidities are treated with single agent immunotherapy to minimize toxicity compared to doublet treatment. However, when these patients progress on single agent treatment, the addition of a CTLA-4 inhibitor such as ipilimumab to existing PD-(L)-1 inhibitor 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 non-sponsored 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 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 & IV melanoma is the current standard of care in Canada. Referring to current clinical practice, they noted that anti-PD1-based regimens, including nivolumab and ipilimumab, nivolumab monotherapy and pembrolizumab monotherapy are used by most advanced/metastatic melanoma patients in a first-line setting.[11] However, the industry noted that except in Canada, physicians worldwide can prescribe nivolumab and ipilimumab combination for the first line treatment of melanoma in the metastatic setting regardless of the timing relative to the last dose of anti-PD1 received as adjuvant treatment, allowing patients to benefit from efficacy associated with dual immunotherapy. They indicated that without this option, patients in Canada who progress to unresectable/metastatic disease on or within 6 months from their last dose of anti-PD1 therapy received in the adjuvant treatment setting (also known as "rapid progressors") are not eligible for the public funding of nivolumab and ipilimumab combination therapy, representing one of the most significant treatment gaps that currently exists in the Canadian melanoma treatment landscape.

Bristol Myers Squibb Canada noted that the current treatment algorithm in Canada limits the use of subsequent first-line anti-PD1 containing regimens including the nivolumab and ipilimumab combination upon progression on or within the 6 months following an anti-PD1 treatment in the adjuvant setting; leaving ipilimumab monotherapy as the only approved treatment option for patients in Canada whose melanoma does not harbor a BRAF-mutation (aka BRAF wild type), as combination targeted therapy is available as an option for those with BRAF-mutated disease. The input suggested that '6-month wash-out period', as stipulated in the treatment algorithm, is not based on strong evidence, but rather on a consultation process with local experts to help better understand appropriate use in clinical practice.[17] They indicated that, currently in Canada patients are faced with the reality of choosing 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 and ipilimumab combination should they progress to unresectable/metastatic disease within a certain timeframe or forego adjuvant treatment to retain access to nivolumab and ipilimumab combination 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-PD1 setting are limited and are based on data from patients treated with anti-PD-(L)1 in the metastatic setting. Further, they emphasized that randomized clinical trials comparing nivolumab and ipilimumab combination with ipilimumab monotherapy are no longer considered an ethical clinical undertaking in the context of the data available to date (that is, a lack of clinical equipoise) and therefore cannot be expected to take place in the future.

Bristol Myers Squibb Canada added that the issue of inaccessibility to nivolumab and ipilimumab combination has also expanded to patients with resected stage IIB/IIC disease and pending a positive CADTH review of pembrolizumab for the neoadjuvant treatment of adult patients with Stage III or Stage IV melanoma, patients in Canada who progress 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-PD1 trials, an estimated 25% of patients receiving an anti-PD1 in the adjuvant setting will experience disease recurrence on or within 6 months. It is estimated that approximately 200 patients in Canada will fall into this category annually and thus a budget impact of extending funding to the combination of nivolumab and ipilimumab is small, as these patients are mostly already receiving ipilimumab.

Clinical Evidence

The clinical evidence included in the review of nivolumab and ipilimumab is presented in two sections. The first section includes studies that were selected according to an a priori protocol. The second section would include indirect evidence selected from the literature that met the selection criteria specified in the review; however, no indirect evidence was considered relevant for inclusion in the review.

Methods

A systematic literature review was performed to identify evidence on the efficacy and harms of nivolumab and ipilimumab for first line treatment of advanced melanoma when patients progress during or within 6 months of adjuvant 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 to be important to patients, clinicians, and drug plans.

In total, 1949 records were identified, 1944 were excluded by title and abstract, while no electronic literature and no grey literature were identified. 5 potentially relevant full text reports were retrieved for scrutiny. In total 5 reports of 5 unique studies are included in the review (Appendix 2 Figure 1).

Table 6: Inclusion Criteria for the Systematic Literature Review

Patient Population	Patients with advanced (unresectable or metastatic) melanoma who progress during or within 6 months of adjuvant PD-1 therapy
Intervention	Nivolumab and ipilimumab *Dosage*: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 cycles, then 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 who progressed during or within 6 months of adjuvant anti-PD-1 therapy and 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 who progressed during any timeframe (i.e.,

during or within 6 months of adjuvant anti-PD-1 therapy, or later) and who were treated with nivolumab and ipilimumab during any line of treatment in the advanced setting.

A total of 5 studies- 2 RCTs and 3 observational studies were included in the review of nivolumab and ipilimumab. These studies included a mix of patients with advanced melanoma who had received prior anti-PD-1 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 who progressed on or within 6 months of prior anti-PD-1 therapy, from those who progressed more than 6 months from prior anti-PD-1 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 agent ipilimumab in patients with metastatic melanoma who had progressed on prior anti-PD-1 therapy are summarized below.

