Canadian Journal of Health Technologies

CADTH

July 2022 Volume 2 Issue 7

CADTH Health Technology Review

Low-Dose Ipilimumab in Combination With Nivolumab or Pembrolizumab for the Treatment of Advanced Melanoma

Rapid Review

CADTH

Authors: Tara Cowling, Heather Neilson, Ransi Nayakarathna, Quenby Mahood

ISSN: 2563-6596

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

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

Questions or requests for information about this report can be directed to **Requests@CADTH.ca**

CADTH

Table of Contents

CADTH

List of Tables

List of Figures

CADTH

Abbreviations

irAE	immune-related adverse event
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee

Key Messages

- The review did not find any studies exclusively on the clinical effectiveness and safety of low-dose ipilimumab in combination with nivolumab for the treatment of advanced melanoma that met the criteria for this review.
- The review found limited evidence, from 1 single-arm phase II trial of 70 adults and 1 retrospective cohort study of 9 adults, on the clinical benefits and safety of low-dose ipilimumab in combination with pembrolizumab (or nivolumab for an unspecified number of patients in the retrospective cohort study) for the treatment of advanced melanoma.
- In the single-arm study, 20 of 70 enrolled patients (29%) achieved a confirmed response, including 5 complete (7.2%) and 15 partial responses (21.4%). In the retrospective cohort study, 3 of 9 patients (33%) achieved a partial response.
- The review did not find any studies on the cost-effectiveness of low-dose ipilimumab in combination with nivolumab or pembrolizumab for the treatment of advanced melanoma that met our criteria for this review.

Context and Policy Issues

In 2021 in Canada, approximately 8,700 people were diagnosed with melanoma skin cancer and 1,250 people were expected to die from this disease.[1] The 5-year survival rate for people with stage 4 melanoma — when melanoma has spread to other, distant sites in the body, also known as metastatic or advanced melanoma — is 15% to 20%.[2] Patients who experience this condition have reported placing high value on controlling their disease progression, death, pain, and other symptoms; they have also reported that the benefits of treatment outweigh the risks of side effects.[3]

In Canada, the current treatment for advanced melanoma includes, but is not limited to, immunotherapy with drugs such as ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda). Ipilimumab is a recombinant human immunoglobulin G1 monoclonal antibody, also known as a CTLA-4-blocking antibody or anti-CTLA-4. Ipilimumab binds to CTL-4, a down-regulator of T-cell activation pathways that enhances the T-cell antitumour response.[4] Nivolumab, a fully human monoclonal immunoglobulin G4 antibody, and pembrolizumab, a humanized monoclonal antibody, are immune checkpoint inhibitors, also known as anti-PD-1 drugs. Both nivolumab and pembrolizumab block PD-1 activity through binding to the PD-1 receptor on T-cells.[5,6] This binding prevents other ligands from binding, thereby releasing inhibition of the T-cell antitumour immune response.[5] Research has shown that the combination of ipilimumab and nivolumab results in a greater enhancement of T-cell function than does either treatment alone.[4]

Health Canada has issued a Notice of Compliance for each drug as follows:

- Ipilimumab is approved as a single drug (3 mg/kg) or in combination with nivolumab (1 mg/kg) for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma. This combination should be administered on the same day every 3 weeks for the first 4 doses or until unacceptable toxicity, whichever occurs earlier. After completion, nivolumab should be administered as a single drug (anti-PD-1 maintenance) for as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[7,8]

- Nivolumab is approved as monotherapy for the treatment of unresectable or metastatic melanoma in patients who have not received prior systemic therapy for unresectable or metastatic melanoma; for patients who experienced disease progression following ipilimumab (and a BRAF inhibitor for patients who are BRAF V600 positive); and as adjuvant therapy for patients with advanced melanoma after complete resection.[8]
- Pembrolizumab is approved as monotherapy for the treatment of unresectable or metastatic melanoma in patients who have not received prior treatment with ipilimumab (patients who are BRAF V600 positive may have received prior BRAF inhibitor therapy); and for patients who experienced disease progression following ipilimumab therapy (and a BRAF or MEK inhibitor for patients who are BRAF V600 positive).[9]

These approvals do not address second-line therapy for patients who complete anti-PD-1 monotherapy but later experience disease progression, or patients who receive an anti-PD-1 drug in the adjuvant setting but later experience a relapse (Figure 1). While the combination of ipilimumab (3 mg/kg) and anti-PD-1 drugs could be an effective option, grade 3 to 4 treatment-related adverse events have been reported in more than 50% of patients receiving this combination.[10] In addition, a CADTH pan-Canadian Oncology Drug Review (pCODR) indicated that the costs of these drugs per patient over 28 days are $1,825 for nivolumab and $32,480 for ipilimumab.[3] An alternative option may be to combine a lower dose of ipilimumab (1 mg/kg) with an anti-PD-1 therapy (nivolumab or pembrolizumab). However, the clinical effectiveness, safety, and cost-effectiveness of this combination are unknown.

