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Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent Melanoma

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A targeted update of the Guideline was conducted in November 2023. As a result of this update, a new recommendation (Recommendation1B) has been added. The PEBC has a formal and standardized process to ensure the currency of each document
PEBC Assessment & Review Protocol

Guideline 8-1 Version 6 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1161

Section 1: Guideline Recommendations
Section 2: Recommendations and Key Evidence
Section 3: Guideline Methods Overview
Section 4: Systematic Review
Section 5: Internal and External Review

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PUBLICATIONS RELATED TO THIS REPORT

Petrella TM, Fletcher GG, Knight G, McWhirter E, Rajagopal S, Song X, Baetz TD. Systemic adjuvant therapy for adult patients at high risk for recurrent cutaneous or mucosal melanoma: An Ontario Health (Cancer Care Ontario) clinical practice guideline. Curr Oncol. 2020;27(1):e43-e52. https://doi.org/10.3747/co.27.5933

Baetz TD, Fletcher GG, Knight G, McWhirter E, Rajagopal S, Song X, Petrella TM. Systemic adjuvant therapy for adult patients at high risk for recurrent melanoma: A systematic review. Cancer Treat Rev. 2020;87(July):102032. https://doi.org/10.1016/j.ctrv.2020.102032.

Petrella T, Verma S, Spithoff K, Quirt I, McCready D; Melanoma Disease Site Group. Adjuvant interferon therapy for patients at high risk for recurrent melanoma: An updated systematic review and practice guideline. Clin Oncol (R Coll Radiol). 2012 Aug;24(6):413-23.

Verma S, Quirt I, McCready D, Bak K, Charette M, Iscoe N; on behalf of the Melanoma Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Systematic review of systemic adjuvant therapy for patients at high risk for recurrent melanoma. Cancer. 2006;106(7):1431-42.

Verma S, Quirt I, McCready D, Charette M, Iscoe N; Melanoma Disease Site Group. Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Curr Oncol. 2005;12(2):31-6.

Guideline Document History*

GUIDELINE VERSION	SYSTEMATIC REVIEW Search Dates	SYSTEMATIC REVIEW Data	PUBLICATIONS	NOTES and KEY CHANGES
Version 4 November 7, 2013	July 2008- September 2013	New data appended in Section 4	CCO website	New data appended in Section 4; 2009 recommendations endorsed
Version 4 December 8, 2017	2013 to October 2017	New data replace previous Section 4	CCO website	Section 4 of 2013 version has been relabelled Appendix 1. Recommendations require updating in a new version
Version 5 August 14, 2019	1996- June 2018 trials; 2013-2018 reviews or guidelines	Guideline rewritten	CCO website	Systematic reviews merged, recommendations rewritten
Update of version 5 June 2023	NA	2 Trials added to Section 1 and Section 2 **Only**	Updated web publication on CCO/OH website	Recommendation 1 was updated with evidence from 2 RCTs. For details see **Appendix 10**

*For full Guideline History since the original publication of May 27, 1998, please see Appendix 9

Table of Contents

List of Tables

Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent 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

To make recommendations regarding the use of adjuvant systemic therapy in adult patients with completely resected cutaneous or mucosal melanoma with a high risk of recurrence.

TARGET POPULATION

Adult patients with cutaneous or mucosal melanoma with high risk of recurrence who are rendered disease-free following resection (including resection of all locoregional or distant metastases, if present). Patients with unresected primary disease or metastases fall outside the scope of this document.

INTENDED USERS

Medical oncologists, surgical oncologists, and other health care providers involved in the management and referral of patients with resected melanoma at high risk for recurrence.

RECOMMENDATIONS

A. Cutaneous Melanoma

Recommendation 1a

1a.1 Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected cutaneous melanoma without *BRAF* V600E or V600K mutations with high risk of recurrence (stage IIIA [>1 mm nodal metastasis] to IIID, IV).

1a.2 Nivolumab, pembrolizumab, or dabrafenib plus trametinib is recommended as adjuvant therapy for patients with completely resected cutaneous melanoma with *BRAF* V600E or V600K mutations and high risk of recurrence (stage IIIA [>1 mm nodal metastasis] to IIID, IV).

1a.3 Molecular testing of high-risk melanoma patients to characterize mutations should be conducted to help guide appropriate treatment decisions.

Qualifying Statements for Recommendation 1

- Nivolumab, pembrolizumab, or the combination dabrafenib plus trametinib (for *BRAF* V600E/K mutated melanoma) are all appropriate treatments; there is currently insufficient evidence to suggest which of these is more effective. These agents were evaluated in different trials [1-3] (see Table 4-4) and have not been directly compared in the adjuvant setting. For nivolumab and pembrolizumab, treatment-related adverse

events (AEs) tended to be mild and manageable, and occurred in 85% and 78% of patients, respectively, with the most common being fatigue, skin reactions (rash, pruritus), diarrhea, nausea, and endocrine disorders. Rates of grade 3+ treatment-related AEs (14.4% and 14.7%) resulting in treatment discontinuation (9.7% vs. 13.8%) were similar. The combination dabrafenib plus trametinib resulted in a higher rate of serious AEs (36%), including pyrexia, hypertension, and hepatic effects, and higher rate of discontinuation due to AEs (25%). The spectrum of adverse effects and contraindications for immunotherapy with nivolumab or pembrolizumab compared with that for dabrafenib plus trametinib should be discussed with the patient when deciding on adjuvant treatment.

- These treatments were evaluated in trials requiring patients to have complete regional lymphadenectomy. The Multicenter Selective Lymphadenectomy Trial-II (MSLT-II) [4] and the Dermatologic Cooperative Oncology Group (DeCOG)-SLT trial [5,6] found that in patients with clinically localized cutaneous melanoma (no satellite, in-transit, regional, or distant metastases) with positive sentinel lymph nodes, immediate completion lymph node dissection compared with nodal observation with ultrasonography and completion lymphadenectomy only upon recurrence did not improve melanoma-specific survival but led to higher morbidity (lymphedema). Based on these results, routine immediate completion lymphadenectomy is no longer standard practice for patients with pathologically node-positive disease by sentinel lymph node biopsy (see guidelines by the Program in Evidence-Based Care/Cancer Care Ontario [7] and the American Society of Clinical Oncology/Society of Surgical Oncology [8]). In the absence of complete lymphadectomy, some patients with positive sentinel lymph nodes assigned as stage IIIA or IIIB may be understaged. These trials and recommendations regarding axillary resection do not apply to patients with clinically positive lymph nodes (by palpation or radiologic investigation), and the standard of care is dissection of lymph nodes in that area (axillary, groin, or head and neck) prior to adjuvant therapy or adjuvant radiotherapy. In the case of unresectable disease, up-front systemic therapy should be considered.
- Patient inclusion in these trials was based on the American Joint Committee on Cancer (AJCC) 7th edition, which subdivides stage III into IIIA, IIIB, and IIIC groups. The AJCC 8th edition now in effect has an additional IIID category; with revised criteria for stage III substages there will be stage migration. For example, using data from the COMBI-AD trial [9], 38% of stage III patients were reclassified to a different subgroup.
- Stage IV patients with completely resected disease were only included in the Eastern Cooperative Oncology Group (ECOG) E1609 trial (abstract only, not reported separately) [10] and the CheckMate 238 trial (see key evidence) [1,11]. Data are therefore more limited for this population.
- The role of radiotherapy was outside the scope of the literature review; adjuvant radiotherapy is the subject of a separate guideline [12]. Patients who received adjuvant radiotherapy were excluded from the trials of immune checkpoint inhibitors and targeted therapy, except for the E1609 trial comparing ipilimumab doses [10].
- The recommendations from the immunotherapy trials are based on interim results for disease-free survival (DFS); most overall survival (OS) results are not yet available but are forthcoming. A recent review by Suciu et al. [13] supports the view that recurrence-free survival is a suitable surrogate for OS. Recommendations should be reevaluated once final results for the relevant studies are reported.

- Data on targeted therapy for *BRAF* mutations other than V600E/K are not available, and therefore adjuvant therapy with nivolumab or pembrolizumab should be considered.

Recommendation 1b (new evidence in 2023)

1b. ***New Recommendation for Stage IIB and IIC: Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected, node-negative cutaneous melanoma with and without BRAF V600E or V600K mutations with high risk of recurrence (Stage IIB and IIC).***

Qualifying Statements for Recommendation 1b

- The recommendations from the immunotherapy trials are based on interim results for recurrence-free survival (RFS) and/or distant metastases-free survival (DMFS); most overall survival (OS) results are not yet available but are forthcoming
- There is currently no data for targeted therapy for BRAF mutated Stage IIB, IIC melanoma. These patients should be offered immunotherapy.

Recommendation 2

2.1 Ipilimumab is not recommended as adjuvant therapy for patients with completely resected cutaneous melanoma with high risk of recurrence.

Qualifying Statements for Recommendation 2

- While ipilimumab may be effective in reducing the risk of melanoma recurrence, this agent has lower efficacy and higher rates of serious adverse effects than nivolumab and is not recommended.

Recommendation 3

3.1 Use of interferon alpha (IFN-α) for adjuvant treatment of cutaneous melanoma outside of a clinical trial is no longer recommended.

Qualifying Statements for Recommendation 3

- The EORTC 18081 trial (NCT01502696) comparing pegylated IFN-α2b for two years to observation in ulcerated stage II melanoma has an estimated completion of April 2019. This trial may confirm results of the individual patient meta-analysis by the International Melanoma Meta-Analysis Collaborative Group [14], which suggested IFN-α is of benefit in ulcerated melanoma.
- IFN may have a limited role in high-risk patients not eligible for other treatments.

Recommendation 4

4.1 Chemotherapy regimens, vaccines, levamisole, bevacizumab, Bacillus Calmette-Guerin, and isolated limb perfusion are not recommended for adjuvant treatment of cutaneous melanoma except as part of a clinical trial.

B. Mucosal Melanoma

Recommendation 5

5.1 Immune checkpoint inhibitors (nivolumab or pembrolizumab) or targeted therapy (in patients with identified mutations) are recommended for adjuvant therapy of mucosal melanoma with high risk of recurrence.

Qualifying Statements for Recommendation 5

- Mutation characterization is required prior to consideration of targeted agents. Mucosal melanoma has a different origin and spectrum of mutations than cutaneous melanoma. *BRAF* mutations are less common than in cutaneous melanoma, and therefore inhibitors are of little value in unselected patients. *KIT* mutations are more prevalent in mucosal melanoma, and inhibitors such as imatinib appear to be of value in advanced melanoma with *KIT* mutations [15]; however, no trials on adjuvant use of KIT inhibitors were found.
- The trials forming the key evidence for cutaneous melanoma (see Recommendations 1-2) excluded mucosal melanoma, with the exception of the CheckMate 238 trial, which included 29 patients (3.2% of total). This small number is insufficient to allow any conclusions specifically for this subgroup.
- There may be a role for chemotherapy, but evidence is not sufficient at this time to make a recommendation. Adjuvant treatment of mucosal melanoma with high-dose IFN-α2b compared with temozolomide plus cisplatin was studied in a phase II trial [16] of patients with stage II/III mucosal melanoma and a subsequent phase III trial in stage I-III mucosal melanoma that has been reported only in abstract form [17]. The phase II study found temozolomide plus cisplatin to result in better OS and DFS than IFN-α2b or placebo. A follow-up phase III study confirmed benefit of temozolomide plus cisplatin compared with IFN-α2b. The available evidence is limited due to lack of full publication and inconsistency with studies in metastatic melanoma [18]

FURTHER QUALIFYING STATEMENTS

The recommended adjuvant therapies have potential for adverse effects (see above key evidence and qualifying statements). While usually manageable and reversible, they may be severe. It was outside the scope of the accompanying systematic review to deal with the management of these adverse effects. The user may refer to other guidelines such as those by the Multinational Association of Supportive Care in Cancer [19], ECOG [20], the American Society of Clinical Oncology/National Comprehensive Cancer Network [21,22], Cancer Care Ontario [23] and others [24,25].

There are several ongoing trials, and the above recommendations may need to be revisited upon their completion.

Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent Melanoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVE

To make recommendations regarding the use of adjuvant systemic therapy in adult patients with completely resected cutaneous or mucosal melanoma with a high risk of recurrence.

TARGET POPULATION

Adult patients with cutaneous or mucosal melanoma with high risk of recurrence who are rendered disease-free following resection (including resection of all locoregional or distant metastases, if present). Patients with unresected primary disease or metastases fall outside the scope of this document.

In determining risk of recurrence, disease with any of the following characteristics was considered high risk:

- Primary melanoma with tumour thickness >4.0 mm (T4 in American Joint Committee on Cancer [AJCC] 6th,7th,8th editions); if node-negative these fall in AJCC stage IIB (no ulceration) or IIC (ulceration)
- Primary melanoma with tumour thickness >2.0 to 4.0 mm with ulceration (T3b; stage IIB if node-negative)
- Primary melanoma with one or more of the following: positive sentinel lymph nodes (micrometastasis), clinically detected positive regional lymph nodes (macrometastasis), or in-transit, satellite or microsatellite metastases. Any combination of these is considered node positive (N1-3) and stages IIIA to IIIC in the AJCC 6th or 7th editions, or stages IIIA-IIID in the AJCC 8th edition.
- Distant metastasis (stage IV)
- Recurrence of melanoma that was previously completely resected

AJCC staging categories are for cutaneous melanoma. Staging for mucosal melanoma varies depending on the primary site, and the AJCC staging designations may not apply.

INTENDED USERS

Medical oncologists, surgical oncologists, and other health care providers involved in the management and referral of patients with resected melanoma at high risk for recurrence.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

A. Cutaneous Melanoma

Recommendation 1

1b. Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected cutaneous melanoma without *BRAF* V600E or V600K mutations with high risk of recurrence (stage IIIA [>1 mm nodal metastasis] to IIID, IV).

1b. Nivolumab, pembrolizumab, or dabrafenib plus trametinib is recommended as adjuvant therapy for patients with completely resected cutaneous melanoma with *BRAF* V600E or V600K mutations and high risk of recurrence (stage IIIA [>1 mm nodal metastasis] to IIID, IV).

1b. Molecular testing of high-risk melanoma patients to characterize mutations should be conducted to help guide appropriate treatment decisions.

Qualifying Statements for Recommendation 1

- Nivolumab, pembrolizumab, or the combination dabrafenib plus trametinib (for *BRAF* V600E/K mutated melanoma) are all appropriate treatments; there is currently insufficient evidence to suggest which of these is more effective. These agents were evaluated in different trials [1-3] (see Table 4-4) and have not been directly compared in the adjuvant setting. For nivolumab and pembrolizumab, treatment-related adverse events (AEs) tended to be mild and manageable, and occurred in 85% and 78% of patients, respectively, with the most common being fatigue, skin reactions (rash, pruritus), diarrhea, nausea, and endocrine disorders. Rates of grade 3+ treatment-related AEs (14.4% and 14.7%) resulting in treatment discontinuation (9.7% vs. 13.8%) were similar. The combination dabrafenib plus trametinib resulted in a higher rate of serious AEs (36%), including pyrexia, hypertension, and hepatic effects, and higher rate of discontinuation due to AEs (25%). The spectrum of adverse effects and contraindications for immunotherapy with nivolumab or pembrolizumab compared with that for dabrafenib plus trametinib should be discussed with the patient when deciding on adjuvant treatment.

- These treatments were evaluated in trials requiring patients to have complete regional lymphadenectomy. The Multicenter Selective Lymphadenectomy Trial-II (MSLT-II) [4] and the Dermatologic Cooperative Oncology Group (DeCOG)-SLT trial [5,6] found that in patients with clinically localized cutaneous melanoma (no satellite, in-transit, regional, or distant metastases) with positive sentinel lymph nodes, immediate completion lymph node dissection compared with nodal observation with ultrasonography and completion lymphadenectomy only upon recurrence did not improve melanoma-specific survival but led to higher morbidity (lymphedema). Based on these results, routine immediate completion lymphadenectomy is no longer standard practice for patients with pathologically node-positive disease by sentinel lymph node biopsy (see guidelines by the Program in Evidence-Based Care [PEBC]/Cancer Care Ontario [CCO] [7] and the American Society of Clinical Oncology/Society of Surgical Oncology [8]). In the absence of complete lymphadectomy, some patients with positive sentinel lymph nodes assigned as stage IIIA or IIIB may be understaged. These trials and recommendations regarding axillary resection do not apply to patients with clinically positive lymph nodes (by palpation or radiologic investigation), and the standard of care is dissection of lymph nodes in that area (axillary, groin, or head and neck) prior to adjuvant therapy or adjuvant radiotherapy. In the case of unresectable disease, up-front systemic therapy should be considered.

- Patient inclusion in these trials was based on the AJCC 7th edition, which subdivides stage III into IIIA, IIIB, and IIIC groups. The AJCC 8th edition now in effect has an additional IIID category; with revised criteria for stage III substages there will be stage migration. For example, using data from the COMBI-AD trial [9], 38% of stage III patients were reclassified to a different subgroup.
- Stage IV patients with completely resected disease were only included in the Eastern Cooperative Oncology Group (ECOG) E1609 trial (abstract only, not reported separately) [10] and the CheckMate 238 trial (see key evidence) [1,11]. Data are therefore more limited for this population.
- The role of radiotherapy was outside the scope of the literature review; adjuvant radiotherapy is the subject of a separate guideline [12]. Patients who received adjuvant radiotherapy were excluded from the trials of immune checkpoint inhibitors and targeted therapy, except for the E1609 trial comparing ipilimumab doses [10].
- The recommendations from the immunotherapy trials are based on interim results for disease-free survival (DFS); most overall survival (OS) results are not yet available but are forthcoming. A recent review by Suciu et al. [13] supports the view that recurrence-free survival (RFS) is a suitable surrogate for OS. Recommendations should be reevaluated once final results for the relevant studies are reported.
- Data on targeted therapy for *BRAF* mutations other than V600E/K are not available, and therefore adjuvant therapy with nivolumab or pembrolizumab should be considered

Key Evidence for Recommendation 1

- The Checkmate 238 trial [1,11] reported two-year RFS of 62.6% for nivolumab (3 mg/kg) versus 50.2% for ipilimumab (10 mg/kg) (hazard ratio [HR]=0.66, p<0.0001). This is the only trial with data for stage IV patients; for this subgroup two-year RFS was 58.0% versus 44.3%, respectively. There were also fewer AEs with nivolumab: grade 3+ AEs occurred in 14.4% versus 45.9% of patients, and deaths in 0% versus 0.4% (2 patients).
- A combined indirect analysis of stage IIIB and IIIC patients from the Checkmate 238 and European Organization for Research and Treatment of Cancer (EORTC) 18071 trials (abstract only [26]) reported 18-month RFS of 70.7% for nivolumab, 54.1% for ipilimumab, and 41.8% for placebo.
- The Keynote 054 trial [2] reported 18-month RFS of 71.4% versus 53.2% for pembrolizumab versus placebo. Grade 3+ AEs occurred in 14.7% versus 3.4% of patients; there was one death on the pembrolizumab arm.
- The COMBI-AD trial [3,9] found that the combination of dabrafenib plus trametinib in patients with *BRAF* V600E/K mutations improved RFS at all time points, with four-year RFS of 54% versus 38%. Benefit was found for all subgroups [27]. This trial included a portion of stage IIIA patients (those with nodal metastases >1 mm); for this group four-year DFS was 69% versus 62% (HR=0.58; 95% CI=0.32 to 1.06). Overall survival at three years was also better (86% vs. 77%), although not statistically significant due to interim boundaries set in the protocol.
- Vemurafenib is being evaluated in the BRIM8 trial [28], which to date found two-year DFS benefit in stage IIC-IIIB patients (cohort 1) but not stage IIIC patients (cohort 2). The study design was such that results for cohort 1 could not be considered significant unless results for cohort 2 found significant DFS benefit. Interim (immature) OS data found no benefit in stage IIIC patients, while there is a trend to benefit (p=0.1) for

cohort 1. Due to the study design, apparently conflicting results according to stage, and preliminary nature of the data, vemurafenib cannot be recommended at this time.

Interpretation of Evidence for Recommendation 1

- The trials noted in the key evidence suggest that nivolumab, pembrolizumab, and (for *BRAF* V600E/K mutations) dabrafenib plus trametinib are all effective in reducing recurrence, and current evidence does not suggest that one is better than the other. Long-term data, as well as results from other ongoing trials may clarify which, if any, is better overall or for subgroups. While direct evidence is only available for stages IIIB, IIIC, IV for nivolumab, and a subset of stage IIIA, IIIB, and IIIC for pembrolizumab (using AJCC 7th edition), it is the authors' opinion that the overall body of evidence suggests these agents should offer similar efficacy in patients with high risk of occurrence, regardless of stage III subgroup. Evidence from the metastatic setting suggests that nivolumab and pembrolizumab are equivalent in efficacy and toxicity profile.

Recommendation 1b (new evidence in 2023)

1b.1 ***New Recommendation for Stage IIB and IIC: Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected, node-negative cutaneous melanoma with and without BRAF V600E or V600K mutations with high risk of recurrence (Stage IIB and IIC).***

Qualifying Statements for Recommendation 1b

- The recommendations from the immunotherapy trials are based on interim results for recurrence-free survival (RFS) and/or distant metastases-free survival (DMFS); most overall survival (OS) results are not yet available but are forthcoming
- There is currently no data for targeted therapy for BRAF mutated Stage IIB, IIC melanoma. These patients should be offered immunotherapy.

Key Evidence for Recommendation 1b

- KeyNote-716 was a multicenter randomized, double blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma [285]. Patients were randomized to pembrolizumab 200 mg or 2 mg/kg intravenously (up to a maximum of 200 mg in pediatric participants) every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. A statistically significant improvement in RFS was shown at the time of the initial interim analysis for patients in the pembrolizumab arm compared with placebo, with a hazard ratio of 0.65 (95% CI: 0.46, 0.92; p=0.0132).

- CheckMate76K was multi-center randomized, double-blind, placebo-controlled study in patients with previously untreated, histologically confirmed resected stage IIB and IIC cutaneous melanoma [286]. 12-month RFS rates among patients with stage IIB melanoma were 93% for nivolumab and 84% for placebo. Among patients with stage IIC melanoma, Nivolumab significantly reduced the risk of recurrence versus placebo, with a stratified HR of 0.42 (95% CI, 0.30-0.59) and 12-month RFS rates of 89% vs 79%. 10% of patients in the nivolumab arm experienced grade 3 or 4 treatment-related adverse effects compared with 2% for those in the placebo arm. Adverse events led to treatment discontinuation in 15% of patients in the nivolumab arm and 3% in the placebo arm.

