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Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

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PUBLICATIONS RELATED TO THIS REPORT

Wright F, Souter LH, Easson A, Murray C, Toye J, McCready D, et al. Primary excision margins and sentinel lymph node biopsy in cutaneous melanoma. Toronto (ON): Cancer Care Ontario; 2017 November 13. Program in Evidence-Based Care Guideline No.: 8-2 Version 2.

Petrella T, Baetz T, Fletcher GG, Knight G, McWhirter E, Rajagopal S, Song X. Systemic adjuvant therapy for adult patients at high risk for recurrent melanoma. Toronto (ON): Cancer Care Ontario; 2019 Aug 14. Program in Evidence-Based Care Guideline No.: 8-1 version 5.

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Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

The objective of this guideline is to provide guidance on the use of systemic therapy in patients with unresectable, metastatic cutaneous melanomas.

PREAMBLE

Immunotherapy

Programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors are immune checkpoint inhibitors used to treat melanoma by boosting the immune system's ability to fight melanoma by blocking specific immune checkpoints. PD-1 inhibitors block the interaction between the PD-1 receptor on T-cells and its ligand PD-L1, enhancing the immune response. Common PD-1 inhibitors used in melanoma treatment include pembrolizumab and nivolumab. CTLA-4 inhibitors work similarly by blocking the CTLA-4 receptor on T-cells. A CTLA-4 inhibitor used in melanoma treatment is ipilimumab. In addition to the above immune checkpoint inhibitors, relatlimab is an immunotherapy drug that targets lymphocyte-activation gene 3 (LAG-3), an inhibitory receptor on T-cells. By blocking LAG-3, it restores T-cell function and enhances the immune response against tumours. For the purpose of this guideline, PD-1 refractory includes both acquired (stopped responding after an initial response) and primary resistance (never responded).

Targeted Therapy

Targeted therapies for metastatic melanoma focus on specific genetic mutations that drive cancer growth. The most common targets are BRAF and MEK proteins, which are part of a signaling pathway that promotes cell division. In patients with BRAF mutations, drugs like vemurafenib or dabrafenib (BRAF inhibitors) are often combined with trametinib or cobimetinib (MEK inhibitors) to block this pathway more effectively and delay resistance.

TARGET POPULATION

These recommendations apply to adult patients (18+) with unresectable lymph node metastasis (American Joint Committee on Cancer [AJCC] TNM stage IIIC/D) and distant metastatic (AJCC TNM stage IV) cutaneous melanoma for whom systemic therapy is indicated. Pathological staging is according to the 8th edition AJCC staging system [1].

INTENDED USERS

The intended users of the guideline are medical oncologists, dermatologists, family doctors and other clinicians who are involved in the treatment and follow-up care of patients with melanoma in the province of Ontario.

RECOMMENDATIONS

RECOMMENDATION 1

1.1 For adults with unresectable Stage IIIC/D or Stage IV distant metastatic BRAF wild-type cutaneous melanoma, the systemic first-line treatments recommended are PD-1/PD-L1 and/or CTLA-4 and/or LAG-3 inhibitors (in no particular order):

- Nivolumab plus ipilimumab
- Nivolumab monotherapy
- Nivolumab plus relatlimab
- Pembrolizumab monotherapy

1.2 Table 1-1 lists the recommended dose, administration, schedule, and duration options of the above-mentioned treatments.

Table 1-1. Dose schedule for systemic treatment options for patients with BRAF wild-type melanoma

Systemic Treatment Option	Recommended Dose, Administration, Schedule and Duration	Reference Trial
Nivolumab plus ipilimumab	Nivolumab 1 mg/kg and ipilimumab 3 mg/kg iv once every 3 weeks for 4 doses followed by nivolumab 3 mg/kg once every 4 weeks until progression, toxicity or physician and/or patient considerations	CheckMate-067 [2-4]
Nivolumab monotherapy	Nivolumab 3 mg/kg iv once every 2 weeks, or nivolumab 6 mg/kg iv once every 4 weeks until progression, toxicity or physician and/or patient considerations	CheckMate 067 [2-4]
Nivolumab plus relatlimab	Nivolumab 480 mg and relatlimab 160 mg iv once every 4 weeks until progression	Relativity-047 [5]
Pembrolizumab monotherapy	Pembrolizumab 2 mg/kg iv once every 3 weeks, or pembrolizumab 6 mg/kg once every 4 weeks for up to 2 years with the possibility of retreatment for 1 year	KeyNote 006 [6] KeyNote 002 [7]

Abbreviations: iv, Intravenous.
Table Notes: Pembrolizumab may be used for up to 2 years with the possibility of retreatment for 1 year.
Nivolumab plus Ipilimumab can be given as 4 treatments every 3 weeks then followed by maintenance nivolumab every 4 weeks, indefinitely
Nivolumab and relatlimab may be given indefinitely until progression, toxicity or physician and/or patient considerations

QUALIFYING STATEMENTS FOR RECOMMENDATION 1

- Clinical trials should be considered if the above systemic targeted therapies are unsuccessful or not acceptable.
- Adjuvant therapy may influence responsiveness in the metastatic setting; however, combination therapy with nivolumab plus ipilimumab should be considered first line regardless of adjuvant treatment choice.
- Chemotherapy may be considered but is not recommended over the immunotherapies listed above.
- For patients with advanced melanoma who experience disease progression after a period off systemic therapy, re-initiation of immunotherapy may be considered

RECOMMENDATION 2

2.1 For adults with unresectable Stage IIIC/D or Stage IV distant metastatic BRAF-mutated cutaneous melanoma, the systemic targeted therapy options recommended are:

- Ipilimumab plus nivolumab
- Nivolumab

- Nivolumab plus relatlimab
- Pembrolizumab
- Dabrafenib plus trametinib
- Encorafenib plus binimetinib
- Vemurafenib plus cobimetinib

2.2 Table 1-2 lists the recommended dose, administration, schedule, and duration options of the above-mentioned treatments.

Table 1-2. Dose schedule for systemic treatment options for patients with BRAF-mutated melanoma

Systemic Treatment Option	Recommended Dose, Administration Schedule and Duration	Reference Trial
Nivolumab plus ipilimumab	Nivolumab plus ipilimumab for up to 4 doses iv every 3 weeks followed by nivolumab 6 mg/kg every 4 weeks indefinitely until progression, toxicity or physician and/or patient considerations	CheckMate-067 [2-4]
Nivolumab monotherapy	Nivolumab 3 mg/kg iv once every 2 weeks, or nivolumab 6 mg/kg iv once every 4 weeks until progression, toxicity or physician and/or patient considerations	CheckMate 067 [2-4]
Nivolumab plus relatlimab	Nivolumab 480 mg and relatlimab 160 mg iv once every 4 weeks until progression	[5] (Relativity-047)
Pembrolizumab monotherapy	Pembrolizumab 2 mg/kg once every 3 weeks iv, or pembrolizumab 4 mg/kg once every 6 weeks iv, or pembrolizumab 6 mg/kg once every 4 weeks for up to 2 years with the possibility of retreatment for 1 year	KeyNote 006 [6] KeyNote 002 [7]
Dabrafenib plus trametinib	Dabrafenib 150 mg orally twice daily plus trametinib 2 mg orally once daily	Combi-v [8] [9]
Encorafenib plus binimetinib	Encorafenib 450 mg orally once daily plus binimetinib 45 mg orally twice daily	COLUMBUS [10-13]
Vemurafenib plus cobimetinib	Cobimetinib (60 mg once daily for 21 days followed by a 7-day rest period in each 28-day cycle) in combination with vemurafenib (960 mg twice daily)	CoBrim [14]

Abbreviations: iv, Intravenous.
Table Notes: Pembrolizumab may be used for up to 2 years with the possibility of retreatment for 1 year.
Nivolumab plus ipilimumab can be administered as 4 treatments every 3 weeks then followed by maintenance nivolumab every 4 weeks, indefinitely
Nivolumab and relatlimab may be given indefinitely until progression, toxicity or physician and/or patient considerations

2.3 Immunotherapy is preferred over targeted therapy as first-line treatment for advanced melanoma, including BRAF-mutant disease, even when administered as single-agent therapy

QUALIFYING STATEMENTS FOR RECOMMENDATION 2

- Clinical trials should be considered if the above systemic targeted therapies are unsuccessful or not acceptable based on patient and physician preferences and values
- Triplet therapy may be discussed for subgroups of patients for which triplet therapy may be beneficial who have not responded well to other treatments

RECOMMENDATION 3

3.1 In adults with stage IIIC/D or stage IV metastatic BRAF wild-type melanoma who are refractory to PD-1 monotherapy the following systemic treatments are recommended:

- Ipilimumab plus nivolumab
- Pembrolizumab plus ipilimumab

3.2 In adults with metastatic BRAF-mutated melanoma who are refractory to PD-1-therapy the following systemic treatments are recommended:

- Ipilimumab plus nivolumab
- Nivolumab plus relatlimab
- Pembrolizumab plus ipilimumab
- Dabrafenib plus trametinib
- Encorafenib plus binimetinib
- Vemurafenib plus cobimetinib

QUALIFYING STATEMENTS FOR RECOMMENDATION 3

- Clinical trials should be considered if the above systemic therapies are unsuccessful or not acceptable based on physician or patient preferences and values.
- Dosing schedules are the same as in Recommendations 1 and 2, for Recommendation 3.1 and 3.2, respectively.

RECOMMENDATION 4

4.1 For adults with unresectable or metastatic melanoma, with the following clinical subtypes: NRAS, KIT, clinical disease subtypes (i.e., brain metastases), the systemic therapy regimens recommended are:

- NRAS: binimetinib (with or without immunotherapy)
- KIT: due to low quality of evidence (no randomized controlled trials) no recommendation can be made – specifically for KIT patients, however, systemic treatment should follow the systemic therapies outlined in Recommendation 2
- Brain metastasis: nivolumab plus ipilimumab

QUALIFYING STATEMENTS FOR RECOMMENDATION 4

- Clinical trials should be considered if the above systemic targeted therapies are unsuccessful or not acceptable based on patient and physician preferences and values
- Brain metastasis: if nivolumab plus ipilimumab cannot be tolerated, nivolumab plus relatlimab, or single-agent nivolumab or pembrolizumab may be considered as per Recommendation 1. If BRAF mutation is present, then BRAF/MEK inhibitors as in Recommendation 2 may be considered. In addition to the recommended systemic therapies, radiation therapy is an important modality of treatment for melanoma brain metastasis. When recommending radiation, stereotactic radiation would be preferred. A multidisciplinary approach is always recommended for optimal patient care.

Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

The objective of this guideline is to provide guidance on the use of systemic therapy in patients with unresectable, metastatic cutaneous melanomas.

PREAMBLE

Immunotherapy

Programmed cell death protein 1/

programmed death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors are immunotherapies used to treat melanoma by boosting the immune system's ability to fight melanoma by blocking specific immune checkpoints. PD-1 inhibitors block the interaction between the PD-1 receptor on T-cells and its ligand PD-L1, enhancing the immune response. Common PD-1 inhibitors used in melanoma treatment include pembrolizumab and nivolumab. CTLA-4 inhibitors work similarly by blocking the CTLA-4 receptor on T-cells. A CTLA-4 inhibitor used in melanoma treatment is ipilimumab. In addition to the above immune checkpoint inhibitors, relatlimab is an immunotherapy drug that targets lymphocyte-activation gene 3 (LAG-3), an inhibitory receptor on T cells. By blocking LAG-3, it restores T-cell function and enhances the immune response against tumours. For the purpose of this guideline, PD-1 refractory includes both acquired (stopped responding after an initial response) and primary resistance (never responded).

Targeted Therapy

Targeted therapies for metastatic melanoma focus on specific genetic mutations that drive cancer growth. The most common targets are BRAF and MEK proteins, which are part of a signaling pathway that promotes cell division. In patients with BRAF mutations, drugs like vemurafenib or dabrafenib (BRAF inhibitors) may be combined with trametinib or cobimetinib (MEK inhibitors) to block this pathway more effectively and delay resistance.

TARGET POPULATION

These recommendations apply to adult patients (18+) with unresectable lymph node metastasis (American Joint Committee on Cancer [AJCC] TNM stage IIIC/D) and distant metastatic (AJCC TNM stage IV) cutaneous melanoma for whom systemic therapy is indicated. Pathological staging is according to the 8th edition AJCC staging system [1].

INTENDED USERS

The intended users of the guideline are medical oncologists, dermatologists, family doctors and other clinicians who are involved in the treatment and follow-up care of patients with melanoma in the province of Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

RECOMMENDATION 1

1.1 For adults with unresectable Stage IIIC/D or Stage IV distant metastatic BRAF wild-type cutaneous melanoma, the systemic first-line treatments recommended are PD-1/PD-L1 and/or CTLA-4 and/or LAG-3 inhibitors (in no particular order):

- Nivolumab plus ipilimumab
- Nivolumab monotherapy
- Nivolumab plus relatlimab
- Pembrolizumab monotherapy

1.2 Table 2-1 lists the recommended dose, administration, schedule, and duration options of the above-mentioned treatments.

Table 2-1. Dose schedule for systemic treatment options for patients with BRAF wild-type melanoma

Systemic Treatment Option	**Recommended Dose,** Administration, **Schedule and Duration**	**Reference Trial**
Nivolumab plus ipilimumab	Nivolumab 1 mg/kg and ipilimumab 3 mg/kg iv once every 3 weeks for 4 doses followed by nivolumab 3 mg/kg once every 4 weeks until progression, toxicity or physician and/or patient considerations	CheckMate-067 [2-4]
Nivolumab monotherapy	Nivolumab 3 mg/kg iv once every 2 weeks, or nivolumab 6 mg/kg iv once every 4 weeks until progression, toxicity or physician and/or patient considerations	CheckMate 067 [2-4]
Nivolumab plus relatlimab	Nivolumab 480 mg and relatlimab 160 mg iv once every 4 weeks until progression	Relativity-047 [5]
Pembrolizumab monotherapy	Pembrolizumab 2 mg/kg iv once every 3 weeks or pembrolizumab 6 mg/kg once every 4 weeks for up to 2 years with the possibility of retreatment for 1 year	KeyNote 006 [6] KeyNote 002 [7]

Abbreviations: iv, Intravenous.

Table Notes: Pembrolizumab may be used for up to 2 years with the possibility of retreatment for one year.

Ipilimumab monotherapy can be used up to 4 doses

Nivolumab plus ipilimumab can be given as 4 treatments every 3 weeks then followed by maintenance nivolumab every 4 weeks, indefinitely

Nivolumab and relatlimab may be given indefinitely until progression, toxicity or physician and/or patient considerations

QUALIFYING STATEMENTS FOR RECOMMENDATION 1

- Clinical trials should be considered if the above systemic targeted therapies are unsuccessful or not acceptable.
- Adjuvant therapy may influence responsiveness in the metastatic setting; however, combination therapy with nivolumab plus ipilimumab should be considered first line regardless of adjuvant treatment choice.
- Chemotherapy may be considered but is not recommended over the immunotherapies listed above.
- For patients with advanced melanoma who experience disease progression after a period off systemic therapy, re-initiation of immunotherapy may be considered.

KEY EVIDENCE FOR RECOMMENDATION 1

The recommendations for systemic immunotherapy are primarily based on a 2018 Cochrane systematic review [15] and several randomized controlled trials (RCTs). These studies evaluated the efficacy and safety of anti-PD-1 (nivolumab and pembrolizumab) and anti-CTLA-4 (ipilimumab) therapies, both as monotherapies and in combination. The Cochrane review found that nivolumab and pembrolizumab significantly improved overall survival (OS) and progression-free survival (PFS) compared to ipilimumab, with reduced toxicity. Combination therapy of nivolumab and ipilimumab showed better PFS but higher toxicity than nivolumab alone [15]. This was confirmed by the results of CheckMate-067, with a minimum follow-up of 10 years, which showed that the combination of nivolumab and ipilimumab significantly improved OS compared with ipilimumab alone. Treatment-related grade 3 or 4 adverse events occurred in 55.0% of patients receiving nivolumab plus ipilimumab, compared to 27.3% with nivolumab alone and 16.3% with ipilimumab alone, indicating a higher toxicity with the combination therapy [2-4]. The CheckMate-511 trial indicated lower toxicity with nivolumab 3 mg/kg and ipilimumab 1 mg/kg versus nivolumab 1 mg/kg and ipilimumab 3 mg/kg [16]. Additionally, a trial reported by Ascierto et al compared ipilimumab 10 mg/kg versus 3 mg/kg and found improved OS (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.70 to 0.99) but with greater toxicity for ipilimumab 10 mg/kg [17]. Additional trials highlighted the efficacy of nivolumab and ipilimumab in treating melanoma brain metastases and the potential benefits of combining nivolumab with relatlimab [18]. Grade 3–4 treatment-related adverse events occurred in approximately 18.9% to 22% of patients receiving the combination therapy, compared to 9.7% to 12% receiving nivolumab alone. Despite the higher toxicity, the combination therapy significantly improved PFS (10.1 vs. 4.6 months) [18]. The Cochrane systematic review evaluating comparisons of ipilimumab and chemotherapy, as well as nivolumab or pembrolizumab and chemotherapy, showed improved survival with immunotherapy but varying toxicity levels [15].

JUSTIFICATION FOR RECOMMENDATION 1

Unfortunately, a limitation of the above evidence is the lack of direct intervention-to-intervention comparisons in RCTs. The choice of therapy should be based on risk and benefit balance, patient characteristics, comorbidities, impact of potential adverse events, and patient and physician preferences. Physician and patient preferences and discussion of potential for toxicity based on the evidence, should occur. Indications above are publicly funded in Ontario. While chemotherapy may be considered, the Working Group recommends the immunotherapy therapies above as they provide survival benefits over traditional chemotherapy [9].

RECOMMENDATION 2

2.1 For adults with unresectable Stage IIIC/D or Stage IV distant metastatic BRAF-mutated cutaneous melanoma, the systemic targeted therapy options recommended are:

- Ipilimumab plus nivolumab
- Nivolumab monotherapy
- Nivolumab plus relatlimab
- Pembrolizumab monotherapy
- Dabrafenib plus trametinib
- Encorafenib plus binimetinib
- Vemurafenib plus cobimetinib

2.2 Table 2-2 lists the recommended dose, administration, schedule, and duration options of the above-mentioned treatments.

Table 2-2. Dose schedule for systemic treatment options for patients with BRAF mutated melanoma

Systemic Treatment Option	Recommended Dose, Administration Schedule and Duration	Reference Trial
Nivolumab plus ipilimumab	Nivolumab plus ipilimumab for up to 4 doses iv every 3 weeks followed by nivolumab 6 mg/kg every 4 weeks indefinitely until progression, toxicity or physician and/or patient considerations	CheckMate-067 [2-4]
Nivolumab monotherapy	Nivolumab 3 mg/kg iv once every 2 weeks, or nivolumab 6 mg/kg iv once every 4 weeks until progression, toxicity or physician and/or patient considerations	CheckMate 067 [2-4]
Nivolumab plus relatlimab	Nivolumab 480 mg and relatlimab 160 mg iv once every 4 weeks until progression	[5] (Relativity-047)
Pembrolizumab monotherapy	Pembrolizumab 2 mg/kg once every 3 weeks iv, or pembrolizumab 4 mg/kg once every 6 weeks iv or pembrolizumab 6 mg/kg once every 4 weeks for up to 2 years with the possibility of retreatment for 1 year	KeyNote 006 [6] KeyNote 002 [7]
Dabrafenib plus trametinib	Dabrafenib 150 mg orally twice daily plus trametinib 2 mg orally once daily	Combi-v [8] [9]
Encorafenib plus binimetinib	Encorafenib 450 mg orally once daily plus binimetinib 45 mg orally twice daily	COLUMBUS [10-13]
Vemurafenib plus cobimetinib	Cobimetinib (60 mg once daily for 21 days followed by a 7-day rest period in each 28-day cycle) in combination with vemurafenib (960 mg twice daily)	CoBrim [14]

Abbreviation: iv, Intravenous.
Table Notes: Pembrolizumab may be used for up to 2 years with the possibility of retreatment for one year.
Nivolumab plus ipilimumab can be given as 4 treatments every 3 weeks then followed by maintenance nivolumab every 4 weeks, indefinitely
Nivolumab and relatlimab may be given indefinitely until progression, toxicity or physician and/or patient considerations

2.3 Immunotherapy is preferred over targeted therapy as first-line treatment for advanced melanoma, including BRAF-mutant disease, even when administered as single-agent therapy

QUALIFYING STATEMENTS FOR RECOMMENDATION 2

- Clinical trials should be considered if the above systemic targeted therapies are unsuccessful or not acceptable based on patient and physician preferences and values
- Triplet therapy may be discussed for patients who have not responded well to other treatments

KEY EVIDENCE FOR RECOMMENDATION 2

The Cochrane review of nine studies on BRAF-mutated melanoma found that combination BRAF and MEK inhibitors offer a survival benefit over single-agent BRAF inhibitors (HR, 0.70; 95% CI, 0.59 to 0.82) without increased toxicity (relative risk [RR], 1.01; 95% CI, 0.85 to 1.20) [15]. The COLUMBUS trial showed significant improvements in PFS and OS with encorafenib plus binimetinib compared to vemurafenib, but not encorafenib alone [10-13]. The combination therapy also had a manageable safety profile, with fewer severe adverse events compared with vemurafenib monotherapy. The EBIN trial evaluated combination encorafenib and binimetinib followed by ipilimumab and nivolumab versus ipilimumab and nivolumab [71].