This report adds to previous CADTH reports on immunotherapy for advanced melanoma. A 2019 Reference List, based on literature published between 2014 and 2019,[11] and a 2019 Technology Review[12] found no relevant evidence of the clinical effectiveness of nivolumab, pembrolizumab, or the combination of ipilimumab and nivolumab in patients who progressed after anti-PD-1 adjuvant therapy. A 2018 Technology Review focused on ipilimumab monotherapy after patient progression on pembrolizumab or nivolumab. In that report, the results from 3 retrospective nonrandomized studies suggested some response from ipilimumab but a high rate of adverse events among patients who received ipilimumab.[13] Two reports from 2012 and 2014 were reimbursement recommendations by the pCODR Expert Review Committee (pERC). In the 2012 report, the committee recommended reimbursement for ipilimumab monotherapy as treatment for patients who received prior systemic therapy;[14] in the 2014 report, the committee recommended ipilimumab as first-line treatment for adults.[15]

The objective of the current report is to summarize evidence regarding the clinical effectiveness, safety, and cost-effectiveness of low-dose ipilimumab (1 mg/kg) in combination with nivolumab or pembrolizumab for patients with advanced melanoma who completed anti-PD-1 monotherapy and later progressed, or those who received an anti-PD-1

Figure 1: Sequence of Events Leading Up to Second-Line Treatment

drug in the adjuvant setting and later relapsed. Therefore, the focus of this report is on anti-PD-1 drugs as second-line treatment (Figure 1).

Research Questions

Among adult patients who progressed after treatment with anti-PD-1 monotherapy or relapsed within 6 months of treatment with an anti-PD-1 drug in the adjuvant setting:

1. What is the clinical effectiveness of low-dose ipilimumab in combination with nivolumab for the treatment of advanced melanoma?
2. What is the clinical effectiveness of low-dose ipilimumab in combination with pembrolizumab for the treatment of advanced melanoma?
3. What is the cost-effectiveness of low-dose ipilimumab in combination with nivolumab for the treatment of advanced melanoma?
4. What is the cost-effectiveness of low-dose ipilimumab in combination with pembrolizumab for the treatment of advanced melanoma?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline and Embase via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ipilimumab (Yervoy) and nivolumab (Opdivo) or pembrolizumab (Keytruda) and advanced melanoma. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, network meta-analyses, any types of clinical trials or observational studies, and economic studies. Where possible, retrieval was limited to the human population. Conference abstracts were omitted from the search results. The search was completed on June 2, 2022, and was limited to English-language documents published since January 1, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients with advanced melanoma who have progressed after treatment with anti-PD-1 monotherapy or have relapsed within 6 months of treatment with an anti-PD-1 drug in the adjuvant setting
Intervention	Q1 and Q3: Four cycles of low-dose ipilimumab (1 mg/kg) in combination with nivolumab (3 mg/kg or maximum of 480 mg) with or without anti-PD-1 maintenance Q2 and Q4: Four cycles of low-dose ipilimumab (1 mg/kg) in combination with pembrolizumab (2 mg/kg or maximum of 200 mg) with or without anti-PD-1 maintenance
Comparator	Standard care or no treatment, ipilimumab (3 mg/kg) alone or in combination with nivolumab or pembrolizumab
Outcomes	Q1 and Q2: Clinical effectiveness (e.g., progression-free survival, overall survival, response rate, duration of response, quality of life, safety [e.g., adverse events of ≥ grade 3 and grade 4, serious adverse events, deaths]) Q3 and Q4: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, incremental cost-effectiveness ratios)
Study designs	Health technology assessments, systematic reviews, randomized-controlled trials, non-randomized studies, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2017. Other exclusion criteria included studies involving other interventions (e.g., surgery) combined with the interventions of interest, and studies focused on comorbid disease populations (e.g., autoimmune diseases).

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Downs and Black checklist[16] applicable to randomized and nonrandomized studies. Summary scores were not calculated for the included study; rather, the strengths and limitations of the included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 808 citations were identified in the literature search. Following screening of titles and abstracts, 738 citations were excluded and 70 potentially relevant reports from the electronic search were retrieved for full-text review. Sixteen potentially relevant publications were retrieved from the grey literature search for full-text review. Of potentially relevant articles, 68 publications were excluded for various reasons, and 2 publications, both nonrandomized studies,[17,18] met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[19] flow chart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two publications met the eligibility criteria and were included in this report.[17,18] Details regarding the characteristics of these publications are provided in Appendix 2.

Study Design

The first included study was a nonrandomized, open-label, single-arm, phase II clinical trial. The objective of the study was to examine the efficacy of pembrolizumab plus low-dose ipilimumab in advanced melanoma in patients, refractory to an anti-PD-1 or PD-L1 antibody.[17] The second study was a retrospective cohort study. The objective of the study was to investigate the safety and efficacy of low-dose ipilimumab plus anti-PD-1 therapy in the second line or above setting.[18]

Country of Origin

The single-arm phase II trial[17] recruited patients from 7 medical centres across the US, and the retrospective cohort study[18] included patients from Germany.

Patient Population

The single-arm phase II trial[17] examined 70 adult patients with unresectable or metastatic melanoma and known BRAF mutation status. Patients had experienced disease progression during treatment with an anti-PD-1 or anti-PD-L1 antibody immediately before accrual to the study or experienced disease progression within 6 months of receiving an adjuvant anti-PD-1 antibody without intercurrent therapy.

The retrospective cohort study[18] examined 9 adult patients with unresectable stage III or IV melanoma. In total, 6 of the 9 patients (66.7%) were in stage M1c or M1d at the initiation of combined immunotherapy. None of the patients had a BRAF V600 mutation. All patients had relevant comorbidities or had experienced severe immune-related side effects during previous immunotherapy.

Interventions and Comparators

The single-arm phase II trial[17] involved participants who received pembrolizumab (200 mg) intravenously along with low-dose ipilimumab (1 mg/kg) intravenously once every 3 weeks for 4 doses, potentially followed by maintenance with pembrolizumab (200 mg) intravenously once every 3 weeks for up to 2 years. Patients who attained a complete response, confirmed on at least 2 scans after a minimum of 24 weeks of study treatment, could discontinue treatment early. No dose reductions of pembrolizumab or ipilimumab were permitted. As this was a single-arm study, there was no comparator treatment group.