Interpretation of Evidence for Recommendation 1b

The above trials [285, 286] in the key evidence suggest that either nivolumab or pembrolizumab are effective in reducing recurrence and improve disease-free survival in patients with Stage IIB and IIC melanoma. Current evidence does not suggest that one regimen is more beneficial over the other and both have a favourable risk-benefit profile. As the current trial data are from interim data analysis, long-term trial results may clarify in the future if any regimen is more effective for any patient subgroups and stages.

Recommendation 2

- Ipilimumab is not recommended as adjuvant therapy for patients with completely resected cutaneous melanoma with high risk of recurrence.

Qualifying Statement for Recommendation 2

- While ipilimumab may be effective in reducing the risk of melanoma recurrence, this agent has lower efficacy and higher rates of serious adverse effects than nivolumab and is not recommended.

Key Evidence for Recommendation 2

- While the EORTC 18071 trial [29-31] reported ipilimumab (10 mg/kg) to improve RFS and OS compared with placebo, there was a high level of AEs. The rate of grade 3 to 4 AEs was 54.1% versus 26.2%. Grade 3 to 4 immune-related AEs were especially prevalent (41.6% vs. 2.7%), with deaths in five patients (1.1% vs. 0%). Discontinuation of treatment due to drug-related AEs occurred in 53% of patients.
- The Checkmate 238 trial [1,11] reported two-year RFS of 62.6% for nivolumab (3 mg/kg) versus 50.2% for ipilimumab (10 mg/kg) (HR=0.66, $p<0.0001$). There were also fewer AEs with nivolumab: grade 3+ AEs 14.4% versus 45.9%, and deaths 0% versus 0.4% (2 patients).
- A combined indirect analysis of these two trials (abstract only [26]) reported 18-month RFS of 70.7% for nivolumab, 54.1% for ipilimumab, and 41.8% for placebo.
- The E1609 trial [10,32] (abstracts only) compared ipilimumab at 3 mg/kg versus 10 mg/kg versus high-dose interferon alpha-2b (HD-IFN-α2b). Preliminary results suggested equal efficacy of 3 mg/kg and 10 mg/kg ipilimumab (3-year RFS 56% vs. 54%). Results at approximately 4.5 years after accrual of the last patient have been reported. OS was significantly better for 3 mg/kg ipilimumab compared with HD-IFN-α2b (HR=0.78, 95.6% CI=0.61 to 1.00; p=0.044) and there was a trend to benefit for RFS (HR=0.0.85, 99.4% CI=0.66 to 1.09, p=0.065). There was also a trend for benefit of 10 mg/kg ipilimumab compared with HD-IFN-α2b for OS (HR=0.88, 95.6% CI=0.69 to 1.12) and RFS (HR=0.84, 99.4% CI 0.65 to 1.09). Grade 3+ AEs (mostly immune-related) for 3 mg/kg ipilimumab versus 10 mg/kg ipilimumab versus HD-IFN-α2b were experienced in 37% versus 58% versus 79% of patients, leading to treatment discontinuation in 35% versus 54% versus 20%. Grade 5 AEs at lease possibly treatment-related occurred in three versus eight versus two patients (0.6% vs. 1.6% vs. 0.3%).

Interpretation of Evidence for Recommendation 2

- As the above trials found nivolumab to be more effective than ipilimumab and with fewer AEs, use of ipilimumab is not supported. This conclusion may need to be reevaluated when final trial results including OS are reported for these trials, as well as the ongoing Checkmate 915 and SWOG 1404 trials.

Recommendation 3

- Use of interferon alpha (IFN-α) for adjuvant treatment of cutaneous melanoma outside of a clinical trial is no longer recommended.

Qualifying Statements for Recommendation 3

- observation in ulcerated stage II melanoma has an estimated completion of April 2019. This trial may confirm results of the individual patient meta-analysis by the International Melanoma Meta-Analysis Collaborative Group (IMMCG) [14], which suggested IFN-α is of benefit in ulcerated melanoma.
- IFN may have a limited role in high-risk patients not eligible for other treatments.

Key Evidence for Recommendation 3

- The Cochrane meta-analysis [33] included 18 randomized controlled trials (RCTs) with 10,499 patients comparing HD-IFN-α to observation or any other treatment in patients with regional lymph node metastasis (and undergoing radical lymph node dissection) or with tumour thickness >1 mm. Adjuvant HD-IFN-α improved DFS (HR=0.83, 95% CI 0.78 to 0.87, p<0.00001) and OS (HR=0.91, 95% CI=0.85 to 0.97, p=0.003). This represents an absolute improvement of about 6% for five-year DFS and 3% for OS.
- The IMMCG [14] conducted an individual patient data (IPD) meta-analysis comparing IFN-α versus no IFN-α (observation only) in high-risk melanoma. It included 15 IFN-α trials with 7744 patients. IPD was available from 11 of these trials (5861 patients) and summary data from the other trials were used. IFN-α resulted in a significant improvement in event-free survival (EFS) (HR=0.86, 95% CI=0.81 to 0.91, p<0.00001) and OS (HR=0.90, 95% CI=0.85 to 0.97, p=0.003). For trials providing IPD, five-year OS was 49.1% versus 46.1% and ten-year OS was 39.9% versus 37.1%; five-year EFS was 37.8% versus 34.3% and ten-year EFS was 31.2% versus 28.5%. While statistically significant, the absolute differences are small.
- IFN benefit did not differ according to dose (no significant trend in effect for high [20 MU/m^2], intermediate [5-10 MU/m^2], low [3 MU/m^2], or very low [1 MU/m^2]) or duration of treatment (≤6, 12 to 18, ≥24 months). Results suggest that low-, intermediate-, or high-dose IFN-α have similar benefit, while data are unclear for very-low-dose IFN (EORTC 18871 and DBG 80-1 trials). For OS, the effect is weaker, and statistically significant only for the low-dose group (HR=0.86, 95% CI=0.77 to 0.96, p=0.007).
- The meta-analysis also did not find a differential IFN benefit according to age, sex, site of primary tumour, disease stage (I/II or III/IV), Breslow thickness, or presence of clinical nodes. For patients with ulcerated tumours there was improved EFS (5-year EFS 32.9% versus 26.9%, 10-year EFS 27.3% versus 20.4%; HR=0.79, 99% CI=0.66 to 0.94, p=0.0006) and OS (5-year OS 46.0% vs. 38.1%, 10-year OS 38.5% vs. 28.0%; HR=0.77, 99% CI=0.64 to 0.92, p=0.0002). The EFS and OS benefits were approximately 6% and 8% at five years, and slightly higher at ten years. There was no significant benefit in patients with non-ulcerated tumours.
- Adverse effects of HD-IFNα and their management based primarily on the E1684, E1690, and 1694 trials has been reviewed by others [34,35] (see also Table 4-5). Dose reduction or delay was required in 28% to 44% of patients during the induction phase and 36% to 52% of patients in the maintenance phase in these trials. Treatment was discontinued due to AEs in 10-26% of patients. Most patients experienced acute flu-like symptoms (fever chills, headache, myalgia, nausea, and vomiting) with grade 3+ AEs in 4-18% of patients. Fatigue, which has been reported in 70% to 100% of patients

(18% grade 3+) and neuropsychiatric symptoms increase in severity over time. Other AEs are anorexia, cardiotoxicity, hepatotoxicity, autoimmunity, ocular toxicity, and altered laboratory findings. While generally manageable with careful monitoring, supportive care, and dose modifications, these AEs often have a profound negative effect on quality of life and may be life-threatening.

Interpretation of Evidence for Recommendation 3

- These meta-analyses indicate that IFN-α results in a small but statistically significant improvement in OS and DFS. For most patients the adverse effects are judged to outweigh the possible small benefit. The IPD meta-analysis suggests IFN-α benefit applies only to ulcerated tumours, and this must be confirmed in a trial designed to test efficacy specifically in ulcerated melanoma. The benefit of nivolumab, pembrolizumab, and (for *BRAF* mutant melanoma) dabrafenib plus trametinib are more than that of IFN-α, and therefore IFN-α is not recommended.

Recommendation 4

- Chemotherapy regimens, vaccines, levamisole, bevacizumab, Bacillus Calmette-Guerin (BCG), and isolated limb perfusion are not recommended for adjuvant treatment of cutaneous melanoma except as part of a clinical trial.

Key Evidence and its Interpretation for Recommendation 4

- The majority of completed trials found no survival benefit. A few trials suggest a possible benefit for some of these agents, but were either too small or discontinued early due to more promising results with IFN-α and were therefore inconclusive. Some trials are ongoing.

B. Mucosal Melanoma

Recommendation 5

- Immune checkpoint inhibitors (nivolumab or pembrolizumab) or targeted therapy (in patients with identified mutations) are recommended for adjuvant therapy of mucosal melanoma with high risk of recurrence.

Qualifying Statements for Recommendation 5

- Mutation characterization is required prior to consideration of targeted agents. Mucosal melanoma has a different origin and spectrum of mutations than cutaneous melanoma. *BRAF* mutations are less common than in cutaneous melanoma, and therefore inhibitors are of little value in unselected patients. *KIT* mutations are more prevalent in mucosal melanoma, and inhibitors such as imatinib appear to be of value in advanced melanoma with *KIT* mutations [15]; however, no trials on adjuvant use of KIT inhibitors were found.
- The trials forming the key evidence for cutaneous melanoma (see Recommendations 1-2) excluded mucosal melanoma, with the exception of the CheckMate 238 trial which included 29 patients (3.2% of total). This small number is insufficient to allow any conclusions specifically for this subgroup.
- There may be a role for chemotherapy, but evidence is not sufficient at this time to make a recommendation. Adjuvant treatment of mucosal melanoma with HD-IFN-α2b compared with temozolomide plus cisplatin was studied in a phase II trial [16] of patients with stage II/III mucosal melanoma and a subsequent phase III trial in stage I-III mucosal melanoma that has been reported only in abstract form [17]. The phase II

study found temozolomide plus cisplatin to result in better OS and DFS than HD-IFN-α2b or placebo. A follow-up phase III study confirmed benefit of temozolomide plus cisplatin compared with HD-IFN-α2b. The available evidence is limited due to lack of full publication and inconsistency with studies in metastatic melanoma [18].

Key Evidence for Recommendation 5

- Targeted agents and immune checkpoint inhibitors have not been evaluated specifically as adjuvant therapy in mucosal melanoma. Key evidence is considered to be the trials supporting their use in cutaneous melanoma [1-3,9,11,26] (see other recommendations), as well as data from trials in advanced or metastatic melanoma where these agents were shown to be effective. D'Angelo et al. [36] conducted a pooled analysis of nivolumab alone or combined with ipilimumab in unresectable stage III or IV mucosal melanoma and found nivolumab plus ipilimumab had greater efficacy than either nivolumab monotherapy or ipilimumab monotherapy (objective response rate 37.1% vs. 23.3% vs. 8.3%) but with much greater rate of grade 3 to 4 AEs (40% vs. 8% vs. not stated). Compared with ipilimumab alone, progression-free survival (PFS) was better for nivolumab plus ipilimumab (HR=0.35, 95% CI=0.19 to 0.64) and for nivolumab alone (HR=0.62, 95% CI=0.39 to 0.98). A post-hoc analysis of patients with advanced mucosal melanoma in the Keynote-001, -002, and -006 trials reported that pembrolizumab provided durable tumour response [37].

Interpretation of Evidence for Recommendation 5

- Recommendations for use of immune-checkpoints inhibitors in mucosal melanoma are based on extrapolation of results from cutaneous melanoma (see Recommendations 1 and 2) and from trials in non-resectable mucosal melanoma.
- For targeted therapy, the authors believe that cutaneous and mucosal melanoma with the same mutations would benefit from the same targeted therapies. Therefore adjuvant therapy with dabrafenib plus trametinib may be considered in mucosal melanoma in which *BRAF* V600E/K mutations are the primary mutations.

FURTHER QUALIFYING STATEMENTS

The recommended adjuvant therapies have potential for adverse effects (see above key evidence and qualifying statements). While usually manageable and reversible, they may be severe. It was outside the scope of the accompanying systematic review to deal with the management of these adverse effects. The user may refer to other guidelines such as those by the Multinational Association of Supportive Care in Cancer (MASCC) [19], ECOG [20], the American Society of Clinical Oncology/National Comprehensive Cancer Network (ASCO/NCCN) [21,22], CCO [23] and others [24,25].

There are several ongoing trials, and the above recommendations may need to be revisited upon their completion.

IMPLEMENTATION CONSIDERATIONS

Most trials on the adjuvant use of immune checkpoint inhibitors and targeted agents in melanoma are ongoing with promising preliminary results. As a result, indications and approvals are changing rapidly. Nivolumab, pembrolizumab, and the combination dabrafenib plus trametinib were approved by Health Canada in early 2019 for adjuvant use in melanoma. At the time of this review immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) and targeted therapies were being evaluated for approval and funding in Ontario. Funding may

be interim pending final results of the trials mentioned in the key evidence sections. Doses for administration of immune checkpoint inhibitors and targeted therapies have not been standardized, and should be according to approved indications.

RELATED PEBC 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.: 8-2V2.

Easson AM, Cosby R, McCready DR, Temple C, Petrella T, Wright F, et al. Surgical management of patients with lymph node metastases from cutaneous melanoma of the trunk or extremities. Easson A, Salerno J, reviewers. Toronto, ON: Cancer Care Ontario; 2012 Dec 4 [Endorsed with partial update 2018 Aug]. Program in Evidence-Based Care Evidence-Based Series No.: 8-6 Version 2 ENDORSED.

Sun A, Souter LH, Hanna TP, Joshua AM, McWhirter E, Rajagopal S, et al. The use of adjuvant radiation therapy for curatively resected melanoma. Toronto (ON): Cancer Care Ontario; 2016 January 4. Program in Evidence-Based Care Guideline No.: 8-9.

Wright FC, Kellett S, Sun A, Hanna T, Nessim C, Look Hong NJ, et al. Guidelines for the management of satellite and in-transit metastasis in melanoma. Toronto (ON): Cancer Care Ontario. In development, expected completion fall 2019. Program in Evidence-Based Care Guideline No.: 8-10.

See Appendix 9 for a listing of the previous versions of this guideline.

Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent 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, Cancer Care Ontario (CCO). 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 CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND

For many years IFN was considered the only effective adjuvant treatment in patients with melanoma. Several trials found IFN had RFS benefit, but marginal or no OS benefit. The small benefit was confirmed in meta-analyses of trials but was offset by significant adverse effects impacting quality of life. Trials in the metastatic setting have found much greater benefit of immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) and targeted therapy (vemurafenib, cobimetinib, dabrafenib, trametinib), and recent trials have confirmed benefit of some of these agents in the adjuvant setting. At the latest assessment of Version 4 of this guideline it was therefore determined that an update was required.

GUIDELINE DEVELOPERS

This guideline was developed by the Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent 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, 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, surgical oncology, and health research methodology. Other members of the 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. Due to a change in policy subsequent to start of the project, the Working Group

members were managed in accordance with the previous version of the *PEBC Conflict of Interest Policy*. The Director of the PEBC waived the requirement that the lead author and 50% of members of the Working Group have no declared interests, with the provision that co-chairs be appointed. The remaining members of the Expert Panel and other reviewers completed the form according to the 2018 revision of 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 [38,39]. This process includes a systematic review (see Section 4), interpretation of the evidence by the Working Group and drafting of recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [40] 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.

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 clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine if an existing guideline could be adapted or endorsed. To this end, the following sources were searched for guidelines that addressed the research questions:

- Practice guideline databases: National Institute for Health and Care Excellence (NICE) Evidence Search; Canadian Partnership Against Cancer Database, Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: NICE, Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), National Health and Medical Research Council Australia, Cancer Council Australia, British Columbia Cancer Agency, and Alberta Health Services.
- Literature Databases: MEDLINE and Embase (see Appendix 2)

The search was for evidence-based guidelines with systematic reviews that addressed at least one research question; guidelines older than five years (published before 2013) and guidelines based on consensus/expert opinion without a systematic review were excluded. Guidelines meeting these criteria are summarized in Appendix 3. Due to recent practice-changing trials, guidelines before 2017 were not considered for endorsement or adaptation, but could be used as systematic reviews for prior evidence or portions of this topic. Only the guidelines by Cancer Council Australia [41] and by the Society for Immunotherapy of Cancer [42] include recent trials and recommendations regarding nivolumab, pembrolizumab, and ipilimumab and recommendations for dabrafenib plus trametinib in patients with *BRAF*

mutations. Results of an evaluation of these two guidelines using the AGREE II tool are in Appendix 3. The Working Group members decided these guidelines had several limitations, including their narrower focus, and could not be endorsed; an update of previous versions of the PEBC/CCO guideline including the systematic review of the evidence (see Section 4) and recommendations (see Section 2) was required.

During the update search (May 2019) it was noted that the French Dermatological Society has a new guideline (French language only) released in November 2018 [43] and published in 2019 [44,45]. It covers stage III melanoma (and stage IV if completely resected), partially replacing the previous guideline on stage I-III cancer found in the initial literature search. The 2019 National Comprehensive Cancer Network (NCCN) guideline on melanoma [now entitled Cutaneous Melanoma] represents a significant revision of previous versions, and now includes immune checkpoint inhibitors and *BRAF*-targeted therapies [46,47]. Recommendations in both these guidelines are similar to those in Sections 1 and 2 of this document. The NCCN guideline includes diagnosis and treatment of stage 0 to stage IV unresectable melanoma, and therefore the section on adjuvant systemic therapy is more limited than in this PEBC/CCO document; in contrast, the NCCN guideline has more details on topics such as principles of molecular testing and management of AEs associated with target therapy.

GUIDELINE REVIEW AND APPROVAL

Internal Review

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

Patient- and Caregiver –Specific Consultation Group

Four cancer patients/survivors participated as Consultation Group members for the project. They reviewed the draft document distributed for internal review and provided feedback on its comprehensibility, appropriateness and feasibility.

External Review

Feedback on the approved draft guideline was obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise were 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 were contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation was intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

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- Frances Wright, who served as a member of the working group in early stages of the project.
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- Sara Miller for copy editing.

Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent Melanoma

Section 4: Systematic Review

BACKGROUND

Incidence

According to the Canadian Cancer Statistics [48,49] the projected number of cases of melanoma in Canada in 2017 was 7200 (18.5 per 100,000) and 1250 deaths, making melanoma the eighth most common cancer and fifteenth in mortality. Of cases with known stage, 67.5% were stage I, 14.9% stage II, 12.7% stage III, and 4.8% stage IV (metastatic). In Ontario, there were predicted to be 4129 cases of melanoma in 2018 (26.4 per 100,000 people), representing 4.6% of cancers [50]. Actual data from 2013 indicated 3409 new cases of melanoma (24.7 per 100,000; 4.4% of all cancers) and 519 deaths (1.9% of all cancer deaths). Five-year survival for the period 2009-2013 was 86.6%.

In the United States, the American Cancer Society estimated 91,270 new cases of melanoma in 2018 and 9,320 deaths [51]. Further information was reported using data from 2007-2013. By stage, 84% was localized (53% in blacks), 9% regional (26% in blacks), and 4% distant metastasis (16% blacks). Five-year survival was 92% (65% blacks) for all stages; when divided by stage of disease survival was 99% for localized diseases (86% blacks), 63% regional metastases (46% blacks), and 20% distant metastasis. Incidence rates for melanoma per 100,000 population increased over the period 1975-2014 (from 10 to 33 for males and 10 to 21 for females). The long-term increase is slowing, with stable rates now reported for age <50 years, but still increasing for those >50 years of age.

Staging and Survival

This systematic review focuses on resected melanoma with a *high risk of recurrence* (defined in Methods section), and therefore incorporates a higher risk subset of stage II plus resectable stage III and IV melanoma. For melanoma, the AJCC 6th edition Cancer Staging Manual (2001 or 2002) was based on factors predicting melanoma-specific survival in 17,600 patients [52]. This was revised for the 7th edition (2009) based on analysis of 30,946 patients with stages I-III melanoma and 7972 patients with stage IV melanoma [53]. The AJCC 8th edition Cancer Staging Manual introduced a revised staging system for cutaneous melanoma based on the International Melanoma Database and Discovery Platform, which includes records of >46,000 patients with stage I-III melanoma diagnosed since 1998 [54]. The cut-off year was chosen to exclude patients treated in the pre-sentinel lymph node era and the early sentinel lymph node era in which techniques were still evolving. For stage IV (metastatic) cancers, the seventh edition AJCC stage IV International Melanoma Database was used, supplemented by data from contemporary clinical trials. Five- and ten-year melanoma-specific survival were 98% and 95% for stage I, 90% and 84% for stage II, and 77% and 69% for stage III, respectively. Survival for stage II and III categories relevant to this review are reported in Table 4-1. Classification of node-positive melanoma into stage groups is more complex and the reader is referred to the staging manual from the AJCC website or melanoma-specific discussions of this topic [54]. It should be noted that while a patient would be considered high risk due to disease features in all systems, the assigned staging subgroup may vary from trial to trial according to the version

of the staging manual used. This should be kept in mind when comparing inclusion criteria and results for various studies.

Table 4-1. Melanoma-specific survival for high-risk melanoma (AJCC 8th edition [54])

Stage	Size	Nodal status	Metastasis	Ulceration	T-group	Melanoma-specific survival	
						5-y (%)	10-y (%)
Node negative (Stage II)							
IIB (T3b subset)	>2.0 to 4.0 mm	N0	M0	Yes	T3b	86	81
IIB (T4a subset)	>4.0 mm	N0	M0	No	T4a	90	83
IIB					T3b/T4a	87	82
IIC	>4.0 mm	N0	M0	Yes	T4b	82	75
Node positive (Stage III)							
IIIA		N1a, N2a	M0	Varies	T1a/b, T2a	93	88
IIIB		N+	M0	Varies	Varies	83	77
IIIC		N+	M0	Varies	Varies	69	60
IIID		N3a-c	M0	Yes	T4b	32	24
Varies		N1	M0	Varies	Varies	82	75
Varies		N2	M0	Varies	Varies	76	68
Varies		N3	M0	Varies	Varies	57	47

Abbreviation: AJCC, American Joint Committee on Cancer

Mucosal Melanoma

Mucosal melanoma is a rare disease, and accounts for approximately 0.03% of all cancers diagnosed [55]. Melanocytes are mostly found in the skin, but are also found in mucous membranes of the respiratory, gastrointestinal, and urogenital tract, and the eye. Characteristics including causative mutations (see *Immune Checkpoint Inhibitors and Targeted Therapies* subsection) and response to treatment differ from that of cutaneous melanoma. Ultraviolet radiation exposure has not been associated with development of mucosal melanoma [56]. The most common sites are head and neck, anorectal areas and vulvovaginal regions; less common sites include the pharynx, larynx, urinary tract, cervix, esophagus, and gallbladder.