The study found no evidence to suggest a longer progression-free survival in the induction group than in the control group (HR 0.87, 90% CI 0.67-1.12; p=0.36) [71]. The coBRIM trial reported better OS and PFS with vemurafenib plus cobimetinib versus vemurafenib monotherapy [14]. Similarly, the combination therapy also had a more tolerable toxicity profile compared to monotherapy. The COMBI-D trial demonstrated improved three-year OS and PFS with dabrafenib plus trametinib compared to dabrafenib monotherapy [8]. Trials involving anti-PD-1 inhibitors, such as IMSPIRE, KEYNOTE-022, and COMBI-i, showed mixed results, with some improvements in PFS and OS. 3 trials investigated targeted therapy in addition to an anti-PD-1 inhibitor [5,9,19-23]. In the IMSPIRE trial, patients were randomly assigned to receive either atezolizumab or placebo; all patients received vemurafenib and cobimetinib. OS was not significantly improved with atezolizumab, vemurafenib, and cobimetinib compared with placebo, vemurafenib, and cobimetinib (HR, 0.84; 95% CI, 0.66 to 1.06; p=0.14) in patients with BRAF mutation-positive advanced melanoma [20,21]. The KEYNOTE-022 trial compared pembrolizumab with placebo in patients who were receiving dabrafenib plus trametinib and reported no significant difference in PFS (HR, 0.66; 95% CI, 0.40 to 1.07) [23]. Grade 3–4 treatment-related adverse events occurred in 58.3% of patients receiving the triplet, compared to 25% in the doublet group. A follow-up publication of KEYNOTE-022 reported PFS (HR, 0.58; 95% CI, 0.34 to 0.83) and OS (HR, 0.64; 95% CI, 0.38 to 1.06) for pembrolizumab and dabrafenib plus trametinib compared to placebo. The COMBI-i trial compared spartalizumab versus placebo in patients who were receiving dabrafenib plus trametinib and reported no significant difference in PFS (HR, 0.82; 95% CI, 0.66 to 1.03) or OS (HR, 0.79; 95% CI, 0.59 to 1.05). The addition of spartalizumab led to an increase in toxicity without a statistically significant improvement in PFS [5,9,19].

Sequencing studies such as DREAMseq and SECOMBIT explored different treatment strategies, with DREAMseq favouring nivolumab plus ipilimumab followed by dabrafenib plus trametinib for better two-year OS and PFS. In a five-year update, nivolumab plus ipilimumab continues to show statistically significant superiority over dabrafenib plus trametinib in both OS and PFS [24]. SECOMBIT evaluated differing treatment approaches in three different arms. After four years of survival data, the SECOMBIT trial demonstrated a survival benefit with first-line immunotherapy with or without an eight-week course of targeted therapy for the treatment of BRAF-mutant metastatic melanoma [25-27]. The INTERIM phase 2 trial evaluated intermittent versus continuous dosing of dabrafenib plus trametinib in patients with BRAFV600-mutant advanced melanoma [28]. The trial found that continuous dosing was superior in terms of PFS, OS, and response rate. Intermittent dosing resulted in fewer treatment-related adverse events but more severe ones. Detection of BRAFV600 circulating tumour DNA (ctDNA) before treatment was linked to worse OS in both groups. Overall, intermittent dosing did not improve the efficacy of BRAF+MEK inhibitors [28].

Triplet Therapy

Three studies evaluated three variations of first-line triplet therapies in BRAF-mutant unresectable metastatic melanoma [22,23,29]. Dummer et al conducted a randomized phase II trial evaluating spartalizumab in combination with dabrafenib and trametinib, versus placebo plus dabrafenib and trametinib in patients with BRAF V600–mutant unresectable or metastatic melanoma. Patients received spartalizumab 400 mg intravenously every four weeks plus dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily or placebo plus dabrafenib and trametinib. Median PFS was 16.2 months (95% CI, 12.7 to 23.9 months) in the spartalizumab plus dabrafenib and trametinib arm versus 12.0 months (95% CI, 10.2 to 15.4 months) in the placebo plus dabrafenib and trametinib arm (HR, 0.82; 95% CI, 0.66 to 1.03; p=0.042) (29). The KEYNOTE-022 trial evaluated the combination of pembrolizumab, dabrafenib, and trametinib versus dabrafenib and trametinib in patients with BRAF-mutant

advanced melanoma. The study found that the triplet therapy improved PFS compared to the doublet therapy, with a median PFS of 16.9 months versus 10.7 months, respectively. OS was not reached with the triplet therapy [23]. The IMSPIRE150 trial evaluated the combination of atezolizumab, cobimetinib, and vemurafenib versus placebo in patients with BRAF V600 mutation-positive advanced melanoma. The study found that the combination therapy significantly improved PFS compared with placebo [22].

JUSTIFICATION FOR RECOMMENDATION 2

As with Recommendation 1, there are no RCTs directly comparing the interventions recommended above. The Working Group determined that due to the lack of comparative evidence, the choice of therapy should be based on risk and benefit balance, patient characteristics, impact of potential adverse events, and patient and physician preferences.

RECOMMENDATION 3

3.1 In adults with stage IIIC/D or stage IV metastatic BRAF wild-type melanoma who are refractory to PD-1 monotherapy the following systemic treatments are recommended:

- Ipilimumab plus nivolumab
- Pembrolizumab plus ipilimumab

3.2 In adults with metastatic BRAF-mutated melanoma who are PD-1-refractory the following systemic treatments are recommended:

- Ipilimumab plus nivolumab
- Nivolumab plus relatlimab
- Pembrolizumab plus ipilimumab
- Dabrafenib plus trametinib
- Encorafenib plus binimetinib
- Vemurafenib plus cobimetinib.

QUALIFYING STATEMENTS FOR RECOMMENDATION 3

- Clinical trials should be considered if the above systemic therapies are unsuccessful or not acceptable based on physician or patient preferences and values
- Dosing schedules are the same as in Recommendations 1 and 2, for Recommendation 3.1 and 3.2, respectively.

KEY EVIDENCE FOR RECOMMENDATION 3

BRAF-Wild-Type Melanoma

The SWOG Cancer Research Network clinical trial S1616-90 of second-line therapy included patients with wild-type unresectable and/or metastatic melanoma who had received one of the options for first-line therapy in Recommendation 1 [30]. Patients were randomly assigned in a 3:1 ratio to receive the combination of the ipilimumab and nivolumab, or ipilimumab alone. The combination of nivolumab and ipilimumab resulted in a statistically significant improvement in PFS when compared to ipilimumab monotherapy (HR, 0.63; 90% CI, 0.41 to 0.97, one-sided p=0.04) [30].

BRAF-Mutant Melanoma

Two randomized trials were identified of second-line or greater therapy that included patients with BRAF-mutant unresectable and/or metastatic melanoma who had received one of the options for first-line therapy in Recommendation 2. The KEYNOTE-002 trial of pembrolizumab versus chemotherapy did not exclude this population but only included 125 patients with BRAF-mutant disease. It found a PFS benefit for pembrolizumab versus

chemotherapy in the prespecified subgroup analysis for 10 mg/kg once every three weeks (HR, 0.44; 95% CI, 0.26 to 0.74) but not 3 mg/kg once every three weeks (HR, 0.74; 95% CI, 0.46 to 1.18). The KEYNOTE-00698 trial also included patients who had BRAF-mutant disease and previous therapy with BRAF/MEK inhibitor combination. In the subgroup analysis, a PFS benefit for pembrolizumab every two weeks versus ipilimumab was found in patients who had received previous BRAF inhibitor therapy (HR, 0.58; 95% CI, 0.34 to 0.97). No benefits were found with pembrolizumab every three weeks.

RECOMMENDATION 4

4.1 For adults with unresectable or metastatic melanoma, with the following clinical subtypes: NRAS, KIT, clinical disease subtypes (i.e., brain metastases), the systemic therapy regimens recommended are:

- NRAS: binimetinib (with or without immunotherapy)
- KIT: due to low quality of evidence (no RCTs) no recommendation can be made specifically for KIT patients, however, systemic treatment should follow the systemic therapies outlined in Recommendation 2
- Brain metastasis: nivolumab plus ipilimumab

QUALIFYING STATEMENTS FOR RECOMMENDATION 4

- Clinical trials should be considered if the above systemic targeted therapies are unsuccessful or not acceptable based on patient and physician preferences and values.
- Brain metastasis: if nivolumab plus ipilimumab cannot be tolerated, nivolumab plus relatlimab, or single-agent nivolumab or pembrolizumab may be considered as per Recommendation 1. If BRAF mutation is present, then BRAF/MEK inhibitors as in Recommendation 2 may be considered. In addition to the recommended systemic therapies, radiation therapy is an important modality of treatment for melanoma brain metastasis. When recommending radiation, stereotactic radiation would be preferred. A multidisciplinary approach is always recommended for optimal patient care.

KEY EVIDENCE FOR RECOMMENDATION 4

NRAS

This recommendation is mainly based on the expert opinion of the Working Group in addition to one RCT. The NEMO study specifically evaluated patients with IIIC or stage IV NRAS-mutant melanoma who were previously untreated or had progressed on or after previous immunotherapy [31]. Patients were randomized to receive either binimetinib 45 mg orally twice daily or dacarbazine 1000 mg/m^2 intravenously every three weeks. Median PFS was 2.8 months (95% CI, 2.8 to 3.6) in the binimetinib group and 1.5 months (range, 1.5 to 1.7) in the dacarbazine group (HR, 0.62; 95% CI, 0.47 to 0.80; one-sided $p<0.001$) [32].

KIT

The recommendation was based on the expert opinion of the Working Group and was supported by one systematic review for the evaluation of KIT-mutated melanoma subtype [33]. Nineteen single-arm studies with an overall sample size of 601 patients were included. No RCTs were found. Interventions included imatinib (n=8), nilotinib (n=7), dasatinib (n=3), and sunitinib (n=1) [33]. Due to the low quality of evidence, and absence of no intervention-to-intervention comparisons of systemic therapies available, a recommendation cannot be made at this time. Subgroup analysis revealed the highest objective response rate (ORR) (20%; 95% CI, 14% to 26%) for nilotinib [33].

Brain Metastases

Three RCTs evaluated subgroups of patients with brain metastases [34-36]. Two studies evaluated nivolumab plus ipilimumab in patients with brain metastases and the recommendation is based on the results of these two studies in addition to the expert opinion of the Working Group [34,36]. Long et al evaluated patients in three cohorts. Patients in cohort A received intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every three weeks for four doses, then nivolumab 3 mg/kg every two weeks; patients in cohort B or cohort C received intravenous nivolumab 3 mg/kg every two weeks. It should be noted that patients in Cohort C were non-randomized, had brain metastases that were symptomatic and in which local therapy had failed, and this distinction had an effect on patient outcomes. Intracranial complete responses occurred in six (17%) patients in cohort A, three (12%) in cohort B, and none in cohort C [34]. Similarly, in the NIBIT-M2 trial, the seven-year OS rates were significantly higher for ipilimumab plus nivolumab arm compared to the fotemustine arm (p=0.011) [36]. The COMBI-MB trial was a Phase II, open-label study that assessed the combination of dabrafenib and trametinib in patients with BRAF V600 mutation-positive melanoma brain metastases [35]. The trial included 125 patients divided into four cohorts based on prior treatments and symptoms. The primary endpoint was the intracranial response rate, which was 58% in the main cohort. The median duration of response was 6.5 months, and the median PFS was 5.6 months. The combination therapy showed promising efficacy, although the responses were less durable compared to those in patients without brain metastases [35].

JUSTIFICATION FOR RECOMMENDATION 4

The evidence suggests that for patients with the above clinical subtypes, the recommended systemic therapies may provide improved PFS and/or OS with tolerable toxicity. Further randomized studies are needed to confirm these findings.

IMPLEMENTATION CONSIDERATIONS

Due to the evolving environment surrounding systematic therapy for unresectable, metastatic melanoma, indications and approvals are changing rapidly. At the time of this review immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab, nivolumab plus relatlimab) are approved for funding for melanoma in Ontario; targeted therapies approved for use in Ontario are dabrafenib plus trametinib, encorafenib plus binimetinib, and vemurafenib plus cobimetinib.

LIMITATIONS OF THE EVIDENCE

The main limitation of this guideline is the lack of head-to-head comparisons between the systemic therapies for both BRAF-wild-type and BRAF-mutated melanoma. Most clinical trials compare new therapies to standard treatments or placebo, rather than directly comparing different active regimens (e.g., immunotherapy vs. targeted therapy), making it difficult to determine the optimal first-line approach. For targeted therapy, there is a shortage of validated predictive biomarkers to guide treatment selection beyond BRAF mutation status, limiting the ability to personalize therapy. Another key limitation of this guideline is that the evidence base did not fully align with the predefined inclusion criteria established for the systematic review; specifically, the evidence surrounding brain metastasis. Studies did not meet the population threshold required for inclusion or were not an RCT, which was a core component of our ad hoc study selection criteria. These criteria were designed to ensure methodological rigor and consistency across the evidence informing our recommendations. The inclusion of these studies, therefore, represent a deviation from these standards and introduces potential bias related to study design and population applicability. While the findings from the studies may provide valuable insights, they should be interpreted with caution given these

limitations. We have acknowledged this gap explicitly to maintain transparency and to support appropriate interpretation of the guideline recommendations.

GUIDELINE LIMITATIONS

The cost-effectiveness of the systemic interventions recommended is beyond the scope of the PEBC guideline. The Working Group members leave resource considerations to other decision makers in Ontario Health (Cancer Care Ontario).

RELATED GUIDELINES

- Wright F, Souter LH, Easson A, Murray C, Toye J, McCready D, et al. Primary excision margins and sentinel lymph node biopsy in cutaneous melanoma. Toronto (ON): Cancer Care Ontario; 2017 November 13. Program in Evidence Based Care Guideline No.: 8-2 Version 2.

- Petrella T, Baetz T, Fletcher GG, Knight G, McWhirter E, Rajagopal S, Song X. Systemic adjuvant therapy for adult patients at high risk for recurrent melanoma. Toronto (ON): Cancer Care Ontario; 2024 March 14. Program in Evidence-Based Care Guideline No.: 8-1 version 6.

FURTHER RESEARCH

Further biomarker-driven investigation may identify patient subpopulations who could benefit from immunotherapy and targeted therapy. High-quality trials are needed to address the therapeutic value of systemic therapies in metastatic, unresectable melanoma disease subtypes. Further research into systemic therapy regimens may also be benefit this patient population. The STOP-GAP trial (ClinicalTrials.gov identifier: NCT02821013) of intermittent versus continuous anti–PD-1 therapy in patients with metastatic melanoma is due to be completed in 2027. There are also ongoing trials in patients with NRAS mutation evaluating pan-RAF inhibitors in combination with MEK inhibitors. Full details of ongoing studies can be found in Appendix 6.

Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

There has been a complete paradigm shift in treatment of unresectable or metastatic melanoma in the past 10 years. Treatment recommendations need to be developed with respect to new systemic agents and their timing (targeted therapy [molecular subtypes – BRAF-mutated, NRAS-mutated, KIT-mutated] and immunotherapy), extent of brain radiation, and optimal timing of surgery, if necessary, so guidance on the appropriate care for patients diagnosed with metastatic melanoma is required.

GUIDELINE DEVELOPERS

This guideline was developed by the Systemic Treatment for Advanced Melanoma GDG (Appendix 1), which was convened at the request of the Melanoma Disease Site Group.

The project was led by a small Working Group of the Systemic Treatment for Advanced Melanoma GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, dermatology, surgical oncology and health research methodology. Other members of the Systemic Treatment for Advanced Melanoma GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [37,38]. This process includes a systematic review, interpretation of the evidence by the Working Group, and draft recommendations; internal review by content and methodology experts; and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [39] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed at least one research question (see Section 4) were included. Guidelines older than three years (published before 2019) were excluded. Guidelines based on consensus or expert opinion were excluded.

The following sources were searched for guidelines in October 2022 with the search term(s) melanoma, skin neoplasms, metastatic stage IV, stage 4: National Institute for Health and Care Excellence Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki.

Based on the criteria listed above, no guidelines were found that met the Working Group's criteria for endorsement.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

Patient and Caregiver-Specific Consultation Group

Three patients/survivors/caregivers participated as Consultation Group members for the Systemic Treatment for Unresectable Metastatic Melanoma Working Group. They reviewed copies of the project plan/draft recommendations and provided feedback on its/their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

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- Sara Miller for copy editing.

Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

Section 4: Systematic Review

INTRODUCTION

Cutaneous melanoma is the most common and aggressive form of melanoma, originating in the melanocytes, which produce the pigment melanin. It typically develops on sun-exposed skin but can occur anywhere on the body. It is estimated that in Canada, in 2024, approximately 11,300 Canadians will be diagnosed with melanoma skin cancer [40]. Additionally, approximately 40-50% of people with cutaneous melanomas have a mutation of the *BRAF* gene.

There has been a complete paradigm shift in treatment of unresectable or metastatic melanoma in the past 10 years with the development of immune checkpoint inhibitors and BRAF/MEK inhibitors. PD-1 and/or PD-L1 inhibitors ipilimumab, nivolumab, and pembrolizumab may be considered in any melanoma. In addition, targeted therapy may be used in patients with specific mutations such as in V600 and similar in the *BRAF* gene (dabrafenib, vemurafenib); these agents are often used in conjunction with MEK inhibitors (trametinib, cobimetinib, and binimetinib). For patients with *BRAF* mutations, it is unclear whether PD-1/PD-L1 inhibitors or targeted therapy is better, and therefore either approach may be used, with switching to the other approach if poor response or unacceptable adverse effects. Consideration may also be given to switching to different immunotherapies (or combinations) within the same class, as toxicity profiles and efficacy may vary. Treatment recommendations are needed with respect to new systemic agents and their timing (targeted therapy [molecular subtypes – BRAF-mutated, NRAS-mutated, KIT-mutated] and immunotherapy), so guidance on the appropriate care for patients diagnosed with metastatic melanoma is required.

Currently, the standard of care for these patients may involve drug therapies, surgery, and/or radiation therapy. Advances in the use of immunotherapy and targeted therapy have improved survival for most patients and are now the preferred treatment options for patients with metastatic melanoma. However, there is no evidence-based guideline in the Ontario context to outline these systemic treatments.

As described in Section 3, the Systemic Treatment for Advanced Melanoma Working Group derived the research questions outlined below, based on the objectives of this guideline (Section 2) and conducted this systematic review to answer these questions.

This systematic review has been registered on the PROSPERO website (International prospective register of systematic reviews) with the following registration number CRD42021246482.

RESEARCH QUESTIONS

Research Question 1

For adult patients (18+) with unresectable lymph node metastasis (AJCC TNM stage IIIC/D) and distant metastatic (AJCC TNM stage IV) cutaneous melanoma:

a. What systemic treatment options (immunotherapies and targeted therapies) with what optimal timing and sequencing, alone or in combination, have demonstrated clinical benefit, compared with traditionally used treatments (chemotherapies, alternative immunotherapies and targeted therapies)?
b. Are there groups of patients with molecular (e.g., BRAF-mutated, NRAS-mutated, KIT-mutated) and/or clinical disease subtypes (e.g., lymph node metastasis, brain metastases) who benefit from certain systemic treatments alone or in combination?

Research Question 2

What is the optimal systemic therapy management of disease progression following treatment breaks in the target population?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

OVID was used to systematically search the MEDLINE and Embase, Cochrane Database of Systematic Reviews and PROSPERO databases for systematic reviews that evaluated systemic therapies (including targeted systemic therapies) for adult patients (18+) with unresectable lymph node metastasis (AJCC TNM stage IIIC/D) and distant metastatic (AJCC TNM stage IV) cutaneous melanoma, published from 2010 to September 2025. The complete literature search strategy can be found in Appendix 2. In addition to the MEDLINE and Embase databases searches, reference lists of included systematic reviews and primary literature was scanned for potentially useful studies.

Systematic reviews were included if they addressed at least one research question and included at least one original study that met the study selection criteria for primary studies (listed below), and if the review had an overall rating as assessed with the AMSTAR 2 Tool [41].

A systematic review conducted by the Cochrane Collaboration was found that met the above selection criteria for Research questions 1a, 1b and 2 [15]. The systematic review identified 122 RCTs published up to 2016; for the purpose of this guideline systematic review, the literature from 2010-2016 will be included. An additional systematic review that evaluated c-KIT inhibitors for unresectable metastatic melanoma that was a subset of research question 2b, also met the study selection criteria [33].The application of the AMSTAR2 tool indicated that there is a high overall confidence in the results of the review and the review presents an accurate summary of the available studies of the research questions When assessed with the AMSTAR 2 tool the systematic review had a high overall confidence in the results of the review (Appendix 5).

Search for Primary Literature

The following databases were searched for relevant RCTs published after the Cochrane review from January 1, 2016, to September 1, 2025: MEDLINE and EMBASE. The full search strategies are reported in Appendix 2

Study Selection Criteria and Process

Inclusion Criteria

Articles were selected for inclusion if they are:

- Published randomized trials related to the guideline question(s) (including full reports or abstracts)
    - Data on the treatment population of interest
    - Data on patients receiving alone or any combination of targeted therapies or immunotherapies
    - Results for one of our outcomes of interest: disease-free survival and/or OS, local control, response, toxicity, and/or quality of life.
- If no/or only low-quality RCTs are available, other comparative studies (e.g., cohort, case-controlled, historically controlled trials, etc.) will be considered if the study investigators tried to control the potential confounders (such as using propensity score

matching method; multivariable analysis to treat the intervention strategy as a variable; and comparing patient characteristics to show no statistically significant differences between the 2 groups at the baseline, etc.)
- Single-arm studies for toxicity/safety outcome only and only if comparative data are unavailable
- Have a minimum study size of 30 analyzed participants in each group for non-randomized comparative studies.

Exclusion Criteria
- Deal with in-transit disease (already covered in PEBC guideline 8-10)
- Abstracts of non-RCT studies (not subsequently published in peer-reviewed journals)
- Are editorials, commentaries, letters, news articles, narrative reviews, and case reports
- Are published in a language other than English where data could not be extracted

A review of the titles and abstracts was conducted by one reviewer (SK). For studies that warranted full-text review, SK reviewed each study, in collaboration with Working Group members when required. The reference lists of eligible papers were manually searched and the eligible papers that were published after 2016 were included.