Study Design

NCT02731729 (*Friedman et al*., 2022)[6] was a randomized phase II open label trial that evaluated ipilimumab alone 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*., 2023)[9] is a randomized phase II study conducted at 39 academic sites across the US, that aims to address whether CTLA-4 blockade, alone or in combination with continued PD-1 blockade, could reverse resistance to prior anti-PD-1, sequentially or concomitantly. All patients had advanced melanoma with primary resistance to anti- PD1-(L)1 treatment, defined as tumours having no objective clinical response (complete or partial response) to the prior use of anti-PD1(L)1 without intervening therapy for advanced disease, or with recurrence while on adjuvant anti-PD-1 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 a PD-1/PD-L1 inhibitor 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/PD-L1 dose. To be eligible, patients needed to have measurable disease based on RECIST v.1.1 criteria, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and adequate kidney, hepatic, and bonne 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 who 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 v.1.1, a Zubrod performance status of 0 to 2, and adequate hepatic, kidney, and hematologic function. Patients must not have had a confirmed partial response (PR) or complete response (CR) prior to 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 four doses, or ipilimumab 3 mg/kg every 3 weeks for up to four doses. Randomization was stratified based on melanoma histological subtype, as well as prior response to PD-1 therapy. Patients with primary refractory disease were those who had anti-PD-1 therapy within 2 months of study enrollment, and patients with progressive disease were those who received their last dose of PD-1 blocking antibody at least 2 months prior to enrollment. Nivolumab and ipilimumab were administered by intravenous infusion. Treatment was continued until disease progression or

unacceptable toxicity. Patients could receive up to four 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 1mg/kg and ipilimumab 3 mg/kg every three weeks for four cycles followed by nivolumab 480 mg every four weeks for up to two years, or to ipilimumab 3mg/kg every three weeks for four 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 four cycles. In the ipilimumab arm, ipilimumab was administered intravenously over 90 minutes on day 1 of the first four cycles only. In the ipilimumab arm treatment continued until disease progression (per RECIST 1.1), development of unacceptable toxicities, or until the completion of four cycles of treatment, whichever was first. In the nivolumab and ipilimumab arm, treatment continued until disease progression, development of unacceptable toxicities, or until two 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 endpoints identified in the CADTH review protocol that were assessed in the two RCTs are summarized below.

In NCT02731729 the primary endpoint was ORR which was defined as either PR or CR defined by RECIST V.1.1 criteria by week 18. Secondary endpoints 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 prior to study treatment, and then at weeks 12 and 18 according to RECIST version1.1. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 during each cycle.

In S1616, the primary endpoint was PFS assessed according to RECIST 1.1 by 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 endpoints included ORR and OS. Tumour response, according to RECIST version 1.1, was assessed by the treating investigator every 12 weeks until disease progression. ORR was defined as a complete or partial response to therapy following RECIST 1.1. Tissue and blood biopsies were collected on or prior to day 1 of protocol treatment and on day 28–35 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 version 5.0.

Statistical Analyses

NCT02731729 was not designed for hypothesis testing between treatment arms. An optimal Simon two-stage design was used for each arm. The study initially planned to enroll 12 patients per arm, with a plan to enroll 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 endpoint analysis was performed once the protocol-specified anticipated number of 78 PFS events had occurred, with data lock 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

	NCT02731729 (Friedman et al, 2022)	S1616 (VanderWalde et al, 2023)
Study design	Randomized multicentre open-label phase II trial	Randomized multicentre open label phase II trial
Locations	USA (4 centres)	USA (39 centres)
Enrollment dates	June 2016 to May 2018	July 2017 to July 2020
Randomization	Ratio 1:1 Stratified by melanoma histological subtype and prior response to PD-1 therapy	Ratio 3:1 No stratification
Number randomized	20 (1 patient withdrew consent prior to 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/PD-L1 inhibitor in the adjuvant or metastatic setting with evidence of clinical or radiological progression • Measurable disease based on RECIST v 1,1 • ECOG performance status score of 0–1 • Adequate kidney, hepatic, and bone marrow function	• At least 18 years old • Pathologically confirmed melanoma that was either stage IV or unresectable stage III • Have measurable disease using RECIST v 1.1. However, if the only measurable disease was cutaneous or subcutaneous, lesions must have been at least 10 mm in greatest dimension and able to be serially recorded using calipers and photographs • Prior treatment with anti-PD-1 or anti-PD-L1 agents • Documented disease progression either while on anti-PD-1/L1 agents or after stopping therapy without intervening therapy • Must not have achieved a confirmed PR or CR to the anti-PD1/L1 agents prior to progression • No active central nervous system metastases unless they were adequately treated and symptom-free without requiring steroids for 14 days prior to registration. • Zubrod performance status of 0–2, and adequate hepatic, kidney, and hematologic function
Exclusion criteria	• Prior treatment with an anti 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 anti 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 four doses)	Nivolumab + Ipilimumab (nivolumab 1mg/kg of body weight and ipilimumab 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab 480 mg every four weeks for up to two years)