For the period 1985-1995, the National Cancer Data Base (United States) [57] reported the distribution of mucosal melanomas as 55% head and neck, 18% female genital tract, 24% anal/rectal, and 3% urinary tract sites. Corresponding five-year survival rates were 31.7%, 11.4%, and 19.8%, respectively; data for urinary sites were not reported. Slightly more recent data from the North American Association of Central Cancer Registries (United States, 1996-2000) [58] are summarized in Table 4-2. Female genital tract cases make up a much larger proportion and head and neck cases a smaller proportion than in the earlier report. For cutaneous melanoma, rates were approximately 16 times higher in whites than blacks; for mucosal melanomas, rates were approximately twice as high in white compared with black patients. Due to the lower incidence of cutaneous melanoma, mucosal melanoma comprises a much higher proportion of all melanomas in black patients (male 4.7% black, 0.7% white; female 13.4% black, 2.1% white) [58], as well as in Hispanic populations compared with white patients [57]. For genital tumours, 67.0% were localized, 23.9% were regional, and 9.0% had distant metastasis. Mucosal melanoma at other sites was diagnosed later and did not vary by sex: 41.3% were localized, 33.0% were regional metastasis (45% to regional lymph nodes and the others with direct extension), and 25.7 % were distant metastasis.

Studies elsewhere have suggested that the proportion of mucosal melanoma compared with cutaneous melanoma is higher in Asia than in the North America or Europe. Chi et al. [59] reported that of 526 patients diagnosed with malignant melanoma in China, 22.6% had mucosal melanoma. Of 5566 patients with melanoma identified from a hospital registry in Japan, 821 (14.8%) had mucosal melanoma, and the crude incidence rate per 100,000 person-years was 0.32 [60].

Table 4-2. Cases of melanoma (all types) and mucosal melanoma in the United States[58] **(1996-2000)**

Type of Melanoma	# of melanoma cases diagnosed	% of melanoma	% of melanoma by sex	% of mucosal	% of mucosal by sex	Incidence per million person years*
All melanoma	133209	100.0				161.7
Male	74296	55.8				202.0
Female	58913	44.2				133.2
All mucosal	1806	1.36				2.19
Male	527	0.40	0.71			1.43
Female	1279	0.96	2.17			2.89
Head and neck	559	0.42		31.0		0.68
Nasal cavity	255	0.19		14.1		0.31
Accessory sinuses	140	0.11		7.8		0.17
Oral cavity	164	0.12		9.1		0.20
Female genital tract	723	0.54	1.23	40.0	56.5	1.63
Vulva	555	0.42		30.7	43.4	1.25
Vagina	143	0.11		7.9	11.2	0.32
Cervix	16	0.01		0.9	1.3	0.04
Male genitals	53	0.04	0.07	2.9	10.1	0.14
Penis	35	0.03		1.9	6.6	0.10
Scrotum	17	0.01		0.9	3.2	0.05
Anal/rectal	299	0.22		16.6		0.36
Other	172	0.13		9.5		0.21

*Rates of female and male genital cancers are based on the number of females and males at risk; data for head and neck, anal/rectal, and other cancers are based on the full population (male + female).

Uveal and Ocular Melanoma

Uveal and other ocular melanomas are outside the scope of the current review; readers may wish to consult guidelines by other organizations [61-65].

Current Standard of Care and Background to Interferon Use

Until recently, IFN-α was the only adjuvant therapy shown to improve OS, and IFN-α2b until 2018 was the only treatment listed on the Cancer Care Ontario Drug Formulary specifically

approved by Health Canada for this indication. Based on the following trials, a high-dose regimen (20 MU/m^2 induction and 10 MU/m^2 maintenance) has been used in Canada.

The North Central Cancer Treatment Group (NCCTG) 83-7052 [66] and the ECOG 1684 and 1690 trials [67,68] were the earliest major trials of IFN-α conducted in the United States. They used what is now considered to be high-dose IFN-α (HD-IFNα) versus observation and the standard regimen as set in the ECOG trials became 20 MU/m^2 administered intravenously 5 days per week for 4 weeks followed by 10 MU/m^2 administered subcutaneously 3 times per week for 48 weeks. ECOG 1694 [69] used the same IFN regimen compared with vaccine and the Sunbelt trial [70] compared this IFN regime with observation in patients clinically node-negative but with positive sentinel lymph nodes. With the exception of the NCCTG trial, which used IFN-α2a and administered it intramuscularly, all trials of HD-IFN used IFN-α2b intravenously (sometimes followed by a lower long-term subcutaneous maintenance dose.

In contrast to the trials conducted in the United States, the early European trials used what is referred to as low-dose IFN-α2a (LD-IFN) administered subcutaneously at 3 MU (flat dose, not per m^2), and this is used in several jurisdictions outside of Canada and the United States. Duration varied among trials. Most trials of LD-IFN used IFN-α2a, with the exception of ECOG 1690, which compared HD-IFN-α2b with LD-IFN-α2b, and the Scottish trial [71] which used LD-IFN-α2b.

In the experience of the authors, IFN is not generally used in Ontario because the small improvements in survival are offset by a high level of AEs. Nivolumab (OPDIVO®), pembrolizumab (KEYTRUDA®), and the combination dabrafenib plus trametinib (TAFINLAR® plus MEKINIST®) have recently been approved by Health Canada as adjuvant therapy in melanoma.

Immune Checkpoint Inhibitors and Targeted Therapies

The most recently studied and promising therapies for both adjuvant use in resectable melanoma and primary treatment of non-resectable melanoma are immune checkpoint inhibitors and targeted therapies. Immune checkpoint inhibitors include the anti-cytotoxic T-lymphocyte antigen-4 (CTLA4) inhibitor ipilimumab (YERVOY®), and the anti-programmed death-1 (PD-1) inhibitors nivolumab and pembrolizumab [29,72]. Ipilimumab is a human monoclonal antibody that blocks CTLA-4 to enhance antibody immune responses. Nivolumab is a human IgG4 monoclonal antibody against PD-1 and acts to block binding of the PD-L1 and PD-L2 ligands. Targeted agents are applicable to a subset of patients with mutations or alterations, and include BRAF inhibitors (vemurafenib [Zelboraf®], dabrafenib), mitogen-activated ERK kinase (MEK) inhibitors (cobimetinib [Cotellic®], trametinib), KIT inhibitors (imatinib mesylate or imatinib [Gleevec® and generic products]), and vascular endothelial growth factor (VEGF) inhibitors (bevacizumab [Avastin® and generic products]).

Signal transduction pathways regulate cell proliferation, cell differentiation, and cell death [73]. The mitogen-activated protein kinase (MAPK) pathway includes the RAS G protein and RAF, MEK, and ERK protein kinases; it is thus also referred to as the RAS-RAF-MEK-ERK pathway [74]. A signal from cell surfaces receptors is communicated through this pathway to DNA, and many of the known mutations result in increased gene expression. Mutations in RAS proteins (HRAS, KRAS, NRAS) are common in cancer, although only *NRAS* mutations are common in melanoma (15-20%). Three RAF proteins are found in mammals, with *BRAF* mutations occurring in many cancers, including 50% to 70% of human melanomas. Approximately 45% to 50% of cutaneous melanomas have activating *BRAF* mutations [1,2,75-79], with 70% to 90% of these having a V600E mutation (formerly labelled V599E). Approximately 5% to 20% of *BRAF* mutations are V600K mutation, while approximately 5% are other mutations [77,80-82]. The proportion of V600K may increase with age and cumulative sun exposure, and vary with

geographic location of patients and body site of melanoma (higher proportion in head and neck cancers and lower for extremities). An analysis of mutations by Iida et al. [83] reported higher rates of *BRAF* (50.0% vs. 12.2%) and *NRAS* (29.2% vs. 17.1%) mutations in cutaneous compared with mucosal melanomas. Vemurafenib and dabrafenib are inhibitors of mutant *BRAF* and effective for both V600E and V600K mutations in unresectable melanoma [81,84-87], although the response to dabrafenib is lower for V600K mutations [87]. Other *BRAF* mutations may also responds to these and other BRAF inhibitors, but due to the low mutation frequency available data are mainly from preclinical or small non-randomized studies.

MEK1 and *MEK2* (*MAPKK1* and *MAPKK2*) are targets in the MAPK pathway downstream from those for *BRAF*. Inhibitors of MEK are also expected to be clinically useful in patients with *BRAF* mutations, thus leading to use in *BRAF* 600E/K mutations. Mutations in the genes corresponding to *MEK1* and *MEK2* were found by Palmieri et al. in 3.9% of cutaneous melanomas [88]. Trametinib is an inhibitor of *MEK1* and *MEK2*. As resistance to BRAF inhibitors develops and disease progression occurs for most patients after six to seven months [87,89], trials evaluating combination therapy have been conducted. As dabrafenib and vemurafenib share similar resistance mechanisms, combination with MEK inhibitors may be more effective [87,90,91]. This may also be the case for *BRAF* mutations other than V600E/K which have lower or unknown response to BRAF inhibitors alone.

The phosphatidylinositol 3-kinase and protein kinase B pathway (PI3K-AKT) [88] is a strong regulator of melanoma growth and survival. The *KIT* gene encodes the c-KIT protein, which is a receptor tyrosine kinase of the cell membrane. *C-KIT* is thought to be involved in activation of both the MAPK and PI3K-AKT pathways. Beadling et al. [92] reported *KIT* mutations in 23% of acral melanomas, 15.6% of mucosal melanomas, and 1.7% of cutaneous melanomas; increased copy number was found in 27.3%, 26.3%, and 6.7% of samples. Palmieri et al. [88] reported similar results in a much larger study restricted to cutaneous melanoma, with 2.2% *KIT* mutations and 3.1% *KIT* amplifications. Iida et al. reported *KIT* mutations in 9.8% of mucosal melanoma and 0% of cutaneous melanoma samples [83]. Ross et al. [93] found *KIT* mutations in 23% of anal melanoma compared with 5% of cutaneous melanoma; corresponding *BRAF* mutations were found in 11% versus 42% of cases. *C-KIT* is not necessarily involved in all cancers for which mutations in this gene are present, and therefore treatment targeting *c-KIT* may only be successful in cases of activating mutations where c-*KIT* is a driver gene/mutation [94]. L576P and K642E are the most detected *c-KIT* mutations in melanoma. Effectiveness of KIT inhibitors in disease with increased copy number but no *KIT* mutations is of interest [92], although a phase II trial in unresectable melanoma suggests imatinib might be effective in tumours with *KIT* mutations but not amplifications only [15].

Bevacizumab is a recombinant human monoclonal antibody VEGF, which is a driver of angiogenesis, and is over-expressed in melanoma [95]. It is approved in Canada for use in combination with chemotherapy for metastatic colorectal cancer; locally advanced, metastatic or recurrent non-small cell lung cancer; recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer; and glioblastoma [96,97]. Conditional approval for use in metastatic breast cancer was withdrawn in 2011 by both Canada and the United States [98]. A review on angiogenesis in advanced/malignant melanoma [99] indicates trials have not found a survival benefit of single agent use of bevacizumab. Several trials evaluating use of bevacizumab combined with chemotherapy or immunotherapy are ongoing.

PURPOSE OF REVIEW

The Working Group of the Melanoma Disease Site Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of

this guideline (Section 2), the Working Group members derived the research questions outlined below.

RESEARCH QUESTIONS

1. What systemic therapy should clinicians recommend to adult patients who have been rendered disease-free following the resection of cutaneous melanomas (including all sites of metastases, if present) and who are at high risk for subsequent recurrence?

2. What systemic therapy should clinicians recommend to adult patients who have been rendered disease-free following the resection of mucosal melanomas?

METHODS

This literature search included clinical practice guidelines, systematic reviews, and RCTs. Practice guidelines were evaluated first, as described in Section 3. In the absence of any guidelines suitable for endorsement, a search for systematic reviews and primary studies was conducted. Details for the review, including the research question, population of interest, interventions and comparators, outcomes, inclusion and exclusion criteria, and databases to search were determined prior to the literature review and documented in the Project Plan.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews and meta-analyses as indicated by the search strategy reported in Appendix 2. The previous version of the PEBC/CCO guideline [100] consisted of several systematic reviews covering different time periods (see Appendix 9). Other systematic reviews were only considered if covering additional topics, or if more recent or comprehensive. Reviews conducted prior to 2013 (the search date for version 4 of the PEBC/CCO guideline) were excluded. Identified systematic reviews were evaluated based on their clinical content and relevance; those incorporated into this review were evaluated for quality using AMSTAR 2 [101-103].

Search for Primary Literature

While some important systematic reviews were found (see IFN section of results), they did not cover the topic completely and therefore a systematic review of the primary literature was necessary.

Literature Search Strategy

The literature search was conducted using Embase, MEDLINE, and EBM Reviews (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) from 1996- June 11, 2018 and updated until May 28, 2019. Complete details of the search are reported in Appendix 2. The search strategy combined terms for melanoma plus terms for chemotherapy, immunotherapy, vaccines, or systemic therapy (including specific agents), plus terms for clinical practice guidelines or systematic reviews or RCTs. Abstracts of the 2018 ASCO Annual Meeting (June 1-5, 2018), ESMO 2018 Congress (October 19-23, 2018), and 33rd Annual Meeting of the Society for Immunotherapy of Cancer (November 7-11, 2018) were also searched. At the time of the literature update, abstracts of the ASCO Annual Meeting 2019 and the ASCO-SITC Clinical Immuno-Oncology Symposium 2019 were also reviewed. Publications cited in previous versions of this guideline, in other reviews, or publications of included trials were

added if more recent or complete publications of the same trials were not found in the database search. Google searching was conducted to locate any recent publications for trials indicated to be ongoing or without outcome data. Clinicaltrials.gov was searched February 27, 2019 to identify trials not otherwise located.

Study Selection Criteria and Process

To be included, studies had to be randomized trials of adjuvant systemic therapy in adult patients with melanoma with high risk of recurrence. For therapy to be considered adjuvant there had to have been complete resection (primary melanoma and known metastases) and no known residual disease. Trials of neoadjuvant therapy plus adjuvant therapy in patients determined prior to therapy to have disease that could be completely resected were included. Studies in metastatic or advanced cancer without resection were excluded. Trials in advanced or metastatic cancer that did not specifically mention adjuvant therapy or complete resection, or that reported response of the tumour to treatment were excluded. Only phase III trials in cutaneous melanoma and phase II or phase III trials in mucosal melanoma were included.

In determining risk of recurrence, disease with any of the following characteristics was considered high risk and therefore met the inclusion criteria if there was complete resection:

- Primary melanoma with tumour thickness >4.0 mm (T4 in AJCC 6th, 7th, or 8th editions); if node-negative these fall in AJCC stage IIB (no ulceration) or IIC (ulceration)
- Primary melanoma with tumour thickness >2.0 to 4.0 mm with ulceration (T3b; stage IIB if node-negative)
- Primary melanoma with one or more of the following: positive sentinel lymph nodes (micrometastasis), clinically detected positive regional lymph nodes (macrometastasis), or in-transit, satellite or microsatellite metastases. Any combination of these is considered node positive (N1-3) and stages IIIA to IIIC in the AJCC 6th or 7th editions, or stages IIIA-IIID in the AJCC 8th edition.
- Distant metastasis (stage IV)
- Recurrence of melanoma that had previously been completely resected.

It is noted that AJCC staging categories are for cutaneous melanoma. Staging for mucosal melanoma varies depending on the primary site, and the AJCC staging categories for cutaneous melanoma may not apply. Stage of mucosal melanoma was not used as either an inclusion or exclusion criterion.

Studies including a range of disease stages were included if at least 50% of patients could be considered at high risk, or if patients meeting the high-risk definition were reported separately. Some studies where insufficient details were reported to assess risk of recurrence according to the above parameters were excluded but reported in Appendix 6; this appendix also summarizes trials included in previous versions of this guideline but not meeting the above inclusion criteria.

Trials that did not report survival data (OS, DFS, RFS, or distant metastasis-free survival [DMFS]) were not included, although ongoing trials are noted in Appendix 7. Letters, comments, editorials, and notes were excluded.

A review of the titles and abstracts that resulted from the search, as well as subsequent full-text review for publications that could not be excluded based on the title or abstract, were conducted by one reviewer (GGF).

Data Extraction

Data extraction for the current review was conducted by a Health Research Methodologist (GGF). As this document is an update, some of the data were reproduced from an earlier version of this document [100] and then verified by consulting the primary literature. All extracted data and information was audited by an independent auditor. Ratios, including HR, were expressed with a ratio <1.0 indicating that the experimental arm (or arm listed first) had better outcome than the control or comparison arm. In assessing the quality of trials, factors such as method of randomization, blinding, use of intent-to-treat analysis, reporting of study withdrawals and loss to follow-up, sources of funding, reporting of expected effect size and power calculations, length of follow-up, and whether baseline characteristics were balance in the different trial arms were considered. Trials on targeted therapy or immune-checkpoint inhibitors were also assessed for risk of bias using the Cochrane risk–of-bias tool [104].

Synthesizing the Evidence

Published meta-analyses were found for use of adjuvant IFN-α versus placebo/control and therefore no other meta-analysis on this topic was conducted. For most other trials, the comparisons were different in each study and results for studies were not combined.

RESULTS

A flowchart/PRISMA diagram indicating the number of publications found in the literature search and those included is provided in Appendix 4.

Systematic Reviews

Fifteen systematic reviews [14,33,35,105-116] plus a protocol for a Cochrane review on neoadjuvant therapy [117] are summarized in Appendix 5. The IPD meta-analysis on adjuvant IFN-α by the IMMCG [14] and the Cochrane systematic review and meta-analysis on adjuvant IFN-α by Mocellin et al. [33] are considered the most relevant, are frequently cited by other authors, and will be summarized in the IFN section.

Most other reviews focused on IFN-α [35,105,106,109,111]; they often included pegylated interferon (PEG-IFN) as well. Most covered the major trials of IFN versus non-treatment control (observation, placebo), but none adequately covered the other trials co paring different doses, forms of IFN, or comparisons to other treatments (chemotherapy, vaccines). Adjuvant trials of immune checkpoint inhibitors in melanoma are very recent and therefore the European Organization for Research and Treatment of Cancer EORTC 18071 trial on ipilimumab [29,30] is the only RCT included in any of the published systematic reviews found in the literature search [35,108,110,112]. Two systematic reviews on adjuvant treatment of brain metastasis from melanoma after stereotactic surgery found no RCTs; cohort studies provided low quality evidence for superiority of ipilimumab plus stereotactic radiosurgery over stereotactic radiosurgery alone [113,114] and suggest further studies of targeted therapy or immunotherapies should be conducted. The systematic reviews identified may be a useful reference to the literature and especially the chronological progression of IFN trials, but are not further discussed in this review and have not been assessed for quality. It was concluded that a full literature search and review was required.

Primary Literature

The literature search identified 63 trials (135 publications) that met the inclusion criteria. Compared with version 3 of this guideline, which was the latest to have evidence

incorporated into the recommendations, this guideline includes 28 new trials and 13 updates of previously reported trials. A breakdown of the number of trials and publications is indicated in Table 4-3.

Table 4-3. Number of included trials and publications by type of treatment

Adjuvant therapy	Number of trials included				Number of publications included ‡
	Trials in previous full version*	Additional trials in current search	Total number of trials	Trials with updated results†	
Immune checkpoint inhibitors or targeted therapy	0	8	8	0	28
Interferon (IFN)					
High-dose IFN-α	7	5	12	6	
Intermittent or pulsed high-dose IFN-α	0	2	2	0	
Intermediate-dose IFN-α	1	2	3	1	
Low-dose IFN-α	10	0	10	2	
Pegylated IFN-α	1	1	2	1	
IFN-gamma	2	0	2	0	
IFN – all studies	19	9	28	9	73
Chemotherapy	8	12	20	0	26
Vaccines	9	4	13	4	24
Immunotherapy (not IFN)	7	2	9	0	11
Total §	35	28	63	13	135

* A small number of trials in previous versions do not meet the current inclusion criteria and have not been included in the numbers in the table. Version 3 (2009) is used as the base version, as Version 4 only contained an assessment with new data summarized in an appendix; the literature review and recommendations were not revised.

† Publications which contain more information or longer follow-up for trials previously identified and included. This would also include publications for which only conference abstracts were available in the earlier version of the guideline. Numbers in this column are already reflected in the first column (number of trials in previous full version) and therefore do not increase the total number of trials.

‡ Multiple publications of trials were retained if they reported different aspects or outcomes, and therefore the number of included publications is greater than the number of trials.

§ Some trials are in more than one category and therefore the total number of trials is less than that obtained by adding the columns.

There were also nine ongoing trials (see Appendix 7). Results for included trials are summarized in Tables 4-4 to 4-8. Trials of targeted therapies and immune checkpoint inhibitors are summarized in Table 4-4 [1-3,9-11,26-32,79,95,118-130]; these trials are recent and some trials are still ongoing. Results for trials of IFN are summarized in Table 4-5 [14,16,17,66-71,131-188]. Trials evaluating chemotherapy, vaccines, and immunotherapy with levamisole or BCG are summarized in Table 4-6 [16,17,149-153,177,180,189-205], Table 4-7 [69,132,133,170,195,206-224], and Table 4-8 [189,191-193,195,206,207,225-228], respectively.

Study Design and Quality

This review included phase III RCTs, plus two phase II trials in patients with mucosal melanoma~~)~~. Large randomized trials are generally considered to provide higher-quality evidence than other study designs. The major IFN trials have been thoroughly described and assessed in the Cochrane review by Mocellin et al. [33]. Authors of the Cochrane review concluded that the quality of evidence (GRADE) was high for both DFS and OS. Many of these studies were also described in previous versions of this review [100,229]. Formal quality assessment beyond that in previous versions of this guidelines was therefore considered unwarranted for trials on these topics. Trials of chemotherapy and vaccines were generally negative and will not be the basis of recommendations; therefore, evaluation was limited to the information reported in Table 4-6 and Table 4-7, as well as the initial determination that they met the inclusion criteria.