Ranking Importance of Outcomes

The survival outcomes OS (effect measure: HR)**,** PFS (local or distant/metastatic) (effect measure: HR), were selected as being "CRITICAL". Toxicity (grade 3 or higher adverse events) from studies that have also reported on OS or PFS (effect measure: RR) were also considered "CRITICAL". Tumour response **(**complete plus partial tumour response) (effect measure: RR), quality-of-life outcomes from studies that have report on our primary outcomes (as described in studies) were selected as being "IMPORTANT".

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction independently by SK, with all extracted data and information audited subsequently by an independent auditor. The Cochrane Collaboration Risk of Bias 2.0 tool was used to assess the risk of bias for each outcome for included RCTs [42].

Synthesizing the Evidence

Meta-analysis or network meta-analysis was not planned or conducted due to the heterogeneity across trials.

RESULTS

Primary Literature Search Results

There were 7418 publications from the medical database searches. After adjusting for publication data and deduplication, 2117 studies remained. After reviewing titles and abstracts, 198 articles required full-text screening and 51 articles met the pre-planned study inclusion criteria. This is in addition to the Cochrane Systematic Review that met the guideline pre-planned study inclusion criteria [15]. Table 4-1 describes the studies in relation to each research question. The PRISMA flow chart and full study characteristics can be found in Appendix 3 and Appendix 4, respectively.

Table 4-1. Studies included in the Evidence Base

Research Question	Included Studies	Citation(s)
What systemic treatment options (**immunotherapies**) with what optimal timing and sequencing, alone or in combination, have demonstrated clinical benefit, compared with traditionally used treatments (chemotherapies, alternative immunotherapies and targeted therapies) for BRAF-wild-type cutaneous melanoma?	1 SR detailing published studies from 2010-2016 10 RCTs (within 17 unique citations) detailing published studies from 2016-2025	[15] [2-4,6,16,17,43-52, 70]
What systemic treatment options (**targeted therapies**) with what optimal timing and sequencing, alone or in combination, have demonstrated clinical benefit, compared with traditionally used treatments (chemotherapies, alternative immunotherapies and targeted therapies) for patients with BRAF-mutated cutaneous melanoma?	1 SR detailing published studies from 2010-2016 17 RCTs (within 25 unique citations) detailing published studies from 2016-2025 NOTE: Some RCTs also evaluated immunotherapy in comparison with targeted therapy	[15] [5,8-14,19-23,25,26,28,35,53-60, 71]
Are there groups of patients with NRAS mutated melanoma who benefit from certain systemic treatments alone or in combination?	1 RCT evaluating patients with unresectable metastatic melanoma with NRAS mutation	[31]
Are there groups of patients with KIT-mutated melanoma who benefit from certain systemic treatments alone or in combination?	1 SR evaluating therapies for patients with unresectable metastatic melanoma with KIT mutation	[33]
Are there groups of patients with brain metastases who benefit from certain systemic treatments alone or in combination?	3 RCTs evaluating systemic therapies for patients with unresectable metastatic melanoma with brain metastases	[34] [36] [35]

Abbreviations: RCT, randomized controlled trial; SR, systematic review

Risk of bias assessment for individual studies

The results of risk of bias assessments for each comparison per outcome of the RCTs are shown in Appendix 5. Overall, the risk of bias for the included studies was "Low" with "Some concerns" being noted due to selection bias, attrition bias and detection bias.

Certainty of the Evidence

The certainty of the evidence per outcome for each comparison, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed using the GRADE approach. Due to the large body of evidence from numerous high-quality RCTs, the evidence certainty for each comparison of interventions was moderate to high. A meta-analysis or network meta-analysis was inappropriate to perform because of the large number of different interventions, patient populations, and outcomes among the included studies in this systematic review,

OUTCOMES

Full details of the study characteristics can be found in Appendix 4. For the study results of the outcomes of interest, due to the length of the tables and their effect on the readability of this guideline, they are grouped together at the end of Section 4.

Immunotherapy

Nivolumab Plus Pembrolizumab Versus Ipilimumab

In the Cochrane systematic review, a statistically significant difference in OS (HR, 0.63; 95% CI, 0.60 to 0.66) and PFS (HR, 0.54; 95% CI, 0.50 to 0.60) was identified for patients treated with nivolumab and pembrolizumab compared to ipilimumab [15]. There was significantly reduced grade 3 and 4 toxicity with anti-PD-1 therapy (RR, 0.70; 95% CI, 0.54 to 0.91) [15].

Nivolumab Plus Ipilimumab Therapy Versus Nivolumab Monotherapy or Ipilimumab Monotherapy

In the Cochrane systematic review, a statistically significant difference in PFS (HR, 0.40; 95% CI, 0.35 to 0.46) was identified for the combination [15]. There was significantly increased grade 3 and 4 toxicity (RR, 1.57; 95% CI, 0.85 to 2.92; two trials) for the combination [15]. The CheckMate 067 trial evaluated the efficacy of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab monotherapy in patients with advanced melanoma [70]. The results, at final analysis of 10 years, showed that the combination of nivolumab and ipilimumab significantly improved OS compared to ipilimumab alone. The median OS was 71.9 months for the combination therapy, 36.9 months for nivolumab alone, and 19.9 months for ipilimumab alone. The 10-year OS rates were 43% for the combination, 37% for nivolumab alone, and 19% for ipilimumab alone. The toxicity profiles differed among the treatment regimens. The combination of nivolumab and ipilimumab had the highest rate of severe (grade 3 or 4) treatment-related adverse events, occurring in 59% of patients. Nivolumab alone had a lower rate of severe adverse events at 21%, whereas ipilimumab alone had severe adverse events in 28% of patients. While the combination therapy showed greater efficacy in improving OS, it also came with a higher risk of significant immune-related toxicities compared to monotherapy regimens [70].

In addition to the Cochrane systematic review, the Checkmate 511 trial reported by Lebbé et al compared ipilimumab 1 mg/kg and nivolumab 3 mg/kg with standard ipilimumab 3 mg/kg and nivolumab 1 mg/kg doses [16]. The trial demonstrated a significantly lower incidence of treatment-related grade 3-5 adverse events with nivolumab 3 mg/kg and ipilimumab 1 mg/kg versus nivolumab 1 mg/kg and ipilimumab 3 mg/kg (p=0.006). The study was not powered to determine efficacy. Additionally, a trial reported by Ascierto et al compared ipilimumab 10 mg/kg versus 3 mg/kg and found improved OS (HR, 0.84; 95% CI, 0.70 to 0.99) but with greater toxicity for ipilimumab 10 mg/kg [17]. One additional trial (Long et al) evaluated the efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with active melanoma brain metastases [34]. intracranial response was achieved by 16 (46%) of 35 patients treated with combined nivolumab and ipilimumab and five (20%) of 25 patients treated with nivolumab monotherapy [34].

Two studies evaluated the sequencing of immunotherapy and targeted therapy [26,27]. The DREAMseq trial evaluated combination nivolumab/ipilimumab or dabrafenib/trametinib and at disease progression patients were enrolled in either a dabrafenib/trametinib arm or nivolumab/ipilimumab arm [56]. Both two-year OS and PFS favoured patients who began in the nivolumab/ipilimumab arm. A second trial to evaluate sequencing of immunotherapy and targeted therapy was the SECOMBIT trial [26]. Patients were randomly assigned to one of three trial arms. It included a sandwich arm that provided eight weeks of encorafenib plus binimetinib before nivolumab plus ipilimumab as first-line therapy. The trial demonstrated no significant differences in PFS (HR, 0.71; 95% CI, 0.44 to 1.14) or OS (HR, 0.73; 95% CI, 0.42 to 1.26).

Nivolumab Plus Relatlimab

One study evaluated relatlimab and nivolumab in patients with untreated unresectable melanoma [18]. Median PFS with nivolumab and relatlimab was superior to nivolumab monotherapy (10.1 vs. 4.6 months; HR, 0.75).

Ipilimumab Versus Chemotherapy

In the Cochrane systematic review, when ipilimumab was compared to chemotherapy, ipilimumab improved OS (HR, 0.42; 95% CI, 0.37 to 0.48); however, ipilimumab may be associated with higher rates of toxicity (RR, 1.69; 95% CI, 1.19 to 2.42) [15].

Nivolumab or Pembrolizumab Versus Chemotherapy

In the Cochrane systematic review, when compared with chemotherapy, nivolumab improved OS in one study (HR, 0.42; 95% CI, 0.37 to 0.48) and was also associated with lower toxicity rates in three studies (RR, 0.55; 95% CI, 0.31 to 0.97) [15].

Targeted Therapy

The Cochrane review included nine studies who evaluated BRAF-mutated melanoma [15]. Three studies compared single-agent BRAF inhibitors with combination BRAF and MEK inhibitors. All trials demonstrated a benefit to combination therapy versus monotherapy [61-65].

In addition to the trials identified in the Cochrane review, an additional four RCTs evaluated targeted therapy for patients with metastatic melanoma and BRAF mutations. The COLUMBUS trial was identified in the systematic review, comparing encorafenib plus binimetinib versus encorafenib alone or vemurafenib alone [10-13]. This trial found significant improvement in PFS with the combination versus vemurafenib (HR, 0.54; 95% CI, 041 to 0.71) but not versus encorafenib (HR, 0.75; 95% CI, 0.56 to 1.00). A significant difference in OS between the combination and vemurafenib (HR, 0.61; 95% CI, 0.47 to 0.79) was found. Grade 3 and 4 toxicity was reported at similar rates among the three arms. The EBIN trial evaluated combination encorafenib and binimetinib followed by ipilimumab and nivolumab versus ipilimumab and nivolumab [71]. The study found no evidence to suggest a longer progression-free survival in the induction group than in the control group (HR 0.87, 90% CI 0.67-1.12; p=0.36) [71]. In addition of the Columbus and EBIN trials, the coBRIM trial of vemurafenib plus cobimetinib versus vemurafenib alone and the COMBI-D trial, and COMBI-V trial investigating dabrafenib plus trametinib were drivers for this recommendation.

Three trials investigated targeted therapy in addition to an anti-PD-1 inhibitor (Keynote 022, Combi-I, IMSPIRE 150). In the IMSPIRE trial, patients were randomly assigned to receive either atezolizumab or placebo plus and cobimetinib. OS was not significantly improved with atezolizumab, vemurafenib, and cobimetinib compared with placebo, vemurafenib, and cobimetinib (HR, 0.84; 95% CI, 0.66 to 1.06; p=0.14) in patients with BRAF-mutation-positive advanced melanoma [20,21]. The KEYNOTE-022 trial compared pembrolizumab with placebo in patients who were receiving dabrafenib plus trametinib and reported no significant difference in PFS (HR, 0.66; 95% CI, 0.40 to 1.07) [23]. A follow-up publication of KEYNOTE-022 reported PFS (HR, 0.58; 95% CI, 0.34 to 0.83) and OS (HR, 0.64; 95% CI, 0.38 to 1.06) for pembrolizumab compared to placebo. However, given the design of the trial, the authors did not consider the PFS HR to be a statistically significant result. The COMBI-i trial compared spartalizumab versus placebo in patients who were receiving dabrafenib plus trametinib and reported no significant difference in PFS (HR, 0.82; 95% CI, 0.66 to 1.03), or OS (HR, 0.79; 95% CI, 0.59 to 1.05) [5,9,19].

Two studies evaluated the sequencing of immunotherapy and targeted therapy. The DREAMseq trial evaluated combination nivolumab plus ipilimumab or dabrafenib plus trametinib

and patients at disease progression were enrolled in either a dabrafenib plus trametinib arm or nivolumab plus ipilimumab arm [27]. Both two-year OS and PFS favoured patients who began in the nivolumab/ipilimumab arm. In a five-year update, nivolumab plus ipilimumab continued to show statistically significant superiority over dabrafenib plus trametinib in both OS and PFS [24]. A second trial to evaluate sequencing of immunotherapy and targeted therapy was the SECOMBIT trial [26]. Patients were randomly assigned to one of three trial arms. Arm A, encorafenib plus binimetinib until disease progression followed by ipilimumab plus nivolumab; Arm B, ipilimumab plus nivolumab until disease progression followed by encorafenib plus binimetinib; and, Arm C, encorafenib plus binimetinib for eight weeks followed by ipilimumab plus nivolumab until disease progression followed by encorafenib plus binimetinib. The trial demonstrated an OS benefit to those patients with BRAFV600-mutant melanoma who had sequential immunotherapy and targeted therapy. After four years of survival data, the SECOMBIT trial demonstrated a survival benefit with first-line immunotherapy with or without an eight-week course of targeted therapy for the treatment of BRAF-mutant metastatic melanoma [25]. The INTERIM phase 2 trial evaluated intermittent versus continuous dosing of dabrafenib plus trametinib in patients with BRAFV-mutant advanced melanoma [28]. The trial found that continuous dosing was superior in terms of PFS, OS, and response rate. Intermittent dosing resulted in fewer treatment-related adverse events but more severe ones. Detection of $BRAFV^{600E}$ ctDNA before treatment was linked to worse OS in both groups. Overall, intermittent dosing did not improve the efficacy of BRAF+MEK inhibitors. [28]

Triplet Therapy

Three studies evaluated three variations of first-line triplet therapies in patients with BRAF-mutant unresectable metastatic melanoma [22,23,29]. Dummer et al conducted a randomized phase II trial evaluating spartalizumab in combination with dabrafenib and trametinib, versus placebo plus dabrafenib and trametinib in patients with BRAF V600–mutant unresectable or metastatic melanoma. Patients received spartalizumab 400 mg intravenously every four weeks plus dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily or placebo plus dabrafenib and trametinib. Median PFS was 16.2 months (95% CI, 12.7 to 23.9 months) in the spartalizumab plus dabrafenib and trametinib arm versus 12.0 months (95% CI, 10.2 to 15.4 months) in the placebo plus dabrafenib and trametinib arm (HR, 0.82; 95% CI, 0.66 to 1.03; p=0.042).

Sequencing of Refractory Patients

BRAF-Wild-Type Melanoma

One trial was identified of second-line therapy that included patients with wild-type unresectable and/or metastatic melanoma who had received one of the options for first-line therapy in Recommendation 1 [30]. In the SWOG Cancer Research Network clinical trial S1616, 90 patients were randomly assigned in a 3:1 ratio to receive the combination of the ipilimumab and nivolumab, or ipilimumab alone. The combination of nivolumab and ipilimumab resulted in a statistically significant improvement in PFS over ipilimumab monotherapy (HR, 0.63; 90% CI, 0.41to 0.97; one-sided p=0.04) [30].

BRAF-Mutant Melanoma

Two randomized trials were identified of second-line or greater therapy that included patients with BRAF-mutant unresectable and/or metastatic melanoma who had received one of the options for first-line therapy in Recommendation 2. The KEYNOTE-002 trial of pembrolizumab versus chemotherapy did not exclude this population but only included 125 patients with BRAF-mutant disease. It found a PFS benefit in the prespecified subgroup analysis for pembrolizumab 10 mg/kg versus chemotherapy once every three weeks (HR, 0.44; 95% CI, 0.26 to 0.74) but not 3 mg/kg once every three weeks (HR, 0.74; 95% CI, 0.46 to 1.18). It was

not clear what proportion of these patients had received BRAF/MEK inhibitor therapy versus ipilimumab-based therapy. The KEYNOTE-00698 trial also included patients who had BRAF-mutant disease and previous therapy with BRAF/MEK inhibitor combination. In the subgroup analysis, a PFS benefit for pembrolizumab every two weeks versus ipilimumab was found in patients who had received previous BRAF inhibitor therapy (HR, 0.58; 95% CI, 0.34 to 0.97). No benefits were found with pembrolizumab every three weeks.

Patient Subtypes

NRAS

The NEMO study evaluated IIIC or stage IV NRAS-mutant melanoma who were previously untreated or had progressed on or after previous immunotherapy [31]. Patients were randomized to receive either binimetinib 45 mg orally twice daily or dacarbazine 1000 mg/m^2 intravenously every three weeks. At a median follow-up of 1.7 months, median PFS was 2.8 months (one-sided 95% CI, 2.8 to 3.6 months) in the binimetinib group and 1.5 months (95% CI, 1.5 to 1.7 months) in the dacarbazine group (p<0.001). While the study has been reported to be completed in 2019 (https://clinicaltrials.gov/study/NCT01763164), no subsequent publications could be found.

KIT

No RCTs were found. One systematic review was found for the evaluation of KIT-mutated melanoma subtype that included 19 single-arm studies with an overall sample size of 601 patients [33]. Interventions included imatinib (n=8), nilotinib (n=7), dasatinib (n=3) and sunitinib (n=1) [33]. The pooled ORR for all inhibitors was 15% (95% CI, 12 to 18%). Subgroup analysis revealed the highest ORR (20%; 95% CI, 14 to 26%) for nilotinib [33].

Brain Metastases

Three RCTs evaluated subgroups of patients with brain metastases [34-36]. NiBIT-2 evaluated fotemustine, ipilimumab plus fotemustine, or ipilimumab plus nivolumab. Compared with fotemustine, ipilimumab plus nivolumab significantly improved OS of patients with melanoma with asymptomatic brain metastases (41.0%; 95% CI, 20.6 to 61.4%) vs. 10.9% (95% CI, 0 to 24.4%; p=0.015) [36]. Long et al also evaluated ipilimumab and nivolumab or nivolumab monotherapy for patients with brain metastases [34]. Patients in cohort A received nivolumab 1 mg/kg with ipilimumab 3 mg/kg, then nivolumab 3 mg/kg every two weeks; patients in cohort B or cohort C received nivolumab 3 mg/kg every two weeks. Responses were achieved by 16 (46%; 95% CI, 29 to 63%) of 35 patients in cohort A, five (20%; 95% CI, 7 to 41%) of 25 in cohort B, and one (6%; 95% CI, 0 to 30%) of 16 in cohort C. Study results for immunotherapy and targeted therapy are summarized in Tables 4-2 and 4-3, respectively.

Table 4-2. Study Results for immunotherapy - Studies published after Cochrane Systematic Review (15)

Citation	Comparison Category	OS (effect measure: HR)	PFS (effect measure: HR)	Toxicity (Grade 3 or higher from studies that also reported on OS or PFS)
[66] Andtbacka, 2016	Im munotherapy	HR: 0.35 (95% CI: 0.04-3.44; p=0.35)	No HR Reported	10mg/kg arm: 36% 3mg/ kg arm: 20%
[17] Ascierto, 2017 [67] Ascierto, 2017	Immunotherapy Imm(Ipi10) vs. Imm(ipi3)	HR 0.84, 95%CI 0.71 to 0.99; p=0.04 *Favours 10mg/kg median OS of 15.7 months*	No HR Reported	10 mg/kg arm: 34% 3 mg/kg: 18%
[68] Chesney, 2018	Immunotherapy Imm(T-VEC+ipi) vs. imm(ipi)	HR 0.82; 95% CI, 0.54-1.25; p=0.36 Median OS was not reached for combination and was 50.1 months	Median PFS was 13.5 months with combination and 6.4 months with ipi (HR 0.81; 95% CI, 0.57-1.15; P=0.23	T-VEC+ipi: 45% ipi: 35%
[50] Hodi, 2016	Immunotherapy imm(niv+ipi) vs imm(ipi)+pla	HR 0.74; 95% CI 0.43–1.26; p=0.26	HR 0.36; 95% CI 0.22–0.56; p<0.0001) Median PFS has not been reached for the combination group and was 3.0	ipi group (51 [54%] vs. 9 [20%] of patients), and led to treatment discontinuation in 28 (30%) of 94 patients and 4 (9%) of 46 patients, respectively
[52] Larkin, 2018 Weber, 2015	Immunotherapy Imm(niv) vs. chem (dac or car)	HR, 0.95; 95.54% CI, 0.73 to 1.24	HR, 1.0; 95.1% CI, 0.78 to 1.436) Median PFS was 3.1 months (95% CI, 2.3 to 3.5) for nivolumab versus 3.7 months (95% CI, 2.3 to 5.3) for ICC	niv: 14% ICC: 34%
[16] Lebbé, 2019	Immunotherapy Imm(niv3+ipi1) vs. Imm(niv1+ipi3)	HR, 1.09; 95% CI, 0.73 to 1.62) Median OS was not reached in either group	HR, 1.06; 95% CI, 0.79 to 1.42 Median PFS was 9.92 months in the niv3+ipi1 group and 8.94 months in the niv1+ipi3 group	niv3+ipi1: 61/180 (33.9%) niv+ipi3: 86/178 (48.3%)

Citation	Comparison Category	OS (effect measure: HR)	PFS (effect measure: HR)	Toxicity (Grade 3 or higher from studies that also reported on OS or PFS)
[34] Long, 2018	Immunotherapy (niv) vs (niv + ipi)	No HR reported	No HR reported	Cohort A1: 9 (54%) Cohort B 4 (16%)
[46] Long, 2019	Immunotherapy (epa)+imm (pem) vs. placebo+imm (pem)	HR 1.13 (0.86−1.49; one-sided p=0.81) *Median not reached in either group*	HR 1.00, 95% CI 0.83–1.21; one-sided p=0.52	epa + pem: n= 85 (24%) placebo + pem: n=84 (24%)
[69] Tarhini, 2019	Immunotherapy Imm (HD ipi + HDI) (Arm A) vs. Imm (ipi) (Arm B) vs. Imm (LD ipi +HDI) (Arm C) vs. Imm (LD ipi) (Arm D)	No HR reported The difference in OS did not reach statistical significance.	No HR reported The difference in PFS did not reach statistical significance.	Arm A 94% (17/18; 95% CI, 72.7%–99.9%) Arm B 64% (14/22; 95% CI, 41%–83%) Arm C 76% (16/22; 95% CI: 50%–89%) Arm D 46% (10/22; 95% CI: 24%–68%)
[43] Tawbi, 2022	Immunotherapy Imm (rel+niv) vs. Imm (niv)	No HR reported	HR, 0.75 [95% CI, 0.62 to 0.92]; p=0.006 by the log-rank test *Favours rel+niv*	Rel+niv: 18.9% niv: 9.7%.
[2] Hodi, 2018 [3], Wolchuk, 2022 [4] Wolchuk, 2017 [XX] Wolchuk, 2025 CheckMate 067	Immunotherapy Imm (niv+ipi) vs. imm (niv)+placebo vs. imm (ipi)+placebo	Combination versus ipi was 0.54 (95% CI 0.44–0.67; p<0.0001) Niv versus ipi was 0.65 (0.53–0.79; p<0.0001).	Combination versus ipi was 0.42 (95% CI 0.35–0.51; p<0.0001) niv versus ipi was 0.53 (0.44–0.64; p<0.0001).	Niv + ipi: 185 (59%) of 313 niv: 70 (22%) of 313 ipi: 86 (28%) of 311