	NCT02731729 (Friedman et al, 2022)	S1616 (VanderWalde et al, 2023)
Comparators	Ipilimumab (3mg/kg every 3 weeks for 4 doses)	Ipilimumab (3mg/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 v 1.1)	PFS (per RECIST v 1.1)
Secondary end points	• Disease control rate • Time-to-treatment failure • OS • Safety	• Change in CD8 T cell infiltrate between responding and non-responding tumours • ORR • OS • Toxicity
Publications	Friedman, et al (2022)	VanderWalde, et al (2023)
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 = National institute 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 (2022),[6] and VanderWalde, et al (2023)[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 which is 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 to the ipilimumab arm, there were more patients aged less than 65 years (51% vs. 39%); fewer patients had elevated LDH at baseline (13% vs. 26%); more patients had Stage IV disease (83% vs. 74%); more patients had not received prior adjuvant therapy (84% vs. 74%); and fewer patients had received priori anti-PD-1 metastatic therapy (78% vs. 87%) whereas more had received other anti-PD-1 combination metastatic therapy (12% vs. 4%). All eligible patients had received prior anti-PD-1 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 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., 2022)

Characteristic	Ipilimumab (N=9)	Nivolumab + Ipilimumab (N=10)
Age (year), median (range)	66 (35–83)	56 (39–66)
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)
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 (152–1800)	214 (157–310)
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 (3–55)	4.3 (2–36)
Best response to prior anti-PD-1 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.PD-1, programmed death 1.
Source: Friedman, et al (2022)[6]

Adapted from 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. Journal for Immunotherapy of Cancer. 2022;10(1):e003853. Distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, see http://creativecommons.org/licenses/by-nc/4.0/. Adaptations include the removal of the "P" column from the original table.

Table 9: Baseline Characteristics – S1616 (VanderWalde et al., 2023)

Characteristic	Ipilimumab (N=23)	Nivolumab + Ipilimumab (N=69)
Age (years)	69 (40, 91)	64 (34, 90)
Age		
<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		
0	15 (65%)	45 (65%)
1	6 (26%)	20 (29%)
2	2 (9%)	4 (6%)
LDH at baseline		
Elevated LDH	6 (26%)	9 (13%)
Normal LDH	5 (22%)	28 (41%)
LDH Not Done	12 (52%)	32 (46%)
AJCC melanoma classification		
Stage III	6 (26%)	12 (17%)
Stage IV	17 (74%)	57 (83%)
Adjuvant therapy		
No prior adjuvant therapy	17 (74%)	58 (84%)
Adjuvant PD-1	3 (13%)	7 (10%)
Adjuvant BRAF/MEK	0 (0%)	2 (3%)
Other Adjuvant Therapy	3 (13%)	2 (3%)
Prior metastatic therapy		
Adjuvant Therapy Only	1 (4%)	6 (9%)
Anti-PD-1 only	20 (87%)	54 (78%)
BRAF/MEK followed by PD-1	1 (4%)	1 (1%)
Other anti-PD-1 combination	1 (4%)	8 (12%)
Duration of prior anti-PD-1/PD-L1 therapy		
<6 Months	15 (65%)	44 (64%)
≥6 months	8 (35%)	25 (36%)

Characteristic	Ipilimumab (N=23)	Nivolumab + Ipilimumab (N=69)
Brain/CNS involvement at baseline		
Yes	2 (9%)	5 (7%)
No	21 (91%)	64 (93%)

CNS = central nervous system; LDH = lactate dehydrogenase.
Patient characteristics among randomized patients. Median (range) and N (%) reported. Two-sided p-values from Wilcoxon (quantitative covariates) and Fisher's exact (categorical covariates) reported.
Source: VanderWalde, et al (2023)[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):2278-2285, 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 below (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, one-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 two patients receiving ipilimumab alone had ongoing responses of 16+ and 33+ months, respectively, while 9 of 19 (47%) patients in the nivolumab plus ipilimumab arm had responses over a range of 6+ to 37+ months. The median duration of response in the nivolumab plus ipilimumab arm was 40.9 months (90% CI: 8 to NR), while it could not be estimated for the patients in the ipilimumab alone 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 two 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 endpoint. At the time of the last data lock (November 3, 3033) 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 alone was 0.63 (90% CI: 0.41 to 0.97, p=0.04, pre-specified one-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

	NCT02731729 (Friedman et al, 2022)		S1616 (VanderWalde et al, 2023)	
	Ipilimumab (N=9)	Nivolumab + Ipilimumab (N=10)	Ipilimumab (N=23)	Nivolumab + Ipilimumab (N=69)
ORR, n (%)	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)	