The SWOG S0008 trial [149] on biochemotherapy versus IFN randomized 432 patients; of these, 402 were eligible and included in the analysis. The trial was randomized but no mention of blinding was reported. Withdrawals and loss to follow-up were included in the CONSORT diagram. Power calculations were provided. Funding was provided by United States National Cancer Institute (NCI) and Novartis; their role beyond funding was not mentioned. The author's assessment based on criteria outlined in the PEBC Handbook is that the trial is of high quality; evaluation using the Cochrane risk-of-bias tool [104] concluded the risk of bias is low for all domains and overall.

For the trials of adjuvant targeted therapy or immune checkpoint inhibitors, items that may be relevant to quality assessment as outlined in the PEBC Handbook are summarized in Appendix 8. These are all large trials and included 498 to 1670 patients. Only abstracts [10,32] have been published for the US Intergroup/ECOG E1609 trial and details required to judge quality were not reported. This is a large multicentre trial (954 locations in the United States and Canada; see clinicaltrials.govhttps://clinicaltrials.gov/ct2/show/NCT01274338) sponsored by the NCI and managed by ECOG. The cut-off date for primary analysis was 2/15/2019. The AVAST-M trial [79,95] received funding from Roche but Roche had no role in study design, analysis, or interpretation. The participants were not blinded in the E1609 and AVAST-M trials. The remaining trials were double blind and funded by pharmaceutical companies; these companies were involved in design and analysis. All trials (other than the E1609 trial for which details are not available) were analyzed on an intent-to-treat basis, noted reasons for withdrawals, and reported on sample size and power calculations. While the role of the pharmaceutical companies in the trials is of some concern, the overall evaluation based on these items stipulated for evaluation in the PEBC Handbook is that these trials provide high-quality evidence. Additional evaluation using the Cochrane risk-of-bias tool [104] concluded that all trials with a complete publication had low overall risk of bias. There was some concern about the selection of reported results for the BRIM8 trial as the investigators amended the protocol due to a slow event rate leading to it being underpowered at time of analysis for Cohort 2. With this exception, all domains for these trials also were rated as low risk of bias. As noted above, the E1609 trial has only been published as an abstract and many details were not reported. There was therefore a rating of "some concerns" overall and for most of the domains for the E1609 trial.

Immune Checkpoint Inhibitors and Targeted Therapies

Ipilimumab versus Placebo

The EORTC 18071 trial [29,30,120] (see Table 4-4) compared ipilimumab at 10 mg/kg to placebo in 951 patients with resected regional lymph-node positive (stage III) cutaneous melanoma. Complete regional lymphadenectomy was required. Treatment was every three weeks for four doses followed by maintenance therapy every three months up to three years. The primary endpoint was RFS, with OS, DMFS, safety, and health-related quality of life (HRQoL) as secondary endpoints. The five-year OS was 65.4% versus 54.4% (HR=0.72, 95.1% CI=0.58 to 0.88, p=0.001). RFS (40.8% vs. 30.3%) and DMFS (48.3% vs. 38.9%) were also significantly improved with ipilimumab. Additional follow-up (median 6.9 years) found the benefit was sustained [31].

Adverse events (AEs) occurred in 98.7% of patients with ipilimumab and 91.1% on placebo. Grade 3 or 4 AEs occurred in 54.1% versus 26.2% of patients. Immune-related AEs were more frequent with ipilimumab (grade 3 to 4 AEs 41.6% vs. 2.7%); gastrointestinal, hepatic, and endocrine AEs were most common. Median onset of grade 2 to 5 immune-related AEs was 4.0 weeks for skin and 13.1 weeks for neurologic events. Grade 2 to 5 endocrine events resolved in 51.5% of patients with a median of 54.3 weeks, while 82-97% of other immune-related AEs resolved in a median of four to eight weeks. Death attributed to ipilimumab occurred in five patients (1.1%): three due to colitis, one due to myocarditis, and one with one multi-organ failure associated with Guillain-Barré syndrome. Ipilimumab had a statistically significant effect on global health scores (77.32 vs. 72.96, p=0.00011 during induction; 76.48 vs. 72.32, p=0.00067 after induction) but these differences were considered not clinically relevant (change of 10 points) on the global health scale of HR QoL [120]. Mean HR QoL scores at week 10 differed by more than 10 points for diarrhea (7.67 vs. 18.17) and insomnia (15.17 vs. 25.60).

In the ipilimumab group 53.3% discontinued due to AEs (51% considered drug-related; 38.6% in the first 12 weeks) compared with 4.6% in the placebo group. In the ipilimumab group, 28.7% discontinued due to recurrence versus 59.5% in the placebo group. Only 13.4% of patients in the ipilimumab group and 30.2% in placebo group completed the three-year treatment period. The authors noted that the trial cannot address the question of maintenance therapy (treatment beyond 3 months).

Ipilimumab versus IFN

The US Intergroup/ECOG E1609 trial [10,32] (see Table 4-4) randomized 1670 adult patients with resected high-risk melanoma (stages IIIB, IIIC, IV or recurrent) to ipilimumab 3 mg/kg versus ipilimumab 10 mg/kg versus HD-IFN-α2b. Primary outcomes were RFS and OS, both to be assessed up to 20 years. Adult recruitment was completed in 2014 (arms for ages 12-17 ongoing) and preliminary results in abstract form have been released Unplanned analysis at median 3.1 years follow-up reported three-year RFS of 56% (95% CI=50% to 61%) with ipilimumab 3 mg/kg versus 54% (95% CI=49% to 60%) with ipilimumab 10 mg/kg. At approximately 4.5 years after accrual of the last patient OS was significantly better for 3 mg/kg ipilimumab compared with HD-IFN-α2b (HR=0.78, 95.6% CI=0.61 to 1.00, p=0.044) and there was a trend to benefit for RFS (HR=0.0.85, 99.4% CI=0.66 to 1.09, p=0.065). There was also a trend for benefit of 10 mg/kg ipilimumab compared with HD-IFN-α2b for OS (HR=0.88, 95.6% CI=0.69 to 1.12] and RFS (HR=0.84, 99.4% CI 0.65 to 1.09). Grade 3+ AEs (mostly immune-related) for ipilimumab 3 mg/kg versus ipilimumab 10 mg/kg versus HD-IFN-α2b were experienced in 37% versus 58% versus 79% of patients, leading to treatment discontinuation in 35% versus 54% versus 20%, respectively. Grade 5 AEs at least possibly treatment-related occurred in three versus eight versus two patients (0.6% vs. 1.6% vs. 0.3%, respectively).

Nivolumab versus Ipilimumab

The CheckMate 238 trial [1,11] (see Table 4-4) randomized 906 patients with complete resection of stage IIIB, IIIC, or IV melanoma to one year of either nivolumab (3 mg/kg every two weeks) or ipilimumab (10 mg/kg every three weeks for four doses then every 12 weeks thereafter starting at week 24). Complete regional lymphadenectomy or resection was required. The primary endpoint was RFS, with secondary endpoints of OS, safety and adverse effects, RFS according to PD-L1 expression, and HRQoL; DMFS was an exploratory endpoint. A full publication reported one-year RFS (overall and by subgroups) and safety results, as well as 18-month RFS [1]. Abstracts provided an update and reported two-year RFS [11,230]. RFS was significantly better for nivolumab (1-year RFS 70.5% vs. 60.8%, HR=0.65 [95% CI=0.51 to 0.83, p<0.001]; 18-month RFS 66.4% vs. 52.7%; two-year RFS 62.6% vs. 50.2%, HR=0.66, p<0.0001). There was RFS benefit for nivolumab in almost all subgroups tested (those defined by age, sex, stage, ulceration, PD-L1 status, or *BRAF* status). Mucosal melanoma is the only subgroup for which results suggest ipilimumab may have greater benefit, although this is based on only 29 cases and results were not statistically significant (RFS 31% nivolumab vs. 54% ipilimumab, HR=1.57, 95% CI=0.57 to 4.33).

There were fewer treatment-related grade 3 to 4 AEs with nivolumab (14.4% vs. 45.9%). Discontinuation due to AEs occurred in 9.7% of patients receiving nivolumab and 42.6% of patients administered ipilimumab. There were two deaths (marrow aplasia and colitis) related to adverse effects of ipilimumab. Full (1 year) treatment was completed by 60.8% versus 26.9% of patients.

Nivolumab versus Placebo

The CheckMate 238 trial [1,11] (see Table 4-4) found lower rates of RFS and AEs with nivolumab than ipilimumab (10 mg/kg); however there have been no adjuvant trials comparing nivolumab and placebo. An indirect comparison was of nivolumab to placebo was conducted based on the EORTC 18071 and CheckMate 238 trials, and reported in two conference abstracts [26,122]. Data for stage IIIB and IIIC cutaneous melanoma from the two trials were pooled using propensity score weighting. They calculated one-year RFS of 74.2% for nivolumab, 61.9% for ipilimumab, and 48.7% for placebo, and 18-month RFS of 70.7%, 54.1%, and 41.8%.

Pembrolizumab versus Placebo

The Keynote 054/EORTC 1325 trial (see Table 4-4) evaluated adjuvant pembrolizumab (200 mg every three weeks for one year) compared with placebo in patients with stage IIIA, IIIB, or IIIC resected melanoma [2]. All patients had complete regional lymphadenectomy. The patient population met the same criteria as in the EORTC 18071 trial of ipilimumab. PD-L1 expression was determined in positive lymph nodes. The primary outcome was RFS overall and in the subgroup with PD-L1-positive tumours, with secondary outcomes of DMFS, OS, safety, and HRQoL. For the overall population, one-year RFS was 75.4% versus 61.0% (HR=0.57, 98.4% CI=0.43 to 0.74, p<0.001) and 18-month RFS was 71.4% versus 53.2%. For the PD-L1-positive subgroup, one-year RFS was 77.1% versus 62.6% (HR=0.54, 95% CI=0.42 to 0.69, p<0.001). Pembrolizumab was also effective in PD-L1-negative tumours (HR=0.47, 95% CI=0.26 to 0.85, p=0.01). RFS was better with pembrolizumab than placebo in all subgroups evaluated.

Treatment was discontinued due to AEs in 13.8% (13% drug-related) of patients on pembrolizumab and 2.2% on placebo (1.6% placebo-related). Trial-related AEs occurred in 77.8% versus 66.1% of patients; grade 3-5 AEs occurred in 14.7% versus 3.4% of patients. One pembrolizumab-related death due to myositis occurred. Immune-related AEs occurred in 37.3% versus 9.0% of patients (grade 3 to 4 AEs 7.1% vs. 0.6%). Endocrine disorders were higher with pembrolizumab (23.4% vs. 5.0%), with the most common ones being hypothyroidism (14.3% vs.

2.8%) and hyperthyroidism (10.2% vs. 1.2%); of these all except one case were grade 1 to 2. Grade 3 to 4 AEs included colitis (2.0% vs. 0.2%), hypophysitis or hypopituitarism (0.6% vs. 0%), and type 1 diabetes mellitus (1.0% vs. 0%). The trial authors indicated that the rate of AEs was similar to that in trials of nivolumab and much lower than for ipilimumab.

Vemurafenib versus Placebo

The BRIM8 trial (see Table 4-4) was designed to test adjuvant use of vemurafenib versus placebo in melanoma with *BRAF* v600 mutations [28]. There was an unusual hierarchical design, in which stage IIIC patients were treated as a separate cohort (Cohort 2) on the assumption that effect, if any, would be greater in more advanced disease. Cohort 1 (stage IIC-IIIB) was only to be analyzed if Cohort 2 DFS was significant. This has led to interpretative difficulty, as there was no significant difference in DFS (although the survival curves suggest benefit up to 18 months but not thereafter) or OS for Cohort 2. In contrast, exploratory analysis (because of restrictions specified in the trial design) of Cohort 1 found numerically better two-year DFS (72.3% vs. 56.6%; HR=0.54, 95% CI=0.37 to 0.78, p=0.0010) and two-year DMFS (81.0% vs. 61.8%; HR=0.58, 95% CI=0.37 to 0.90, p=0.0133). For the two cohorts combined, there was improved DFS (HR=0.65, 95% CI=0.50 to 0.85, p=0.0013). Effect, if any, on two-year OS was less than for DFS. In Cohort 2 OS was 83.7% versus 85.4% (p=0.86) and in Cohort 1 was 93.4% versus 86.8% (p=0.10). AEs were reported in 99% versus 89% of patients, and most were grade 1 to 2 in severity and manageable. Grade 3 to 4 AEs occurred in 57% of patients administered vemurafenib versus 15% with placebo, with serious events in 16% versus 10%. Of the grade 3 to 4 AEs, squamous cell carcinoma of the skin occurred in 7% versus 1%, keratoacanthoma in 10% versus 1%, arthralgia in 7% versus 0%, and rash in 6% versus 1%. Treatment was discontinued due to AEs in 20% versus 2% of patients. Dose was modified in 63% of patients in the vemurafenib group and 15% in the placebo group.

Dabrafenib plus Trametinib versus Placebo

The COMBI-AD trial (see Table 4-4) used dabrafenib, which is a BRAF inhibitor, together with the MEK inhibitor trametinib in patients with resected stage III melanoma with *BRAF* V600E or V600K mutations [3,9]. All patients had undergone completion lymphadenectomy. There was a significant improvement in four-year RFS with dabrafenib plus trametinib compared with placebo (54% vs. 38%, HR=0.49, 95% CI=0.40 to 0.59), as well as DMFS. There was also improved three-year OS (86% vs. 77%; HR=0.57, 95% CI=0.42 to 0.79, p=0.0006), although this was considered not significant due to the interim analysis boundary set, and therefore follow-up is continuing. RFS with dabrafenib plus trametinib was better than for placebo in all subgroups (T1, T2, T3, T4; N1, N2, N3; with or without in-transit metastases; superficial spreading melanoma, nodular melanoma) [27]. AEs occurred in 97% versus 88% of patients. Grade 3 to 4 AEs occurred in 41% versus 14% of patients, of which 36% versus 10% were considered serious. This included one death due to pneumonia in the treatment arm. Rates of AEs were highest in the first 3 months and then declined [130].

A follow-up paper compared the COMBI-AD trial for patient distribution using AJCC 7th versus AJCC 8th edition [9]. For stage IIIA (7th), 40% were reassigned to stage IIIB and 12% to stage IIIC. For stage IIIB (7th), 4% were reassigned to stage IIIA and 42% to stage IIIC. For stage IIIC (7th), <1% were reassigned to stage IIIA, 13% to stage IIIB, and 11% to stage IIID. While the differences in staging according to AJCC 7th or AJCC 8th do not affect the classification as being "high-risk", they may affect eligibility for treatment if eligibility is narrowly defined by substage.

Bevacizumab versus Observation

The AVAST-M trial ([79,95], see Table 4-4) tested adjuvant bevacizumab in patients with resected stage IIB, IIC, or III cutaneous melanoma. The primary endpoint was detection of an 8% difference in 5% OS compared with standard observation, with DFS or DMFS (both defined to include only melanoma-related deaths) as secondary outcomes, and assessment of biological predictive and prognostic markers as tertiary endpoints. The trial found no difference in five-year OS (64% for both groups, p=0.78). The bevacizumab group did have better five-year DFS (51% vs. 45%, HR=0.85, 95% CI=0.74 to 0.99, p=0.03).

BRAF mutation status was determined in 48% of patients, and of these, 45% had V600 mutations. In this subgroup, there was a trend suggesting bevacizumab may have benefit (OS 63% vs. 55%, HR=0.80, 95% CI=0.57 to 1.13; DFI 48% vs. 40%, HR=0.81, 95% CI=0.60 to 1.10); this would need to be confirmed in a larger trial of patients with this mutation.

Interferon

Twenty-eight trials of IFN are summarized in Table 4-5. Nineteen of these were included and discussed in detail in earlier versions of this review [229,231]; only a brief summary is included here. More recent or complete publications were found for nine of the previously included trials. Most trials studied IFN-α2a (Roferon®-A) or IFN-α2b (Intron® A); these two forms differ in a single amino acid at position 23 [33] and were not directly compared in any of the included studies. It was the contention of the authors in the previous versions of this review that there is not enough evidence to suggest these two forms should be viewed differently.

Published Meta-analyses

Due to the existence of many trials of HD-IFN or LD-IFN with contradictory or non-significant effects, several meta-analyses of the data have been undertaken. The most recent and comprehensive, as noted earlier, are the IPD by Ives et al. [14], and the Cochrane meta-analysis by Mocellin et al. [33] and their conclusions will replace those of the meta-analyses on IFN conducted for previous versions of this review [100,229]. Many of the other trials (i.,e., trials not included in these meta-analyses) evaluated combinations of IFN with other agents (chemotherapy, vaccines, immunomodulators) or different schedules or doses of IFN and were therefore too diverse to be included in the meta-analyses; these trials are summarized in the next section.

Based on evaluation using the AMSTAR 2 tool [101-103] there is high confidence in the Cochrane systematic review, with an exception being a lack of reporting of the sources of funding for included trials. The IPD meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data (PRISMA-IPD) guidelines [232], suggesting the authors considered the requirements, although many are not reported in the actual publication. Despite these shortfalls in reporting, it is considered an important and high-quality IPD meta-analysis. This is based on knowledge from other reviews (including the current one) that most major trials were included, the data collection and analysis procedures described, and the meta-analysis results reported.

The IMMCG IPD meta-analysis [14] and Cochrane meta-analysis [33] cover most of the trials of IFN versus observation and some comparing two doses/durations of IFN. The trials included in these reviews are clearly indicated in Table 4-5. Both used 17 of the same trials in their meta-analyses. EORTC 18871 and German Cancer Society (DKG) 80-1 trials were published together [179] and counted as one trial in the Cochrane review but two in the IMMCG IPD meta-analysis. In addition, the Cochrane group added the E1697 trial (4 weeks IFN vs. none) and noted an Italian trial [233] met the inclusion criteria but was not used in the meta-analysis. This Italian trial was also excluded from the current review. Both meta-analyses included the

ECOG 2696 trial [234]. This was a small vaccine trial (107 patients) comparing GM2-KLH/QS-21 vaccine plus IFN starting either day 1 or day 28 versus GM2-KLH/QS-21 vaccine; as a phase II trial it did not meet the inclusion criteria of the current review.

The reader should be cognizant of the fact that the Cochrane and IPD meta-analyses represent analyses of the same set of studies. While it could be argued that only one of these should be mentioned, we consider that comparison of the IPD meta-analysis and published data meta-analysis is useful. The Cochrane review, but not the IPD, includes details for individual studies and their quality, as well as AEs, while the IPD allows subgroup analysis not possible using the separate trial publications.

Cochrane Systematic Review and Meta-analysis [33]

The Cochrane meta-analysis [33] included 18 RCTs with 10,499 patients; of these, 17 trials were used in the meta-analysis for DFS and 15 for OS. The report indicates that a search in September 2015 found no relevant new results. The meta-analysis included trials comparing IFN-α to observation or any other treatment in patients with regional lymph node metastasis (and undergoing radical lymph node dissection) or with tumour thickness >1 mm. Adjuvant IFN improved DFS (HR=0.83, 95% CI=0.78 to 0.87, p<0.00001) and OS (HR=0.91, 95% CI=0.85 to 0.97, p=0.003). This represents an absolute improvement of approximately 6% for five-year DFS and 3% for OS. They calculated that 35 patients would need to be treated to prevent one death (5-year survival). Subgroup analysis did not answer whether IFN duration and dose impacted efficacy, or whether subgroups (positive or negative lymph node status) would benefit more. The authors noted that there were several RCTs that randomized patients to different IFN doses, but these did not meet their inclusion criteria and could not be pooled due to heterogeneous study designs. Grade 3 and 4 AEs varied greatly, with no grade 3 fever or fatigue in some trials, and up to 8% fever and 23% fatigue in others. Grade 4 fever or fatigue occurred in less than 1% of patients. Adverse effects impaired quality of life but disappeared after treatment discontinuation. The authors concluded that "the results of this meta-analysis support the therapeutic efficacy of adjuvant IFN-α for the treatment of people with high-risk (AJCC TNM stage II-III) cutaneous melanoma in terms of both disease-free survival and, although to a lower extent, overall survival."

The meta-analysis used data from abstracts for the Sunbelt [235] and E1697 [236] trials, and a report for the EORTC 18952 at median 4.6 years follow-up [160]. Full publications of the Sunbelt [70] and E1697 trials [148], and longer-term follow-up of the EORTC trial (median 11 years, [158]) were found in the current search. The updated publications are not expected to alter the meta-analysis conclusions.

Individual patient data meta-analysis of adjuvant IFN-α

The IMMCG conducted an IPD meta-analysis on the use of adjuvant IFN-α in high-risk melanoma, with full publication in 2017 [14]. The preliminary report had been published a decade earlier in abstract form [237] and has been often cited, including in the previous version of this guideline. The updated meta-analysis [14] included studies comparing IFN-α versus no IFN-α (observation only), and did not consider comparisons to other agents or vaccines for the primary analysis. It included 15 IFN trials (14 trials of IFN and 1 of PEG-IFN) with 7744 patients (7699 analyzed); IPD was available from 11 of these trials (5861 patients) and summary data from the other trials were used. Included trials are noted in Table 4-5. Two vaccine trials, namely ECOG 1694 [69] (IFN-α2b versus GM2-KLH/QS-21 vaccine) and ECOG 2696 [234] (a phase II trial excluded from the current review; GM2-KLH/QS-21 vaccine plus IFN starting either day 1 or day 28 versus GM2-KLH/QS-21 vaccine) were not included in the primary analyses, but it was reported that adding in IPD from these trials gave the same results.

Primary outcomes were EFS and OS. IFN-α resulted in a significant improvement in EFS (HR=0.86, 95% CI=0.81 to 0.91, p<0.00001) and OS (HR=0.90, 95% CI=0.85 to 0.97, p=0.003). For trials providing IPD, five-year OS was 49.1% versus 46.1% and ten-year OS was 39.9% versus 37.1%; five-year EFS was 37.8% versus 34.3% and ten-year EFS was 31.2% versus 28.5%. While statistically significant, the absolute differences are small.