Citation	Comparison Category	OS (effect measure: HR)	PFS (effect measure: HR)	Toxicity (Grade 3 or higher from studies that also reported on OS or PFS)
[6] Schachter, 2017 KEYNOTE-066, Various Citations doi: 10.1016/S1470-2045(19)30388-2. Epub 2019 Jul 22.	Immunotherapy Imm(pem2) vs. Imm(pem3) vs. Imm(ipi)	OS in pem groups were superior to the ipi group (HR 0.68; 95% CI 0.53–0.87; p=0.0009 for the 2-week schedule and HR 0.68; 95% CI 0.53–0.86; p=0.0008 for the 3-week schedule vs ipilimumab There was no difference between the two pembrolizumab schedules (HR 1.01; p=0.93)	PFS was longer with pem than with ipi (HR 0.61; 95% CI 0.50–0.75; p<0.0001 for both pem schedules vs ipi). There was no difference in PFS between the two pem schedules (HR 0.95; 95% CI 0.77–1.17; p=0.62)	3% in the 2-week pem group (6 of 236 patients) 1% in the 3-week pem group (3 of 232 patients) 3% in the ipi group (4 of 160 patients)

Abbreviations: car, carboplatin; CDC-chem, chemosensitivity-directed combination chemotherapy; chem, chemotherapy; CI, confidence interval; dac, dacarbazine; epa, epacadostat; HD, high-dose; HDI, high-dose interleukin -2; HR, hazard ratio; ICC, investigator's choice chemotherapy; ipi, ipilimumab; LD, low dose; niv, nivolumab; OS, overall survival; pem, pembrolizumab; PFS, progression-free survival; rel, relatlimab; T-VEC, talimogene laherparepvec

Table 4-3. Study Results for Targeted Therapy- Studies published after Cochrane Systematic Review (15)

Citation	Comparison Category	OS (effect measure: HR)	PFS (effect measure: HR)	Toxicity (Grade 3 or higher from studies that also reported on OS or PFS)
[56] Atkins, 2023	Targeted Therapy Dabrafenib and trametinib versus combination nivolumab and ipilimumab	HR within 5 months was 2.35 (95% CI: 0.70,8.00) favoring arm B and > 5 months was 0.29 (95% CI: 0.17, 0.48) favouring arm A HRs were biphasic	NR	Arm A 59.5% Arm B 53.1% Arm C 53.8% Arm D 50.0%
[55] Gogas, 2021	Targeted Therapy (cobi)+Imm (ate) vs. Imm (pem)	NR	HR 1.15; 95% CI 0.88-1.50; P = 0.30) *No significant difference between arms*	cobi + ate 147/220 (66.8%) pembro: 72/216 for
[60] Long, 2018	Targeted Therapy TT (dab) vs. TT (dab+tra/1) vs. TT (dab+tra/2)	HR, 0.76; 95% CI, 0.49 to 1.18 *Favours dab+tra arms*	HR, 0.44; 95% CI, 0.28 to 0.67 *favours dab+tra arms*	(dab+tra (150/2): n=67(37%) (dab+tra (150/1): n=29 (54%) dab monotherapy: n=25 (47%)
[54] Robert, 2019 METRIC Study, Various Citations	Targeted Therapy TT (tra) vs. chem (dac+pac)	HR: 0.84, 95% CI, 0.63-1.11 *Favours tra*	HR: 0.54; 95% CI, 0.41-0.73 *Favours tra*	tra: n=37 [12%] chem: n=11 [11%]
[5], Tawbi, 2022 [9], Dummer, 2022 [19], Dummer 2020	Targeted Therapy sparta-dab+tra or placebo-dab+tra	A total of 90 of 267 patients (34%) treated with sparta-dab+tra and 103 of 265 patients (39%) treated with placebo-dab+tra had died as of the data cut-off (HR, 0.79 [95% CI, 0.59 to 1.05]	Sparta-dab+tra arm had a PFS event versus 165 of 265 patients (62%) in the placebo-dab+tra arm (HR, 0.82 [95% CI, 0.66 to 1.03]; p=0.042 [one-sided; nonsignificant])	sparta-dab+tra arm 55% (146 of 267) placebo-dab+tra arm 33% (88 of 264),

Citation	Comparison Category	OS (effect measure: HR)	PFS (effect measure: HR)	Toxicity (Grade 3 or higher from studies that also reported on OS or PFS)
[58], Robert 2020	Targeted Therapy Imm (niv) vs chem (dac)	5-year OS rates of 39% and 17%, respectively, and an HR of 0.5 (95% CI, 0.40 to 0.63; p<0.0001 *Favours niv*	5-year PFS rates of 28% and 3%, respectively, and an HR of 0.4 (95% CI, 0.33 to 0.54; p<0.0001 *Favours niv*	niv: 16% dac:18%
[8] Long, 2017 COMBI-D, Various Citations	Targeted Therapy TT (dab+tra) vs. TT (dab)+placebo	3-year OS 54% in dab+tra arm; 41% in monotherapy arm [HR, 0.74 (95% CI, 0.53–1.03)	3-year PFS 27% in dab+tra arm; 17% in monotherapy arm HR, 0.70 (95% CI, 0.53–0.93)	
[53] Algazi, 2020	Targeted Therapy TT (dab+tra)cont vs. TT (dab+tra)inter (BRAF+MEK inhibitors)	median = 29.2 months in both arms, HR=1.02,80%CI 0.78–1.33, p=0.93	HR=1.36 inter/cont, 80% CI 1.10–1.66, p=0.063, two-sided α=0.2 *Favours cont*	Cont therapy arm: grade 3 - n=38 (36%) grade 4 - n=7 (7%) Inter therapy arm: grade 3 - n=31 (31%) grade 4 - n=3 (3%) (p=0.46 for grade 3; p=0.33 for grade 4
[26] Ascierto, 2022	Targeted Therapy TT (enc+bin) > imm (ipi+niv) vs. imm (ipi+niv) > TT (enc+bin) vs. TT (enc+bin) > imm (ipi+niv) > TT (enc+bin)	arm B vs. arm A HR = 0.73 (95% CI, 0.42 to 1.26) arm C vs. arm A was HR = 0.81 (95% CI, 0.48 to 1.37)	arm B vs. arm A TPFS HR = 0.71 (95% CI, 0.44 to 1.14) and arm C vs. A TPFS HR =0.74 (95% CI, 0.46 to 1.18), respectively	Arm A: 27 (39%, 95% CI, 28 to 51), Arm B 41 (59%, 95% CI, 48 to 71), Arm C 26 (38%, 95% CI, 27 to 50)
[59] Chapman, 2017	Targeted Therapy TT (vem) vs. Chem (dac)	Median OS HR 0.81 [95% CI 0.7–1.0]; P =0.03 (favours vem)	NR	vem: 336 patients (49%) dac: 52 of 287 patients (18%)

Citation	Comparison Category	OS (effect measure: HR)	PFS (effect measure: HR)	Toxicity (Grade 3 or higher from studies that also reported on OS or PFS)
[14] Dreno, 2018	Targeted Therapy TT (cobi+vem) vs. placebo+TT (vem)	0.70 (95% CI 0.55–0.90), favours combination of cobi and vem compared to vem alone	0.51 (95% CI 0.39–0.68), *Favours combination therapy*	
[22] Gutzmer, 2020	Targeted Therapy TT (cobi) + Imm (ate) vs. Imm (pem)	93 (36%) of 256 patients in the ate group and 112 (43%) of 258 patients in the control group (HR 0.85; 95% CI 0.64–1.11; logrank p=0.23)	ate (16.1 months; 95% CI 11.3–18.5) control (12.3 months; 95% CI 10.8–14.7) HR 0.85; 95% CI 0.67–1.07; logrank p=0.16 *Favours ate*	Ate: 182 (79%) of 230 Control: 205 (73%) of 281
[11,12] Dummer, 2018 [10,13] Dummer, 2022 Ascierto, 2020	Targeted Therapy TT+TT (enc+bin) vs. TT (enc) vs. TT (vem)	enc+bin vs enc: HR, 0.93; 95% CI, 0.72 to 1.19 enc vs vem: HR, 0.71; 95% CI, 0.56 to 0.91	enc+bin vs enc: HR, 0.79; 95% CI, 0.61 to 1.02; enc vs vem: HR, 0.68; 95% CI, 0.52 to 0.88).	enc+bin: 70%, enc: 66%, and vem: 70%
[71] Robert et al, 2025	Targeted Therapy TT+TT>Imm (enc +bin>nivo+ipi) vs. Imm (nivo+ipi)	NR	HR = 0.87, 90% [CI] 0.67-1.12, p = 0.36	(enc +bin>nivo+ipi):58% (nivo+ipi): 51%

Abbreviations: ate, atezolizumab; bin, binimetinib; CI, confidence interval; cobi, cobimetinib; cont, continuous; dab, dabrafenib; dac, dacarbazine; enc, encorafenib; HR, hazard ratio; inter, intermittent; ipi, ipilimumab; niv, nivolumab; NR, not reported; OS, overall survival; pac, paclitaxel; pem, pembrolizumab; PFS, progression-free survival; sparta, spartalizumab; tra, trametinib; TPSF, toxicity-free, PFS, progression-free survival; vem, vemurafenib

DISCUSSION

Recent treatments for melanoma, such as small-molecule targeted drugs, show better efficacy than traditional chemotherapy, particularly for specific gene mutations. The Cochrane systematic review and various trials have provided significant insights into the efficacy and safety of different immunotherapy combinations for advanced melanoma. Nivolumab and pembrolizumab, when compared to ipilimumab, showed a statistically significant improvement in OS and PFS, with reduced grade 3 and 4 toxicities. The combination of nivolumab and ipilimumab also demonstrated better PFS compared to monotherapies, although it came with higher grade toxicity rates. The CheckMate 067 trial highlighted that the combination therapy significantly improved OS over ipilimumab alone, with median OS of 71.9 months for the combination, 36.9 months for nivolumab alone, and 19.9 months for ipilimumab alone. However, the combination had the highest rate of severe adverse events. The CheckMate 511 trial found that a specific dosing regimen of nivolumab and ipilimumab reduced severe adverse events. Additional trials, such as those by Ascierto et al and Long et al, explored different dosing and combinations, showing varying efficacy and toxicity profiles. The DREAMseq and SECOMBIT trials evaluated the sequencing of immunotherapy and targeted therapy, with DREAMseq favoring initial nivolumab/ipilimumab treatment followed by BRAF and MEK inhibitor therapy. Lastly, studies on nivolumab plus relatlimab and comparisons of ipilimumab or nivolumab/pembrolizumab with chemotherapy further underscored the benefits and risks of these therapies in improving survival outcomes for melanoma patients.

The Cochrane review included nine studies evaluating BRAF-mutated melanoma, with three studies comparing single-agent BRAF inhibitors to combination BRAF and MEK inhibitors. All trials demonstrated a benefit to combination therapy over monotherapy. Additional RCTs evaluated targeted therapy for patients with metastatic melanoma and BRAF mutations. The COLUMBUS trial found significant improvement in PFS and OS with encorafenib plus binimetinib compared to vemurafenib alone, but not versus encorafenib alone. The coBRIM and COMBI-D/COMBI-V trials also supported the recommendation for combination therapy. Three trials investigated targeted therapy with an anti-PD-1 inhibitor, with mixed results. The DREAMseq and SECOMBIT trials evaluated the sequencing of immunotherapy and targeted therapy, showing benefits for initial nivolumab/ipilimumab treatment. Lastly, three studies on triplet therapies in patients with BRAF-mutant unresectable metastatic melanoma showed varying degrees of efficacy, with the spartalizumab combination showing a median PFS of 16.2 months compared to 12.0 months for the placebo combination.

Future research for stage IIIC/D and IV cutaneous melanoma should focus on several key areas to improve patient outcomes. First, there is a need for more personalized treatment approaches, leveraging genetic and molecular profiling to tailor therapies to individual patients. Additionally, further studies are required to optimize the sequencing and combination of existing therapies, such as immunotherapy and targeted therapy, to enhance efficacy and minimize toxicity.

Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the six members of the GDG Expert Panel, five members voted and none abstained, for a total of 100% response in May 2025. Of those who voted, all (n=5) approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Is fianlimab plus cemiplimab funded in Ontario? Should this be included?	Due to the early nature of the evidence, we have removed this from the recommendation. As the evidence matures, this combination will be monitored in future updates.

RAP Review and Approval

Three RAP members reviewed this document in March 2025. One member of the RAP committee approved and two members conditionally approved in March 2025. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
Two comments – to provide context – efficiently summarize all treatments presented in this document – right now you have only three; efficiently justify why patients are demarcated by Recommendation 1, 2 and 4 (preambles can be very short, and expand in the main document)	We have included both immunotherapies as well as targeted therapies in the preamble. While still on the longer side we agree in that it helps contextualize the patients that may fall into each category.
It may make more sense to label refractory recommendations as Recommendations 1b and 2b, and the then recommendations for subtype become Recommendation 3 – minor point – but I think more intuitive.	The figure was unclear to multiple reviewers, as a result we have made the decision to remove it from the Guideline. Regarding numbering the Recommendations differently, with the elimination of the figure, we feel that the numbering is clearer.

All table notes have this extra 'is'	Extra "is" have been removed from all tables.
Why do you not outline how long other agents in the above table can be used for – (not my clinical area, so may not be relevant?	At this time, only pembrolizumab is recommended to stop at 2 years, all other therapies are until disease progression or toxicity
Onus is on the reader to ferret out strengths and limitations from the presented evidence, requires expertise as a melanoma clinician and an epidemiologist – in the summary it may be good to have a separate section on 'Limitations of the evidence' where the experts can explicitly report the limitations of the evidence – in the main body, a 'Limitations of the evidence' paragraph can be at the end of each recommendation section, and in an expanded format versus the summary. There is a future research section, but this is generic	A section on the limitations of the evidence has been created at the end of Section 2.
An edit suggestion: minor If no/or only low-quality RCTs are available	Thank you, this is true, and we have edited this statement in the Guideline.
The guideline covers a complex set of data. For the reader who is less familiar with the different classes of immunotherapies and targeted therapies, I suggest adding some sentences to orient the reader (beyond providing the names of these therapies) could be helpful. Similarly, the specific mutations and the rationale for different targeted therapies may be helpful. Reason for why patients with brain metastases need special consideration for systemic therapy again can be contextualized. I can suggest doing this in section 4 introduction section	Thank you, we have added some more context to the various therapies in the preamble in Sections 1 and 2
Various comments for clarification and simplification of the tables	The tables in Section 4 of the guideline have been edited to improve consistency across outcomes, and succinctness. We have also shorted the citations in the tables to improve readability
As discussed above, I find the recommendations focus strongly on OS and PFS. I appreciate toxicity is nuanced and decision making individualized, but at least some discussion on what the factors are involved guiding decision making in the narrative in Section 4, or the discussions	We have elaborated on the toxicity data available from the included trials as well as emphasized the need for extensive patient/physician discussion when choosing an appropriate therapy. This was done in each of the key evidence sections for the recommendations as well as in the key evidence and discussion in Section 4. We have also added

section could add to the implementability of the guideline.	a section on Limitations of the evidence at the end of Section 2.

Patient and Caregiver-Specific Consultation Group

Three patients/survivors/caregivers participated as Consultation Group members for the Working Group. They reviewed the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The main comments from the Consultation Group are summarized in Table 5-3.

Table 5-3. Summary of the Working Group's responses to comments from the Patient Consultation Group.

Comments	Responses
What happens after progression - do they go to a trial?	Yes, patients can switch to an alternate therapy listed, or to a clinical trial based on patient and physician preferences.
Nivolumab 1 mg/kg and ipilimumab 3 mg/kg iv once weekly for four doses followed by nivolumab 3 mg/kg once every two weeks – both of them? Not clear.	Nivolumab plus ipilimumab is once every 3 weeks for 4 cycles then nivolumab maintenance every 4 weeks
Recommendation 2 – the table does not talk further about the bottom 2 in the schedule. Can they be used beyond two years or until progression – please clarify how long.	Pembrolizumab may be used for up to 2 years with the possibility of retreatment for one year. Nivolumab plus ipilimumab can be given as four treatments every three weeks then followed by maintenance nivolumab every four weeks, indefinitely. Nivolumab and relatlimab may be given indefinitely until progression, toxicity or physician and/or patient considerations.
What does PD-1-refractory mean?	PD-1-refractory is a term used to describe when a patient's cancer does not respond to PD-1 immunotherapy.
What do you mean by toxicity?	Toxicity means how harmful the side effects of a drug or therapy can be to your body
How about adverse effects and OS?	We have elaborated on these outcomes in various spots in the text, as well as in the evidence tables
The timing of treatment was not clear or convenient - maybe better clarification	The systemic treatments commence after the melanoma has been clinically determined to be unresectable and metastatic.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Four targeted peer reviewers from Ontario who are considered to be clinical and methodological experts on the topic were identified by the Working Group. Two agreed to be the reviewers (Appendix 1). Two responses were received. Results of the feedback survey are

summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1.**Rate the guideline development methods.**	0	0	0	1	1
2.**Rate the guideline presentation.**	0	0	1	1	0
3.**Rate the guideline recommendations.**	0	0	1	1	0
4.**Rate the completeness of reporting.**	0	0	0	2	0
5.**Does this document provide sufficient information to inform your decisions? If not, what areas are missing?**	0	0	0	2	0
6.**Rate the overall quality of the guideline report.**	0	0	0	2	0
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7.**I would make use of this guideline in my professional decisions.**	0	0	1	1	0
8.**I would recommend this guideline for use in practice.**	0	0	0	1	1
9.**What are the barriers or enablers to the implementation of this guideline report?**	Correlation / linkage and/or future updates with any guidance on sequencing of metastatic therapies will be useful. Needs to be easily searchable/findable on the OH/CCO website. Funding implications for systemic therapies discussed in this guideline				

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
Was the EBIN study (EORTC 1612-MG) Robert et al. not included because it was presented ASCO 2024 in June and the search performed in May 2024? Or because it had only been presented in abstract form?	A subsequent 2025 update of the literature search has included this paper https://pubmed.ncbi.nlm.nih.gov/40449497/
While the randomized brain metastasis study (Long et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19:672–681.) was included where 36 patients received ipi/nivo and 27 receive nivo (in randomized portion), the Tawbi study (Tawbi et al. Combined Nivolumab and Ipilimumab in	This study did not meet the population threshold of the literature review. Additionally, the Tawbi et al. study was not an RCT and therefore did not meet the ad hoc study selection criteria. We have recognized that this is a limitation to our guideline and have addressed this gap in the limitations of the guideline.

Comments	Responses
Melanoma Metastatic to the Brain. New Engl J Med 2018;379:722–730.), with 94 patients was not. It seems to me that the Tawbi data, in as far as it significantly confirms the Long data should be included rather than excluded. However, the methodology that elevates small RCTs over large phase II single arms studies may represent a methodological process that needs to be considered by treating physicians	
Recommendation 1.3 is regarding BRAF mutated melanoma, but appears in a section for BRAF WT. Page 10 includes discussion of references regarding the triplet in the first paragraph. This information needs to be combined with the section on triplet therapy (third paragraph). Otherwise, you are repeating the same information. The section on triplet therapy should outline the PFS and OS data for the three studies and conclude that there are mixed results where PFS is superior in some studies, but not OS. There may be select patients where triplet would be discussed (funding is outside the scope I believe). Page 10 should also have a section on sequencing in BRAF mutated patients. This separate section would use the references DreamSeq and SECOMBIT to justify recommending combination ipilimumab/nivolumab over targeted therapy. If we are going to have a section on triplet, then a paragraph talking about the short "run in" of targeted therapy and switch to ipilimumab/nivolumab should be discussed. SECOMBIT (and EBIN) would justify this statement and there are some patients who would be clinically appropriate for this.	We have removed this statement as it does not pertain to BRAF WT We decided to discuss the literature regarding triplet therapy as the Working Group felt it was an important distinction. A paragraph discussing sequencing therapies is included in the guideline on page 9.
In the dosing of nivolumab the 6 mg/kg dose every 4 weeks is recommended, but the pembrolizumab 4 mg/kg every 6 weeks is not recommended. Why the different treatment of these regimens? PD1 refractory is not defined. There are different definitions that also include acquired resistance, primary resistance. It is understood that progression off therapy (even off therapy for a few months) is different biologically than progression off therapy for several years. I suspect the guideline is silent due to the requirement of RCT as there are no RCT data for these types of patients. The authors must	We agree and this has been added to the dosing In the context of this guideline the definition of PD-1 refractory includes both acquired (stopped responding after an initial response) and primary resistance (never responded). We have clarified this in the body of the guideline.