	NCT02731729 (Friedman et al, 2022)		S1616 (VanderWalde et al, 2023)	
	Ipilimumab (N=9)	Nivolumab + Ipilimumab (N=10)	Ipilimumab (N=23)	Nivolumab + Ipilimumab (N=69)
			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; NA = not applicable; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.
[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 endpoint.
Note: P-values were not adjusted for multiple comparisons.
Source: Friedman, et al (2022),[6] and VanderWalde, et al (2023)[9]

Harms

Of the 19 patients in NCT02731729 who received at least one dose of study drug and were evaluable for safety, all but one experienced at least one treatment-related AE (TRAE) as assessed by the investigator. More patients in the nivolumab plus ipilimumab arm experienced treatment-related diarrhea (60% vs. 33%), AST increase (50% vs. 22%), ALT increase (40% vs. 11%), hypophysitis (30% vs. 11%), and hypotension (20% vs. 0%), whereas fewer experienced treatment-related colitis (10% vs. 22%) and hypokalemia (10% vs. 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 one 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), and 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 TRAE, 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 increased 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

	Ipilimumab (N=9)		Nivolumab + Ipilimumab (N=10)	
Event	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

	Ipilimumab (N=9)		Nivolumab + Ipilimumab (N=10)	
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
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 (2022)[6]
Adapted from 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. Journal for Immunotherapy of Cancer. 2022;10(1):e003853. Distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, see http://creativecommons.org/licenses/by-nc/4.0/. Adaptations include the removal of the "Total" column from the original table.

Table 12: Grade 3 or Higher Treatment-Related Toxicities in at Least 4% of Patients in Either Arm - S1616

Event	Ipilimumab (N=23)	Nivolumab + Ipilimumab (N=68)
Diarrhea	3 (13)	9 (13)
AST Increased	2 (7) [a]	5 (7)
ALT 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] 1 each of these events was grade 4.
Source: VanderWalde, et al (2023)[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):2278-2285, 2023, reproduced with permission from Springer Nature. https://www.nature.com/nm/

Characteristics of Included Observational Studies

Study Design and Patient Population

The earliest study identified that evaluated the efficacy of ipilimumab alone or in combination with nivolumab after treatment failure to anti-PD-therapy was a retrospective study of patients with advanced melanoma from 12 centres in the US and Europe by *Zimmer, et al* (2017). Patients with stage III or IV melanoma (per AJCC 7th edition criteria) who had received at least one 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 the electronic medical records and pharmacy databases of the participating centres.

The second study by *Baron, et al* (2021) was a retrospective cohort study using real-world data from the Flatiron Health database including deidentified electronic health record data from over 265 cancer clinics across the US. This study compared the overall survival of patients with unresectable or metastatic melanoma treated in the frontline 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* (2021) was a multicentre retrospective cohort study done at 15 melanoma centres in Australia, Europe and the US which 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 while or after anti-PD-(L)1 therapy (nivolumab, pembrolizumab, atezolizumab) in the adjuvant or metastatic setting.

Treatments

Two of the retrospective studies compared single agent ipilimumab to combination ipilimumab and 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 treatment failure (Table 13).

Endpoints and Statistical Analyses

ORR defined as the proportion of patients with a partial or complete response to treatment, was reported in two of the studies (Zimmer, et al and Pires da Silva, et al). All three studies reported OS and PFS. PFS was defined as time from the first dose of ipilimumab or ipilimumab and 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 (2017) estimated PFS and OS using the Kaplan-Meier method. Between-group differences were not tested.

Baron, et al (2021) compared OS from the initiation of second line therapy between the two 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 (2021) 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 endpoints 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 Common Terminology Criteria for Adverse Events (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 χ^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

	Zimmer, et al (2017)	Baron, et al (2021)	Pires da Silva, et al (2021)
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort
Country and data source(s)	USA, Europe (12 tertiary referral centres)	USA real world data: Flatiron Health (Electronic health records data from over 265 cancer clinics)	Australia, Europe, USA (15 centres)
Study year	Jan 2010 to June 2016	Not reported	Feb 2011 to Feb 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 and ipilimumab or ipilimumab alone after anti-PD-1 treatment failure.* • histologically-proven unresectable stage III or IV melanoma (AJCC 7th edition) • received at least one dose of ipilimumab or ipilimumab and nivolumab either on or off a trial • documented disease progression on prior anti-PD-1 therapy as per RECIST1.1	*Patients with unresectable/metastatic melanoma treated with single agent anti-PD1 in the frontline setting and who subsequently received second line ipilimumab or combination ipilimumab plus nivolumab.*	*Patients with metastatic melanoma who were resistant to anti-PD-(L)1 in the adjuvant or metastatic setting, and who received ipilimumab alone or ipilimumab plus anti-PD-1.* • Age 18 years and older • Metastatic melanoma (unresectable stage III and IV) • Received anti-PD-(L)1 (nivolumab, pembrolizumab, atezolizumab) in the adjuvant or metastatic setting • Progression (per RECIST v 1.1 on prior anti-PD-(L)1 monotherapy (no confirmatory scans) • No prior use of ipilimumab (previous systemic treatments including BRAF inhibitors plus MEK inhibitors, other immune checkpoint inhibitors, and chemotherapy was allowed)
Treatments (dosage)	• Ipilimumab (3 mg/kg every 3 weeks for 4 intravenous infusions) • Ipilimumab + nivolumab (3 or 1 mg/kg) given in combination with nivolumab (1or 3 mg/kg); the combination was typically administered for up to 4 infusions followed	• 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)