IFN benefit did not differ according to dose (no significant trend in effect for high [20 MU/m^2], intermediate [5-10 MU/m^2], low [3 MU/m^2], very low [1 MU/m^2]) or duration of treatment (≤6, 12 to 18, ≥24 months). Given the difference in usage of HD-IFN and LD-IFN by jurisdiction and toxicity of long-term HD-IFN, this finding may be especially important. For EFS, HR=0.83 for high dose (95% CI=0.72 to 0.96, p=0.01), HR=0.84 for intermediate dose (95% CI=0.74 to 0.95, p=0.006), HR=0.85 for low dose (95% CI=0.77 to 0.94, p=0.001), and HR=0.99 for very low dose (95% CI=0.80 to 1.23, p=1.0). These results suggest that low-, intermediate-, or high-dose IFN have similar benefit, while data are unclear for very low doses (EORTC 18871 and DBG 80-1 trials). For OS, the effect is weaker, and statistically significant only for the low-dose group (HR=0.86, 95% CI=0.77 to 0.96, p=0.007); however, non-significant for the intermediate dose group (HR=0.91, 95% CI=0.79 to 1.04, p=0.2) and for the high-dose group (HR=0.93 , 95% CI=0.80 to 1.08, p=0.3).

The meta-analysis also did not find a differential IFN benefit according to age, sex, site of primary tumour, disease stage (I/II or III/IV), Breslow thickness, or presence of clinical nodes. For patients with ulcerated tumours there was improved EFS (5-year EFS 32.9% vs. 26.9%, ten-year EFS 27.3% vs. 20.4%; HR=0.79, 99% CI=0.66 to 0.94, p=0.0006) and OS (5-year OS 46.0% vs. 38.1%, ten-year OS 38.5% vs. 28.0%; HR=0.77, 99% CI=0.64 to 0.92, p=0.0002). In contrast, in patients with non-ulcerated tumours there was no benefit for EFS (5-year EFS 43.2% vs. 40.7%, ten-year EFS 35.5% vs. 34.5%; HR=0.95, 99% CI=0.82 to 1.10, p>0.1, p=0.04 for interaction) or OS (5-year OS 53.7% vs. 53.2%, ten-year OS 44.7% vs. 43.4%; HR=1.02, 99% CI=0.87 to 1.20, p>0.1, p=0.002 for interaction). The ongoing EORTC 18081 (NCT01502696) trial being conducted in patients with ulcerated melanoma may confirm this finding.

Adverse Effects of IFN

An analysis of quality of life [134] found that for the E1684 trial rates of toxicity were 0.7% none, 25.2% mild-moderate, 67.1% severe, and 7.0% laboratory toxicity (severe myelosuppression, hematoxicity, or renal dysfunction requiring dose reduction or discontinuation). Corresponding data from the 1690 trial were 1.9% none, 16.7% mild-moderate, 52.6% severe, and 28.8% laboratory toxicity. A quality of life analysis of the AIM-high study [176] found LD-IFN-α2a (compared with placebo) resulted in worse HRQoL (role functioning, emotional functioning, cognitive functioning, social functioning, global health status), symptom scores (fatigue, nausea and vomiting, appetite loss, constipation, diarrhea), and more financial difficulty. The Nordic trial [165] found that patients receiving intermediate-dose IFN (compared with observation only) had decreased functioning and quality of life and more AEs (alopecia, fever, headache, chills, stiff muscles); most improved after IFN completion.

Adverse effects of HD-IFNα and their management based primarily on the E1684, E1690, and 1694 trials has been reviewed by others [34,35]. Dose reduction or delay was required in 28% to 44% of patients during the induction phase and 36% to 52% of patients in the maintenance phase in these trials. Treatment was discontinued due to AEs in 10-26% of patients. Flu-like symptoms such as fever chills, headache, myalgia, nausea, and vomiting are common acute symptoms, occurring in 66% to 81% of patients (4-18% grade 3+). Tolerance may develop if HD-IFNα is administered daily, but otherwise recurs with each cycle. Fatigue, which has been reported in 70% to 100% of patients (18% grade 3+) and neuropsychiatric symptoms increase in

severity over time. Other AEs are anorexia, cardiotoxicity, hepatotoxicity, autoimmunity, erectile dysfunction, ocular toxicity, and altered laboratory findings (hematologic parameters, hypertriglyceridemia). These AEs often have a profound negative effect on quality of life, and may be life-threatening. With careful monitoring, supportive care, and dose modifications, most AEs are manageable.

Other IFN Trials

Short-term IFN

The Hellenic Cooperative Oncology Group (HeCOG) trial [145] compared IFN-α2b for 4 weeks versus 52 weeks, while the larger E1697 trial [148] compared HD-IFN-α2b for 4 weeks versus observation. E1697 found no survival benefit of IFN but worse quality of life. While the HeCOG study found no significant difference for longer or shorter duration, there was no observation arm and the study was designed as a non-inferiority study to detect >15% difference in three-year RFS. As the benefit of IFN is generally less than this (see meta-analyses above), the lack of difference in these arms is not unexpected.

IFN dose or duration

The DeCOG MM-ADJ-5 [154] and IMI Mel.A trials [155,156] administered HD-IFN-α2b in an intensified or pulsed manner, with one month treatment either every four months for three cycles (MM-ADJ-5) or every other month for four cycles (IMI-Mel.A), with the comparison arm being standard HD-IFN in both studies. There was no difference in OS in either study. RFS was worse in the MM-ADJ-5 trial but not the IMI Mel-A trial, and in a pooled analysis of these two trials [157] there was no significant differences in RFS or OS. The pulsed treatment had fewer adverse effects and lower rates of treatment discontinuation.

The ECOG 1690 trial compared LD-IFN-α2b and HD-IFN-α2b with observation [68]. There were no differences in OS, while for RFS HD-IFN (5-year RFS 44% vs. 35%, p=0.054 vs. observation) appeared more effective than LD-IFN (5-year RFS 40% vs. 35%, p=0.171 vs. observation). However, this needs to be interpreted in light of the IPD meta-analysis which found no dose-response relationship. AEs were common: 1.9% none, 16.7% mild-moderate, 52.6% severe, and 28.8% laboratory toxicity (severe myelosuppression, hematoxicity, or renal dysfunction requiring dose reduction or discontinuation).

EORTC 18952 [158,160] compared IFN-α2b at 10 MU followed by either 5 MU for two years or 10 MU for one year (same planned total dose in both arms). This trial found the longer duration resulted in numerically better (but not statistically significant) ten-year RFS (p=0.06) and OS (p=0.08) compared with observation. In subgroup analysis, there was no benefit of IFN in non-ulcerated melanoma (HR≥1). In ulcerated cases, the longer duration was significantly better than observation for OS (HR=0.59, p=0.0007), RFS (HR=0.61, p=0.0003), and DMFS (HR=0.57, p=0.0008); 13 months of IFN appeared to have intermediate effect, and results were not statistically significant (OS p=0.13, RFS p=0.16, DMFS p=0.06). IFN benefit was also greater in patients with stage IIB/III-N1 than stage III-N2 patients (palpable nodes).

The Nordic trial compared IFN-α2b at 10 MU for 25 months versus 13 months to observation and found RFS benefit (significant only for 13 month arm) but not OS benefit [164]. These results were incorporated into the IPD meta-analysis.

Pegylated IFN

The EORTC 18991 [181] used pegylated IFN-α2b (PEG-IFN; Sylatron™) versus observation, and found RFS benefit (4-year RFS 45.6% vs. 38.9%, p=0.01; 7-year RFS 39.1% vs. 34.6%, p=0.055) but no difference in OS. In subgroup analysis, PEG-IFN had OS benefit in stage III-N1 ulcerated melanoma (OS 52.6% vs. 34.5%; HR=0.59, 99% CI=0.35 to 0.97, p=0.006). It was approved in the United States based on the RFS benefit in this trial [181,238]. The DeCOG trial comparing PEG-IFN-α2a versus IFN-α2a [187] found PEG-IFN did not significantly improve DMFS, OS, or DFS compared with IFN, but had higher rates of dose reduction or discontinuation and higher rates of grade 3 to 4 neutropenia.

Ulcerated Melanoma (Meta-Analysis of EORTC 18952 and EORTC 18991)

Both EORTC 18952 [158,160] and EORTC 18991 [181,239] stratified patients by stage and ulceration and these factors were explored in a meta-analysis of the two trials [159]. As indicated in the previous sections, ulceration was found to be a predictive of IFN or PEG-IFN efficacy, as well as a prognostic factor. Efficacy was also greater in stage IIb/III-N1 disease and not significant in stage III-N2 disease. Due to the post hoc nature of the analysis, the authors indicate it to be hypothesis generating, and initiated the EORTC 18081 trial of PEG-IFN in patients with stage II ulcerated tumours (see Appendix 7). These two trials comprise a large portion of those with ulcerated melanoma (849 patients out of 1443 total) in the IPD meta-analysis summarized earlier [14], which also found benefit of IFN in ulcerated melanoma, and none in non-ulcerated cases.

IFN-gamma versus Observation

The Southwest Oncology Group (SWOG) 8642 trial [188] and the EORTC 18871 plus DKG 80-1 trials [179] compared interferon-gamma (IFN-γ) to observation. Both trials found no clinical benefit for adjuvant treatment with low-dose IFN-γ.

Chemotherapy

Twenty trials of chemotherapy are summarized in Table 4-6. Dimethyl triazeno imidazole carboxamide (DTIC; drug name dacarbazine) was evaluated in seven trials [177,180,189-193]. No significant benefit was found for most trials, and outcomes were worse than the control arm in the COG 7040 trial [190]. A DeCOG trial [177] found IFN alone improved OS and DFS, but IFN plus DTIC for 2 years did not; it appeared DTIC may have a negative effect. A German study found benefit of IFN (6 months) plus DTIC (2 doses) as indicated by improved OS and DFS. The different results of these two trials may be in the dose/duration of DTIC. Overall these trials suggest DTIC is not an effective adjuvant treatment.

Trials of methyl-CCNU [195], vindesine [198], isotretinoin [197], or megestrol acetate [196] found no benefit of these agents. BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea; carmustine] plus actinomycin-D plus vincristine improved DFS and had a non-significant OS benefit [194]; the trial authors suggested nitrosoureas may have a weak effect as adjuvant treatment, although no additional trials were located.

The SWOG S0008 trial [149] and an earlier MD Anderson trial [153] studied biochemotherapy with cisplatin plus vinblastine plus DTIC plus interleukin-2 plus LD-IFN compared with high and/or intermediate-dose IFN alone. The MD Anderson trial did not find a difference in RFS or OS and was terminated early. The SWOG S0008 trial found improved RFS with biochemotherapy but no difference in OS and more AEs; the authors concluded biochemotherapy (3 cycles) may provide a shorter alternative to 1 year of HD-IFN. Grossmann

[240] suggests that while biochemotherapy was the first treatment to improve DFS compared with IFN, the complexity, cost, and toxicity has prevented it from being widely used.

Two trials in mucosal melanoma found temozolomide plus cisplatin was significantly better than IFN or observation for RFS and that chemotherapy or IFN were both better than observation for OS. These trials will be discussed in a subsequent section on mucosal melanoma.

While isolated limb perfusion has been studied mostly in patients as primary treatment, four trials were identified that used hyperthermic perfusion with melphalan as adjuvant therapy [199-201,203,204]. All trials were conducted in the 1980s. A Swedish trial [199,200] in patients with recurrent melanoma of extremities found no significant survival benefit; it only randomized 69 patients and was underpowered to detect differences. In contrast, small studies in the United Kingdom [203] and Germany [204,205] found isolated limb perfusion improved DFS and OS. The much larger EORTC 18832 trial found a significant improvement in disease-free interval in the first two to three years (trend but no longer significant at longer follow-up) but no difference in OS [201,202]. Two relatively old systematic reviews [241,242] identified the same four studies; as there appears to be no more recent trials these reviews are still considered useful. They concluded adjuvant isolated limb perfusion cannot be recommended for routine use due to lack of survival benefit, and note it was a costly technically and surgically complex procedure conducted in only a few centres worldwide. Management of satellite and in-transit metastasis in melanoma is the topic of a separate PEBC/CCO guideline to be completed in 2019 [243].

Vaccines

Thirteen adjuvant vaccine trials are summarized in Table 4-7. Nine of these were included in the previous version of this review, including four with updated results. None found statistically significant OS or DFS benefit of vaccine treatment. Most promising was the New York trial of GM2 vaccine [213] which found four-year OS of 48% versus 29% (p=0.09) and four-year DFS 56% versus 43% (p=0.22) plus significant results in subsets with GM2 antibody detected or when excluding patients with GM2 antibody prior to treatment. The EORTC 18961 [214] and ECOG 1694 [69] trials used GM2-KLH/QS-21 vaccine, which is based on GM2 vaccine but modified to improve immunogenicity. The EORTC 18961 trial was stopped at interim analysis for futility. ECOG 1694 also closed at interim analysis as it found the RFS and OS with the vaccine to be inferior to IFN. A trial of polyvalent shed antigen vaccine [221] showed longer time to disease progression (p=0.03) and three-year OS of 53% versus 33% (not significant) but closed early due to positive IFN trials. A trial in Australia by Hersey et al. [208] reported five-year OS of 60.6% with vaccinia melanoma cell lysates versus 54.8% for control and ten-year OS 53.4% versus 41% (p=0.068). In the Ad Hoc Melanoma Working Group trial [170], combination LD-IFN and Melacine (an allogenic melanoma lysate) resulted in OS and DFS rates indistinguishable from those of HD-IFN, and with fewer severe neuropsychiatric effects. The trial authors indicated the number of patients was insufficient to demonstrate either equivalency or small differences. Given the small effect of IFN, possible equivalency of LD-IFN and HD-IFN (see meta-analyses summarized earlier in this document), and lack of non-treatment control, it is not possible to determine which (if any) agent was effective.

I*mmunotherapy (other than IFN) and Gene Therapy*

Nine trials of immunotherapy (other than IFN) or gene therapy are summarized in Table 4-8. Four trials of levamisole (three trials included in Table 4-8 plus one not meeting the current inclusion criteria; see Appendix 6) were discussed in detail in previous versions of this review [100,231]. Meta-analysis of five-year death rates yielded a risk ratio of 0.94 (95% CI=0.75

to 1.20, p=0.6). The conclusion was that if levamisole has an impact on the clinical course of malignant melanoma when given in the adjuvant setting, that effect is marginal. Approval for human use was revoked in the United States (1999/2000) and Canada (2003) due to adverse effects (https://www.drugbank.ca/drugs/DB00848; https://en.wikipedia.org/wiki/Levamisole).

Six of the included trials evaluated BCG, either alone or together with chemotherapy or vaccines. Five of these trials were included in previous versions of the review due to the chemotherapy or vaccine arms, but BCG was not evaluated. None of the trials in the current review found a statistically significant benefit for BCG use.

The other trial in Table 4-8 is a phase II trial of rAd-p53 in oral mucosal melanoma and will be discussed in the mucosal melanoma section.

Mucosal Melanoma

HD-IFN-α2b versus temozolomide plus cisplatin were studied in a phase II trial [16] of patients with stage II/III mucosal melanoma and a subsequent phase III trial in stage I-III mucosal melanoma that has been reported only in abstract form [17] (see Table 4-5 and Table 4-6). The phase II trial found temozolomide plus cisplatin to result in better OS and RFS than either HD-IFN or observation. The preliminary phase III trial data appear to confirm these results, reporting better RFS and DMFS with temozolomide plus cisplatin compared with HD-IFN. Estimated median OS was 41.20 months versus 35.73 months (p=0.083); further publication at longer follow-up with actual survival data are required.

A small phase II trial (n=57) on use of recombinant adeno-viral human p53 (rAd-p53) gene therapy [228] (see Table 4-8) found improved two-year survival (39.6% vs. 16.7%) in patients with melanomas of the oral mucosa. Only an abstract publication of this trial was located. A review on Gendicine [244], a product approved in China to treat head and neck cancer, includes this trial.

No other adjuvant trials specifically in patients with mucosal melanoma were located. The Checkmate 238 trial [1] included patients with mucosal melanoma (29 patients, 3.2% of total) and suggests RFS may be better with ipilimumab than nivolumab for mucosal melanoma; this result is not statistically significant due to the small number of patients and events (HR=1.57 nivolumab vs. ipilimumab, 95% CI=0.57 to 4.33). This is in contrast to the overall results for trial, which found nivolumab to result in better RFS. Most other trials on adjuvant therapy in melanoma have been conducted on patients with cutaneous melanoma or melanoma with no further specification. A few trials allowed mucosal melanoma but these were a small portion of the cases and results were not reported separately. E1697 [148] had 28 patients with mucosal melanoma (2.4% of total), E4697 [222] had 30 patients (3.7% of total), and University of California [226] had 2 patients (1.8%); COG 7040 [190] allowed mucosal melanoma as part of the inclusion criteria but did not specify how many patients with mucosal melanoma were included. A few other trials did not specifically allow mucosal melanoma but reported a few cases in the patient/disease characteristics table (HeCOG [145], German trial [180], NCCTG [196], and SWOG 7521 [245]).

Ongoing, Unpublished, or Incomplete Studies

Ongoing trials are summarized in Appendix 7.

DISCUSSION AND CONCLUSIONS

Chemotherapy, Vaccines, and IFN

Despite the large number of phase III RCTs evaluating adjuvant systemic treatments for cutaneous melanoma, trials of chemotherapy, vaccines, or IFN found only small or inconsistent benefits. The additional long-term follow-up results and data from new trials of vaccines or chemotherapy indicate there is still insufficient evidence for their routine use. Several trials were terminated based on more promising results with IFN comparing IFN to no other treatment.

The meta-analyses of trials comparing IFN with placebo/observation found 3-6% improvement in DFS and OS [14,33]. The benefits of IFN appear weak, with optimal dosage and patient factors still unclear. This small OS and DFS benefit must be balanced against the known adverse effects, such as fever and other flu-like symptoms, fatigue, mood change, hematologic and hepatic effects, and overall decreased quality of life. While the ECOG 1690 trial [68] reported high-dose IFN to be better, meta-analyses found low dose and shorter duration to be as effective as longer and higher doses; no optimal dose or duration was indicated. The only patient or disease factor found in the IPD meta-analysis to be relevant in determining IFN benefit was ulceration, generating the hypothesis that IFN may only benefit patients with ulcerated melanoma. The ongoing EORTC 18081 (NCT01502696) trial (estimated completion date April 2019) is being conducted in patients with ulcerated melanoma. The experience of the authors is that IFN is rarely used as adjuvant therapy in Ontario, and this appears to be consistent with the evidence that IFN is of low benefit in unselected patients.

Immune Checkpoint Inhibitors

Ipilimumab has been found to have a survival benefit, with approximately 10% improvement in OS and RFS compared with placebo in the EORTC 18071 trial [29,30,120]. AEs occurred in more than 90% of patients (treatment and placebo), which calls into question the classification of outcomes as AEs, other than immune-related AEs (grade 3 to 4 AEs in 41.6% vs. 2.7% of patients) and deaths (1.1% of those treated with ipilimumab). Ipilimumab appears more effective than IFN, but with more severe adverse effects. Preliminary results from the ECOG 1609 trial [10] comparing ipilimumab (10 mg/kg or 3 mg/kg) versus HD-IFNα suggested equivalent RFS for the two ipilimumab arms but much higher rate of deaths for the higher dose. Later analysis confirmed the superiority of 3 mg/kg ipilimumab compared with HD-IFNα [32].

The CheckMate 238 trial [1,11] compared nivolumab to ipilimumab (10 mg/kg). Nivolumab was found to result in significantly better two-year RFS (62.6% vs. 50.2%) and resulted in fewer treatment-related grade 3 to 4 AEs (14.4% vs. 45.9%) and less treatment discontinuation. Two deaths occurred in the ipilimumab arm. An indirect comparison of the CheckMate 238 and EORTC trials (reported as abstracts [26,122]) found one-year RFS of 74.2% for nivolumab, 61.9% for ipilimumab, and 48.7% for placebo. The better safety profile and lesser toxicity of nivolumab makes it preferred over ipilimumab.

Pembrolizumab is a third immune checkpoint inhibitor evaluated for adjuvant use. The Keynote 054/EORTC 1325 trial compared pembrolizumab with placebo [2] and found one-year RFS of 75.4% versus 61.0% ($p<0.001$).Trial-related AEs occurred in 77.8% versus 66.1% of patients; grade 3-5 AEs occurred in 14.7% versus 3.4% of patients. One pembrolizumab-related death due to myositis occurred. The trial authors indicated that the rate of AEs was similar to that in trials of nivolumab and much lower than for ipilimumab.

Based on RFS data, nivolumab and pembrolizumab appear more effective than ipilimumab, and result in fewer adverse effects. While OS results are not yet available, based on the OS benefit of ipilimumab and results for nivolumab and pembrolizumab in the metastatic setting it is expected that they will have a positive effect on OS as well. All three appear more effective than IFN in the populations studied.

Targeted Therapy

The BRIM8 trial tested vemurafenib versus placebo in patients with melanoma having *BRAF* v600 mutations [28]. While the intent was to include any V600 mutations and an exploratory objective was to assess outcomes in *BRAF* mutations other than V600E, the study used the Cobas *BRAF*^{V600} Mutation Test to identify patients. This test identifies primarily V600E mutations, and does not reliably detect others [82,246]. Of patients tested, 91% had V600E mutations, and results were not reported separately for non-V600E mutations. For stage IIC-IIIB patients (Cohort 1) there was better two-year DFS (72.3% vs. 56.6%, p=0.0010) and two-year DMFS (81.0% vs. 61.8%, p=0.0133), while for stage IIIC patients (Cohort 2) survival curves are suggestive of DFS benefit up to 18 months but not thereafter. An unusual design specified that results for Cohort 1 would not be considered significant unless results for Cohort 2 were significant. Thus while there is extremely low probability (p=0.0010) of the improved DFS in Cohort 1 being due to chance, it cannot be labelled statistically significant. Both DFS and OS results suggest vemurafenib is more effective in those with less disease burden. Grade 1 to 2 AEs were reported in most patients, grade 3 to 4 AEs in 57% versus 15% of patients, and serious events in 16% versus 10%. While vemurafenib appears to have some benefit, the preliminary nature of the results, inconsistency in effect according to disease stage, and hierarchical study design all make interpretation difficult. The current evidence does not support use of vemurafenib in the adjuvant setting.