Comments	Responses
define PD1 refractory for clarity of this recommendation.	
How should patients with advanced melanoma be treated upon relapse off treatment. Physicians should be aware that IO retreatment is a valid choice. However, this may be out of scope due to the methodology of PEBC.	Thank you for highlighting this. When patients with advanced melanoma progress after a treatment-free interval, re-starting IO therapy is a clinically recognized option. We will ensure this is reflected in our guideline as a qualifying statement, noting that IO retreatment upon relapse is appropriate when clinically indicated.
Relatlimab/nivolumab is presented, but new data are evolving that confirm the improvement of PFS, Response rate and numerical OS (later data analysis showing confidence intervals not crossing 1). I think the data are more recent and a relook at the literature relatively soon may be needed.	. This consideration will be incorporated into future guideline updates as appropriate. The Program in Evidence-Based Care (PEBC) conducts annual reviews to evaluate the relevance and accuracy of all recommendations, ensuring alignment with current evidence and best practices
In considering first line, the guidance has statements of ipilimumab/nivolumab over encorafenib/binimetinib. There have been meta-analyses suggesting that monotherapy with anti-PD1 is also superior, but these data are not included due to the lack of RCT data	Noted.
Given that RCT data supports use of targeted therapy “run in” (ie SECOMBIT), the report should discuss this option. Currently there are barriers to funding by private and provincial insurers. The PEBC discussion regarding the run in (i.e., SECOMBIT) may alleviate these barriers.	The SECOMBIT trial was a relatively small study, and its findings require confirmation in larger, adequately powered studies to validate these results.
Triplet therapy is discussed. These regimens are currently not funded but may be appropriate in certain select patient populations or through self pay as the treatment costs decrease with the arrival of generic drugs.	The Working Group is in agreement with this comment
No major concerns. Consistency with other OH guidelines is key for readability and ease of access for readers. If possible, would be helpful to somehow highlight (underline, bold etc) that RECOMMENDATION 1 applies to BRAF wild type, and RECOMMENDATION 2 applies to BRAF mutated – as this is a key distinction when readers are looking for guidance.	Thank you, we have tried to make this distinction clearer in Section 1 and 2 of the Guideline.
For the TARGET POPULATION – since this guideline represents IIIC/IIID patients, I think this applies not only to unresectable lymph node metastases, but ALSO to unresectable in transit/satellite disease. Inclusion should be widened.	In-transit and satellite disease are covered in Guideline 8-10
	We have added LAG-3 to recommendation 1.1

Comments	Responses
For RECOMMENDATION 1.1, it states… "the systemic first-line treatments recommended are PD-1/PD-L1 and/or CTLA-4 inhibitors…", but Nivo/Rela is also in the list. Should LAG-3 inhibitors be added to this statement? Also, since there are no PD-L1 inhibitors included (i.e. atezolizumab), should PD-L1 be excluded?	
For Tables 1-1 and 1-2, the recommended MAINTENANCE Nivo dosing for Ipi/Nivo is different (q2 weeks in 1-1 and q4 weeks in 1-2). Is this deliberate? I know the footnote states q4 weeks is ok for both, but it reads inconsistently overall.	Thank you. The tables have been edited for consistency.
-Is RECOMMENDATION 1.3 necessary given that ALL of RECOMMENDATION 1 talks about BRAF wild type? May cause more confusion.	The table titles have been updated for consistency.
Titles for TABLES 1-1 and 1-2 should be consistent.	
For RECOMMENDATION 2.1, is the list also in "no particular order"? Or is the listing of immunotherapies before targeted therapies deliberate? If deliberate order, this should be indicated.	Immunotherapy is preferred over targeted therapy for first-line therapy as indicated in Recommendation 2.3
For RECOMMEDATION 2.3, I think the message is that immunotherapy is preferred over targeted therapy as first line. Does this imply ONLY Ipi/Nivo as written, OR is Nivo or Pembro monotherapy ALSO preferred over targeted therapy for BRAF mutant patients? OR, is the principle that COMBINATION therapy is preferred over MONOTHERAPIES in general?	Immunotherapy is preferred over targeted therapy as first-line treatment for patients with advanced melanoma, including those with BRAF mutations. This preference applies even when immunotherapy is administered as a single agent (e.g., nivolumab or pembrolizumab), not exclusively in combination regimens such as ipilimumab/nivolumab. While combination immunotherapy may offer enhanced efficacy in certain scenarios, the overarching principle is that immunotherapy—whether as monotherapy or combination—is generally favoured over targeted therapy in the first-line setting
For RECOMMENDATION 3.1 and 3.2 – should this be clarified that it refers to patients who are "refractory to PD-1 MONOTHERAPY"?	Thank you for your comment, we have edited recommendation 31- to include patients refractory to PD-1 monotherapy.
For RECOMMENDATION 3.1 and 3.2 – is Ipi/Pembo funded in Ontario?	Determining if treatments are funded in Ontario is outside the scope of this guideline; however, it is acknowledged this this is a barrier to implementation.
For RECOMMENDATION 3.1 and 3.2 – Should Ipi monotherapy be included? ▫ recognizing it is poorer efficacy than combination therapy but it was included in the trials and is funded as a second-line therapy.	

Comments	Responses
For RECOMMENDATION 3.2 – I believe that Nivo/Rela is ONLY funded for second-line therapy IF BRAF targeted therapy was the first line. This should be clarified, as patients who receive first line PD-1 monotherapy (I think…) will NOT be eligible for nivolumab/relatlimab second line. Several issues of minor language inconsistency and could improve readability – 1. Sometimes ipilimumab plus nivolumab, sometimes nivolumab plus ipilimumab. 2. Sometimes nivolumab OR pembrolizumab MONOTHERAPY, sometimes just nivolumab or pembrolizumab.	The guideline has been improved for consistency
Was there inclusion or deliberate EXCLUSION of CAR T cell therapy for metastatic melanoma ▫ I know it is not approved in Canada/Ontario but should it be mentioned somewhere given its prominence in the literature/trials and approval by the FDA?	CAR-T therapies were not under the scope of this guideline
I am not a medical oncologist or primary user of systemic treatments, but I think this guideline provides appropriate guidance for the questions asked. Although I recognize that this is a systemic therapy guideline, the use of medical treatments is closely tied and often sequenced with surgery and with radiation therapy. It may not be in scope, but it would be useful to indicate a recommendation somewhere where referral to surgical and/or radiation oncology is recommended to discuss optimal treatment sequencing and/or options. Perhaps adjacent to the statements on 'consideration of clinical trials' in the QUALIFYING STATEMENTS. If there is guidance on WHICH patients to refer (e.g., oligometastatic, isolated progression, sustained response on treatment etc), that would be even better. Needs to be easily searchable/findable on the OH/CCO website. Should link to the In transit melanoma guideline also, as the content closely related and may overlap. The landscape of approved therapies and trials is RAPIDLY changing, so the MAJOR issue will be keeping this guideline up to date with relevant drug approvals over time in Ontario. The risk is	All feedback has been noted. The PEBC evaluates the relevancy of the recommendations on a yearly basis to address rapidly evolving nature of systemic therapies.

Comments	Responses
that recommendations and sequencing will dynamically become out of date and incomplete	

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Contacted professionals included oncologists within the PEBC contact database with an interest in melanoma. Eighty-five professionals were contacted (82 professionals practicing in Ontario and 3 who practice outside Ontario). Of these, 24 (28%) responses were received of which 10 stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 14 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number 14 (16%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1.**Rate the overall quality of the guideline report.**	0	0	0	5	9
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2.**I would make use of this guideline in my professional decisions.**	1	0	0	3	10
3.**I would recommend this guideline for use in practice.**	0	0	0	2	12
4.**What are the barriers or enablers to the implementation of this guideline report?**	Barriers: Access to drugs, access to health care providers, access to guidelines, patient compliance with medications. Not all recommendations are necessarily publicly funded in Ontario. Some of this is new so need to ensure good dissemination Enablers: Streamline referral process for Cutaneous Melanoma patients to an oncology service once criteria are met. Up-to-date guideline information for health care providers, self referral would be the most enabling.				

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses

1. Recommendation 3-should the guidelines help to define or specify "PD1-refractory disease"? Does this mean progression/recurrent on PD1 or within three versus six versus 12 months? This was a query also raised by an internal reviewer.	Thank you, a definition of PD-1 refractory melanoma has been added into the preamble in Sections 1 and 2
2. Recommendation #4: CNS metastases are common/challenging in melanoma and warrants a separate recommendation point rather than grouping it with KIT/NRAS molecular subtypes.	We agree that CNS metastases represent a distinct and clinically significant challenge in melanoma management. However, CNS disease was outside the defined scope of this guideline, which focused on systemic therapy recommendations for molecular subtypes such as KIT and NRAS. We recognize the importance of this topic and will consider addressing CNS involvement in a future, dedicated guideline or update
3. Systemic recommendations should include a comment regarding symptomatic vs asymptomatic CNS disease. Similarly, distinction between symptomatic vs asymptomatic CNS disease should be included in the section regarding Key Evidence (page 14). In the Long et al study (ref 34), cohort C patients had symptomatic or treated brain metastases.	Thank you we have clarified this in the key evidence section and indicated that in the qualifying statements if BRAF mutation is present then targeted therapies may be an option for some patients in consultation with their clinical team.
4. Other evidence in CNS disease that could be included: 2025 update for the Long et al (ABC trial) with seven-year PFS/OS data which could be included. For BRAF+ patients with brain metastases, there is evidence of use in asymptomatic brain metastases (Menzies et al) and this evidence could be included.	Thank you, this has been noted and any future updates will be evaluated

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table 1. Members of the Metastatic Melanoma Working Group.

Name	Affiliation	Declarations of interest
Teresa Petrella Working Group Chair Medical Oncologist	Odette Cancer Centre Toronto, Ontario	$500 or more in a single year to act in a consulting capacity: Merck, BMS, Sanofi, Novartis Grants or research support: Merck, Roche, Novartis, BMS Principal Investigator: multiple clinical trials involving ipilimumab, nivolumab, dabrafenib, trametinib
Tara Baetz Medical Oncologist	BC Cancer Victoria, British Columbia	$500 or more in a single year to act in a consulting capacity (Advisory Boards: Merk, Novartis, BMS, Sun pharma, Abbvie, Gilead, Asta Zeneca, Roche, Pfizer, Sanofi, Seattle genetics) Received any grants or other research support, either as principal or co-investigator, in any amount, from a relevant business entity? Seattle genetics Been a principal investigator for a clinical trial involving any of the objects of study, regardless of the source of funding? If so, please provide the name of the trial in the comment box. "Study" The procedures, drugs, techniques, tests, modalities, systems, or other activities that are covered by the topic of the document being developed by the PEBC. This includes both the objects of study of primary interest and possible competing objects of study: Amgen (MasterKey 265) BMS (CA-209 76K) Morphosys (BMIND)
Gregory Knight Medical Oncologist	Grand River Regional Cancer Centre, Kitchener, Ontario	$500 or more in a single year to act in a consulting

		capacity? "Consulting capacity" includes such work as consultant, investigator, advisory board member, lobbyist, speaker: Advisory Boards: multiple boards
Elaine McWhirter Medical Oncologist	Juravinski Cancer Centre, Hamilton, Ontario	$500 or more in a single year to act in a consulting capacity? "Consulting capacity" includes such work as consultant, investigator, advisory board member, lobbyist, speaker: Advisory Boards: Merck, BMS, Novartis, EMD Serono, Sanofi-Genzyme, Pfizer Grants or other research support: Roche Other: Merck 2021 – donated $20,000 to enclosed fund for the surgical oncologist fellowship which will pay international fellow salary) at the University of Toronto
Alexander Sun Radiation Oncologist	Princess Margaret Cancer Centre, Toronto, Ontario	None Declared
Xinni Song Medical Oncologist	The Ottawa Hospital, Ottawa, Ontario	
Frances Wright Medical Oncologist	Sunnybrook Cancer Centre, Toronto, Ontario	$500 or more in a single year to act in a consulting capacity? "Consulting capacity" includes such work as consultant, investigator, advisory board member, lobbyist, speaker: Novartis
Sarah Kellett Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None Declared

Table 2. Members of the Metastatic Melanoma Expert Panel

Name, Expertise	**Affiliation**	**Declarations of interest**
David McCready, Surgical Oncologist	Princess Margaret Hospital, Toronto, Ontario	Stock, bonds or stock options valued at $500 or more: Yes
Annette Cyr, Patient Representative	Not available	None declared
Christian Murray, Dermatologist	Skin Surgery Centre, University of Toronto, Toronto, Ontario	None declared

Caroline Hamm, Medical Oncologist	Windsor Regional Cancer Centre, Windsor, Ontario	None declared
Sudha Rajagopal, Medical Oncologist	Credit Valley Hospital Peel Regional Cancer Centre Mississauga, Ontario	None declared
Dr. Alexandra Easson Surgical Oncologist	Princess Margaret Cancer Centre, Toronto, Ontario	None declared

Table 3. Members of the Patient Consultation Group

Name	Declaration of Interest
Lise Craig	None declared
Sharon Tan	None declared
Randall Conrod	None declared
Helen Alexander	None declared

Table 4. Members of the Report Approval Panel

Name, Expertise	Affiliation	Declarations of interest
Dr. Jonathan Sussman	Juravinski Cancer Centre Radiation Oncologist Hamilton, Ontario	None Declared
Dr. Rebecca Wong	University of Toronto Radiation Oncologist Toronto, Ontario	None Declared
Dr. Marko Simunovic	Juravinski Cancer Centre Surgical Oncologist Hamilton, Ontario	None Declared

Table 5. Targeted Peer Reviewers

Name, Expertise	Affiliation	Declarations of interest
Dr. Marcus Butler	Medical Oncologist Princess Margaret Cancer Centre in Toronto, Canada	Advisory board to the following entities: BMS, Merck, Pfizer, Novartis, Sanofi, Regeneron, Medison, Immunocore, Ideaya Bio, Iovance, Sun pharma, Adaptimmune. Advisory board reimbursement from BMS, Merck, Pfizer, Novartis, Sanofi, Regeneron, Medison, Immunocore, Ideaya Bio, Iovance, Sun pharma, Adaptimmune. Grant to institution to conduct investigator initiated clinical trials from Merck and Takara Bio. Quality improvement funds to institution from Novartis.

		Principal site investigator for several phase 3 trials
Dr. Nicole Look-Hong	Surgical Oncologist Sunnybrook Health Sciences Center	Current skin cancer lead for Ontario Health (OH)

Appendix 2: Literature Search Strategy

MEDLINE (Ovid) search strategy

1. exp Melanoma/
2. exp Skin Neoplasms/
3. melanoma.ti,ab.
4. or/1-3
5. (metastatic or metastas$).ti,ab.
6. exp Neoplasm Metastasis/
7. ("stage iv" or "stage 4").ti,ab.
8. or/5-7
9. 4 and 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animals/ not humans.sh.
19. 17 not 18
20. 9 and 19

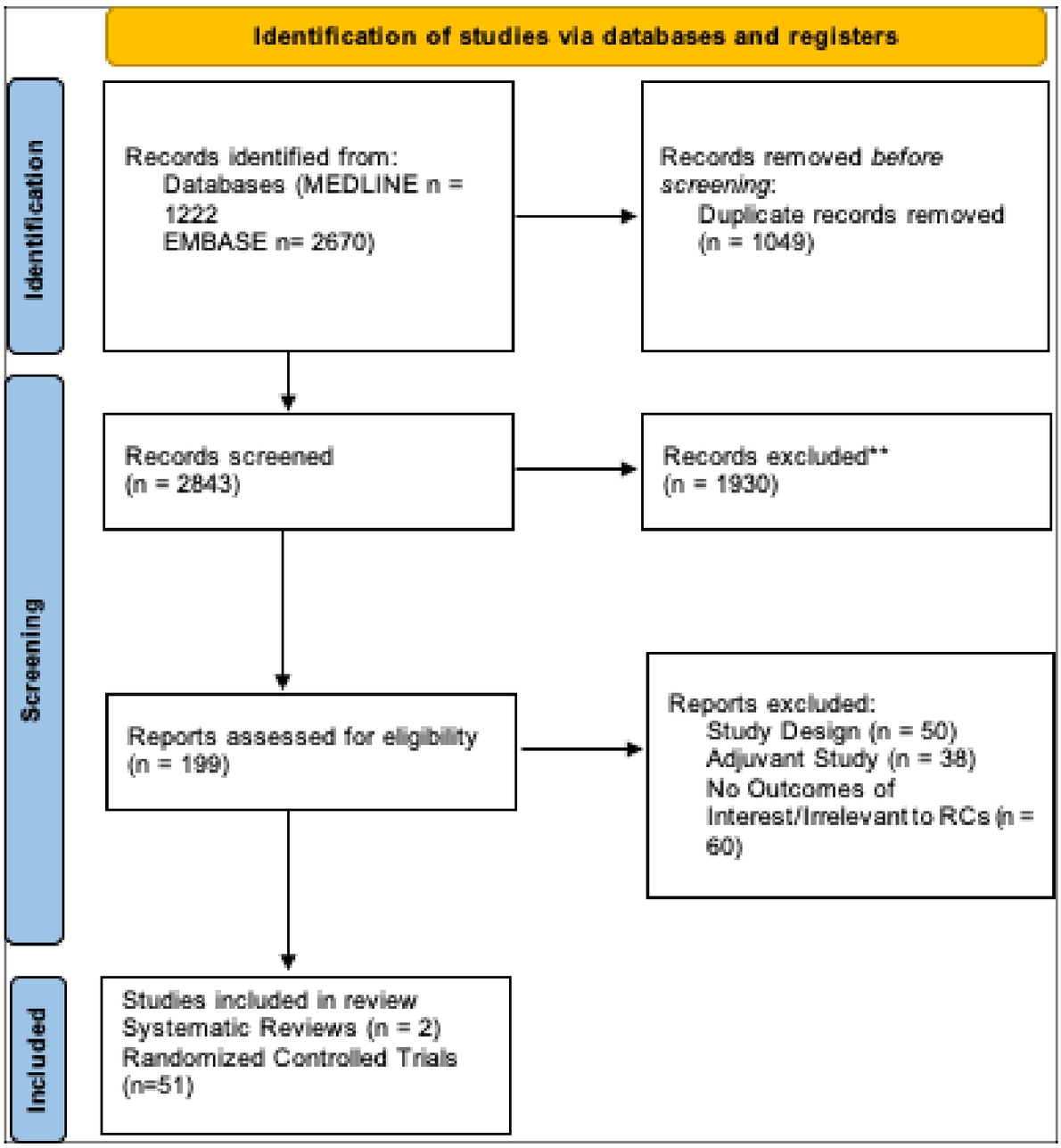
[Lines 10-19: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Embase (Ovid) search strategy

exp melanoma/
2. melanoma.ti,ab.
3. 1 or 2
4. (metastatic or metastas$).ti,ab.
5. metastasis/ or exp skin metastasis/
6. ("stage iv" or "stage 4").ti,ab.
7. 4 or 5 or 6
8. crossover procedure.sh.
9. double-blind procedure.sh.
10. single-blind procedure.sh.
11. (crossover$ or cross over$).tw.
12. placebo$.tw.
13. (doubl$ adj blind$).tw.
14. allocat$.tw.
15. trial.ti.
16. randomized controlled trial.sh.
17. random$.tw.
18. or/8-17
19. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
20. human/ or normal human/
21. 19 and 20

22. 19 not 21
23. 18 not 22
24. 3 and 7 and 23

Appendix 3: PRISMA Flow Diagram



Appendix 4: Study Characteristics
Studies published after the Cochrane Systematic Literature Review (Pasquali et al, 2018)

TABLE 4-1. Studies Evaluating Immunotherapy

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
Andtbacka R.H, M. Ross, I. Puzanov, M. Milhem, F. Collichio, K. A. Delman, et al. Patterns of Clinical Response with Talimogene Laherparepvec (T-VEC) in Patients with Melanoma Treated in the OPTiM Phase III Clinical Trial Annals of Surgical Oncology 2016 Vol. 23 Issue 13 Pages 4169-4177	Andtbacka, et al., 2019 Andtbacka, et al., 2015 Recruitment: 2009-2011 **OPTiM Trial** Trial ID: NCT01515189.	Phase III RCT open-label multicentre: 64 sites in 4 countries	Unresectable, bidimensionally measurable stage IIIB/C/IV melanoma	imm (T-VEC) vs. other (GM-CSF)	F-U: Med. 49 mos. Age: 63 (22-94) vs. 64 (26-91) %male: 59% vs. 55%
Ascierto P.A., M. Del Vecchio, C. Robert, A. Mackiewicz, V. Chiarion-Sileni, A. Arance, et al Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2017 Vol. 18(5) Pages 611-622 Ascierto P.A, M. Del Vecchio, A. Mackiewicz, C. Robert, V. Chiarion-Sileni, A. Arance, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. J Immunother Cancer 2020 Vol. 8(1) (no pagination)	Ascierto, et al., 2020a Ascierto, et al., 2017 Recruitment: Feb. 2012 – July 2012 Trial ID: NCT01515189	Phase III RCT double-blind multicentre: 87 centres in 21 countries	Untreated or previously treated unresectable stage III or IV melanoma, without previous treatment with BRAF inhibitors or immune checkpoint inhibitors	Imm(Ipi10) vs. Imm(ipi3)	F-U: Med. 14.5 (IQR 4.6–42.3) vs. 11.2 (IQR 4.9-29.4) mos. Age: Mean 62 (49-70) vs. 62 (51-71) %male: 60% vs. 64%