	Zimmer, et al (2017)	Baron, et al (2021)	Pires da Silva, et al (2021)
	by nivolumab maintenance therapy at 3 mg/kg every 2 weeks)		
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
Endpoints	• 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, 2017	Baron et al, 2021	Pires da Silva et al, 2021
Funding	None	None	None

AJCC = American Joint Committee on Cancer; ORR = overall response rate; OS = overall survival; PFS = progression free survival; RECIST = Response Evaluation Criteria in Solid Tumours.
Source: Zimmer, et al (2017),[10] Baron, et al (2021),[5] Pires da Silva, et al (2021)[8]

Results of the Included Observational Studies

Patient Characteristics and Disposition

Zimmer, et al (2017) included 47 patients who were treated with at least one dose of ipilimumab and 37 patients with at least one dose of ipilimumab and 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 and nivolumab (41% versus 11%) compared with ipilimumab-treated patients. 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 ± 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 three 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 retreated (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 four doses of ipilimumab, 21 patients (45%) stopped treatment early due to side-effects and/or clinical deterioration. In the combination-group, 15 patients (41%) received less 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 and 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 (2017)

Characteristic	Ipilimumab (N=47)	Ipilimumab + Nivolumab (N=37)
Age in years, median (range)	65 (29-80)	56 (27-81)
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)
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 x ULN	28 (59)	27 (73)
≥2 x 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)

Characteristic	Ipilimumab (N=47)	Ipilimumab + Nivolumab (N=37)
≥3	14 (30)	19 (51)
Sequential treatment, n (%)[a]		
Yes	42 (89)	22 (59)
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 combined with nivolumab followed directly after progression of prior anti-PD-1 therapy.
Source: Zimmer, et al (2017)[10]
Reprinted from Eur J Cancer, 75, 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, Pages No. 47-55, Copyright 2017, with permission from Elsevier

Baron, et al (2021) included 57 patients with metastatic or unresectable melanoma who had received treatment with front line anti-PD-1 antibodies 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 frontline anti-PD-1 therapy was 3.9 months (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 alone had an ECOG performance status greater than 1 (4% versus 21% based on data from 39 patients), fewer had 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 (2021)

Characteristic	Ipilimumab (N=22)	Ipilimumab plus Nivolumab (N=35)
Age, mean	73	67
ECOG >I % (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)
Frontline treatment % (n/N)		
Nivolumab	72 (16/22)	65 (23/35)
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 (2021)[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, 27(3), pp. 555-559, copyright © 2021 by SAGE Publications, Reprinted by Permission of SAGE Publications.

Pires da Silva, et al (2021) included 355 patients with metastatic melanoma, resistant to anti-PD-(L)1 monotherapy (29.5% nivolumab, 69.5% pembrolizumab, 1% atezolizumab), who had been treated with ipilimumab alone (n=162 [46%]) or ipilimumab plus nivolumab or pembrolizumab (n=193 [54%]). Most patients (n=311 of 355) were receiving anti-PD-(L)1 in the metastatic setting; most of these patients (72% in both treatment groups) had innate resistance to anti-PD-(L)1. There were some differences in patient characteristics between the two treatment groups. Compared to 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-(L)1 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-(L)1 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 (2021)

Characteristic	Ipilimumab plus anti-PD-1 (n=193)	Ipilimumab (N=162)
Age, years		
Median (IQR)	61.0 (51.5–70.0)	67.0 (58.0–74.0)
Range	22.0–91.0	21.0–85.0
Sex, n (%)		
Male	124 (64)	103 (64)
Female	69 (36)	59 (36)
Geographical location, n (%)		
Australia	93 (48)	22 (14)
Europe	55 (28)	113 (70)
USA	45 (23)	27 (17)
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 (2.1–6.7)	3.0 (2.5–5.7)
Range	0.5–42.3	1.0–24.4
ECOG performance status, n (%)		
0	130 (69)	64 (40)
≥1[b]	58 (31)	95 (60)
Missing values	5	3
Staging, n (%)		

Characteristic	Ipilimumab plus anti-PD-1 (n=193)	Ipilimumab (N=162)
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.

[a] Patients treated in the adjuvant setting (n=44: n=36 in the ipilimumab plus anti-PD-1 group and n=8 in the ipilimumab group); therefore, best response to anti-PD-L1 was not available for this subgroup.

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

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

Source: Pires da Silva, et al (2021)[8]

Efficacy

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

Objective response rate

In the study by *Zimmer et al* (2017), the ORR was 16% for the ipilimumab group and 21% for the combination group.