Combination treatment of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in patients with *BRAF* V600E/K mutations was evaluated in the COMBI-AD trial [3,9]. This combination resulted in significant improvement in four-year RFS and DMFS compared with placebo. There was also improved three-year OS (86% vs. 77%; HR=0.57, 95% CI=0.42 to 0.79, p=0.0006), although this was considered not significant due to the interim analysis boundary set, and therefore follow-up is continuing. AEs occurred in 97% versus 88% of patients. Grade 3 to 4 AEs occurred in 41% versus 14% of patients, of which 36% versus 10% were considered serious. Both vemurafenib and the combination dabrafenib plus trametinib appear to be promising treatments, with the latter combination appearing to be more effective for OS. There were slight differences in the patient population that may need to be further evaluated.

Mucosal Melanoma

Data are extremely limited for mucosal melanoma and it has usually been treated as for cutaneous melanoma, despite know differences in causative mutations. The Checkmate 238 trial [1] allowed mucosal melanoma (29 patients, 3.2% of total) and suggests RFS may be better with ipilimumab than nivolumab for mucosal melanoma; this result is not statistically significant due to the small number of patients and events (HR=1.57 nivolumab vs. ipilimumab, 95% CI=0.57 to 4.33). The trial, however, does suggest a role for immune checkpoint inhibitors. Phase II and preliminary phase III results suggest temozolomide plus cisplatin may be more effective than IFN, although a review by Tyrrell et al. [18] concluded this combination was not effective in metastatic mucosal melanoma.

Table 4-4. Adjuvant targeted therapy or immune checkpoint inhibitors

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
AVAST-M ISRCTN 81261306 Corrie, 2014, 2018 [79,95]	2007-2012 N=1343	IIB, IIC or IIIA-C (AJCC 7th ed)	Cutaneous melanoma	Bevacizumab vs. observation	Bevacizumab (7.5 mg/kg iv 3 weekly for 1 y) vs. observation	6.4 y	OS 62% vs. 61% 5-y OS 64% vs. 64%, HR=0.98 (95% CI=0.82 to 1.16), p=0.78) By subtype: *BRAF* mutant HR=0.80 (95% CI=0.57 to 1.13), p=0.21; *BRAF* wild-type HR=1.17 (95% CI=0.82 to 1.61), p=0.34	DFS: 50% vs. 45% 5-y DFS: 51% vs. 45%, HR=0.85 (95% CI=0.74 to 0.99), p=0.03 5-y DMFS 58% vs. 54%, HR=0.91 (95% CI=0.78 to 1.07), p=0.25	No difference in overall QoL Lee, 2018 [118] [circulating tumour cells]	Bevacizumab improved DFS but not OS
EORTC 18071, NCT00636168 Eggermont, 2016, 2015 [29,30] Barker, 2017 [119] [abstract, subgroup] Coens, 2017 [120] [QoL] Eggermont, 2019 [31] [abstract, longer follow-up]	2008-2011 N=951	Stage III (metastasis to regional lymph nodes; AJCC 7th 2009) Stage IIIA and N1a: only included if nodal metastasis >1 mm	Cutaneous melanoma (excluded ocular or mucosal) Randomization stratified by AJCC 2009 stage (IIIA vs. IIIB vs. IIIC [1-3 positive nodes] vs. IIIC [4+ positive nodes]) and geographic region All had complete regional lymphadenectomy; RT to LN dissection field not allowed	Ipilimumab vs. placebo Reported pt characteristics by both AJCC 2009 and AJCC 2002 criteria; used 2002 criteria in case-report forms	Ipilimumab (10 mg/kg every 3 wk for 4 doses then every 3 mo for up to 3 y or recurrence or unacceptable level of adverse effects) vs. placebo	5.3 y 6.9 y	5-y OS 65.4% vs. 54.4%, HR=0.72 (95.1% CI=0.58 to 0.88), p=0.001 7-y OS 60.0% vs. 51.3%, HR=0.73 (95% CI=0.60 to 0.89), p=0.0021	5-y RFS 40.8% vs. 30.3%, HR=0.76 (95% CI=0.64 to 0.89, p<0.001) 3-y RFS 46.5% vs. 34.5% (HR=0.75, 95% CI 0.64 to 0.90), p=0.0013 5-y DMFS 48.3% vs. 38.9%, HR=0.76 (95.8% CI=0.64 to 0.92), p=0.002 7-y RFS 39.2% vs. 30.9%, HR=0.75 (95% CI=0.63 to 0.88), p=0.0004; median 2.7 y vs. 1.5 y 7-y DMFS 44.5% vs. 36.9%, HR=0.76 (95% CI=0.64 to 0.90),	Grade 3 to 4 AEs 54.1% vs. 26.2% Immune-related AEs grade 3-4: 41.6% vs. 2.7% Deaths due to immune-related AEs: 5 pts (1.1%) vs. 0 Discontinuation of treatment in 53% of pts due to AEs (51% drug-related)	Higher RFS, OS, DMFS but more immune-related adverse effects with ipilimumab

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
			No in-transit metastasis No RT (except for non-invasive cancer) prohibited during screening and treatment phases					p=0.0018; median 5.0 y vs. 2.4 y		
US Intergroup E1609, ECOG E1609; NCT01274338 Tarhini, 2017 [10] [abstract] Tarhini, 2019 [32] [abstract]	2011-2014 N=1670	High-risk melanoma, stratified by AJCC 7th 2009 stages IIIB, IIIC, IV (M1a, M1b); or with recurrence; or unknown primary	Cutaneous melanoma Excluded stage IV with M1c (visceral metastases other than lung, or elevated serum lactate dehydrogenase) Lymphadenectomy of sites with clinically positive lymph nodes or identified by lymphoscintigraphic or dye techniques Disease-free by physical exam and total body imaging (PET-CT, CT, and/or MRI) at time of randomization Previous RT allowed if ≥21 d prior to adjuvant systemic treatment	Ipilimumab 10 mg/kg vs. 3 mg/kg vs. HD-IFN-α2b; 1 y treatment	Ipilimumab 3 mg/kg vs. ipilimumab 10 mg/kg vs. HD-IFN-α2b Ipilimumab: iv over 90 min d1, repeated q21d for 4 courses; starting wk 24 give iv every 90 d for max 4 courses) IFN: high-dose (20 MU/m^2/d) iv days 1-5, 8-12, 15-19, 22-26 then maintenance high-dose (10 MU/m^2/d) sc on days 1, 3, 5; treatment repeated every week for 48 weeks IFN dose from physician fact sheet	3.1 y. Ongoing Minimum 4.5 y	Ipi3 vs. HD-IFN: HR=0.78 (95.6% CI=0.61 to 1.00), p=0.044 Ipi10 vs. HD-IFN: HR=0.88 (95.6% CI=0.69 to 1.12)	3-y RFS 56% vs. 54% vs. not reported [unplanned analysis at 3 y] Ipi3vs. HD-IFN: HR=0.85 (99.4% CI=0.66 to 1.09), p=0.065 Ipi10 vs. HD-IFN: HR=0.84 (99.4% CI=0.65 to 1.09)	Accrual to 10 mg/kg ipilimumab suspended 9/23-11/16/2013 due to toxicity Treatment-related AEs: grade 3+ 37% vs. 58% vs. 79%; grade 5 (at least possibly related) 3 pts vs. 8 pts vs. 2 pts; leading to treatment discontinuation 35% vs. 54% vs. 20%	Toxicity higher at 10 mg/kg vs. 3 mg/kg ipilimumab; at 3.1y no difference in RFS between these arms

CheckMate 238, NCT02388906 Weber, 2017 [1] Weber, 2018 [11] [abstract] Mandalà, 2019 [121] [abstract]	Mar-Nov 2015 N=1325 (NCT) or 906 [11]	Stage IIIB/C or IV (AJCC 7th ed, 2009)	All melanomas except ocular/uveal allowed; mucosal are eligible Mucosal: 29 pts (3.2%) Age ≥15 y Randomization stratified by stage and PD-L1 status Complete regional lymphadenectomy or resection was required Prior RT allowed only as adjuvant therapy after neurosurgical resection for CNS lesions; during trial RFS data censored if pt received tumour-directed RT or surgery without recurrence	Nivolumab vs. ipilimumab	Nivolumab (3 mg/kg q2w for 1 y) + placebo vs. Ipilimumab (10 mg/kg q3w for 4 doses then q12w from wk 24 for up to 1 y or disease recurrence or unacceptable toxicity) plus placebo	Minimum 24 mo	Not yet reported; primary completion Nov 2018; estimated final completion Nov 2019	2-y RFS 62.6% vs. 50.2%, HR=0.66 (p<0.0001) -18-mo RFS 66.4% vs. 52.7% -Stage IIIB/C: 67.3% vs. 55.5%, HR=0.65 (95% CI=0.51 to 0.82) -stage IV 59.8% vs. 50.6%, HR=0.70 (95% CI=0.45 to 1.10) -1-y RFS 70.5% vs. 60.8% (HR=0.65, 97.56% CI=0.51 to 0.83, p<0.001) 2-y RFS higher for nivolumab in all subgroups (stage IIIB, stage IIIC, stage IV, PD-L1 ≥5%, PD-L1 <5%, *BRAF* mutant, *BRAF* wild-type), significance not reported Stage IIIB/C: RFS HR=0. At earlier (18 mo), hazard ratios (95% CI) indicated nivolumab better overall and for most subgroups. Based on only 29 pts, for mucosal subtype HR=1.57 (95% CI 0.57 to 4.33) DMFS 70.5% vs. 63.7%, HR=0.76, p=0.034	At earlier follow-up (minimum 18 mo): Any AEs 96.9% vs. 98.5%, grade 3-5 AEs 25.4% vs. 55.2% Deaths 0% vs. 0.4% (1 each of marrow aplasia and colitis) Treatment related AEs (any grade) Overall 85.2% vs. 97% Fatigue 34% vs. 33% Pyrexia 1.5% vs. 12% Arthralgia 13% vs. 11% Headache 9.7% vs. 17% Gastrointestinal 25.2% vs. 48.3% Diarrhea 24% vs. 46% Colitis 2.0% vs. 9.9% Nausea 15% vs. 20% Abdominal pain 6.4% vs. 10% Skin 44.5% vs. 59.8% Pruritus 23 % vs. 34% Rash 20% vs. 29% Maculopapular rash 5.3% vs. 11% Endocrine Hypothyroidism 11% vs. 6.8% Hyperthyroidism 8.0% vs. 4.0% Hypophysitis 1.5% vs. 11% Hepatic 9.1% vs. 21.2% Increased ALT 6.2% vs. 15% Increased AST 5.5% vs. 13% Treatment related AEs (grade 3+) in > 1% of pts Any 14.4% vs. 45.9% Diarrhea 1.5% vs. 9.5% Pruritus 0% vs. 1.1% Rash 1.1% vs. 3.1% Headache 0.2% vs. 1.5% Increased ALT 1.1% vs. 5.7% Increased AST 0.4% vs. 4.2%	Significant RFS benefit for nivolumab and fewer adverse effects. For mucosal, non-significant recurrence benefit for ipilimumab

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
									Maculopapular rash 0% vs. 2.0% Hypophysitis 0.4% vs. 2.4% Treatment discontinued due to AEs in 9.7% vs. 42.6% First onset of treatment-related AEs with nivolumab was highest in the first 3 mo: 28% fatigue, 16% pruritus, 15% diarrhea. Most resolved within 3 mo except endocrine (median 48 weeks) and skin events (median 22 weeks) No clinically meaningful changes in QoL	
CheckMate 238 and EORTC 18071 (indirect comparison /pooled data) Shoushtari, 2018 [26] [abstract] Hemstock, 2019 [123,124] [abstracts]		Stage IIIB or IIIC		Indirect comparison of nivolumab vs. placebo	Indirect treatment comparison of nivolumab vs. placebo for stage IIIB or IIIC cutaneous melanoma See individual trials for dose and schedule of administration			1-y RFS: 74.2% nivolumab vs. 61.9% ipilimumab vs. 48.7% placebo 18-mo RFS: 70.7% vs. 54.1% vs. 41.8% Number needed to treat to achieve 1 additional recurrence-free survivor: -at 1 y: 3.9 nivolumab vs. placebo; 8.1 nivolumab vs. ipilimumab -at 18 mo: 3.5 nivolumab vs. placebo; 6.0 nivolumab vs. ipilimumab Other group [124] estimated RFS HR as 0.50 to 0.53 and DMFS HR as 0.57 to 0.62 for nivolumab vs. placebo	Value (cost) analysis: Freeman, 2018 [122] [abstract].	Nivolumab gave highest RFS compared with placebo or ipilimumab

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
Keynote 054, EORTC 1325-MG, NCT02362594, EudraCT 2014-004944-37 Eggermont, 2018 [2] Coens, 2018 [125] [126] [QoL abstract/ poster]	2015-2016 N=1019	Stage IIIA, IIIB, IIIC AJCC 7th ed, 2009 Stage IIIA and N1a: only included if nodal metastasis >1 mm	Cutaneous melanoma (excluded mucosal or ocular melanoma) Randomization stratified by stage and geographic region. Analysis overall and by PD-L1 expression Complete regional lymphadenectomy was required No prior therapy except surgery (or IFN for thick primary melanoma without lymph node involvement)	Pembrolizumab vs. placebo	Pembrolizumab (200 mg iv q3w for 18 doses [≈1y] or until recurrence or unacceptable toxic effects) vs. placebo	15 mo	Not yet reported (follow-up ongoing, estimated final completion July 2025)	1-y RFS 75.4% vs. 61.0%, HR=0.57 (98.4% CI=0.43 to 0.74, p<0.001) 18-mo RFS 71.4% vs. 53.2% PD-L1 positive subgroup: 1-y RFS 77.1% vs. 62.6%, HR=0.54 (95% CI=0.42 to 0.69, p<0.001) PD-L1 negative HR=0.47 (95% CI=0.26 to 0.85), p=0.01	Any AEs 93.3% vs. 90.2%, grade 3+ AEs 31.6% vs. 18.5% Treatment-related AEs (any grade) Overall 77.8% vs. 66.1% Fatigue or asthenia 37% vs. 33% Skin reactions 28% vs. 18% Rash 16% vs. 11% Pruritus 18% vs. 10% Diarrhea 19% vs. 17% Nausea 11% vs. 8.6% Dyspnea 5.9% vs. 3.0% Treatment-rated AEs, grade 3-5 Overall: 14.7% vs. 3 .4% Nausea 11% vs. 8.6% All others < 1% 1 death due to myositis in pembrolizumab group Immune-related AEs, any grade Overall 37.3% vs. 9.0% Endocrine 23% vs. 5.0% Respiratory (pneumonitis, sarcoidosis) 4.7% vs. 0.6% Vitiligo or skin 5.3% vs. 1.6% Gastrointestinal 3.9% vs. 0.8% Hepatitis 1.8% vs. 0.2% Immune-related AEs, grade 3+ Overall 7.1% vs. 0.6% Endocrine 1.8% vs. 0% Diabetes 1.0% vs. 0% Gastrointestinal 2.0% vs. 0.4% Colitis 2.0% vs. 0.2% Hepatitis 1.4% vs. 0.2%	Significantly longer RFS Pembrolizumab maintains HRQoL

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
									Mean Global Health/QoL: overall 75.1 vs. 77.3 (p=0.042); during treatment 76.9 vs. 78.0 (p=0.263); after treatment 75.0 vs. 77.2 (p=0.160); difference <5 points and well below clinical relevance threshold	
BRIM8, NCT01667419 Maio, 2018 [28] Schadendorf, 2018 [127] [abstract]	2012-2015 N=498 (N=184 cohort 2; N=314 cohort 1)	Stage IIC, IIIA, IIIB (cohort 1) or stage IIIC (cohort 2) AJCC 7th ed, 2009) For IIIA pts, nodal metastases had to be >1 mm diameter	Cutaneous melanoma *BRAFV*^{v600} mutation positive by Cobas *BRAF*^{V600} mutation test Hierarchical testing of DFS in cohort 2 before cohort 1 was prespecified, cohort 1 could only be significant if cohort 2 had p≤0.05 Cohort 1 randomization stratified by stage Complete regional lymphadenectomy if clinical or radiological evidence of regional lymph node involvement, positive SLN, or SLNB could not be done or SLN not detected	Vemurafenib vs. placebo	Oral vemurafenib (960 mg twice a day for 52 wk in 13×28d cycles) vs. placebo	Cohort 1: 33.5 mo cohort 2: 30.8 mo	Interim analysis only, data immature: Cohort 1 (stage IIC-IIIB): 2-y OS 93.4% vs. 86.8%, HR= 0.60 (95% CI=0.32 to 1.11). p=0.0969 Cohort 2 (stage IIIC): 2-y OS 83.7% vs. 85.4%, HR=0.95 (95% CI=0.50 to 1.79), p=0.8633	Cohort 1 (stage IIC-IIIB): median DFS not reached vs. 36.9 mo, 2-y DFS 72.3% vs. 56.6%, HR=0.54 (95% CI=0.37 to 0.78), p=0.0010; 1-y DFS 84.3% vs. 66.2% Cohort 1: 2-y DMFS 81.0% vs. 66.9%, HR=0.58 (95% CI=0.37 to 0.90), p=0.013; 1-y DFMS 83.2% vs. 77.0% Results for cohort 1 not significant due to prespecified hierarchical prerequisite that Cohort 2 must have significant DFS benefit in order to analyze Cohort 1 Cohort 2 (stage IIIC): median DFS 23.1 mo vs. 15.4 mo, 2-y DFS 46.3% vs. 47.5%, HR=0.80 (95% CI=0.54 to 1.18), p=0.26; 1-y DFS 78.9% vs. 58.0% Cohort 2: median DMFS 37.2 vs. 30.7 mo, 2-y DMFS 57.5% vs. 62.4%, HR=0.91 (95% CI 0.57 to 1.44), p=0.68; 1-y DMFS 83.2% vs. 77.0% Pooled analysis (exploratory): 2-y DFS 62.2% vs. 53.1%	Grade 3 to 4 AEs 57% vs. 15%; most common were keratoacanthoma, arthralgia, squamous cell carcinoma, rash, elevated ALT. Serious AEs 16% vs. 10% Underpowered as placebo arm had much better DFS than expected and analysis conducted early Poor prognosis if low CD8+; vemurafenib DFS benefit significant only in pts with <1% CD8+ T cells in tumour centre (HR=0.56, 95% CI=0.34 to 0.92) or <5% PD-L1+ immune cells (HR=0.36, 95% CI=0.24 to 0.56)	Primary endpoint of DFS in cohort 2 not met; exploratory analysis of cohort 1 suggests possible DFS benefit

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
			Exclude if history or RT for melanoma treatment including RT to resected nodal basin; or if RT for prostate, cervical, or rectal cancer RT prohibited during study treatment period					(HR=0.65, p=0.0013), 1-y DFS 82.2% vs. 63.1%		
COMBI-AD; NCT01682083 Hauschild, 2018 [9]; Long, 2017 [3]; Schadendorf, 2019 [128] Abstracts Schadendorf, 2018 [129] [QoL]; Atkinson, 2018 [130] [AEs]; Schadendorf 2019 [27] [RFS by baseline characteristics]	2013-2014 N=870	Stage III (AJCC 7th ed) with *BRAF* V600E or V600K mutations For IIIA pts, nodal metastases had to be >1 mm diameter	Cutaneous melanoma, stage IIIA, IIIB, or IIIC *BRAF* V600E or *BRAF* V600K mutations All patients had completion lymphadenectomy Excluded if pt had prior RT for melanoma	Dabrafenib + trametinib vs. placebos	Oral dabrafenib (150 mg twice daily) + trametinib (2 mg once daily) vs. placebos for 12 mo	43 mo	3-y OS 86% vs. 77%, HR=0.57 (95% CI=0.42 to 0.79), p=0.0006 OS did not cross prespecified interim analysis boundary of p=0.000019	Median RFS not reached vs. 16.6 mo 4-y RFS 54% vs. 38%, HR=0.49, 95% CI=0.40 to 0.59; RFS significantly better for all subgroups as well 3-y RFS (calculated at median 34 mo follow-up) 58% vs. 39%, HR=0.47, p<0.001 2-y RFS 67% vs. 44% 1-y RFS 88% vs. 56% 4-y DMFS 67% vs. 56%, HR=0.53, 95% CI=0.42 to 0.67) Estimated cure rate 54% vs. 37% Treatment benefit also found for all subgroups analyzed (V600K, V600E; disease stage by AJCC 7th or 8th edition; micro/macrometastasis ±ulceration; number of positive nodes, T stage, in-transit or no in-transit metastases,	Trial not powered to detect difference on basis of type of *BRAF* mutation AEs, any grade Overall 97% vs. 88 Pyrexia 63% vs. 11% Fatigue 47% vs. 28% Nausea 40% vs. 20% Headache 39% vs. 24% Chills 37% vs. 4% Diarrhea 33% vs. 15% Vomiting 28% vs. 10% Arthralgia 28% vs. 14% Rash 24% vs. 11% Cough 17% vs. 11% Myalgia 16% vs. 9% Elevated ALT 15% vs. 1% Elevated AST14% vs. 2% Influenza-like illness 15% vs. 7% Limb pain 14% vs. 9% Asthenia 13% vs. 10% Edema 13% vs. 4% Dry skin 13% vs. 7% Acneiform dermatitis 12% vs. 2% Constipation 12% vs. 6% Hypertension 11% vs. 8%	Dabrafenib + trametinib group had improved RFS and OS Benefit if independent of baseline factors