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
Chesney, I. Puzanov, F. Collichio, P. Singh, M. M. Milhem, J. Glaspy, et al. Randomized, Open-Label Phase II Study Evaluating the Efficacy and Safety of Talimogene Laherparepvec in Combination with Ipilimumab Versus Ipilimumab Alone in Patients with Advanced, Unresectable Melanoma. J Clin Oncol 2018 Vol. 36 Issue 17 Pages 1658-1667	Chesney, et al., 2018 Puzanov, et al., 2020 (Abstract) Recruitment: Aug. 2013 – Feb. 2016	Phase II RCT Open-label Multicentre	Unresectable stages IIIB to IV melanoma, with no more than one prior therapy if BRAF wild-type, no more than two prior therapies if BRAF mutant, measurable/injectable disease, and without symptomatic autoimmunity or clinically significant immunosuppression	Imm(T-VEC+ipi) vs. imm(ipi)	F-U (MED): 48.3 TVEC+ipi; 35.7 IPI alone Med. Age: 65 (23-93) vs 64 (23-90) Male%: 63% vs 55%
Hodi, J. Chesney, A. C. Pavlick, C. Robert, K. F. Grossmann, D. F. McDermott, et al.Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 2016 Vol. 17 Issue 11 Pages 1558-1568 Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, Giguere JK, Agarwala SS, Shaheen M, Ernstoff MS, Minor D, Salama AK, Taylor M, Ott PA, Rollin LM, Horak C, Gagnier P, Wolchok JD, Hodi FS. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015 May 21;372(21):2006-17. doi: 10.1056/NEJMoa1414428. Epub 2015 Apr 20. Erratum In: N Engl J Med. 2018 Nov 29;379(22):2185.	Hodi et al 2016 Postow et al 2015 *Postow et al included in Cochrane review* *Updated Survival Results available* **CHECKMATE-069 Trial** Trial ID: NCT01927419	Phase II RCT. Double-blind, multicentre trial 19 sites in 2 countries	Previously untreated, unresectable stage III or IV melanoma	imm(niv+ipi) vs imm(ipi)+pla	F-U: Med. 24.5 months (IQR 9.1-25.7) Age: NR %male: NR

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
Larkin, D. Minor, S. D'Angelo, B. Neyns, M. Smylie, W. H. Miller, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. J Clin Oncol 2018 Vol. 36(4) Pages 383-390`  Weber, S. P. D'Angelo, D. Minor, F. S. Hodi, R. Gutzmer, B. Neyns, et al.Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015 Vol. 16 Issue 4 Pages 375-384`	Larkin et al, 2022 Weber et al 2015 *(this pub is included in Cochrane review)* *UPDATED SURVIVAL RESULTS* **CHECKMATE 037** Trial ID: NCT01721746	Phase III RCT Open-label Multi-centred 90 sites; 14 countries	Pts with unresectable stage IIIC or IV metastatic melanoma	Imm(niv) vs. chem(dac or car)	F-U: 2 yrs Med age: 59 (23-83) vs. 62 (29-85) %male: 65% vs. 64%
Lebbé, N. Meyer, L. Mortier, I. Marquez-Rodas, C. Robert, P. Rutkowski, 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 Vol. 37 Issue 11 Pages 867-875	Lebbé, et al., 2019 Recruitment: Apr. 2016 – Mar. 2017 **CheckMate 511** Trial ID: NCT02714218	Phase IIIb/IV RCT Double-blind Multi-centred: 57 sites, 13 countries	Previously untreated, unresectable stage III or IV melanoma	Imm(niv3+ipi1) vs. Imm(niv1+ipi3)	F-U med. 12 mos. Med. Age: 58.5 (19-85) vs. 58.5 (26-85) %male: 58.3% vs. 56.7%
Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, Wilmott JS, Edwards J, Gonzalez M, Scolyer RA, Menzies AM, McArthur GA. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018 May;19(5):672-681. doi: 10.1016/S1470-2045(18)30139-6. Epub 2018 Mar 27.	Long et al, 2018 **ABC Trial** Trial ID: NCT02374242	Phase II RCT open-label, multicentered: 4 sites in Australia	AJCC Stage IV (any T, any N, M1c) histologically confirmed melanoma or unknown primary melanoma. Patients must have at least 1 radiological definitive brain metastasis that is ≥5mm and ≤40mm measurable		F-U-med: 17 months (IQR 8–25) Age: 59 (53-68) vs 63 (52-74) vs 51 (48-56) Male %: 83% vs 76% vs 69%

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
Long, R. Dummer, O. Hamid, T. F. Gajewski, C. Caglevic, S. Dalle, et al. Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. Lancet Oncol 2019 Vol. 20(8) Pages 1083-1097	Long, et al., 2019 Recruitment: June 2016 – Aug. 2017 **ECHO-301/KEYNOTE-252 Trial** Trial ID: NCT02752074	Phase 3 RCT Double-blind parallel-group International study	Unresectable stage III or IV melanoma previously untrreated with PD-1 or PD-L1 checkpoint inhibitors	Other(epa+imm(pem) vs. pl+imm(pem)	F-U:. Med. 12.4 (IQR 10.3 – 14.5) mos. Age:64 (52-72) vs, 63 (54-72) %male: 61% vs. 59%
Tarhini, S. J. Lee, X. Li, U. N. M. Rao, A. Nagarajan, M. R. Albertini, et al. E3611-A Randomized Phase II Study of Ipilimumab at 3 or 10 mg/kg Alone or in Combination with High-Dose Interferon-alpha2b in Advanced Melanoma. Clinical Cancer Research 2019 Vol. 25 Issue 2 Pages 524-532	Tarhini et al 2019 **E3611 Trial** Trial ID: NCT01708941	Phase II RCT; open label	Unresectable stage III or stage IV melanoma	Imm (HD ipi + HDI) vs. Imm (ipi) vs. Imm (LD ipi +HDI) vs. Imm (LD ipi)	F-U: every 3 months for 2 years, every 6 months for 3 years, annually for up to 5 years med age: 60 (20-74) vs 57 (27-83) vs 65 (29-77) %male: 44% vs 64% vs 68%

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
Tawbi, D. Schadendorf, E. J. Lipson, P. A. Ascierto, L. Matamala, E. C. Gutierrez, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med 2022 Vol. 386(1) Pages 24-34	Tawbi et al 2022 **REALTIVITY-047** TRIAL ID: NCT03470922	Phase II/III RCT, double-blind, multicenter trial; 127 sites; 25 countries	Previously untreated metastatic or unresectable melanoma	Imm(rel+niv) vs. Imm(niv)	F-U: 5.6 mos. vs. 4.9 mos. Age: 63 (20-94) vs 62 (21-90) %male: 59.2 vs 57.4
Ugurel, C. Loquai, P. Terheyden, D. Schadendorf, E. Richtig, J. Utikal, et al. Chemosensitivity-directed therapy compared to dacarbazine in chemo-naive advanced metastatic melanoma: A multicenter randomized phase-3 DeCOG trial. Oncotarget 2017 Vol. 8(44) Pages 76029-76043	Ugurel, et al., 2017 Recruitment: Nov. 2008 – Oct. 2012 **DeCOG trial** Trial ID:	Phase III RCT multicentered	Chemo-naive advanced metastatic melanoma:	chem vs. imm (dac)	F-U: 26.4 months Age: NR %male: NR
Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank C, Petrella TM, Hamid O, Zhou H, Ebbinghaus S, Ibrahim N, Robert C. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017 Oct 21;390(10105):1853-1862. doi: 10.1016/S0140-6736(17)31601-X. Epub 2017 Aug 16. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372(26):2521-32. doi: 10.1056/NEJMoa1503093. Epub 2015 Apr 19. Hamid O, Robert C, Daud A, Carlino MS, Mitchell TC, Hersey	Various Citations Recruitment: Sep. 2013 – Mar. 2014 *Robert et al (2015) included in Cochrane review. Updated results available in Schacter et al (2017)* **KEYNOTE-006 Trial** Trial ID: NCT01866319	Phase III RCT Open-label Multicentred: 87 institutions in 16 countries	Unresectable stage III or IV melanoma (excluding ocular melanoma	Imm(pem2) vs. Imm(pem3) vs. Imm(ipi)	F-U: at least 21 mos. Med. age: 61 (18-89) vs. 63 (22-89) vs. 62 (18-88) %male: 58% vs. 63% vs. 58%

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
P, Schachter J, Long GV, Hodi FS, Wolchok JD, Arance A, Grob JJ, Joshua AM, Weber JS, Mortier L, Jensen E, Diede SJ, Moreno BH, Ribas A. Long-term outcomes in patients with advanced melanoma who had initial stable disease with pembrolizumab in KEYNOTE-001 and KEYNOTE-006. Eur J Cancer. 2021 Nov;157:391-402. doi: 10.1016/j.ejca.2021.08.013. Epub 2021 Sep 25. Robert C, Hwu WJ, Hamid O, Ribas A, Weber JS, Daud AI, Hodi FS, Wolchok JD, Mitchell TC, Hersey P, Dronca R, Joseph RW, Boutros C, Min L, Long GV, Schachter J, Puzanov I, Dummer R, Lin J, Ibrahim N, Diede SJ, Carlino MS, Joshua AM. Long-term safety of pembrolizumab monotherapy and relationship with clinical outcome: A landmark analysis in patients with advanced melanoma. Eur J Cancer. 2021 Feb;144:182-191. doi: 10.1016/j.ejca.2020.11.010. Epub 2020 Dec 24. Lala M, Li TR, de Alwis DP, Sinha V, Mayawala K, Yamamoto N, Siu LL, Chartash E, Aboshady H, Jain L. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer. 2020 May;131:68-75. doi: 10.1016/j.ejca.2020.02.016. Epub 2020 Apr 15. Erratum In: Eur J Cancer. 2021 Feb;144:400. van Vugt MJH, Stone JA, De Greef RHJMM, Snyder ES, Lipka L, Turner DC, Chain A, Lala M, Li M, Robey SH, Kondic AG, De Alwis D, Mayawala K, Jain L, Freshwater T. Immunogenicity of pembrolizumab in patients with advanced tumors. J Immunother Cancer. 2019 Aug 8;7(1):212. doi: 10.1186/s40425-019-0663-4. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil CM, Lotem M, Larkin JMG, Lorigan P, Neyns B, Blank CU, Petrella TM, Hamid O, Su SC, Krepler					

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
C, Ibrahim N, Long GV. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019 Sep;20(9):1239-1251. doi: 10.1016/S1470-2045(19)30388-2. Epub 2019 Jul 22. Wang M, Chen C, Jemielita T, Anderson J, Li XN, Hu C, Kang SP, Ibrahim N, Ebbinghaus S. Are tumor size changes predictive of survival for checkpoint blockade based immunotherapy in metastatic melanoma? J Immunother Cancer. 2019 Feb 8;7(1):39. doi: 10.1186/s40425-019-0513-4. Hamid O, Robert C, Ribas A, Hodi FS, Walpole E, Daud A, Arance AS, Brown E, Hoeller C, Mortier L, Schachter J, Long J, Ebbinghaus S, Ibrahim N, Butler M. Antitumour activity of pembrolizumab in advanced mucosal melanoma: a post-hoc analysis of KEYNOTE-001, 002, 006. Br J Cancer. 2018 Sep;119(6):670-674. doi: 10.1038/s41416-018-0207-6. Epub 2018 Sep 11. Carlino MS, Long GV, Schadendorf D, Robert C, Ribas A, Richtig E, Nyakas M, Caglevic C, Tarhini A, Blank C, Hoeller C, Bar-Sela G, Barrow C, Wolter P, Zhou H, Emancipator K, Jensen EH, Ebbinghaus S, Ibrahim N, Daud A. Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: A randomised clinical trial. Eur J Cancer. 2018 Sep;101:236-243. doi: 10.1016/j.ejca.2018.06.034. Epub 2018 Aug 7. Petrella TM, Robert C, Richtig E, Miller WH Jr, Masucci GV, Walpole E, Lebbe C, Steven N, Middleton MR, Hille D, Zhou W, Ibrahim N, Cebon J. Patient-reported outcomes in KEYNOTE-006, a randomised study of pembrolizumab versus ipilimumab in patients with advanced melanoma. Eur J					

Citation	Study Citation and Trial Name	Study Methodology	Population	Treatment Summary	Follow-up
Cancer. 2017 Nov;86:115-124. doi: 10.1016/j.ejca.2017.08.032. Epub 2017 Oct 4.					
D'Angelo, O. A. Hamid, A. Tarhini, D. Schadendorf, B. Chmielowski, F. A. Collichio, et al.A phase 2 study of ontuxizumab, a monoclonal antibody targeting endosialin, in metastatic melanoma. Invest New Drugs 2018 Vol. 36 Issue 1 Pages 103-113	D'Angelo, et al., 2018 Recruitment: May 2011 – Dec. 2013	Phase II RCT Open-label Multicentre	Patients with disease progression after receiving at least 1 prior systemic treatment for metastatic melanoma	Imm(ont2) vs. Imm(ont4)	F-U: NR Mean age: 65.1 (27–91) vs. 61.2 (35–83) %male: 55% vs. 75%

Abbreviations: AJCC, American Joint Committee on Cancer; car, carboplatin; chem, chemotherapy; dac, dacarbazine; epa, epacadostat; F-U, follow-up; GM-CSF, granulocyte-macrophage colony-stimulating factor; HD, high-dose; HDI, high-dose interleukin-2; imm, immunotherapy; ipi, ipilimumab; IQR, interquartile range; LD, low dose; med, median; mos, months; niv, nivolumab; NR, not reported; ont, ontuxizumab; pem, pembrolizumab; RCT, randomized controlled trial; rel, relatlimab; T-VEC, talimogene laherparepvec; yrs, years

TABLE 4-2. Studies Evaluating Targeted Therapy

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Atkins, S. J. Lee, B. Chmielowski, A. A. Tarhini, G. I. Cohen, T. G. Truong, et al Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: The DREAMseq Trial - ECOG-ACRIN EA6134. J Clin Oncol 2022 Pages 101200JCO2201763	Atkins et al, 2023 **DREAMseq** Trial ID: NCT02224781	Phase III RCT; multicenter	Unresectable stage III or stage IV; BRAF V600 mutation	Sequential	F-U: every 3 months for 2 years and then every 6 months for 3 years. Age: 61 (25-85) vs 61 (30-84) Male%: 60.9% vs 65.3%
Gogas, B. Dréno, J. Larkin, L. Demidov, D. Stroyakovskiy, Z. Eroglu, et al.Cobimetinib plus atezolizumab in BRAFV600 wild-type melanoma: primary results from the randomized phase III IMspire170 study. Annal Oncol 2021 Vol. 32 Issue 3 Pages 384-394	Gogas, et al., 2021 Recruitment: Dec. 2017 – Jan. 2019 **IMspire170 study**	Phase III RCT Open label International	Previously untreated BRAFV600 wild-type advanced melanoma	TT(cobi)+Imm(ate) vs. Imm(pem)	F-U: med. 7.1 mos. (IQR 4-8-9.9) vs. 7.2 mos. (IQR 4.9-10.1) Med. Age: 66 (54-73) vs. 66 (55-73) %male: 58.1% vs. 62.9%

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Long, Z. Eroglu, J. Infante, S. Patel, A. Daud, D. B. Johnson, et al.Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma who received dabrafenib combined with trametinib. J Clin Oncol 2018 Vol. 36(7) Pages 667-673	Long, et al., 2018 Recruitment NR - Oct. 2016 **BRF113220 Trial; Part C** Trial ID: NCT02374242	Phase II RCT Open-label Multicentred: 16 centres	BRAF inhibitor-naive patients with BRAF V600-mutant MM	TT(dab) vs. TT(dab+tra/1) vs. TT(dab+tra/2)	F-U: 5 yrs. Med. age: 50 (18-82) vs. 49 (23-85) vs. 58 (27-79) %male: 54% vs. 56% vs. 63%
Robert C, Flaherty K, Nathan P, Hersey P, Garbe C, Milhem M, Demidov L, Mohr P, Hassel JC, Rutkowski P, Dummer R, Utikal J, Kiecker F, Larkin J, D'Amelio A Jr, Mookerjee B, Schadendorf D. Five-year outcomes from a phase 3 METRIC study in patients with BRAF V600 E/K-mutant advanced or metastatic melanoma. Eur J Cancer. 2019 Mar;109:61-69. doi: 10.1016/j.ejca.2018.12.015. Epub 2019 Jan 25. Latimer NR, Bell H, Abrams KR, Amonkar MM, Casey M. Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer Med. 2016 May;5(5):806-15. doi: 10.1002/cam4.643. Epub 2016 Jan 27. Santiago-Walker A, Gagnon R, Mazumdar J, Casey M, Long GV, Schadendorf D, Flaherty K, Kefford R, Hauschild A, Hwu P, Haney P, O'Hagan A, Carver J, Goodman V, Legos J, Martin AM. Correlation of BRAF Mutation Status in Circulating-Free DNA and Tumor and Association with Clinical Outcome across Four BRAFi and MEKi Clinical Trials. Clin Cancer Res. 2016 Feb 1;22(3):567-74. doi: 10.1158/1078-0432.CCR-15-0321. Epub 2015 Oct 7. Schadendorf D, Amonkar MM, Milhem M, Grotzinger K, Demidov LV, Rutkowski P, Garbe C, Dummer R, Hassel JC, Wolter P, Mohr P, Trefzer U, Lefeuvre-Plesse C, Rutten A,	Robert et al., 2019 Recruitment: Dec. 2010 – Jul. 2011 **METRIC Trial** Trial ID: NCT01245062	Phase III RCT Open-label Multicentred	BRAF V600 E/K-mutant metastatic melanoma	TT(tra) vs. chem (dac+pac)	F-U: med. 14.7 (0-70) vs. 8.7 (0-70) Med. age: 54.5 (23-85) vs. 54 (21-77) %male: 56% vs. 49%

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Steven N, Ullenhag G, Sherman L, Wu FS, Patel K, Casey M, Robert C. Functional and symptom impact of trametinib versus chemotherapy in BRAF V^{600E} advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Ann Oncol. 2014 Mar;25(3):700-706. doi: 10.1093/annonc/mdt580. Epub 2014 Feb 6.					
Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480-92. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022;40(2):127-37. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017;377(14):1345-56. Wolchok JD, Chiarion-Sileni V, Rutkowski P, Cowey CL, Schadendorf D, Wagstaff J, et al. Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med. 2025;392(1):11-22.	Various Citations **CHECKMATE-067 Trial** Trial ID: NCT01844505	Phase III RCT Double-blind Multicentred: 137 centres from 21 countries	Previously untreated, unresectable, stage III or stage IV melanoma, known BRAFV600 mutation status, and an Eastern Cooperative Oncology Group performance status of 0 or 1.	Imm(niv+ipi) vs. imm(niv)+placebo vs. imm(ipi)+placebo	F-U: 4-yrs Age: 61 {51-70) vs. 60 (50-68) vs. 62 (52-71) %male: 66% vs. 64% vs. 64%

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Tawbi HA, Robert C, Brase JC, Gusenleitner D, Gasal E, Garrett J, Savchenko A, Gorgun G, Flaherty KT, Ribas A, Dummer R, Schadendorf D, Long GV, Nathan PD, Ascierto PA. Spartalizumab or placebo in combination with dabrafenib and trametinib in patients with BRAF V600-mutant melanoma: exploratory biomarker analyses from a randomized phase 3 trial (COMBI-i). J Immunother Cancer. 2022 Jun;10(6):e004226. doi: 10.1136/jitc-2021-004226. Dummer R, Long GV, Robert C, Tawbi HA, Flaherty KT, Ascierto PA, Nathan PD, Rutkowski P, Leonov O, Dutriaux C, Mandala M, Lorigan P, Ferrucci PF, Grob JJ, Meyer N, Gogas H, Stroyakovskiy D, Arance A, Brase JC, Green S, Haas T, Masood A, Gasal E, Ribas A, Schadendorf D. Randomized Phase III Trial Evaluating Spartalizumab Plus Dabrafenib and Trametinib for BRAF V600-Mutant Unresectable or Metastatic Melanoma. J Clin Oncol. 2022 May 1;40(13):1428-1438. doi: 10.1200/JCO.21.01601. Epub 2022 Jan 14. Dummer R, Lebbe C, Atkinson V, Mandala M, Nathan PD, Arance A, Richtig E, Yamazaki N, Robert C, Schadendorf D, Tawbi HA, Ascierto PA, Ribas A, Flaherty KT, Pakhle N, Campbell CD, Gusenleitner D, Masood A, Brase JC, Gasal E, Long GV. Combined PD-1, BRAF and MEK inhibition in advanced BRAF-mutant melanoma: safety run-in and biomarker cohorts of COMBI-i. Nat Med. 2020 Oct;26(10):1557-1563. doi: 10.1038/s41591-020-1082-2. Epub 2020 Oct 5.	Various Citations **COMBI-i Trial** Trial ID: NCT02967692	Phase II RCT. Double-blind, multicentre trial; 179 sites in 29 countries	Histologically confirmed, unresectable or metastatic melanoma with BRAF V600 mutation		F-U med: 27.2 (IQR 25.4-29.0) med Age: sparta-dab-tra: 56 (46-66) Placebo-dab-tra: 55 (47-65)