The retrospective cohort study[18] examined the safety profile and efficacy of low-dose ipilimumab (1 mg/ kg) combined with anti-PD-1 immunotherapy in patients who progressed after anti-PD-1 monotherapy. Seven of 9 patients received anti-PD-1 maintenance therapy, either with nivolumab or pembrolizumab; the median number of doses was 7.5 (range = 2 to 17).

Outcomes

The primary outcome in the single-arm phase II trial[17] was the objective response rate from pembrolizumab and low-dose ipilimumab following initial progression on an anti-PD-1 or anti-PD-L1 antibody in advanced melanoma. Secondary outcomes were progression-free survival (defined as time on study treatment until immune-related progressive disease, clear

clinical progression, or death), and safety. Exploratory outcomes included the associations of baseline tumour gene expression patterns with clinical outcomes. Although not prespecified end points in the study protocol, overall survival (defined as the time from enrolment to death from any cause) and duration of response (defined as the time from first evidence of response until disease progression or death) were also assessed.

The primary outcome of the retrospective cohort study[18] was the rate of severe (grade 3 to 5) immune-related adverse events (irAEs), graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0). These events were assessed from the first dose of combined immunotherapy to November 1, 2020. Safety was assessed based on the frequency and severity of irAEs, and whether treatment discontinuation or death occurred. Exploratory outcomes included resistance to previous PD-1–based immunotherapy and following response to combined immunotherapy; best overall response, progression-free survival, and overall survival were also examined as outcomes.

Summary of Critical Appraisal

The 2 included nonrandomized studies were critically appraised using the Downs and Black tool.[16] The following summary highlights the strengths and limitations from each study, with additional details provided in Appendix 3.

A number of strengths were identified for the 2 included studies.[17,18] Both studies addressed clearly focused research objectives. In both studies the outcomes were measured objectively, the follow-up period of participants was sufficiently long, and statistical tests for assessing the main outcomes were appropriate. The single-arm phase II trial[17] had well-defined eligibility criteria for the study population, whereas the retrospective cohort study's inclusion and exclusion criteria[18] were not adequately described.

In terms of methodological limitations, both studies had nonrandomized, single-arm designs and the retrospective cohort study[18] had a limited number of participants (n = 9). Therefore, both studies were prone to selection bias and neither study accounted for confounding factors. Due to the lack of a control group, randomization, and blinding, there is an inability to distinguish between the effect of the treatment, a placebo effect, and the effect of natural history. In addition, it is difficult to interpret the magnitude of response without a frame of reference for comparison, such as the effect of ipilimumab alone.

Furthermore, the single-arm phase II study excluded patients who were refractory to an anti-PD-1 or anti-PD-L1 antibody and experienced high-grade toxicity; therefore, the authors noted that observed toxicity rates may have been subject to selection bias. The study authors also noted a lack of formal consensus on how they defined progression on an anti-PD-1 or anti-PD-L1 antibody at the time of study.[17]

Given the methodological limitations of these 2 studies, the results reported should be interpreted with caution.

Summary of Findings

A summary of findings is presented in the following text according to the research questions posed by this report. Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Low-Dose Ipilimumab in Combination With Nivolumab

One retrospective cohort study was identified that assessed the clinical effectiveness of low-dose ipilimumab combined with either nivolumab or pembrolizumab in 9 adult patients with advanced melanoma who had a history of disease progression following immunotherapy.[18] The number of patients who received nivolumab (as opposed to pembrolizumab) in combination therapy was unspecified; therefore, the results of this study are presented in the Clinical Effectiveness of Low-Dose Ipilimumab in Combination With Pembrolizumab section, where this limitation is noted.

No studies were identified that exclusively assessed the clinical effectiveness of low-dose ipilimumab combined with nivolumab in adult patients with advanced melanoma who progressed after treatment with anti-PD-1 monotherapy or relapsed within 6 months of treatment with an anti-PD-1 drug in the adjuvant setting; therefore, no summary can be provided.

Clinical Effectiveness of Low-Dose Ipilimumab in Combination With Pembrolizumab

Two studies were identified that reported on the clinical effectiveness of low-dose ipilimumab in combination with pembrolizumab.[17,18] The trials were both nonrandomized studies of patients with advanced melanoma refractory to an anti-PD-1 or anti-PD-L1 antibody.

In the single-arm phase II trial,[17] 60 of 70 patients had received prior treatment with an anti-PD-1 antibody monotherapy and 10 patients had prior treatment with an anti-PD-1 or anti-PD-L1 antibody–based combination therapy, with a median of 4.8 months on a prior anti-PD-1 or anti-PD-L1 antibody treatment. In the retrospective cohort study,[18] 9 patients had prior treatment with an anti-PD-1 therapy for a median duration of 5.3 months.

In the retrospective cohort study of 9 patients, the combination therapy either included nivolumab or pembrolizumab as the anti-PD-1 drug; the number of patients who received pembrolizumab (as opposed to nivolumab) was unspecified.[18]

Response

In the single-arm phase II trial,[17] 20 of 70 enrolled patients (29%) achieved a confirmed response (95% confidence interval [CI], 18.4 to 40.6), including 5 complete (7.2%) and 15 partial responses (21.4%). Among patients who responded, the median duration of response was 16.6 months (95% CI, 7.9 to not reached). Responses were observed across all clinical subgroups, including patients with elevated lactate dehydrogenase levels and brain and liver metastases, and patients who progressed on an anti-PD-1 or anti-PD-L1 antibody in the adjuvant setting. Fifteen percent of responses (2 of 13) were among patients who progressed on a prior anti-PD-1 or anti-PD-L1 antibody within 6 months, although responses were also observed among those with longer prior treatment. Additionally, these responses occurred predominantly among patients with intermediate to non-T-cell–inflamed and PD-L1–negative tumours.