In the study by *Pires da Silva et al* (2021), 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 geographic location, ECOG performance status, lung metastasis, liver metastasis, AJCC v8 staging, platelet count, and neutrophil-lymphocyte ratio (NLR), 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

	Zimmer, et al (2017)		Pires da Silva, et al (2021)	
	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%)

	Zimmer, et al (2017)		Pires da Silva, et al (2021)	
	Ipilimumab + Nivolumab (n=47)	Ipilimumab (n=37)	Ipilimumab + anti-PD-1 (n=193)	Ipilimumab (n=162)
	p-value not reported		p<0.0001[a]	

[a] **Estimated using Pearson χ^2 test with Yate's correction.**
Source: Zimmer, et al (2017),[10] Pires da Silva, et al (2021)[8]

Overall survival

In the study by *Zimmer, et al* (2017), the 1-year OS rate after initiation of ipilimumab or ipilimumab and nivolumab was 54% (95% CI: 35 to 70) for the ipilimumab group and 55% (95% CI: 26 to76) for the combination-group. The between-group difference with its CI was not reported.

In the study by *Baron, et al* (2021), 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 patient treated with ipilimumab plus nivolumab (p=0.99).

In the study by *Pires da Silva, et al* (2021), 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, geographic location, mutation status, PD-L1 treatment setting, length of time on PD-L1, time to progression with PD-L1, ECOG performance status, lung metastasis, liver metastasis, bone metastasis, number of metastases, AJCC staging, lymphocyte count, neutrophil count, platelet count, LDH, and NLR, the adjusted HR for treatment with ipilimumab plus anti-PD-1 compared with ipilimumab was 0.67 (95% CI: 0.45 to 0.99) (P = 0.042).

Table 18: Overall Survival

Zimmer, et al (2017)		Baron, et al (2021)		Pires da Silva, et al (2021)	
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 (95% CI), months	
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; IQR = interquartile range; HR = hazard ratio; OS = overall survival.
[a] **Estimated using the log rank test.**
Source: Zimmer, et al (2017),[10] Baron, et al (2021),[5] Pires da Silva, et al (2021)[8]

Progression-free survival

In the study by *Zimmer, et al* (2017) 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* (2021), 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* (2021) 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 (2017)		Baron, et al (2021)		Pires da Silva, et al (2021)	
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 (95% CI), months		Time to next treatment or death (used as proxy for PFS) Median (IQR)		Median PFS (95% CI), months	
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 (2017),[10] Baron, et al (2021),[5] Pires da Silva, et al (2021)[8]

Subgroup analyses by prior anti-PD-1 treatment

Pires da Silva reported subgroup analyses by prior anti-PD-1 treatment comparing ORR, PFS and OS between patients who received prior anti-PD-1 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 two treatment groups in this subpopulation (Table 20).

Table 20: Subgroup Analyses by Prior anti-PD-1 Treatment in the Adjuvant versus Metastatic Setting

	Ipilimumab + anti-PD-1			Ipilimumab		
	Full cohort (N=193)	Prior anti-PD-1 in the adjuvant setting (N=36)	Prior anti-PD-1 in metastatic setting (N=157)	Full cohort (N=162)	Prior anti-PD-1 in the adjuvant setting (N=8)	Prior anti-PD-1 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, 3.6)	3.3 (2.5, NR)	3.0 (2.3, 3.5)	2.6 (2.4, 2.9)	2.5 (1.8, NR)	2.6 (2.4, 2.9)
12- month PFS	24%	47%	22%	12%	25%	13%
Median OS, month (95% CI)	20.4 (12.7, 34.8)	NR	16.7 (10.7, 32.8)	8.8 (6.1, 11.3)	11.2 (9.2, NR)	8.5 (5.6, 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 (2021)[8]

Harms

Of the three observational studies included, only *Pires da Silva, et al* (2021) reported AEs. In this study 32% of patients had at least one grade 3–5 AE, with similar rates in both treatment groups (33% with ipilimumab and 31% with ipilimumab plus anti-PD-1). The most common grade 3–5 AE were diarrhoea or colitis (20% with ipilimumab and 12% with ipilimumab plus anti-PD-1) followed by increased alanine aminotransferase or aspartate aminotransferase (9% versus 12%). Grade 1-2 AEs were reported for 43% of patients in the ipilimumab group and 53% of patients in the combination arm. Grade 3 and grade 4 AEs were reported in 31% and 2% of patients in the ipilimumab arm, respectively, and 22% and 10% of patients in the combination arm, respectively. One death occurred with ipilimumab 26 days after the last treatment: a colon perforation due to immune-related pancolitis.