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
								superficial spreading, nodular melanoma) 4-y DFS AJCC 7th Stage IIIA: 69% vs. 62%, HR=0.58 (95% CI=0.32 to 1.06) Stage IIIB: 56% vs. 37%, HR=0.49 (95% CI=0.37 to 0.66) Stage IIIC: 46% vs. 30%, HR=0.46 (95% CI=0.34 to 0.61) 4-y DFS AJCC 8th Stage IIIA: 75% vs. 71%, HR=0.63 (95% CI=0.26 to 1.56) Stage IIIB: 60% vs. 40%, HR=0.48 (95% CI=0.34 to 0.67) Stage IIIC: 47% vs. 33%, HR=0.50 (95% CI=0.38 to 0.64) Stage IIID: 43% vs. 18%, HR=0.34 (95% CI=0.14 to 0.79)	Decreased appetite 11% vs. 6% Erythema 11% vs. 3% AEs, grade 3 or 4 Overall 41% vs. 14% Pyrexia 5% vs. < 0.5% Fatigue 4% vs. 0.2% Elevated ALT 4% vs. 0.2% Elevated AST 4% vs. 0.2% Hypertension 6% vs. 2% New primary melanoma 3% vs. 2% Other cutaneous cancers 6% vs. 5% Non-cutaneous cancers 2% vs. 1% Deaths: One fatal pneumonia vs. 0 Dose interruption due to AEs in 66% vs. 15% and discontinuation due to AEs in 26% vs. 3% Most AEs occurred during first 3 mo and then declined Visual analogue scale of HR QoL found no clinically meaningful differences between arms; no meaningful change from baseline during treatment or long-term follow-up. Pts from both groups had significant decrease in scores if recurrence occurred	

Abbreviations: AEs, adverse events; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; HRQoL, health-related quality of life; IFN, interferon; iv, intravenous; LN, lymph node; MRI, magnetic resonance imaging; OS, overall survival; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PET-CT, positron emission tomography-computed tomography; pt, patient; pts, patients; QoL, quality of life; RFS, recurrence-free survival; RT, radiation therapy

Back to Results

Table 4-5. Adjuvant IFN trials

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
High-dose IFN											
NCCTG 83-7052 (North Central Cancer Treatment Group) Creagan, 1995 [66]	v3, M1, M2	1984-90 N=264 (103 stage I, 161 stage II)	Stage I (>1.69 mm and N0) or II (N+); Ives [14] redefined as IIA-B or III based on nodal status	Melanoma (subtype not specified) Regional lymph node dissection in stage II pts not mandatory	HD-IFN-α2a (im) vs. observation	20 MU/m^2 im 3×/wk for 12 wk	6.1 y	Median OS 6.0 y vs. 4.4 y, p=0.53; stage II median 4.1 y vs. 2.7 y, p=0.44 5-y OS 54% vs. 48%, p=0.53 (log rank) or p=0.28 (Cox); for stage II subgroup 5-y OS 47% vs. 39%, p=0.44 (log rank) or p=0.25 (Cox)	Median DFS 2.4 y vs. 2.0 y, p=0.19 overall; 17 mo vs. 10.8 mo for stage II 5-y DFS 43% vs. 36%, p=0.24 log rank, p=0.09 cox; stage II subgroup 40% vs. 30%, p=0.09 (log-rank) or p=0.04 (Cox)	Flu-like toxicity in 99% IFN (44% grade 3) vs. 3% observation; grade 3 adverse effects were fever (24%), chills (21%), lethargy (20%) Weight loss ≥10% of baseline weight: 13% vs. 3%, p=0.003 ECOG score decrease 45% vs. 16%, p<0.0001 Data are from text/figures; some data in abstract does not match	Possible DFS and OS benefit for selected pts, need confirmation in larger trial
ECOG 1684 Kirkwood, 1996 [67]; Cole, 1996 [131] Update in pooled analyses: Kirkwood, 2004 [132] and Najjar, 2019 [133]	v3*, M1, M2	1984-90 N=287	AJCC Stage IIB or III: >4 mm, cN0 but pN+, cN+, or regional lymph node recurrence	Cutaneous melanoma Regional lymph node dissection if T4cN0; no prior adjuvant RT, chemo, immunotherapy	HD- IFN-α2b vs. observation	20 MU/m^2 iv 5 d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk	6.9 y	Median OS 3.82 y vs. 2.78 y 36.3% vs. 32.1%, HR=0.82, p=0.18 5-y OS 46% vs. 37%, p=0.0237	Median RFS 1.72 y vs. 0.98 y 34.9% vs. 24.3%, HR=0.72, p= 0.02 5-y RFS 37% vs. 26%, p=0.0023	QoL in pooled analysis, Kilbridge, 2002 [134]: toxicity 0.7% none, 25.2% mild-moderate, 67.1% severe, and 7.0% laboratory toxicity (severe myelosuppression, hematoxicity, or	Significant RFS and OS benefit Benefit at long-term follow-up less than at 5 y; this may be due to competing causes of death in old age

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
							17.9 y	2-y OS 63% vs. 57% HR=0.82 (95% CI=0.62 to 1.08)	HR=0.73 (95% CI=0.56 to 0.97), p=0.28	renal dysfunction requiring dose reduction or discontinuation).	
ECOG 1690, S9111, C9190 Kirkwood, 2000 [68] Kirkwood, 2002 [135]; Rao, 2002 [136] Update in pooled analyses, Kirkwood, 2004 [132] and Najjar, 2019 [133]	v3*, M1, M2	1991-95 N=642 accrued, 608 eligible	Stage IIB or III	Cutaneous melanoma (2 pts vulvar and 4 pts anogenital melanoma) Regional lymph node dissection if T4cN0 not mandatory	HD- IFN-α2b (1 y) vs. LD-IFN-α2b (2 y) vs. observation	HD-IFN (20 MU/m^2 iv 5 d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk) vs. LD-IFN (3 MU sc 3×/wk for 2 y)	6.6 y 12.2 y	49.8% HD-IFN vs. 51.6% LD-IFN vs. 51.4%, HR=1.0 , p=0.98 5-y OS 52% vs. 53% vs. 55% HD-IFN vs. observation HR=1.0, p=0.995 LD-IFN vs. observation, HR=0.96, p=0.813 2-y OS 72% vs. 78% vs. 68% HD-IFN vs. observation: HR=0.94 (95% CI=0.73 to 1.21)	44.2% HD-IFN vs. 40.0% LD-IFN vs. 39.6%, HR=0.81, p=0.09 5-y RFS 44% vs. 40% vs. 35; HD-IFN vs. observation HR=0.78, p=0.054 LD-IFN vs. observation HR=0.84, p=0.171 HD-IFN vs. observation: HR=0.82 (95% CE=0.64 to 1.05), p=0.12	QoL in pooled analysis, Kilbridge, 2002 [134]. Toxicity: 1.9% none, 16.7% mild-moderate, 52.6% severe, and 28.8% laboratory Also in LD-IFN section	Dose-dependent RFS benefit, significant for HD-IFN At relapse, was significantly more frequent use of IFN (31% vs. 15%, p=0.003) and biochemotherapy (17% vs. 6%, p=0.013) in observation arm, and may have confounded OS results
E1684 and E1690 combined [132] Update in Najjar, 2019 [133]							7.2 y	HD-IFN vs. control: HR=0.93, p=0.42	HD-IFN vs. control: HR=0.77, p=0.006		

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
							13.3 y	HR=0.88 (95% CI=0.73 to 1.07), ns	HR=0.78 (95% CI=0.64 to 0.94), p=0.008		
ECOG 1694 Kirkwood, 2001 [69]. Update in pooled analysis, Kirkwood, 2004 [132] and Najjar, 2019 [133]	v3*, M1, M2	1996-99 N=880; 774 eligible for efficacy analysis	Stage IIB/III; or clinically node positive from unknown primary; or nodal recurrence	Cutaneous melanoma Allowed deep lesions (>4 mm) with microscopic satellite lesions within 2 cm; excluded T4 with gross SC invasion or grossly apparent satellite lesions	GM2-KLH/QS-21 vaccine vs. IFN-α2b	Vaccine (1mL sc on days 1, 8, 15, 22; then q12w for weeks 12-96) vs. IFN (20 MU/m^2 iv 5 d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk)	2.1 y (16 mo at un-blinding) 16.0 y	71.1% GMK vs. 76.7% IFN, Calculated at median 16 mo: 2-y OS 73% vs. 78%, HR=1.52, p=0.009 IFN vs. vaccine: HR=0.85 (95% CI=0.71 to 1.01), p=0.068	54.0% GMK vs. 64.2% IFN, Calculated at median 16 mo: 2-y RFS 49% vs. 62%, HR=1.47, p=0.0015 IFN vs. vaccine: HR=0.82 (95% CI=0.68 to 0.98), p=0.34	Trial closed after interim analysis due to GMK inferiority Also in vaccine table	IFN group had better RFS and OS then vaccine group
Sunbelt, UAB-9735, NCT00004196 McMasters, 2016 [70]; Egger, 2016 [137] [QoL]	(v3), M1*, (M2)	1997-2003 N=218+556=774	≥1mm, clinically node-negative, SLN+ allowed	Cutaneous melanoma Randomized if 1 positive SLN (arms 1-2); separate randomization if SLN negative (arms 4-6) A. 1 positive node by SLNB: CLND then observation vs. HD-IFN	HD-IFN-α2b vs. observation (SLN+) Or CLND + IFN vs. CLND vs. observation (SLN- but RT-PCR LN+)	Protocol A: 20 MU/m^2 iv, 5 d/wk for 4 wk, then 10 MU/m^2 sc 3×/wk, 48 wk Protocol B: IFN the same as protocol A initially for 46 pts; from 1999 received only 4 wk iv treatment (138 pts)	71 mo	Protocol A (1 positive SLN): 5-y OS 71.4% vs. 74.8%, HR=1.10 (95% CI 0.69 to 1.76), p=0.68) Protocol B: (SLN- and RT-PCR LN+): CLND + IFN vs. CLND vs. observation, 5-y OS 86.9% vs. 85.9% vs. 85.5%, p=0.77	Protocol A: 5-y DFS 70.9% vs. 67.1%, HR=0.82 (95% CI 0.50 to 1.36), p=0.45 Protocol B: CLND + IFN vs. CLND vs. observation, 5-y DFS 83.9% vs. 84.0% vs. 79.4%, p=0.069	No survival benefit for IFN DFS benefit for CLND vs. observation Several other papers on prognostic factors [138-144]	1 positive SLN: no OS or DFS benefit SLN- but RT-PCR positive nodes: no OS benefit for CLND or CLND + HDI;

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				B. 0 positive nodes by SLNB: staging by RT-PCR: if positive, randomized to observation vs. CLND vs. CLND + HD-IFN				CLND + IFN vs. observation: HR=0.86 (95% CI 0.52 to 1.40), p=0.55 CLND vs. observation: HR=1.00 (95% CI 0.634 to 1.59), p=0.99	CLND + IFN vs. observation: HR=0.68 (95% CI 0.42 to 1.09), p=0.11 CLND vs. observation: HR=0.58 (95% CI 0.35 to 0.94), p=0.0277		
Hellenic Cooperative Oncology Group (HeCOG) Pectasides, 2009 [145] Gogas, 2004 [146]	(v3), v4	1998-2004 N=364, 353 eligible	Stage IIB, IIC, III	Cutaneous melanoma; 12 pts (3%) mucosal melanoma in pt characteristics table but not reported separately	IFN-α2b 4 wk vs. IFN-α2b 4 wk + 48 wk	15 MU/m^2 iv 5d/wk for 4 wk Same as above followed by 10 MU sc (flat dose) 3×/wk, 48 wk	63 mo	Median OS 64.4 mo vs. 65.3 mo, p=0.49 5-y OS 56% vs. 54%; 3-y OS 70% vs. 63%	Median RFS 24.1 mo vs. 27.9 mo, p=0.9 5-y RFS 37% vs. 35% 3-y RFS 44.26% vs. 45.10% (deemed equivalent) 5-y DMFS 42% vs. 38%; 3-y DMFS 55% vs. 50%	Prognostic factors: Gogas, 2006 [147] No statistical difference in grade3-4 AEs; more grade 1 to 2 AEs in 52 week arm	No significant difference in OS or RFS; more adverse effects with longer treatment This is a non-inferiority study and conclude equivalence within limits of study; see E1697 trial
E1697 NCT00003641 Agarwala, 2017 [148]	(v4), (M2)	1998-2010 N=1150	T2bN0, T3a-bN0, T4a-bN0, T1-4N1a-2a	Allowed mucosal melanoma (28 pts, 2.4%) but not reported separately 34% ulceration, 15% >4 mm, 19% node positive	HD-IFN-α2b (4 wk) vs. observation	HD-IFN (20 MU/m^2 iv for 5d/wk×4 wk) vs. observation	7 y	5-y OS 83% vs. 83%, HR=1.08 (95% CI=0.82 to 1.41), p=0.558	5-y RFS 70% vs. 70%, HR=0.98 (95% CI=0.79 to 1.22), p=0.964	Grade 3+ AEs 57.9% vs. 4.6%, p<0.001 Ended early for futility	4 wk IFN not better than observation: same OS but worse QoL

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
SWOG S0008, NCT00006237 Flaherty, 2014 [149]	(v4)	2000-2007 N=432	Stage IIIA-N2a to Stage IIIC-N3 (ulcerated plus SLN+; non-ulcerated plus 2+ positive SLN; regional LN macrometastasis; satellite or in-transit metastasis; regional nodal recurrence)	Excluded mucosal and uveal primaries 53% stage III, 9% stage IIb, 34% stage IIa; Complete regional lymphadenectomy required	Biochemotherapy (cisplatin, vinblastine, DTIC, interleukin-2, IFN) vs. HD-IFN-α2b	Biochemotherapy q21d for 3 cycles (cisplatin 20 mg/m^2 iv d 1-4, vinblastine 1.2 mg/m^2 iv d1-4, DTIC 800 mg/m^2 iv d1, IL-2 9 MU/m^2 iv over 96 h, IFN 5 MU/m^2 d1-5) vs. HD-IFN (20 MU/m^2 iv 5d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk)	7.2 y	Median OS 9.9 y vs. 6.7 y, HR=0.98 (95% CI=0.74 to 1.31), p=0.55 5-y OS 56% vs. 56%	Median RFS 4.0 y vs. 1.9 , HR=0.75 (95% CI=0.58 to 0.97), p=0.029 5-y RFS 48% vs. 39%	Grade 3+ AEs 76% biochemotherapy vs. 64% IFN; profile varied by arm Also in chemotherapy table Publications on minimal residual disease [150], unknown primary melanoma [151], brain metastases [152]	Biochemotherapy shorter alternative to HDI, with improved RFS but no difference in OS and more toxicity than IFN alone
NCT00002882 USA, MD Anderson Kim, 2009 [153]	v4	1995-2003 N=138 (200 planned); stopped for futility	Regional lymph node metastasis with complete lymphadenectomy	Melanoma, subtype not specified in criteria; no pts had mucosal melanoma Stratified by prognosis: favorable (1 involved LN), intermediate (2-4 involved lymph nodes); unfavourable (>4 involved LN, extranodal tumour extension, or tumour recurrence in regional lymph	Biochemotherapy (cisplatin, vinblastine, DTIC, IFN-α2b, interleukin-2) vs. IFN-α2b; IFN patients randomized again to high-does vs. intermediate-dose IFN	Biochemotherapy q3w for 4 cycles (cisplatin 20 mg/m^2 iv d1–4; vinblastine 1.5 mg/m^2 iv d1-4; DTIC 800 mg/m^2 iv d1; IFN 5MU/m^2 sc d1–5; IL-2 9 MU/m^2 iv over 96 h) vs. HD-IFN (20 MU/m^2 iv 5d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk) vs. ID-IFN (10 MU/m^2 sc 3×/wk for 52 wk)	49.3 mo	Median OS 72 mo vs. 66 mo vs. >108 mo HD-IFN vs. ID-IFN, p=0.67 Biochemotherapy vs. IFN (groups combined): 5-y OS 61% vs. 65%, p=0.45	Median RFS >108 mo vs. 58 mo vs. >108 mo HD-IFN vs. ID-IFN, p=0.54 Biochemotherapy vs. IFN (groups combined): 5-y RFS 59% vs. 57%; 2-y RFS 68% vs. 65%, p=0.86	Also in chemotherapy table; also in intermediate dose IFN section Majority of biochemotherapy group had grade 4 hematologic AEs vs. none in IFN group; gastrointestinal and dermatologic AEs more severe in biochemotherapy group; depression and liver enzyme elevation common with IFN	Median RFS and OS not reached. No significant differences in median RFS or OS between HDI and IDI and therefore groups combined (although numbers too small to reveal a modest survival benefit) Concluded biochemotherapy more toxic and not more effective than IFN; trial terminated early based on futility analysis. Trial not

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
				node basin despite prior lymph node dissection)							designed to prove equivalency. See larger SWOG S0008 trial
NCT03435302, BCHMMAT00 (Phase 3) Lian, 2018 [17] [abstract]		2014-2016 N=204	Mucosal Stage I-III	Mucosal melanoma Lymphadenectomy if involved regional lymph nodes	Temozolamide + cisplatin vs. HD-IFN-α2b	Chemotherapy: 200 mg/m^2/d temozolomide po days 1-5 plus 75 mg/m^2 cisplatin iv divided into 3 d and repeated q3w for 6 cycles HDI: 15 MU/m^2/d IFN-a2b iv days 1 to 5 each wk for 4 wk, then 9 MU sc 3×/wk for 48 wk	23.7 mo	Median OS 41.20 vs. 35.73 mo, p=0.083	Median RFS 15.53 mo vs. 9.47 mo, HR=0.56 (95% CI=0.40 to 0.77, p<0.001) Median DMFS 16.80 mo vs. 9.57 mo, HR=0.53 (95% CI=0.38 to 0.74, p<0.001)	Also in chemotherapy table	RFS and distant-metastasis-free survival better in chemotherapy group
ChiCTR-TRC-11001798 (Phase 2) Lian, 2013 [16]	v4	2007-2009 N=189	Mucosal Stage II/III	Mucosal melanoma	Temozolomide + cisplatin vs. HD-IFN-α2b vs. observation	Chemotherapy q3w for 6 cycles: temozolomide (200 mg/m^2/d po d1-5) + cisplatin (75 mg/m^2 divided into 3 d) vs. HD-IFN (15MU/m^2 d1-5 for 4 wk then 9 MU 3×/wk for 48 wk) vs. observation	26.8 mo	Median OS 48.7 mo vs. 40.4 mo vs. 21.2 mo, p<0.001 for chemo vs. observation; p<0.001 for IFN vs. observation; p=0.009 chemo vs. IFN ≈3-y OS: 66.7% vs. 52.4% vs. 25.4%	Median RFS 20.8 mo vs. 9.4 mo vs. 5.4 mo; p<0.001 for chemo vs. observation; p<0.001 for IFN vs. observation; p<0.001 chemo vs. IFN ≈3-y RFS 27% vs. 8% vs. 0%	Also in chemotherapy table Fever, fatigue, hepatotoxicity higher with IFN then chemo (p<0.001); anorexia, nausea/vomiting higher with chemo then IFN (p<0.001). All adverse effects were mild-moderate and managed by dose reduction or	RFS better with chemotherapy; chemotherapy and IFN both better than observation for OS Chemotherapy may be better for mucosal melanoma

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
										interruption, or supportive care	
Intermittent or Pulsed HD-IFN											
DeCOG MM-ADJ-5 NCT00226408 Mohr, 2015 [154]	(v4)	Sept 2003-Jul 2009 N=649; 627 analyzable	Stage III Resected lymph node or in-transit metastasis	Cutaneous melanoma	Intermittent intensified HD-IFN-α2b (5 d a wk for 4 wk every 4 mo) vs. std HD-IFN	Intermittent (20 MU/m^2 iv 5×/wk for 4 wk, every 4 mo for 3 cycles) vs. std HD-IFN (20 MU/m^2 iv 5d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk)	55 mo	OS 62.9% vs. 64.1% HR=1.01 (95% CI=0.78 to 1.36), p=0.85	RFS 42.6% vs. 48.5% HR=1.27 (95% CI=1.02 to 1.59), p=0.03 5-y DMFS 49.2% vs. 53.1%, HR=1.21 (95% CI=0.95 to 1.53), p=0.12	Termination of treatment due to AEs or QoL: 14.8% vs. 26.0%, p<0.001 Anemia 30.9% vs. 48.1%, p<0.001; grade 3 to 4 fatigue 11.9% vs. 21.2%, p=0.004	No significant difference in DMFS or OS RFS better with standard HD-IFN, although with more adverse effects Intermittent IFN not superior
IMI Mel.A (Italian Melanoma Group), ISRCTN75125874 Chiarion-Sileni, 2011 [155] [abstract] Chiarion-Sileni, 2006 [156] [tolerability]	v4	1998-2010 N=336, 330 evaluable	Stage III (AJCC 2002) primary or recurrent; excluded satellite or in-transit metastases or extra capsular nodal involvement or recurrence	Cutaneous melanoma	Intensified (pulsed) HD-IFN-α2b vs. standard HD-IFN	Intensified IFN: (20 MU/m^2 iv 5 d/wk for 4 wk every other month for 4 cycles) vs. HD-IFN (20 MU/m^2 iv 5 d/wk for 4 weeks then 10 MU/m^2 sc 3×/wk for 48 wk		Median OS 88.7 mo vs. 82.6 mo 5-y OS: 60.1% vs. 52.7%, not significant	Median RFS 47.9 mo vs. 35.6 mo 5-y RFS 45.8% vs. 44.3%, not significant	Discontinuation due to toxicity or refusal 20% vs. 28%; full dose treatment received in 66% vs. 49%, p=0.0026	No significant differences in relapse, RFS, OS; see meta-analysis with DeCOG MM-ADJ-5 Shorter more intensive HDI is feasible
Pooled: DeCOG MM-ADJ-5 and IMI Mel.A Weichenthal, 2013 [157] [abstract]	v4	N=627 DeCOG + 330 IMI MeI.A			Intermittent HD-IFN-α2b vs. standard HD-IFN		4.6 y DeCOG, 7.2 y IMI	OS: HR=1.04 (95% CI=0.84-1.29)	RFS: HR=1.11 (95% CI=0.93-1.33)		No significant differences for RFS or OS; favorable safety profile and less overall toxicity in intermittent (pulsed) regimen
Intermediate-dose IFN											