In the retrospective cohort study,[18] 3 of 9 patients had a partial response (accounting for the objective response rate of 33.3%) and the disease control rate was 66.7%. The number of patients who received pembrolizumab (as opposed to nivolumab) was unspecified.

Progression-Free Survival

The median progression-free survival was 5 months (95% CI, 2.8 to 8.3) in the single-arm phase II trial[17] and 5.7 months in the retrospective cohort study.[18] In the latter study, the number of patients who received pembrolizumab (as opposed to nivolumab) was unspecified.

Overall Survival

The median overall survival was 24.7 months (95% CI, 5.2 to not reached) in the single-arm phase II trial[17] and 21.6 months in the retrospective cohort study.[18] In the latter study, the 12-month overall survival rate was 79% (95% CI, 56.9% to 100%); the number of patients who received pembrolizumab (as opposed to nivolumab) was unspecified.[18]

Adverse Events

In the single-arm phase II trial,[17] grade 3 to 4 adverse events—most commonly colitis, diarrhea, rash, and transaminase elevations—occurred in 27% of patients.

In the retrospective cohort study,[18] 5 of 9 patients (55.6%) experienced irAEs of any grade. Grade 3 irAEs occurred in 3 of 9 patients (33.3%). No patients experienced a grade 4 or 5 irAE. The number of patients who received pembrolizumab (as opposed to nivolumab) was unspecified.

Cost-Effectiveness of Low-Dose Ipilimumab in Combination With Nivolumab

No studies were identified that assessed the cost-effectiveness of low-dose ipilimumab combined with nivolumab in adult patients with advanced melanoma who progressed after treatment with anti-PD-1 monotherapy or relapsed within 6 months of treatment with an anti-PD-1 drug in the adjuvant setting; therefore, no summary can be provided.

Cost-Effectiveness of Low-Dose Ipilimumab in Combination With Pembrolizumab

No studies were identified that assessed the cost-effectiveness of low-dose ipilimumab combined with pembrolizumab in adult patients with advanced melanoma who progressed after treatment with anti-PD-1 monotherapy or relapsed within 6 months of treatment with an anti-PD-1 drug in the adjuvant setting; therefore, no summary can be provided.

Limitations

There are several limitations worth noting. First, there was no evidence identified on the cost-effectiveness of low-dose ipilimumab in combination with nivolumab or pembrolizumab, respectively. In addition, the evidence on clinical effectiveness was limited to only 2 studies with a low number of participants.[17,18]

In terms of generalizability to the Canadian context, the single-arm phase II trial[17] included participants from 7 medical centres across the US, and the retrospective cohort study included 9 patients from Germany. Although patients living in Canada were not included in these studies, the characteristics of the patient population would not necessarily be different, but the delivery of care in other countries, including treatment pathways for patients with melanoma and lack of comparison to the standard of care in Canada, may

limit generalizability.[18] Furthermore, the low-dose regimen is not currently approved for use in Canada.

Due to the limitations related to volume of evidence, methodological concerns, and generalizability, caution should be used when interpreting the results of these 2 studies.

Conclusions and Implications for Decision- or Policy-Making

Two studies met the inclusion criteria of this review, comprising a single-arm phase II trial of 70 patients[17] and a retrospective cohort study of 9 patients.[18] All patients were adults with advanced melanoma who had experienced progression or relapse following anti-PD-1 therapy. Both studies reported on the clinical effectiveness of low-dose ipilimumab combined with pembrolizumab (or nivolumab in the retrospective cohort study[18]), and both included some patients who received anti-PD-1 maintenance for up to 2 years (7 of 9 patients received anti-PD-1 maintenance therapy in the retrospective cohort study; an unknown number of patients received maintenance therapy in the single-arm phase II trial). No evidence was identified that met the eligibility criteria in this report for studying the cost-effectiveness of low-dose ipilimumab combined with either pembrolizumab or nivolumab.

In general, the combination of low-dose ipilimumab and pembrolizumab (or nivolumab) was associated with antitumour activity and tolerability. Response rates ranged from 29%[17] to 33%,[18] and among responders, the median duration of response was 16.6 months.[17] Adverse event rates (grade 3 to 4 or 3+) ranged from 27%[17] to 33%.[18] The median progression-free survival ranged from 5 months[17] to 5.7 months.[18] The overall survival ranged from 21.6 months[18] to 24.7 months.[17]

Additional studies that did not meet the eligibility criteria are provided in Appendix 5. Notably, a phase IIIb and IV randomized trial of nivolumab plus low- versus high-dose ipilimumab in adult patients (n = 360), known as the CheckMate 511 Trial, did not have an eligible patient population given that all patients were previously untreated.[20] Moreover, an international retrospective cohort study of patients resistant to anti-PD-1 drugs who received ipilimumab alone or ipilimumab plus anti-PD-1 therapy (n = 355) did not have an eligible intervention given that the dose of ipilimumab was 3 mg/kg.[21]

Previous, related CADTH reports have been published in this population but with different interventions of interest (e.g., ipilimumab monotherapy[13-15]), a higher dose of ipilimumab (e.g., 3 mg/kg[13-15]), or in the first-line treatment setting.[15] Another related CADTH report was nonspecific to dose.[12] The sparse evidence for the clinical effectiveness of low-dose ipilimumab in combination with nivolumab for the treatment of advanced melanoma is consistent with the lack of evidence noted previously by CADTH, based on literature published up to and including 2019.[11,12]

This report offers limited evidence regarding the clinical effectiveness of low-dose ipilimumab in combination with nivolumab or pembrolizumab following treatment with anti-PD-1 monotherapy, and no evidence was identified regarding the cost-effectiveness of these treatments. Future studies are needed with robust study designs, such as randomized-controlled trials with a higher number of recruited patients, in the second-line setting, that

include patient populations of those in Canada and a comparator treatment group that is the Canadian standard of care, to address the clinical and cost-effectiveness of low-dose ipilimumab in combination with pembrolizumab or nivolumab.