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Robert C, Long GV, Brady B, Dutriaux C, Di Giacomo AM, Mortier L, Rutkowski P, Hassel JC, McNeil CM, Kalinka EA, Lebbe C, Charles J, Hernberg MM, Savage KJ, Chiarion-Sileni V, Mihalcioiu C, Mauch C, Arance A, Cognetti F, Ny L, Schmidt H, Schadendorf D, Gogas H, Zoco J, Re S, Ascierto PA, Atkinson V. Five-Year Outcomes With Nivolumab in Patients With Wild-Type BRAF Advanced Melanoma. J Clin Oncol. 2020 Nov 20;38(33):3937-3946. doi: 10.1200/JCO.20.00995. Epub 2020 Sep 30. Ascierto PA, Long GV, Robert C, Brady B, Dutriaux C, Di Giacomo AM, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage KJ, Hernberg MM, Lebbe C, Charles J, Mihalcioiu C, Chiarion-Sileni V, Mauch C, Cognetti F, Ny L, Arance A, Svane IM, Schadendorf D, Gogas H, Saci A, Jiang J, Rizzo J, Atkinson V. Survival Outcomes in Patients With Previously Untreated BRAF Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. JAMA Oncol. 2019 Feb 1;5(2):187-194. doi: 10.1001/jamaoncol.2018.4514. Erratum In: JAMA Oncol. 2019 Feb 1;5(2):271. Long GV, Tykodi SS, Schneider JG, Garbe C, Gravis G, Rashford M, Agrawal S, Grigoryeva E, Bello A, Roy A, Rollin L, Zhao X. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. Ann Oncol. 2018 Nov 1;29(11):2208-2213. doi: 10.1093/annonc/mdy408. Long GV, Weber JS, Larkin J, Atkinson V, Grob JJ, Schadendorf D, Dummer R, Robert C, Marquez-Rodas I, McNeil C, Schmidt H, Briscoe K, Baurain JF, Hodi FS, Wolchok JD. Nivolumab for Patients With Advanced Melanoma Treated Beyond Progression: Analysis of 2 Phase 3 Clinical Trials. JAMA Oncol. 2017 Nov 1;3(11):1511-1519. doi: 10.1001/jamaoncol.2017.1588. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L,	Various Citations *Robert et al 2015 previously incuded in Cochrane Review* *UPDATED 5-YEAR SURVIVAL RATES AVAILABLE* **CheckMate 066** Trial ID: NCT01721772	Phase III RCT Double blind Multicentre	Previously untreated, unresectable, stage III/IV, wild-type BRAF melanoma	imm(niv) vs chem(dac)	F-U: Med. 9 mos. Age: 64 (18-86) vs. 66 (26-87) %male 57.6% vs. 60.1%

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage KJ, Hernberg MM, Lebbe C, Charles J, Mihalcioiu C, Chiarion-Sileni V, Mauch C, Cognetti F, Arance A, Schmidt H, Schadendorf D, Gogas H, Lundgren-Eriksson L, Horak C, Sharkey B, Waxman IM, Atkinson V, Ascierto PA. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015 Jan 22;372(4):320-30. doi: 10.1056/NEJMoa1412082. Epub 2014 Nov 16.					
Long, K. T. Flaherty, D. Stroyakovskiy, H. Gogas, E. Levchenko, F. de Braud, et al.. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V^{600E}/ K-mutant melanoma: Long-term survival and safety analysis of a phase 3 study. Annals of Oncology 2017 Vol. 28(7) Pages 1631-1639 Schadendorf D, Robert C, Dummer R, Flaherty KT, Tawbi HA, Menzies AM, Banerjee H, Lau M, Long GV. Pyrexia in patients treated with dabrafenib plus trametinib across clinical trials in BRAF-mutant cancers. Eur J Cancer. 2021 Aug;153:234-241. doi: 10.1016/j.ejca.2021.05.005. Epub 2021 Jul 2. Syeda MM, Wiggins JM, Corless BC, Long GV, Flaherty KT, Schadendorf D, Nathan PD, Robert C, Ribas A, Davies MA, Grob JJ, Gasal E, Squires M, Marker M, Garrett J, Brase JC, Polsky D. Circulating tumour DNA in patients with advanced melanoma treated with dabrafenib or dabrafenib plus trametinib: a clinical validation study. Lancet Oncol. 2021 Mar;22(3):370-380. doi: 10.1016/S1470-2045(20)30726-9. Epub 2021 Feb 12.	Various Citations Recruitment: NR - Feb. 2016 *Long et al was previously incuded in Cochrane review; updated results available* **COMBI-d trial** Trial ID: NCT01584648	Phase 3 RCT Double-blind Multi-centred	Previously untreated BRAF V^{600E}/K-mutant unresectable stage IIIC or stage IV melanoma.	TT(dab+tra) vs. TT(dab)+placebo	F-U: ≥ 36 mos. Age: NR %male: NR

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, Chiarion Sileni V, Schachter J, Garbe C, Bondarenko I, Gogas H, Mandala M, Haanen JBAG, Lebbe C, Mackiewicz A, Rutkowski P, Nathan PD, Ribas A, Davies MA, Flaherty KT, Burgess P, Tan M, Gasal E, Voi M, Schadendorf D, Long GV. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med. 2019 Aug 15;381(7):626-636. doi: 10.1056/NEJMoa1904059. Epub 2019 Jun 4. Long GV, Grob JJ, Nathan P, Ribas A, Robert C, Schadendorf D, Lane SR, Mak C, Legenne P, Flaherty KT, Davies MA. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol. 2016 Dec;17(12):1743-1754. doi: 10.1016/S1470-2045(16)30578-2. Epub 2016 Nov 16. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion-Sileni V, Lebbe C, Mandala M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Swann S, Legos JJ, Jin F, Mookerjee B, Flaherty K. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015 Aug 1;386(9992):444-51. doi: 10.1016/S0140-6736(15)60898-4. Epub 2015 May 31. Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, Grob JJ, Bondarenko I, Garbe C, Lebbe C, Larkin J, Chiarion-Sileni V, Millward M, Arance A, Mandala M, Flaherty KT, Nathan P, Ribas A, Robert C, Casey M, DeMarini DJ, Irani JG, Aktan G, Long GV. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib					

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer. 2015 May;51(7):833-40. doi: 10.1016/j.ejca.2015.03.004. Epub 2015 Mar 17. Menzies AM, Ashworth MT, Swann S, Kefford RF, Flaherty K, Weber J, Infante JR, Kim KB, Gonzalez R, Hamid O, Schuchter L, Cebon J, Sosman JA, Little S, Sun P, Aktan G, Ouellet D, Jin F, Long GV, Daud A. Characteristics of pyrexia in BRAFV^{600E}/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. Ann Oncol. 2015 Feb;26(2):415-21. doi: 10.1093/annonc/mdu529. Epub 2014 Nov 18. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion Sileni V, Lebbe C, Mandala M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Casey M, Ouellet D, Martin AM, Le N, Patel K, Flaherty K. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014 Nov 13;371(20):1877-88. doi: 10.1056/NEJMoa1406037. Epub 2014 Sep 29.					
Algazi A.P, M. Othus, A. I. Daud, R. S. Lo, J. M. Mehnert, T. G. Truong, et al. Continuous versus intermittent BRAF and MEK inhibition in patients with BRAF-mutated melanoma: a randomized phase 2 trial. Nat Med 2020 Vol. 26 Issue 10 Pages 1564-1568	Algazi, et al., 2020 Recruitment: Sep. 2014 - 16 April 2019 Trial ID: NCT02196181	phase II RCT open-label multicentre: 68 academic and community sites	Metastatic and unresectable BRAF V600 melanoma	TT(dab+tra)cont vs. TT(dab+tra)inter (BRAF+MEK inhibitors)	F-U: med. 2 yrs. Age: 61 (range: 20-88) %male: 64

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Ascierto P.A, M. Mandala, P. F. Ferrucci, M. Guidoboni, P. Rutkowski, V. Ferraresi, et al. Sequencing of Ipilimumab Plus Nivolumab and Encorafenib Plus Binimetinib for Untreated BRAF-Mutated Metastatic Melanoma (SECOMBIT): A Randomized, Three-Arm, Open-Label Phase II Trial. J Clin Oncol 2022 Pages JCO2102961	Ascierto, et al., 2022 Recruitment: Nov 2016 to May 2019 **SECOMBIT Trial** Trial ID: NCT02631447	Phase II RCT Multicentre: 37 centers in 9 countries	Untreated, metastatic BRAFV600 mutated melanoma	TT(enc+bin)>imm(ipi+niv) vs. Imm(ipi+niv)>TT(enc+bin) vs. TT(enc+bin) >imm(ipi+niv)>TT(enc+bin)	F-U: 1 yr Age: 55 (19-77) vs 55 (18-81) vs 51 (28-80) %male:~~NR~~ 60.9% vs 47.9% vs 60.9% median follow-up of 32.2 months (interquartile range, 27.9-41.6 months)
Chapman, C. Robert, J. Larkin, J. B. Haanen, A. Ribas, D. Hogg, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol 2017 Vol. 28 Issue 10 Pages 2581-2587	Chapman, et al., 2017 Recruitment: NR Jan. 2010 - Dec. 2010 **BRIM-3 Trial** Trial ID: NCT01006980	Phase III RCT Open-label Multicentre	BRAFV600 mutation-positive metastatic melanoma	TT(vem) vs. Chem(dac)	F-U: NR Med. Age: 52 (17–86) vs. 56 (21–86) %male: 54% vs. 59%

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Dreno, P. A. Ascierto, V. Atkinson, G. Liszkay, M. Maio, M. Mandala, et al.. Health-related quality of life impact of cobimetinib in combination with vemurafenib in patients with advanced or metastatic BRAFV600 mutation-positive melanoma. British Journal of Cancer 2018 Vol. 118(6) Pages 777-784 Larkin J, Ascierto PA, Dre´no B, Atkinson V, Liszkay G, Maio M, Demidov L, Stroyakovskiy D, Thomas L, de la Cruz-Merino L, Dutriaux C, Garbe C, Sovak MA, Chang I, Choong N, Hack SP, McArthur GA, Ribas A (2014) MEK pathway inhibition effect on QOL in melanoma Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 371: 1867–1876.	Dreno, et al., 2018 Recruitment: Jan. 2013 – Jan. 2014 **coBRIM Trial** Trial ID: NCT01689519	Phase III RCT Closed-label Multicentre: 133 sites in 19 countries	advanced or metastatic BRAFV600 mutation-positive melanoma	TT(cobi+vem) vs. plac+TT(vem)	F-U: NR Age: NR %male: NR
Gutzmer, D. Stroyakovskiy, H. Gogas, C. Robert, K. Lewis, S. Protsenko, et alAtezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF^{V600} mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020 Vol. 395(10240) Pages 1835-1844	Gogas, et al., 2021 Recruitment: Dec. 2017 – Jan. 2019 **IMspire170 Trial**	Phase III RCT Open label International	previously untreated BRAFV600 wild-type advanced melanoma	TT(cobi)+Imm(ate) vs. Imm(pem)	F-U: med. Overall 18.9 mo (IQR 10.4-23.8) Med. Age: 54 (54-73) vs. 53.5 (55-73) %male: 59% vs. 58%

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19(10):1315-27. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603-15 Dummer R, Flaherty KT, Robert C, Arance A, de Groot JWB, Garbe C, et al. COLUMBUS 5-Year Update: A Randomized, Open-Label, Phase III Trial of Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With BRAF V600-Mutant Melanoma. J Clin Oncol. 2022:JCO2102659 Ascierto PA, Dummer R, Gogas HJ, Flaherty KT, Arance A, Mandala M, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. Eur J Cancer. 2020;126:33-44.	Various Citations **COLOMBUS Trial** Trial ID: NCT01909453	Phase III RCT Open-label Multicentred: 162 hospitals in 28 countries	Patients with advanced/metastatic BRAF V600-mutant melanoma untreated or progressed after first-line immunotherapy	TT+TT(enc+bin) vs. TT(enc) vs. TT(vem)	F-U: med. 36.8 mos. (35.9-37.5) Med. Age: 57 (20-89) vs. 54 (23-88) vs. 56 (21-82) %male: 60% vs. 56% vs. 58%

Citation	Study Citation and Trial Name	Study Type	Population	Treatment Summary	Follow-up
Dummer, D. Schadendorf, P. A. Ascierto, A. Arance, C. Dutriaux, A. M. Di Giacomo, et al.Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017 Vol. 18(4) Pages 435-445	Dummer, et al., 2017 Recruitment: Aug. 2013 – Apr. 2015 **NEMO Trial** Trial ID: NCT01763164	Phase III RCT Open-label Multicentred: 118 hospitals in 26 countries.	advanced, unresectable, American Joint Committee on Cancer stage IIIC or stage IV NRAS-mutant melanoma who were previously untreated or had progressed on or after previous immunotherapy	TT(bin) vs. Chem(dac)	F-U: 1.7 mos. (IQR 1.4 – 4.1) Med. age: 65 (18-90) vs. 62 (27-89) %male: 62% vs. 64%

Abbreviations: ate, atezolizumab; bin, binimetinib; cobi, cobimetinib; cont, continuous; dab, dabrafenib; dac, dacarbazine; enc, encorafenib; F-U, follow-up; imm, immunotherapy; inter, intermittent; ipi, ipilimumab; IQR, interquartile range; ivo, med, median; mos, months; niv, nivolumab; NR, not reported; pac, paclitaxel; pem, pembrolizumab; RCT, randomized controlled trial; sparta, spartalizumab; tra, trametinib; TT, targeted therapy; vem, vemurafenib

TABLE 4-3. Studies Evaluating Dosing and Administration Schedules

Citation	Author	Methods	Population	Treatment Summary	Follow-up patient Characteristics
Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480-92. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022;40(2):127-37. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017;377(14):1345-56.	Various Citations **CHECKMATE-067 Trial** Trial ID: NCT01844505	Phase III RCT Double-blind Multicentred: 137 centres from 21 countries	Previously untreated, unresectable, stage III or stage IV melanoma, known BRAFV600 mutation status, and an Eastern Cooperative Oncology Group performance status of 0 or 1.	Imm(niv+ipi) vs. imm(niv)+placebo vs. imm(ipi)+placebo	F-U: 4-yrs Age: 61 {51-70) vs. 60 (50-68) vs. 62 (52-71) %male: 66% vs. 64% vs. 64%

Citation	Author	Methods	Population	Treatment Summary	Follow-up patient Characteristics
Atkins MB, Carlino MS, Hill AG, McNeil CM, Long GV, Atkinson V, et al. KEYNOTE 029: A phase I/II randomized trial of pembrolizumab (pembro) plus 2 dose regimens of ipilimumab (ipi) for advanced melanoma. Cancer Research Conference: American Association for Cancer Research Annual Meeting. 2017;77(13 Supplement 1). Carlino MS, Menzies AM, Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, et al. Long-term Follow-up of Standard-Dose Pembrolizumab Plus Reduced-Dose Ipilimumab in Patients with Advanced Melanoma: KEYNOTE-029 Part 1B. Clin Cancer Res. 2020;26(19):5086-91.	**KEYNOTE-029** NCT02089685	Phase 1b trial	Adults with histologically confirmed unresectable stage III–IV melanoma	pem 2 mg/kg i.v. once every 3 weeks with ipi 1 mg/kg i.v. once every 3 weeks for four doses, followed by pem 2 mg/kg once every 3 weeks for up to 2 years or until disease progression	

Citation	Author	Methods	Population	Treatment Summary	Follow-up patient Characteristics
Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19(10):1315-27. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603-15 Dummer R, Flaherty KT, Robert C, Arance A, de Groot JWB, Garbe C, et al. COLUMBUS 5-Year Update: A Randomized, Open-Label, Phase III Trial of Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With BRAF V600-Mutant Melanoma. J Clin Oncol. 2022:JCO2102659 Ascierto PA, Dummer R, Gogas HJ, Flaherty KT, Arance A, Mandala M, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. Eur J Cancer. 2020;126:33-44.	Various Citations **COLOMBUS Trial** Trial ID: NCT01909453	Phase III RCT Open-label Multicentred: 162 hospitals in 28 countries	patients with advanced/metastatic BRAF V600-mutant melanoma untreated or progressed after first-line immunotherapy	TT+TT(enc+bin) vs. TT(enc) vs. TT(vem)	F-U: med. 36.8 mos. (35.9-37.5) Med. Age: 57 (20-89) vs. 54 (23-88) vs. 56 (21-82) %male: 60% vs. 56% vs. 58%

Citation	Author	Methods	Population	Treatment Summary	Follow-up patient Characteristics
Lebbé, N. Meyer, L. Mortier, I. Marquez-Rodas, C. Robert, P. Rutkowski, 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 Vol. 37 Issue 11 Pages 867-875	Lebbé, et al., 2019 Recruitment: Apr. 2016 – Mar. 2017 **CheckMate 511** Trial ID: NCT02714218	Phase IIIb/IV RCT Double-blind Multi-centred: 57 sites, 13 counties	Previously untreated, unresectable stage III or IV melanoma	Imm(niv3+ipi1) vs. Imm(niv1+ipi3)	F-U med. 12 mos. Med. Age: 58.5 (19-85) vs. 58.5 (26-85) %male: 58.3% vs. 56.7%
Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908-18.	KEYNOTE-002	International RCT phase 2 clinical trial		Patients were randomly assigned (1:1:1) to pem 2 mg/kg or pem 10 mg/kg i.v. every 3 weeks or investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin [eliminated with protocol amendment one], dacarbazine, or oral temozolomide)	

Citation	Author	Methods	Population	Treatment Summary	Follow-up patient Characteristics
Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390(10105):1853-62.	KEYNOTE-006	KEYNOTE-006 was a multi-centre, open-label, randomized, controlled, phase 3 study done at 87 academic institutions, cancer centres, and hospitals in 16 countries	Aged at least 18 years, with an Eastern Cooperative Oncology Group (ECOG) perfor- mance status of 0 or 1, at least one measurable lesion per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), unresectable stage III or IV melanoma	Patients were randomly assigned 1:1:1 to receive intravenous pem 10 mg/kg every 2 or 3 weeks or i.v. ipi 3 mg/kg every 3 weeks for four doses (ipi only). Treatment was given for 2 years (pem groups only) or until disease progression, intolerable toxicity, complete response, patient withdrawal of consent, or investigator decision to discontinue treatment.	Med. follow-up was 22.9 months

Abbreviations: bin, binimetinib; enc, encorafenib; imm, immunotherapy; ipi, ipilimumab; i.v., intravenous; med, median; mos, months; niv, nivolumab; pem, pembrolizumab; RCT, randomized controlled trial; TT, targeted therapy; vem, vemurafenib

TABLE 4-5. Studies Evaluating Sequencing

Citation	Author	Methods	Population	Treatment Summary	Followup patient Characteristics
Ascierto P.A, M. Mandala, P. F. Ferrucci, M. Guidoboni, P. Rutkowski, V. Ferraresi, et al. Sequencing of Ipilimumab Plus Nivolumab and Encorafenib Plus Binimetinib for Untreated BRAF-Mutated Metastatic Melanoma (SECOMBIT): A Randomized, Three-Arm, Open-Label Phase II Trial. J Clin Oncol 2022 Pages JCO2102961	Ascierto, et al., 2022 Recruitment: Nov 2016 to May 2019 **SECOMBIT Trial** Trial ID: NCT02631447	Phase II RCT Multicentre: 37 centers in 9 countries	Untreated, metastatic BRAFV600 mutated melanoma	TT(enc+bin)>imm(ipi+niv) vs. Imm(ipi+niv)>TT(enc+bin) vs. TT(enc+bin) >imm(ipi+niv)>TT(enc+bin)	F-U: 1 yr Age: NR %male:NR median follow-up of 32.2 months (interquartile range, 27.9-41.6 months)
Atkins, S. J. Lee, B. Chmielowski, A. A. Tarhini, G. I. Cohen, T. G. Truong, et al Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: The DREAMseq Trial - ECOG-ACRIN EA6134. J Clin Oncol 2022 Pages 101200JCO2201763	Atkins et al, 2023 **DREAMseq** Trial ID: NCT02224781	Phase III RCT; multicenter	Unresectable stage III or stage IV; BRAF V600 mutation	Sequential	F-U: every 3 months for 2 years and then every 6 months for 3 years.
Olson DJ, Eroglu Z, Brockstein B, Poklepovic AS, Bajaj M, Babu S, et al. Pembrolizumab Plus Ipilimumab Following Anti-PD-1/L1 Failure in Melanoma. J Clin Oncol. 2021;39(24):2647-55.	Trial ID: NCT02743819.	Open-label, single-arm phase II trial	Unresectable or metastatic melanoma with known BRAF mutation status. All patients must have experienced disease progression during treatment with an anti-PD-1/L1 antibody immediately before accrual to this study or disease progression within 6 months of adjuvant anti-PD-1 antibody without intercurrent therapy.	Patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody as immediate prior therapy (including non-anti-CTLA-4 antibody combinations) were eligible. Patients eceived pem 200 mg plus ipi 1 mg/kg once every 3 weeks for four doses, followed by pem monotherapy.	Med F-U 12.0 months

Citation	Author	Methods	Population	Treatment Summary	Followup patient Characteristics
Betof Warner A, Palmer JS, Shoushtari AN, Goldman DA, Panageas KS, Hayes SA, et al. Long-Term Outcomes and Responses to Retreatment in Patients With Melanoma Treated With PD-1 Blockade. J Clin Oncol. 2020;38(15):1655-63.	-	Retrospective	Confirmed diagnosis of advanced melanoma (unresectable stage III or stage IV), and received >1 dose of single- agent anti-PD-1 therapy (niv or pem), followed by >1 scan that could be evaluated for response to therapy	Single-agent anti-PD-1 therapy at Memorial Sloan Kettering from 2009-2018 who had discontinued treatment and had at least 3 months of follow-up after discontinuation (n = 396).	