Critical Appraisal

Internal validity

RCTS

In the two 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 such, it is possible that the observed effects were over- or under-estimated and may have been driven by prognostic differences between the two treatment arms.[19] Phase II trials typically include fewer patients and aim to provide preliminary evidence about the efficacy and harms of a drug, later to be confirmed in a larger phase III trial. In S1616, a randomization ratio of 3:1 was used. This unbalanced randomization ratio was explained by the authors to power 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 combination ipilimumab and nivolumab arm. This was to test the hypothesis that primary anti-PD-1 resistance could be reversed by the addition of anti-CTLA-4 therapy to continued anti-PD-1 therapy as evidenced by increases in infiltrating CD8 T cells and 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 v.1.1 in both trials. All reported outcomes (ORR, PFS, OS) were appropriate for this setting. NCT02731729 was not designed for hypothesis testing between arms. As such, there was no statistical testing and no between-group differences with their measure of precision provided for relevant outcomes, precluding conclusions as to 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 endpoints were appropriate. S1616 was not powered to detect differences in OS, and survival data were collected as a secondary endpoint as 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 as to whether the between-group differences appeared clinically important. In addition, no adjustments for multiple testing were performed so there is an increased risk of type I error. Neither study conduced a true ITT analysis as patients found to be ineligible or non evaluable after randomization were excluded from some analyses.

Observational studies

All three observational studies were retrospective analyses and are prone to selection bias because healthier patients would be 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 three 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 favorable 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 such, there is a risk of bias due to confounding. All

patients had unresectable or metastatic melanoma and had progressed on prior anti-PD(L)-1 therapy and were retreated with either ipilimumab monotherapy or ipilimumab plus anti-PD-1 therapy. In the study by *Zimmer, et al* (2017), patients did not consistently receive these regimens directly after anti-PD-1 therapy, and patients could have received and lost response to single agent anti-PD-1 treatment on any line of therapy.

All three 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 version 1.1 In the two studies that reported this outcome. *Zimmer, et al* did not report if confirmatory scans were performed. In the study by *Pires da Silva, et al* response was according to physicians best estimate but with no confirmatory scans to exclude potential pseudoprogressions. 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 non-proportional hazards. The authors noted that for the PFS analysis, the proportional hazards assumption was violated (Schoenfeld p=0.019); as such, the HR may be unreliable. In addition, this study reported AEs, but these may be prone to recall bias if the AEs were not recorded and graded at the time of occurrence.

External validity

RCTS

In both RCTs, the trial inclusion and exclusion criteria were clinically relevant and included patients who had received anti-PD-1 therapy in the adjuvant or metastatic setting. The trials restricted combination treatment to patients without an active CNS metastases and good performance status. This is consistent with clinical practice where 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 where (except for reimbursement restrictions) patients who have failed anti-PD-1 therapy in the adjuvant or metastatic setting may be retreated with ipilimumab or combination ipilimumab and nivolumab. 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 who progressed during or within 6 months of adjuvant PD-1 therapy, now being treated in the first line advanced setting) and it is unclear whether the results are generalizable to this subgroup of patients.

Observational studies

Like the RCTS, the populations of the three observational studies are different from the reimbursement request (i.e., patients with advanced melanoma who progressed during or within 6 months of adjuvant PD-1 therapy, now being treated in the first line advanced setting). As such 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 Canadian setting, but 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 progressing during or within 6 months of anti-PD-1 therapy.

Indirect Evidence

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

Economic Evidence

The economic review consisted of only a cost comparison for nivolumab and 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 who progress during or within 6 months of adjuvant PD-1 therapy.

CADTH Analyses

The comparators presented in **Error! Reference source not found.** have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs, unless otherwise indicated and validated by clinical experts. The price of nivolumab and ipilimumab was obtained from 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 dosed 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. As such, results of the cost-comparison demonstrate 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 sub-group of BRAF positive patients with advanced melanoma, current therapies include dabrafenib plus trametinib, cobimetinib plus vemurafenib and encorafeni plus binimetinib. Compared 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. As such, 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 should prices differ from those presented in Table 3.

Table 21: CADTH Cost Comparison Table for Advanced Melanoma

Treatment	Strength / 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
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

Note: 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.
Dosing is based on respective 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 and 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 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 intravenous infusion compared with orally administered BRAF targeted therapies.

Discussion

Summary of Available Evidence

The objective of this CADTH non-sponsored review was to evaluate evidence regarding the efficacy of ipilimumab and nivolumab in patients with advanced (unresectable or metastatic) melanoma who progress during or within 6 months of adjuvant PD-1therapy (i.e., treatment in the first-line advanced setting). CADTH could identify 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 who failed anti-PD-1 in the metastatic setting only or a mix of patients who failed anti-PD-1 in the adjuvant or metastatic setting; no study included only patients who received PD-1 therapy. Second, none of the studies differentiated patients who progressed during or within 6 months of adjuvant PD-1 therapy from those who progressed more than 6 months after PD-1 therapy. All the available studies compared nivolumab and ipilimumab (or pembrolizumab and ipilimumab) to ipilimumab. No evidence was identified that compared nivolumab and ipilimumab to BRAF-targeted therapies.