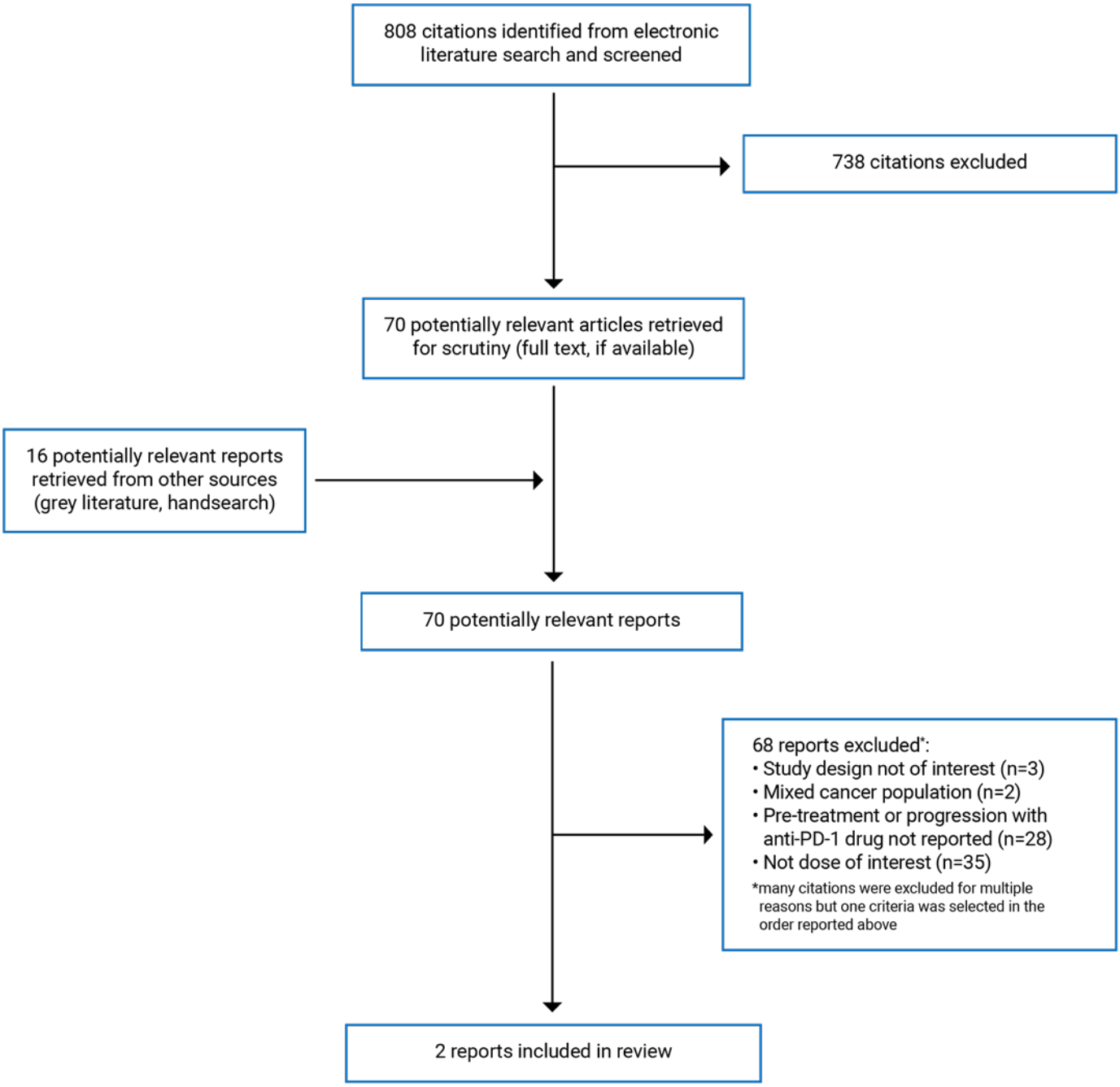
References

1. Canadian Cancer Statistics Advisory Committee, Canadian Cancer Society, Statistics Canada, Public Health Agency of Canada. Canadian cancer statistics. Toronto, ON: Canadian Cancer Society; 2021: www.cancer.ca/Canadian-Cancer-Statistics-2021-EN. Accessed 2022 Jun 20.
2. Canadian Cancer Society. *Survival statistics for melanoma skin cancer.* 2022; https://cancer.ca/en/cancer-information/cancer-types/skin-melanoma/prognosis-and-survival/survival-statistics.
3. Pan-Canadian Oncology Drug Review. pCODR Expert Review Committee (pERC) final recommendation for Nivolumab (Opdivo) plus Ipilimumab (Yervoy) for metastatic melanoma. Ottawa (ON): PCODR; 2017: https://www.cadth.ca/sites/default/files/pcodr/pcodr_opdivo_yervoy_metmela_fn_rec.pdf. Accessed 2022 Jun 20.
4. Ipilimumab: drug information. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2022: www.uptodate.com. Accessed 2022 Jun 3.
5. Nivolumab: drug information. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2022: www.uptodate.com. Accessed 2022 Jun 3.
6. Pembrolizumab: drug information. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2022: www.uptodate.com. Accessed 2022 Jun 3.
7. Yervoy (ipilimumab for injection): intravenous infusion, 5 mg i;ilimumab/mL, 10 mL and 40 mL vials, antineoplastic [product monograph including patient medication information]. Montreal, Canada: Bristol-Myers Squibb Canada Co.; 2012: https://www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf.
8. Opdivo: nivolumab for injection: intravenous infusion, 10 mg nivolumab/ml, 40 mg and 100 mg single use vials: antineoplastic (anatomical therapeutic chemical index code: L01XC17) [product monograph, including patient information]. Montreal, Canada: Bristol-Myers Squibb Canada Co.; 2015: https://www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf.
9. Keytruda (pembrolizumab): powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial, antineoplastic agent, monoclonal antibody [product monograph including patient medication information]. Kirkland, QC: Merck Canada Inc.; 2017: https://pdf.hres.ca/dpd_pm/00040232.PDF. Accessed 2022 Jun 20.
10. Hodi FS, Chapman PB, Sznol M, et al. Safety and efficacy of combination nivolumab plus ipilimumab in patients with advanced melanoma: results from a North American expanded access program (CheckMate 218). *Melanoma Res.* 2021;31(1):67-75. PubMed
11. Cancer immunotherapy after adjuvant immunotherapy: clinical effectiveness and guidelines. *(CADTH rapid response report: reference list)*. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RA1056%20Cancer%20Immunotherapies%20Final.pdf. Accessed 2022 Jun 20.
12. Dosing and timing of immuno-oncology drugs *(CADTH Technology Review)*. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/dosing-and-timing-immuno-oncology-drugs. Accessed 2022 Jul 5.
13. Metastatic melanoma gap analysis *(CADTH Technology Review)*. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/HE0004_Metastatic_Melanoma_Gap_Analysis_TR_Final.pdf. Accessed 2022 Jun 20.
14. Pan-Canadian Oncology Drug Review. pCODR Expert Review Committee (pERC) final recommendation for ipilimumab (Yervoy) for advanced melanoma. Ottawa (ON): pCODR; 2012: https://www.cadth.ca/sites/default/files/pcodr/pcodr-yervoy-adv-mel-fn-rec.pdf. Accessed 2022 Jun 20.