Abbreviations: bin, binimetinib; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; enc, encorafenib; ipi, ipilimumab; i.v., intravenous; med, median; mos, months; niv, nivolumab; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pem, pembrolizumab; RCT, randomized controlled trial; TT, targeted therapy; vem, vemurafenib

Appendix 5: AMSTAR and Risk of Bias Assessments

ITEM	Pasquali et al, 2018	Steeb et al, 2021
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y	Y
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Y	Y
4. Did the review authors use a comprehensive literature search strategy?	Y	Y
5. Did the review authors perform study selection in duplicate?	Y	Y
6. Did the review authors perform data extraction in duplicate?	Y	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Y	Y
8. Did the review authors describe the included studies in adequate detail?	Y	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y	Y
10. Did the review authors report on the sources of funding for the studies included in the review?	Y	Y
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y	-
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y	-
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y	Y
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y	Y
AMSTAR ASSESSMENT	**HIGH**	**HIGH**

Risk of bias for included randomized controlled trials assessed using Cochrane's Risk of Bias tool (RoB2)

Study	Type of Systemic Therapy	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall Assessment
AlgaziOCE, et al., 2020 Recruitment: Sep. 2014 - 16 April 2019 Trial ID: NCT02196181	Targeted Therapy	TT(dab+tra)cont vs. TT(dab+tra)inter (BRAF+MEK inhibitors)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Andtbacka, et al., 2019 Andtbacka, et al., 2015 Recruitment: 2009-2011 OPTiM Trial Trial ID: NCT01515189.	Immunotherapy	imm (T-VEC) vs. other (GM-CSF)	PFS	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
			OS	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Ascierto, et al., 2020a Ascierto, et al., 2017 Recruitment: Feb. 2012 – July 2012 Trial ID: NCT01515189	Immunotherapy	Imm(Ipi10) vs. Imm(ipi3)	PFS	NA	NA	NA	NA	NA	NA	NA
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Ascierto, et al., 2022 Recruitment: Nov 2016 to May 2019 SECOMBIT Trial Trial ID: NCT02631447)	Targeted Therapy	TT(enc+bin)>imm(ipi+niv) vs. Imm(ipi+niv)>TT(enc+bin) vs. TT(enc+bin)>imm(ipi+niv)>TT(enc+bin)	PFS	Low	Some Concerns	Some Concerns	Low	Some Concerns	Low	Some Concerns
			OS	Low	Some Concerns	Some Concerns	Low	Some Concerns	Low	Some Concerns
			AE	Low	Some Concerns	Some Concerns	Low	Some Concerns	Low	Some Concerns
Atkins et al, 2023	Targeted Therapy	Arm A: combination nivolumab/ipilimumab	PFS	NA	NA	NA	NA	NA	NA	NA

Study	Type of Systemic Therapy	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall Assessment
DREAMseq Trial ID: NCT02224781		(Arm A) or Arm B: dabrafenib/trametinib At disease progression were enrolled in Step 2 Arm C: dabrafenib/trametinib Arm D: nivolumab/ipilimumab	OS	NA	NA	NA	NA	NA	NA	NA
			AE	Low	Low	Some Concerns	Some Concerns	Some Concerns	Some Concerns	Some Concerns
Chapman, et al., 2017 Recruitment: NR Jan. 2010 - Dec. 2010 BRIM-3 Trial Trial ID: NCT01006980	Targeted Therapy	TT(vem) vs. Chem(dac)	PFS	NA	NA	NA	NA	NA	NA	NA
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Chesney, et al., 2018 Puzanov, et al., 2020 (Abstract) Recruitment: Aug. 2013 – Feb. 2016	Immunotherapy	Imm(T-VEC+ipi) vs. imm(ipi)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
D'Angelo, et al., 2018 Recruitment: May 2011 – Dec. 2013	Immunotherapy (second-line)	Imm(ont2) vs. Imm(ont4)	PFS	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
			OS	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Dreno, et al., 2018 Larkin et al, 2014 Recruitment: Jan. 2013 – Jan. 2014 coBRIM Trial Trial ID: NCT01689519	Targeted Therapy	TT(cobi+vem) vs. plac+TT(vem)	Assessed in Pasquali et al (2018)							

Study	Type of Systemic Therapy	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall Assessment
Dummer, et al., 2017 Recruitment: Aug. 2013 – Apr. 2015 NEMO Trial Trial ID: NCT01763164	Targeted Therapy (NRAS)	TT(bin) vs. Chem(dac)	PFS	Low	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns
			OS	Low	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns
			AE	Low	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns
Gutzmer, et al., 2020 Recruitment: Dec. 2017 – Jan. 2019 IMspire150 Trial	Targeted Therapy/Immunotherapy	TT(obi)+Imm(ate) vs. Imm(pem)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	High	Low	Low	Low	Low
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Gogas, et al., 2021 Recruitment: Dec. 2017 – Jan. 2019 IMspire170 study	Targeted Therapy/Immunotherapy	TT(cobi)+TT(ate)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	NA	NA	NA	NA	NA	NA	NA
			AE	Low	Low	Low	Low	Low	Low	Low
Hodi et al 2016 Postow et al 2015	Immunotherapy	imm(niv+ipi) vs imm(ipi)+placebo	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Some Concern	Low	Low	Low	Some Concerns
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Larkin et al, 2022 Weber et al 2015 CHECKMATE 037 Trial ID: NCT01721746	Immunotherapy	Imm(niv) vs. chem(dac or car)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Lebbé, et al., 2019	Immunotherapy	Imm(niv3+ipi1) vs. Imm(niv1+ipi3)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low

Study	Type of Systemic Therapy	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall Assessment
Recruitment: Apr. 2016 – Mar. 2017 CheckMate 511 Trial ID: NCT02714218			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Long et al, 2018 ABC Trial Trial ID: NCT02374242	Immunotherapy	Imm (niv1+ipi3/3 weeks)+(niv3/2 weeks) vs. Imm (niv3/2 weeks)	PFS	NA	NA	NA	NA	NA	NA	NA
			OS	NA	NA	NA	NA	NA	NA	NA
			AE	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns	Some Concerns
Long, et al., 2018 Recruitment NR - Oct. 2016 BRF113220 Trial; Part C Trial ID: NCT02374242	Targeted Therapy	TT(dab) vs. TT(dab+tra/1) vs. TT(dab+tra/2)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Long, et al., 2019 Recruitment: June 2016 – Aug. 2017 ECHO-301/KEYNOTE-252 Trial Trial ID: NCT02752074	Immmunotherapy	Other(epa+imm(pem) vs. pl+imm(pem)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Robert et al., 2019 Recruitment: Dec. 2010 – Jul. 2011 METRIC Trial	Targeted Therapy	TT(tra) vs. chem (dac+pac)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	High	Low	Low	Low	Low
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns

Study	Type of Systemic Therapy	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall Assessment
Trial ID: NCT01245062										
Tarhini et al 2019 E3611 Trial Trial ID: NCT01708941	Immunotherapy	Imm (HD ipi + HDI) vs. Imm (ipi) vs. Imm (LD ipi +HDI) vs. Imm (LD ipi)	PFS	NA	NA	NA	NA	NA	NA	NA
			OS	NA	NA	NA	NA	NA	NA	NA
			AE	Low	Some Concerns	Some Concerns	Some Concerns	Some Concerns	Some Concerns	Some Concerns
Twabi et al 2022 REALTIVITY-047 TRIAL ID: NCT03470922	Immunotherapy	Imm(rel+niv) vs. Imm(niv)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	NA	NA	NA	NA	NA	NA	NA
			AE	Low	Low	Low	Some Concerns	Low	Low	Low
Ugurel, et al., 2017 Recruitment: Nov. 2008 – Oct. 2012 DeCOG trial	Immunotherapy	chemo vs. imm (dac)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Some Concerns	Low	Low	Low	Some Concerns
			AE	Low	Low	Low	Some Concerns	Low	Low	Some Concerns
Various Citations CHECKMATE-067 Trial Trial ID: NCT01844505	Targeted Therapy	Imm(niv+ipi) vs. imm(niv)+placebo vs. imm(ipi)+placebp	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Various Citations COLOMBUS Trial Trial ID: NCT01909453	Targeted Therapy	TT+TT(enc+bin) vs. TT(enc) vs. TT(vem)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Various Citations COMBI-i Trial	Targeted Therapy	Spartalizumab or placebo in combination with dab and tra	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low

Study	Type of Systemic Therapy	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall Assessment
Trial ID: NCT02967692			AE	Low	Low	Low	Low	Low	Low	Low
Various Citations Robert et al 2015 previously included in Cochrane Review UPDATED 5-YEAR SURVIVAL RATES AVAILABLE CheckMate 066 Trial ID: NCT01721772	Targeted Therapy	imm(niv) vs chem(dac)	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Various Citations Recruitment: NR - Feb. 2016 Long et al was previously included in Cochrane review; updated results available COMBI-d trial Trial ID: NCT01584648	Targeted Therapy	TT(dab+tra) vs. TT(dab)+placebo	PFS	Low	Low	Low	Low	Low	Low	Low
			OS	Low	Low	Low	Low	Low	Low	Low
			AE	Low	Low	Low	Low	Low	Low	Low
Various Citations Recruitment: Sep. 2013 – Mar. 2014	Immunotherapy	Imm(pem2) vs. Imm(pem3) vs. Imm(ipi)	PFS	Low	Low	Low	Low	Low	Low	

Study	Type of Systemic Therapy	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall Assessment
Robert et al (2015) included in Cochrane review. Updated results available in Schacter et al (2017) KEYNOTE-006 Trial Trial ID: NCT01866319			OS	Low	Low	Low	Low	Low	Low	
			AE	Low	Low	Low Lw	Some Concerns	Low	Low	Low
Algazi, et al., 2020 Recruitment: Sep. 2014 - 16 April 2019 Trial ID: NCT02196181	Targeted Therapy	TT(dab+tra)cont vs. TT(dab+tra)inter (BRAF+MEK inhibitors)	PFS	Low	Low	Some Concerns	Low	Low	Low	Some Concerns
			OS	Low	Low	Some Concerns	Low	Low	Low	Some Concerns
			AE	Low	Low	Some Concerns	Low	Low	Low	Some Concerns

Abbreviations: AE, adverse events; ate, atezolizumab; bin, binimetinib; car, carboplatin; chem, chemotherapy; cobi, cobimetinib; cont, continuous; dab, dabrafenib; dac, dacarbazine; enc, encorafenib; epa, epacadostat; GM-CSF, granulocyte-macrophage colony-stimulating factor; HD, high-dose; HDI, high-dose interleukin-2; imm, immunotherapy; inter, intermittent; ipi, ipilimumab; LD, low dose; NA, not available; ont, ontuxizumab; OS, overall survival; pac, paclitaxel; pem, pembrolizumab; PFS, progression-free survival; rel, relatlimab; TT, targeted therapy; tra, trametinib; T-VEC, talimogene laherparepvec; vem, vemurafenib

Appendix 6: Future Research (Detailed Table)

NCT Number	Study Title	Study URL	Study Status	Conditions	Interventions	Sponsor	Collaborators	Study Type
NCT06346067	A Study to Assess Naporafenib (ERAS-254) Administered with Trametinib in Patients With NRAS-mutant Melanoma (SEACRAFT-2)	https://clinicaltrials.gov/study/NCT06346067	RECRUITING	Advanced or Metastatic NRAS-mutant Melanoma	DRUG: Naporafenib|DRUG: Dacarbazine|DRUG: Temozolomide|DRUG: Trametinib	Erasca, Inc.		INTERVENTIONAL
NCT06320353	Study —Comparing the Efficacy and Safety of RPH-075 and Keytruda® in Patients with Unresectable or Metastatic Skin Melanoma	https://clinicaltrials.gov/study/NCT06320353	ACTIVE_NOT_RECRUITING	Skin Melanoma	DRUG: RPH-075|DRUG: Keytruda®	R-Pharm	Data Management 365|Exacte Labs LLC|Federal State Budgetary Institution of the Central Research Institute of Epidemiology of Rospotrebnadzor	INTERVENTIONAL
NCT06054555	A Study to Evaluate ABP 206 Compared With OPDIVO® (Nivolumab) in Subjects with Unresectable or Metastatic Melanoma	https://clinicaltrials.gov/study/NCT06054555	RECRUITING	Melanoma	DRUG: ABP 206|DRUG: Nivolumab	Amgen		INTERVENTIONAL
NCT05933577	A Clinical Study of V940 Plus Pembrolizumab in People with High-Risk Melanoma (V940-001)	https://clinicaltrials.gov/study/NCT05933577	RECRUITING	Melanoma	BIOLOGICAL: V940|BIOLOGICAL: Pembrolizumab|OTHER: Placebo	Merck Sharp & Dohme LLC	ModernaTX, Inc.	INTERVENTIONAL
NCT05783882	Prolgolimab 250 mg Q3W in Patients with Unresectable or Metastatic Melanoma	https://clinicaltrials.gov/study/NCT05783882	ACTIVE_NOT_RECRUITING	Unresectable or Metastatic Melanoma	DRUG: Prolgolimab	Biocad		INTERVENTIONAL
NCT05732805	A Clinical Study of BCD-217 (Nurulimab + Prolgolimab) Followed by Anti-PD-1 Compared to Anti-PD-1 Monotherapy as First-Line Treatment in Subjects with Unresectable/Metastatic Melanoma	https://clinicaltrials.gov/study/NCT05732805	RECRUITING	Melanoma|Melanoma (Skin)|Melanoma Stage III|Melanoma Stage IV|Melanoma Unresectable|Melano	BIOLOGICAL: BCD-217|BIOLOGICAL: BCD-100|BIOLOGICAL: Placebo	Biocad		INTERVENTIONAL

NCT Number	Study Title	Study URL	Study Status	Conditions	Interventions	Sponsor	Collaborators	Study Type
				ma Metastatic|Melanoma Advanced				
NCT05727904	Study to Investigate Lifileucel Regimen Plus Pembrolizumab Compared with Pembrolizumab Alone in Participants with Untreated Advanced Melanoma.	https://clinicaltrials.gov/study/NCT05727904	RECRUITING	Metastatic Melanoma|Unresectable Melanoma|Melanoma	BIOLOGICAL: Lifileucel plus Pembrolizumab|BIOLOGICAL: Pembrolizumab with Optional Crossover Period	Iovance Biotherapeutics, Inc.		INTERVENTIONAL
NCT05625399	A Study of Subcutaneous Nivolumab + Relatlimab Fixed-dose Combination (FDC) in Previously Untreated Metastatic or Unresectable Melanoma	https://clinicaltrials.gov/study/NCT05625399	RECRUITING	Melanoma	DRUG: Nivolumab + Relatlimab|DRUG: rHuPH20	Bristol-Myers Squibb		INTERVENTIONAL
NCT05522660	Immunotherapy or Targeted Therapy with or Without Stereotactic Radiosurgery for Patients with Brain Metastases rrom Melanoma or Non-small Cell Lung Cancer	https://clinicaltrials.gov/study/NCT05522660	RECRUITING	Non-Small Cell Lung Cancer|Melanoma	RADIATION: Stereotactic radiosurgery|DRUG: Immune checkpoint inhibitor	ETOP IBCSG Partners Foundation	USZ Foundation	INTERVENTIONAL
NCT05352672	Clinical Study of Fianlimab in Combination with Cemiplimab Versus Pembrolizumab in Adolescent and Adult Patients with Previously Untreated Unresectable Locally Advanced or Metastatic Melanoma	https://clinicaltrials.gov/study/NCT05352672	RECRUITING	Melanoma	DRUG: Fianlimab|DRUG: Cemiplimab|DRUG: Pembrolizumab|DRUG: Placebo	Regeneron Pharmaceuticals		INTERVENTIONAL
NCT05155254	IO102-IO103 in Combination with Pembrolizumab Versus Pembrolizumab Alone in Advanced Melanoma (IOB-013 / KN-D18)	https://clinicaltrials.gov/study/NCT05155254	ACTIVE_NOT_RECRUITING	Metastatic Melanoma|Unresectable Melanoma	DRUG: IO102-IO103|DRUG: Pembrolizumab	IO Biotech	Syneos Health|Merck Sharp & Dohme LLC	INTERVENTIONAL
NCT05022901	An Open-Label Expanded Access Study of the Melphalan/Hepatic Delivery System (HDS) in Patients	https://clinicaltrials.gov/study/NCT05022901	ACTIVE_NOT_RECRUITING	Metastatic Ocular Melanoma|Metastatic	COMBINATION_PRODUCT: Melphalan (3 mg/kg IBW) with	Delcath Systems Inc.		INTERVENTIONAL

NCT Number	Study Title	Study URL	Study Status	Conditions	Interventions	Sponsor	Collaborators	Study Type
	wth Hepatic Dominant Ocular Melanoma			Uveal Melanoma	Hepatic Delivery System (HDS)			
NCT04695977	CMP-001 in Combination with Nivolumab Compared to Nivolumab Monotherapy in Subjects with Advanced Melanoma	https://clinicaltrials.gov/study/NCT04695977	ACTIVE_NOT_RECRUITING	Melanoma|Advanced Melanoma|Metastatic Melanoma|Unresectable Melanoma	DRUG: CMP-001|DRUG: Nivolumab	Regeneron Pharmaceuticals	Bristol-Myers Squibb	INTERVENTIONAL
NCT04674683	Study Comparing Investigational Drug HBI-8000 + Nivolumab vs. Placebo + Nivolumab in Patients with Advanced Melanoma	https://clinicaltrials.gov/study/NCT04674683	ACTIVE_NOT_RECRUITING	Unresectable or Metastatic Melanoma|Progressive Brain Metastasis	DRUG: HBI-8000 in combination with nivolumab|DRUG: Placebo in combination with nivolumab	HUYABIO International, LLC.	Bristol-Myers Squibb	INTERVENTIONAL
NCT04657991	A Clinical Trial of Three Study Medicines (Encorafenib, Binimetinib, and Pembrolizumab) in Patients with Advanced or Metastatic Melanoma	https://clinicaltrials.gov/study/NCT04657991	ACTIVE_NOT_RECRUITING	Melanoma	DRUG: Encorafenib|DRUG: Binimetinib|DRUG: Pembrolizumab	Pfizer	Merck Sharp & Dohme LLC	INTERVENTIONAL
NCT03715205	Study to Evaluate the Safety of Pembrolizumab in Participants with Unresectable or Metastatic Melanoma or Non-small Cell Lung Cancer in India (MK-3475-593/KEYNOTE-593)	https://clinicaltrials.gov/study/NCT03715205	ACTIVE_NOT_RECRUITING	Carcinoma, Non-Small-Cell Lung|Melanoma	DRUG: Pembrolizumab	Merck Sharp & Dohme LLC		INTERVENTIONAL
NCT03470922	A Study of Relatlimab Plus Nivolumab Versus Nivolumab Alone in Participants with Advanced Melanoma	https://clinicaltrials.gov/study/NCT03470922	ACTIVE_NOT_RECRUITING	Melanoma	BIOLOGICAL: Relatlimab|BIOLOGICAL: Nivolumab	Bristol-Myers Squibb		INTERVENTIONAL
NCT03430297	A Randomized, Controlled, Multi-center, Phase III Clinical Study to Investigate Recombinant Humanized PD-1 Monoclonal Antibody Injection (JS001) Versus Dacarbazine as the 1st-line Therapy	https://clinicaltrials.gov/study/NCT03430297	ACTIVE_NOT_RECRUITING	Metastatic Melanoma|Unresectable Melanoma	BIOLOGICAL: JS001 240mg Q2W|DRUG: Dacarbazine 1000mg/m2 Q3W	Shanghai Junshi Bioscience Co., Ltd.		INTERVENTIONAL

NCT Number	Study Title	Study URL	Study Status	Conditions	Interventions	Sponsor	Collaborators	Study Type
	for Unresectable or Metastatic Melanoma							
NCT02967692	A Study of the Anti-PD-1 Antibody PDR001, in Combination with Dabrafenib and Trametinib in Advanced Melanoma	https://clinicaltrials.gov/study/NCT02967692	ACTIVE_NOT_RECRUITING	Melanoma	BIOLOGICAL: Spartalizumab|OTHER: Placebo|DRUG: Dabrafenib|DRUG: Trametinib	Novartis Pharmaceuticals		INTERVENTIONAL
NCT02821013	Duration of Anti-PD-1 Therapy in Metastatic Melanoma	https://clinicaltrials.gov/study/NCT02821013	RECRUITING	Unresectable/Metastatic Melanoma	DRUG: Intermittent PD-1 inhibitor therapy|DRUG: Continuous PD-1 inhibitor therapy	Canadian Cancer Trials Group	Melanoma and Skin Cancer Trials Limited	INTERVENTIONAL
NCT02278887	Study Comparing TIL to Standard Ipilimumab in Patients with Metastatic Melanoma	https://clinicaltrials.gov/study/NCT02278887	ACTIVE_NOT_RECRUITING	Metastatic Melanoma	PROCEDURE: Translational research|DRUG: Cyclophosphamide|DRUG: Fludarabine|DRUG: Interleukin-2|DRUG: Ipilimumab infusion	The Netherlands Cancer Institute	Copenhagen University Hospital at Herlev	INTERVENTIONAL
NCT02224781	Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients with Stage III-IV BRAFV600 Melanoma	https://clinicaltrials.gov/study/NCT02224781	ACTIVE_NOT_RECRUITING	Clinical Stage III Cutaneous Melanoma AJCC v8|Clinical Stage IV Cutaneous Melanoma AJCC v8|Metastatic Melanoma|Recurrent Melanoma|Unresectable Melanoma	PROCEDURE: Biospecimen Collection|PROCEDURE: Computed Tomography|DRUG: Dabrafenib Mesylate|PROCEDURE: Echocardiography|BIOLOGICAL: Ipilimumab|PROCEDURE: Multigated Acquisition Scan|BIOLOGICAL: Nivolumab|OTHER: Quality-of-Life Assessment|DRUG:	National Cancer Institute (NCI)		INTERVENTIONAL

NCT Number	Study Title	Study URL	Study Status	Conditions	Interventions	Sponsor	Collaborators	Study Type
					Trametinib Dimethyl Sulfoxide			
NCT02068196	A National Phase IV Study with Ipilimumab for Patients with Advanced Malignant Melanoma.	https://clinicaltrials.gov/study/NCT02068196	ACTIVE_NOT_RECRUITING	Malignant Melanoma	PROCEDURE: Blood sampling for Pre-existing immunity|DRUG: Ipilimumab	Oslo University Hospital		INTERVENTIONAL
NCT01844505	Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma (CheckMate 067)	https://clinicaltrials.gov/study/NCT01844505	ACTIVE_NOT_RECRUITING	Unresectable or Metastatic Melanoma	BIOLOGICAL: Nivolumab|BIOLOGICAL: Ipilimumab|BIOLOGICAL: Placebo for Nivolumab|BIOLOGICAL: Placebo for Ipilimumab	Bristol-Myers Squibb		INTERVENTIONAL