Interpretation of Results

Efficacy

In one of the RCTs (NCT 0231729) evaluating ipilimumab alone 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 CI for ORR was not reported. As such the precision of the between-arm difference could not be assessed. The larger RCT (S1616) showed that combination therapy with ipilimumab and nivolumab may be associated with better ORR and PFS than ipilimumab alone after failure to 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 to most phase III trials in melanoma and lacked power to test between group differences in OS. The hazard ratio 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 KM plot, it appears that the hazard ratio may not be reliable. In addition, although a benefit on PFS was observed despite the small sample size, the confidence intervals around the hazard ratio are wide so there is uncertainty as to the magnitude of the effect.

Of the three observational studies included in this review, two 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 which setting prior anti-PD-1 treatment resistance occurred, and *Baron et al*, evaluated anti-PD-1 retreatment in the second line metastatic setting only. The Study by *Pires da Silva, et al*, although benefits from a larger sample size and more extensive statistical analyses, it is affected by a critical risk of bias due to confounding as some baseline characteristics and prognostic factors differed between the two 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 alone. 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 to 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 such, the reported HR may not be reliable. Although results need to be interpreted with caution given that it was retrospective and non-randomized study with baseline prognostic imbalances between treatment groups, it does provide more reliable evidence on 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 to ipilimumab alone 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 in a similar range 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 alone in S1616 trial. The two studies also reported similar hazard ratios 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 of these studies. In addition, ORR is unlikely to be a valid surrogate for OS which is an important clinical outcome.

International melanoma guidelines (NCCN)[1] recognize that 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 and ipilimumab combination for patients who relapse during or within 6 months of PD-1 therapy is considered a standard in other countries. In addition, the NCCN guidelines do not exclude the use of ipilimumab and nivolumab combination in patients who have progressed on or within 6 months of ati-PD-1 therapy. Therefore, the 6-month recurrence free interval for retreatment 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. Of note, the Australian Pharmaceutical Benefits Scheme (PBAC) recently rereviewed 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 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 were 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 two treatment arms but in S1616 the combination of nivolumab and 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 to 22% in the ipilimumab only group. In NCT02731729 all patient in the ipilimumab arm and all but one patient in the combination group experienced at least one AE. These AE rates are consistent with previously published RCT data for ipilimumab and combination ipilimumab and nivolumab.[3]

The proportions of patients with AEs in the only observational study that reported safety results were lower than those observed in the two RCTs. In the study by *Pires da Silva, et al*, a similar proportion of patients in the two treatment groups (33% in the ipilimumab group and 31% in the combination group) had Grade 3-5 AEs. While this may suggest that ipilimumab plus nivolumab is not associated with worse toxicity than ipilimumab alone, 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 due to possibly higher risk of recurrence of AEs.

Cost Information

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). As such, the incremental per patient cost of nivolumab plus ipilimumab combination therapy 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 used 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 combination 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 alone among patients with advanced melanoma who progressed during or within 6 months of adjuvant PD-1 therapy is uncertain. No evidence comparing combination ipilimumab and nivolumab to BRAF-targeted therapy in this population was identified. Although some studies showed the potential for improved objective response rate, progression free survival, or overall survival with combination therapy compared to ipilimumab alone, 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 alone specifically in patients who progress 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 PD-1 inhibitor treatment for advanced melanoma due to their prior exposure

to anti-PD-1 therapy in the adjuvant setting and experiencing 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 retreatment interval of more than 6-month for patients with advanced melanoma who experience disease recurrence after anti-PD-1 therapy.

Results of the cost-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 such, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced (unresectable or metastatic) melanoma who progress during or within 6 months of adjuvant PD-1 therapy, will increase overall treatment costs compared with ipilimumab monotherapy given 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 alone in patients who progress during or within 6 months of adjuvant anti-PD-1 therapy. As such, nivolumab plus ipilimumab is associated with incremental costs and unknown clinical benefit compared with ipilimumab monotherapy alone in patients who progress during or within 6 months of adjuvant anti-PD-1 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 combination therapy to 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 sub-group 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. As such, compared with BRAF targeted therapies, the reimbursement of nivolumab plus ipilimumab for the treatment of patients with advanced melanoma who progress during or within 6 months of adjuvant PD-1 therapy is expected to lead to incremental costs in the first 4 cycles and result in 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.

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Appendix 1: Literature Search Strategy

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 multi-file search. Duplicates were manually removed in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were nivolumab and ipilimumab and melanoma. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

CADTH-developed search filters were applied to limit retrieval to 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. See Appendix 1 for the detailed search strategies.

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

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

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 (ITCs) 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 one 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)
.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 U.S. 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 the World Health Organization. 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

Alt text: 1949 records were identified, 1944 were excluded by title and abstract, while no electronic literature and no grey literature were identified. 5 potentially relevant full text reports were retrieved for scrutiny. In total 5 reports of 5 unique studies are included in the review.