15. Pan-Canadian Oncology Drug Review. pCODR Expert Review Committee (pERC) final recommendation for ipilimumab (Yervoy) for first line advanced melanoma. Ottawa (ON): pCODR; 2014: https://www.cadth.ca/sites/default/files/pcodr/pcodr-yervoy1st-fn-rec.pdf. Accessed 2022 Jun 20.
16. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. PubMed
17. Olson DJ, Eroglu Z, Brockstein B, et al. Pembrolizumab plus ipilimumab following anti-PD-1/L1 failure in melanoma. *J Clin Oncol.* 2021;39(24):2647-2655. PubMed
18. Klee G, Kurzhals J, Hagelstein V, et al. Low-dose ipilimumab combined with anti-PD-1 immunotherapy in patients with metastatic melanoma following anti-PD-1 treatment failure. *Melanoma Res.* 2021;31(5):464-471. PubMed
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7):e1000100. PubMed
20. Lebbé C, Meyer N, Mortier L, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV CheckMate 511 Trial. *J Clin Oncol.* 2019;37(11):867-875. PubMed
21. Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. *Lancet Oncol.* 2021;22(6):836-847. PubMed

Appendix 1: Selection of Included Studies

Note that this appendix has not been copy-edited.

Figure 2: Selection of Included Studies



[a] Many citations were excluded for multiple reasons but 1 criteria was selected (in the order reported in the box).

Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Olson et al. (2021),[17] United States, Merck Investigator Studies Program	Open-label, single-arm phase II trial	70 adult patients with unresectable or metastatic melanoma with known BRAF mutation status. Median patient age was 64 years (range: 27-87); 47 of 70 patients (67%) were male. 62 patients (89%) had cutaneous melanoma; 20 patients (29%) had BRAF V600 mutations; 34 patients (49%) had M1c or M1d disease; 22 patients (31%) had elevated serum lactate dehydrogenase concentrations. All patients had experienced disease progression during treatment with an anti-PD-1/L1 antibody immediately before accrual to the study or disease progression within 6 months of adjuvant anti-PD-1 antibody without intercurrent therapy. Patients had previous grade 3-4 toxicity from anti-PD-1/L1 antibody therapy leading to treatment discontinuation; patients with active CNS metastases were excluded.	Pembrolizumab (200 mg) intravenously along with low-dose ipilimumab (1 mg/kg) intravenously once every 3 weeks for four doses, followed by pembrolizumab intravenously 200 mg once every 3 weeks for up to 2 years	Primary: Objective response rate of pembrolizumab with low-dose ipilimumab following initial progression on an anti-PD-1/L1 antibody in advanced melanoma. Secondary: Progression-free survival (defined as time on study treatment until immune related progressive disease, clear clinical progression, or death) and safety. Exploratory: Associations of baseline tumor gene expression patterns with clinical outcomes. Additional: Overall survival (time from enrollment to death from any cause) and duration of response (defined as the time from first evidence of response until disease progression or death) Follow-up: up to 2 years

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Klee et al. (2021),[18] Germany, source of funding not reported	Retrospective cohort	9 patients with inoperable stage III (n=2) or IV (n=7) metastatic melanoma. 6 of 9 patients (66.7%) were in M-stage M1c or M1d at the initiation of combined immunotherapy. None of the patients had a BRAF V600 mutation. 6 patients had cutaneous melanoma, 2 had melanoma of unknown primary and one patient had mucosal melanoma. Average patient age was 79.4 ± 8.03 years; 6 of 9 (66.7%) were male. All patients had relevant co-morbidities or had experienced severe irAEs during previous immunotherapy. All patients had a history of disease progression following immunotherapy	Ipilimumab (1 mg/kg) with nivolumab 3 mg/kg or pembrolizumab 200 mg every 3 weeks for four doses. After four doses of combined immunotherapy staging examinations (computer tomography/ MRI) were performed to assess treatment response. Following combined immunotherapy, patients received anti-PD-1 monotherapy with nivolumab or pembrolizumab or were switched to another therapy.	Primary: Rate of severe (grade 3–5) irAEs. irAEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), assessed from the first dose of combined immunotherapy to 1 November 2020. Safety was assessed based on the frequency of irAEs, their severity and whether they led to treatment discontinuation or death. Exploratory: resistance to previous PD-1-based immunotherapy, clinical outcomes following response to combined immunotherapy, including best overall response, progression-free survival, and overall survival Follow-up: median 13.1 months

BRAF = BRAF 600, a specific mutation in the BRAF gene; irAE = immune-related adverse events; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[16]

Strengths	Limitations
Olson et al. (2021)[17]	
• The objectives of the study are clearly described • The main outcomes to be measured are clearly described and accurate • The characteristics of the patients included in the study are clearly described • The intervention of interest is clearly described • The main findings of the study are clearly described • Study provides estimates of the random variability in the data for the main outcomes • Important adverse events that may be a consequence of the intervention are reported • The characteristics of patients lost to follow-up are described • The different lengths of follow-up were adjusted by using Kaplan-Meier method • The statistical tests used to assess the main outcomes are appropriate • Loss of patients to follow-up was considered	• The authors did not address or account for confounding factors • Actual probability values are not reported for the main outcomes • Unable to determine the external validity • Internal validity bias associated with study design (non-randomized, unblinded, and single-arm) • • No power calculations were provided
Klee et al. (2021)[18]	
• The objectives of the study are clearly described • The main outcomes to be measured are clearly described and accurate • The intervention of interest is clearly described • The main findings of the study are clearly described • Study provides estimates of the random variability in the data for the main outcomes • Important adverse events that may be a consequence of the intervention are reported • The characteristics of patients lost to follow-up are described • The different lengths of follow-up were adjusted by using Kaplan-Meier method • The statistical tests used to assess the main outcomes are appropriate • Loss of patients to follow-up was considered	• Inclusion and exclusion criteria not adequately described • The authors did not address or account for confounding factors • Unable to determine the external validity • Internal validity bias associated with study design (non-randomized, unblinded, and single-arm) • • No power calculations were provided

Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Table 4: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Olson et al. (2021)[17]	
• Among the 70 patients enrolled, 60 had prior treatment with an anti-PD-1 antibody monotherapy and 10 had prior treatment with an anti-PD-1/L1 antibody–based combination therapy, with a median of 4.8 months on a prior anti-PD-1/L1 antibody treatment. • The median follow-up was 12.0 months (interquartile range [IQR], 6.0- 22.6 months); among patients still alive, the median follow-up time was 13.3 months (IQR, 6.2-23.1 months). • At the time of the analysis, 5 patients (7%) were continuing to receive pembrolizumab monotherapy and 1 patient had completed 2 years of study therapy. All other patients discontinued due to the following reasons: clinical or radiographic disease progression in 47 patients (67%), adverse events in 9 patients (13%), elective discontinuation of therapy after complete response in 4 patients (6%), death unrelated to study therapy in 2 patients (3%), or withdrawal of consent in 2 patients (3%). • Fifty-three patients (76%) received four or more doses of pembrolizumab plus low dose ipilimumab. Of those who did not complete four cycles of study therapy, median number of cycles was 2 (IQR, 1.75-2.25) and reasons for discontinuation included progressive disease (n = 11), adverse events (n = 4), and death (n = 2). • For patients continuing pembrolizumab monotherapy, the median number of cycles was 9 (IQR, 5.0-15.8) • Among 70 enrolled patients, 20 confirmed responses were observed (response rate 29% [95% CI, 18.4 to 40.6]) including five complete (7.2%) and 15 partial responses (21.4%) with a median duration of response of 16.6 months. • Three patients had unconfirmed responses, all with subsequent disease progression; 8 were non-evaluable for radiographic assessment of the primary end point but are included in the overall analysis for objective response rate (as non-responders) and secondary end points. • Of the 8 non-evaluable patients, 5 had clear clinical progression before first response assessment, 2 died of complications related to disease progression before restaging, and 1 withdrew consent after experiencing grade 3 immune-related hepatitis after one dose of study therapy. • Responses were observed across clinical and biomarker subgroups, including patients who progressed on an anti-PD-1/L1 antibody in the adjuvant setting (2 of 13, 15%),	"The combination of pembrolizumab plus low-dose ipilimumab demonstrated significant antitumor activity and tolerability in a multicenter clinical trial. This study demonstrated long-term responses, suggesting that durable survival—a hallmark of immunotherapy activity—may be possible even after failure of an anti-PD-1/L1 antibody (p. 2653)."[17]

Main study findings	Authors' conclusion
patients with liver metastases and previously treated CNS metastases (6 of 25, 17%), and patients with an elevated LDH at study entry (6 of 22, 27%). • The median time between prior anti-PD-1/L1 treatments and initiating pembrolizumab plus low-dose ipilimumab was 1.5 months in responders, vs 1.4 months in non-responders. • Treatment-related adverse events occurred in 62 of 70 patients (87%), with the most frequent events including pruritis, rash, diarrhea, fatigue, nausea, and transaminase elevations. • Grade 3-4 treatment-related adverse events occurred in 19 of 70 patients (27%) with the most common being colitis or diarrhea, rash, and transaminase elevations. • One patient experienced a grade 4 treatment-related adverse event, which was a concurrent lipase elevation in a patient with grade three pancreatitis. Four other patients also experienced concurrent grade 3 treatment-related adverse events. • There were no deaths related to study treatment. • The median time to onset of grade 3-4 adverse events was 55 days. • The median progression-free survival was 5 months (95% CI, 2.8 to 8.3). • In responding patients, the median duration of response was 16.6 months (95% CI, 7.9 to not reached). • The median overall survival was 24.7 months (95% CI,15.2 to not reached) • • At the time of data lock, 14 of 20 responses (70%) were ongoing	
Klee et al. (2021)[18]	
• Eight of 9 patients (89%) tolerated 4 doses of low-dose ipilimumab (1 mg/kg) plus nivolumab 3 mg/kg or low-dose ipilimumab plus pembrolizumab 200 mg. • One of 9 patients discontinued combined immunotherapy due to immune related colitis • Two of 9 patients underwent concurrent radiotherapy • after the combined immunotherapy had been initiated. • Seven of 9 patients received maintenance therapy with nivolumab or pembrolizumab with a median of 7.5 doses (range: 2–17 doses). • Three of 9 patients (33.3%) died during the observation period due to tumor progression. • The proportion of patients with irAEs of any grade was 55.6% (5 of 9 patients); the proportion with grade 3 irAEs was 33.3% (3 of 9 patients). There were no grade 4 or 5 irAEs. Four out of the 5 patients with irAEs developed several organ-specific toxicities.	"Dual inhibition of anti-cytotoxic T-lymphocyte–associated antigen 4 (with low-dose ipilimumab) and PD-1 may be a useful treatment option for patients with advanced melanoma who have progressed following anti-PD-1 monotherapy. The irAE profile may also be more favorable than that seen with standard IPI3+NIVO1 therapy. As a result, this dosing regimen could be considered for selected patient populations, for example, elderly patients, patients with multiple co-morbidities or those who have suffered from severe irAEs during previous immunotherapy." (p.470)

Main study findings	Authors' conclusion
• The mean time to the onset of grade 3 irAEs was 14.3 weeks. • The objective response rate was 33.3% (3 of 9 patients had a partial response) • The disease control rate was 66.7% (6 of 9 patients) • Median progression-free survival was 5.7 months • Median overall survival was 21.6 months. • 12-month overall survival was 79% (95% CI 56.9%– 100%) • Median progression-free survival was different between the second-line and "greater than second-line" treatment groups (*P*-value = 0.0018). • Median overall survival was different between the second-line and "greater than second-line" treatment groups (*P*-value = 0.027).	

irAE = immune-related adverse events; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; PD-L1 = programmed cell death ligand-1.

Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

Cancer immunotherapy after adjuvant immunotherapy: clinical effectiveness and guidelines. *(CADTH Rapid Response Report: Reference List)*. Ottawa, ON: CADTH;2019: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RA1056%20Cancer%20Immunotherapies%20Final.pdf. Accessed 2022 Jun 23.

Dosing and timing of immune-oncology drugs. *(CADTH Technology Review: Optimal Use 360 Report)*. Ottawa, ON: CADTH; 2019: https://www.cadth.ca/dosing-and-timing-immuno-oncology-drugs. Accessed 2022 Jul 5.

Metastatic melanoma gap analysis. (CADTH Technology Review; no.9). Ottawa, ON: CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/HE0004_Metastatic_Melanoma_Gap_Analysis_TR_Final.pdf. Accessed 2022 Jun 23.

Yervoy for first line advanced melanoma: details. *(CADTH Reimbursement Review)*. Ottawa, ON: CADTH; 2014: https://www.cadth.ca/yervoy-first-line-advanced-melanoma-details. Accessed 2022 Jun 23.

Yervoy for advanced melanoma: details. *(CADTH Reimbursement Review)*. Ottawa, ON: CADTH; 2012: https://www.cadth.ca/yervoy-advanced-melanoma-details. Accessed 2022 Jun 23.

Review Articles

Karlsson AK, Saleh SN. Checkpoint inhibitors for malignant melanoma: a systematic review and meta-analysis. Review. *Clin Cosmet Investig Dermatol*. 2017;10:325-339. PubMed

Additional References

Higher dose of ipilimumab (3 mg/kg)

Friedman CF, Spencer C, Cabanski CR, et al. Ipilimumab alone or in combination with nivolumab in patients with advanced melanoma who have progressed or relapsed on PD-1 blockade: clinical outcomes and translational biomarker analyses. *J Immunother Cancer.* 2022;10(1):01. PubMed

Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. *Lancet Oncol.* 2021;22(6):836-847. PubMed

Ineligible due to previous treatment

Lebbé C, Meyer N, Mortier L, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV CheckMate 511 trial. *J Clin Oncol.* 2019;37(11):867-875. PubMed

Kirchberger MC, Moreira A, Erdmann M, Schuler G, Heinzerling L. Real world experience in low-dose ipilimumab in combination with PD-1 blockade in advanced melanoma patients. *Oncotarget.* 2018;9(48):28903-28909. PubMed

Long GV, Atkinson V, Cebon JS, et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. *Lancet Oncol.* 2017;18(9):1202-1210. PubMed