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
EORTC 18952, NCT00002763 Eggermont, 2016 [158] [long-term follow-up] Eggermont, 2012, 2005 [159,160]	(v3), M1, (M2)	1996-2000 N=1388	Stage IIB or III	Cutaneous melanoma Regional lymph node dissection if T4cN0 not mandatory	IFN-α2b intermediate/ low dose for 2 y vs. intermediate dose for 1 y vs. observation (2:2:1 ratio)	10 MU iv 5d/wk for 4 wk, then 5 MU 3×/wk sc for 2 y vs 10 MU iv 5d/wk for 4 wk, then 10 MU 3×/wk sc for 1 y [note total planned IFN same in both arms; stepwise dose reductions to adjust for toxicity and maintain ECOG status of 0-1]	11 y	10-y OS: 44.0% vs. 38.3% vs. 36.1%, p=0.15; 25 mo vs. observation: HR=0.84 (99% CI=0.66 to 1.08), p=0.08; 13 mo vs. observation: HR=0.95 (99% CI=0.75 to 1.21), p=0.58 4.5-y OS 53.1% vs. 48.3% vs. 47.7%; HR=0.85 (95% CI=0.68 to 1.07), p=0.12 [25 mo vs. observation]; HR=0.97 (97.5% CI=0.77 to 1.21), p=0.73 [13 mo vs. observation]	10-y RFS: 33.0% vs. 29.3% vs. 27.4%, p=0.14; 25 mo vs. observation: HR=0.84 (99% CI=0.67 to 1.06), p=0.06; 13 mo vs. observation: HR=0.94 (99% CI=0.75 to 1.17), p=0.46 10-y DMFS: 38.9% vs. 33.8% vs. 32.1%; 25 mo vs. observation HR=0.84 (99% CI=0.66 to 1.07), p=0.07; 13 mo vs. observation HR=0.95 (99% CI=0.75 to 1.20), p=0.57	For ulcerated subgroups, 25 mo was significantly better than control for OS (p=0.0007), RFS (p=0.0008), and DMFS (p=0.0003). 13 mo IFN appeared to have effect, but results were not statistically significant (OS p=0.13, RFS p=0.16, DMFS p=0.06) Neither duration had benefit for non-ulcerated subgroups Grade 3+ AEs (influenza-like symptoms, anorexia, dizziness, headache, mood) higher in IFN groups than observation Prognostic factors: Bouwhuis, 2011, 2009 [161-163]	25 mo better; ulceration is primary factor for IFN sensitivity

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
Nordic Adjuvant interferon trial, NCT01259934 Hansson, 2011 [164]; Brandberg, 2012, 2013 [165] [QoL]	(v4), M1*, M2	1996-2004 N=855	Stage IIB-IIC (T4N0) or III (TxN1-3)	Cutaneous melanoma; excluded non-cutaneous	IFN-α2b (25 vs. 13 mo) vs. control (intermediate-dose)	IFN (10 MU sc [flat dose] 5d/wk for 4 wk then 10 MU sc 3d/wk for 24 mo) vs. IFN (10 MU sc 5d/wk for 4 wk then 10 MU sc 3d/wk for 12 mo)	72.4 mo QoL: 24 mo, but only reported results at 6 and 16 mo	1+24 mo vs. 1+12 mo vs. observation: median OS 64.3 vs. 72.1 vs. 56.1 mo, p=0.600 1+24 vs. observation: HR=0.91 (0.72 to 1.15), p=0.858 1+12 vs. observation: HR=0.91 (0.72 to 1.14), p=0.652 IFN groups combined vs. observation: HR=0.91 (95% CI=0.74 to 1.10), p=0.642	Median RFS 28. 6 mo vs. 37.8 mo vs. 23.2 mo 1+24 vs. observation: RFS HR=0. 83 (0.68 to 1.03), p=0.178 1+12 vs. observation: RFS HR=0.77 (0.63 to 0.96), p=0.034 Combined vs. observation: RFS HR=0.80 (0.67 to 0.96), p=0.030	Prognostic factors: Brandberg, 2013 [166]; Vihinen, 2014 [167]; Prasmickaite, 2015 [168]; Krogh, 2016 [169] [163] Significant negative effect on QoL (global health; physical, role, emotional, cognitive, and social functioning; fatigue; nausea; pain; dyspnea; appetite loss; constipation; diarrhea; alopecia, fever; headache; chills; stiff muscles). These were mostly reversed for 13 mo IFN group at 16 mo; did not measure after end of 25 mo	RFS but not OS benefit for IFN; no indication that extending IFN (25 vs. 13 mo) is beneficial Negative but reversible effect on QoL
Ad Hoc Melanoma Working Group (Melacine) Mitchell, 2007 [170]	(v3)	1997-2003 N=604	LN+, AJCC 1988 Stage III	Excluded ocular or mucosal melanoma; 3 pts had melanoma on vulva	Allogeneic melanoma lysates (Melacine) + LD-IFN-α2b (2 y) vs. HD-IFN-α2b (1 y)	IFN (5 MU/m^2 sc 3×/wk for 104 weeks) + allogeneic melanoma vaccine (Melacine;	32 mo overall; 42 mo for surviving pts	Vaccine + LD-IFN vs. HD-IFN: median >84 mo vs. 83 mo, p=0.56; 5-y OS 61% vs. 57%	Median RFS 58 vs. 50 mo, p=0.61; 5-y RFS 50% vs. 48%, p=0.80	More neuropsychiatric toxicity in HD-IFN arm, other serious AEs same in both arms	OS and DFS indistinguishable; more neuropsychiatric toxicity with HD-IFN

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
						weekly for 1 mo, at week 8, then every 2 mo for 104 wk total) HD-IFN (20 MU/m^2 iv for 5 d then 10 MU/m^2 sc 3×/wk for 52 weeks total)				Data in Table 3 does not match data in text or figures; data from text has been extracted Also in vaccine table	
NCT00002882 USA, MD Anderson Kim, 2009 [153]	v4	1995-2003 N=138 (200 planned); stopped for futility	Regional lymph node metastasis with complete lymphadenectomy	Melanoma, subtype not specified in criteria; no pts had mucosal melanoma Stratified by prognosis: favorable (1 involved LN), intermediate (2-4 involved lymph nodes); unfavourable (>4 involved LN, extranodal tumour extension, or tumour recurrence in regional lymph node basin despite prior lymph node dissection)	Biochemotherapy (cisplatin, vinblastine, DTIC, IFN-α2b, interleukin-2) vs. IFN-α2b; IFN patients randomized again to high-does vs. intermediate-dose IFN	Biochemotherapy q3w for 4 cycles (cisplatin 20 mg/m^2 iv d1–4; vinblastine 1.5 mg/m^2 iv d1-4; DTIC 800 mg/m^2 iv d1; IFN 5MU/m^2 sc d1–5; IL-2 9 MU/m^2 iv over 96 h) vs. HD-IFN (20 MU/m^2 iv 5d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk) vs. ID-IFN (10 MU/m^2 sc 3×/wk for 52 wk)	49.3 mo	Median OS 72 mo vs. 66 mo vs. >108 mo HD-IFN vs. ID-IFN, p=0.67 Biochemotherapy vs. IFN (groups combined): 5-y OS 61% vs. 65%, p=0.45	Median RFS >108 mo vs. 58 mo vs. >108 mo HD-IFN vs. ID-IFN, p=0.54 Biochemotherapy vs. IFN (groups combined): 5-y RFS 59% vs. 57%; 2-y RFS 68% vs. 65%, p=0.86	Also in chemotherapy table; also in HD-IFN section Majority of biochemotherapy group had grade 4 hematologic AEs vs. none in IFN group; gastrointestinal and dermatologic AEs more severe in biochemotherapy group; depression and liver enzyme elevation common with IFN	Median RFS and OS not reached. No significant differences in median RFS or OS between HD-IFN and intermediate-dose-IFN and therefore groups combined (although numbers too small to reveal a modest survival benefit) Concluded biochemotherapy more toxic and not more effective than IFN; trial terminated early based on futility analysis. Trial not designed to prove equivalency. See larger SWOG S0008 trial
LD-IFN											

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
ECOG 1690, S9111, C9190 Kirkwood, 2000 [68] Kirkwood, 2002 [135]; Rao, 2002 [136] Update in pooled analyses: Kirkwood, 2004 [132] and Najjar, 2019 [133]	v3*, M1, M2	1991-95 N=642 accrued, 608 eligible	Stage IIB or III	Cutaneous melanoma Regional lymph node dissection if T4cN0 not mandatory	HD-IFN-α2b (1 y) vs. LD-IFN-α2b (2 y) vs. observation	HD-IFN (20 MU/m^2 iv 5 d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk) vs. LD-IFN (3 MU sc 3×/wk for 2 y)	6.6 y 12.2 y	49.8% HD-IFN vs. 51.6% LD-IFN vs. 51.4%, HR=1.0, p=0.98 5-y OS 52% vs. 53% vs. 55% HD-IFN vs. observation HR=1.0, p=0.995 LD-IFN vs. observation, HR=0.96, p=0.813 2-y OS 72% vs. 78% vs. 68% HD-IFN vs. observation: HR=0.94 (95% CI=0.73 to 1.21)	44.2% HD-IFN vs. 40.0% LD-IFN vs. 39.6%, HR=0.81, p=0.09 5-y RFS 44% vs. 40% vs. 35; HD-IFN vs. observation HR=0.78, p=0.054 LD-IFN vs. observation HR=0.84, p=0.171 HD-IFN vs. observation: HR=0.82 (95% CE=0.64 to 1.05), p=0.12	QoL in pooled analysis, Kilbridge, 2002 [134]: toxicity 1.9% none, 16.7% mild-moderate, 52.6% severe, and 28.8% laboratory Also in HD-IFN section	Dose dependant RFS benefit, significant for HD-IFN No OS benefit, but more pts on observation arm received IFN at relapse
French Cooperative Group on Melanoma (CGM) Grob, 1998 [171] Lafuma, 2001 [172]	v3, M1*, M2	1990-about 1994 N=499 enrolled, 489 eligible	Stage IIA-B (>1.5 mm), clinically node negative	Cutaneous melanoma Regional lymph node dissection not mandatory	IFN-α2a (18 mo) vs. observation	3 MU sc 3×/wk for 18 mo	5.0 y	OS HR=0.72 (0.51 to 1.01), p=0.059; adjusted HR=0.70 (0.50 to 0.99), p=0.046 5-y OS 76% vs. 68%; 3-y OS 85% vs. 79%; 1-	Relapse: p=0.035, HR=0.75 (0.57 to 0.98); adjusted HR=0.74 (0.56 to 0.98), p=0.033 Relapse: 5-y 43% vs. 51%, 3-y 432% vs.	Estimate about 53% meet our definition of high risk	Improved relapse-free interval and trend to improved OS (p=0.059) which was significant after adjustment for predetermined prognostic factors

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
								y OS 97% vs. 96% 2-y OS 92% vs. 88%	44%, 1-y 16% vs. 20%,		
Austrian Malignant Melanoma Cooperative Group (MMCG) Pehamberger, 1998 [173]	v3, M1*, M2	1990-94 N=311	Stage IIA-B (≥1.5 mm), clinically node negative	Cutaneous melanoma Regional lymph node dissection not mandatory; used lymph node ultrasound	IFN-α2a (3 wk + 49 wk) vs. observation	3 MU sc daily for 3 wk, then 3×/wk for 1 y	41 mo (mean)	OS 90.0% vs. 86.6% (ns)	5-y DFS 64% vs. 46%, p=0.02 Relapse 24.0% vs. 36.3%	Estimate about 60% meet our definition of high risk Number of events and follow-up period too small to give significant OS results	Improved DFS
[Scottish Melanoma Group] Cameron, 2001 [71]	v3, M1, M2	1989-93 N=96	High risk: Stage IIA-B (>3 mm) or stage III (node positive)	Melanoma (subtype not specified) Regional lymph node dissection not mandatory in Stage II pts	IFN-α2b (6 mo) vs. observation	3 MU sc 3×/wk for 6 mo	6.5 y	Median OS 39 mo vs. 27 mo, 5-y OS 42% vs. 29%, p>0.2 2-y OS 60% vs. 56%	Median DFS 22 mo vs. 9 mo 5-y DFS 35% vs. 34% 2-y DFS 48% vs. 36%, p=0.05	Trial underpowered due to low recruitment	Improved DFS up to 24 mo but not significant at 6 y; need larger trials
WHO 16 Cascinelli, 2001 [174]	v3, M1, M2	1990-1993 N=444 randomized; 424 entered study	Stage III	Cutaneous melanoma Matted nodes or extracapsular extension allowed; had complete lymphadenectomy for regional nodal spread	LD-IFN-α2a vs. observation	3 MU sc 3×/wk for 3 y	88 mo	5-y OS 35% vs. 37%, p=0.72 2-y OS 60% vs. 53%	5-y DFS 27.5% vs. 28.4%, p=0.50		No improvement in DFS or OS

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
UKCCCR AIM-High [United Kingdom Coordinating Committee on Cancer Research AIM HIGH] NCT00002892 Hancock, 2004 [175]; Dixon, 2006 [176] (QoL)	v3, M1, M2	1995-2000 N=674	Stage IIB (≥4 mm) or III or recurrent regional nodal involvement	Cutaneous melanoma Matted nodes or extracapsular extension allowed. Regional nodal dissection in stage II not mandatory	LD-IFN-α2a (2 y) vs. observation	3 MU 3×/wk for 2 y	3.1 y	5-y OS 46% vs. 42%, OR=0.94 (95% CI=0.75- to 1.18), p=0.6 2-y OS 64% vs. 64%	5-y RFS 33% vs. 30%, OR=0.91 (95% CI=0.75 to 1.10), p=0.3	Grade 3 toxicity 15% vs. 4%,; fatigue (grade 3) p<0.005 LD-IFN-α2a (compared with placebo) resulted in worse HRQoL (role functioning, emotional functioning, cognitive functioning, social functioning, global health status), symptom scores (fatigue, nausea and vomiting, appetite loss, constipation, diarrhea), and more financial difficulty	No significant difference in OS or RFS; 15% of pts on IFN withdrew due to toxicity
DeCOG (Dermatologic Cooperative Oncology Group) Garbe, 2008 [177]	v3, M1, M2	1997-2001 N= 444 (148 in each of 3 arms); 441 eligible	pN+ (microscopic or macroscopic)	Cutaneous melanoma Complete lymphadenectomy, no satellite, in - transit, or distant metastases	LD-IFN-α2a (2 y) vs. IFN + DTIC (DTIC) vs. observation	IFN (3 MU sc 3×/wk for 2 y) vs IFN (2 y) + DTIC (850 mg/m^2 iv d1 q28d for 6 mo then q42 d mo 7-12 then q56d mo 13-24)	47 mo	IFN vs. none: 4-y OS 59.0% vs. 42.4%, HR=0.62 (97.5% CI=0.42 to 0.89), p=0.0045 DTIC + IFN vs. none: 4-y OS 45.2% vs. 42.4%, HR=0.96 (97.5% CI=0.67	IFN vs. none: 4-y DFS 39.0% vs. 27.3%, HR=0.69 (97.5% CI=0.49 to 0.96), p=0.018 DTIC + IFN vs. none: 4-y DFS 29.4% vs. 27.3%, HR=1.01 (97.5% CI=0.72	Grade 3 to 4 AEs: 13 pts IFN, 25 IFN + DTIC Also in chemotherapy table	IFN improved OS and DFS; DTIC reversed (eliminated) IFN benefit.

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
								to 1.33), p=0.76	to 1.36), p=0.97		
DeCOG Hauschild, 2010 [247] Heinze, 2010 [178] [mood, psychiatric symptoms]	(v3), v4	March 2001-March 2004 N=850	≥1.5 mm (pT2a); clinically LN-; SLNB performed in most pts, 18% SLN+	Mucosal and ocular melanoma excluded	LD-IFN-α2a 18 mo vs. 60 mo	3 MU 3×/wk sc for 18 mo vs. 3 MU 3×/wk sc for 60 mo	4.3 y	5-y OS: 85.9% vs. 84.9%, HR=1.03 (95% CI=0.71 to 1.50), p=0.86	RFS: 75.6% vs. 72.6%, HR= 1.05 (95% CI=0.80 to 1.39), p=0.72; DMFS: 81.9% v 79.7%, HR=1.10 (95% CI=0.80 to 1.52), p=0.56	Most not high-risk, but include as reported recurrence by SLN status Recurrence, SLN+ subgroup (n=114): 51.7% vs. 51.8%, not significant Treatment discontinuation 17.8% vs. 37.9%, p=0.001	Prolonged IFN showed no clinical benefit (RFS, DMFS, OS) compared with 18 mo
EORTC 18871 plus DKG 80-1 Kleeberg, 2004 [179]	v3, M1, M2	1988-96 N=830 (423 EORTC; 407 DKG)	Stage IIA-B (>3 mm) or stage III	Melanoma (subtype not specified) Regional lymph node dissection not mandatory in Stage II pts	LD-rIFN-α2b (1 y) vs. rIFN-γ versus Iscador M (DKG 80-1 only) versus observation	rIFN-α2b (1 MU sc every other day) vs. rIFN-γ (0.2 mg sc every other) vs. Iscador M (escalated dose from 0.01 to 1.0 mg/mL qod over 2 wk, 3 d without treatment then resumed for 14 doses of 20 mg/mL then 7 d no treatment) vs. none	8.2 y	OS (vs. control): HR=0.96 (95% CI=0.76 to 1.21), p=0.72; HR=0.87 (95% CI=0.69 to 1.10), p=0.25; HR=1.21 (95% CI=0.84 to 1.75), p=0.31 OS: 42.9% IFNα vs. 46.7% IFNγ vs. 39.3% control	Disease-free interval (vs. control): HR=1.04 (95% CI=0.84 to 1.30), p=0.71; HR=0.96 (95% CI=0.77 to 1.20), p=0.73; HR=1.32 (95% CI=0.93 to 1.87), p=0.12	Also in IFN-gamma section Data from the two trials was combined for comparisons of IFN rIFN-α2b vs. control and rIFN-γ vs. control; for ICADOR M vs. control, data was not combined	No clinical benefit (DFI or OS) of any treatments

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
						All treatments for 1 y or until progression		OS: 41.2% Iscador M vs. 47.2% control			
[Germany] Stadler, 2006 [180]	v3	1993-1997 N=252; n=236 per protocol	Stage II-III	Cutaneous melanoma (3 pts had location of mucous membrane or genito-anal region) Radical lymphadenectomy and excision of all satellite metastases and/or in-transit metastases	DTIC + natural human LD-IFN-α (HuIFN-aLe) vs. none HuIFN-aLe comprises several IFN-a subtypes	DTIC 850 mg/m^2 d2 of wk 1 and 5. 4 wk after 2nd DTIC injection, HuIFN-αLe 3 MU 3×/wk for 6 mo	5.5 y (2001) 8.5 y long-term (2003/2004)	OS (2003/04): 58.6% vs. 41.9%, HR=0.71 (95% CI 0.49 to 1.00), p=0.052; Per protocol analysis: OS 59.6% vs. 41.8%, HR=0.66 (95% CI=0.46 to 0.96), p=0.029; High-risk subgroup (stage IIb-III): OS 52.4% vs. 25%, HR=0.58 (95% CI=0.38 to 0.86), p=0.008 Lower risk (stage IIa): p=0.93	Median RFS 1002 d vs. 461 d, p=0.068; stage IIB-III subset RFS p=0.002 Melanoma-related deaths: analysis in 2001, p=0.97; analysis in 2003-2004, 35.2% vs. 54.0%, HR=0.65 (95% CI=0.46 to 0.97), p=0.022; p=0.002 after adjustment	46 serious AEs in treatment arm (11 during DTIC, 22 during IFN, and 13 post-treatment) and 11 in control arm Also in chemotherapy table	Results strongly suggest that DTIC + IFN is beneficial
Pegylated IFN											
EORTC 18991, NCT00006249 Eggermont, 2012 [181] [long-term results]	(v3), v4, M1, M2	2000-2003 N=1256	Stage III	Ocular or mucous membrane melanoma ineligible	PEG-IFN-α2b vs. observation	6 µg/kg/wk, sc 8 wk, then 3 µg/kg/wk for 5 y or until distant metastases	7.6 y	Median OS 6.2 y vs. 5.6 y 7-y OS:47.8% vs. 46.4%, HR=0.96 (95%	Median RFS 3.0 vs. 2.2 y 7-y RFS 39.1% vs. 34.6%, HR=0.87 (95%	Prognostic factors [183-186] 7-y DMFS 41.7% vs. 40.0%, HR=0.93 (95%	RFS benefit; no difference in OS overall OS benefit in stage III-N1 ulcerated

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
Bottomley, 2009 [182] [QoL)				Regional lymph node involvement		(median treatment duration was 12 mo)		CI=0.82 to 1.11), p=0.57; subgroup stage III-N1 ulcerated 52.6% vs. 34.5%, HR=0.59 (99% CI=0.35 to 0.97), p=0.006	CI=0.76 to 1.00), p=0.055; subgroup stage III-N1 ulcerated 34.4% vs. 22.9%, HR=0.72 (99% CI=0.46 to 1.13), p=0.06	CI=0.81 to 1.07), p=0.33; stage III-N1 ulcerated subgroup HR=0.65 (99% CI=0.41 to 1.04), p=0.02 Decreased global HRQoL at month 3 and year 2; clinical differences for 5 scales (social, role functioning, appetite, fatigue, dyspnea)	
DeCOG, NCT00204529 Eigentler, 2016 [187]		Oct 2004-Sept 2007 N=909	IIA(T3a)-IIIB (AJCC 2002) "high-risk" melanoma	Mucosal or ocular melanoma excluded	PEG-IFN-α2a vs. IFN-α2a	PEG-IFN (180 µg sc q1w) vs. IFN (3 MU 3×/wk); both for 24 mo	65.1 mo	5-y OS: 73.2% vs. 75.2%; HR=1.0524 (95% CI=0.81 to 1.37, p= 0.7017)	5-y DFS 57.3% vs. 60.9%; HR=1.09 (95% CI=0.89 to 1.35), p=0.4012 5-y DMFS 61.0% vs. 67.3%; HR=1.16 (95% CI=0.92 to 1.46), p=0.2147	Grade3-4 neutropenia higher with PEG-IFN (25.0% vs. 5.1%) Quality of life was identical for most domains. New trial, may affect recommendation, as old rec indicated no trials of this completed or expected	PEG-IFN did not significantly improve outcome (DMFS, OS, DFS) compared with IFN PEG-IFN had higher rates of dose reduction or discontinuation (26.2% vs. 13.3%)
IFN gamma											
SWOG 8642 Meyskens, 1995 [188]	v3	1987-1989	AJCC Stage II (≥1.5 mm, M0,	Cutaneous melanoma	IFN-γ vs. observation	0.2 mg/d sc for 1 y or until recurrence		2.5-y OS: RR=1.31 (95%	2.5-y DFS: RR=1.18 (95%		IFNγ did not improve OS or DFS

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
		N=284, 202 eligible	M0) or III (any T, N1-2, M0)					CI=0.88 to 1.95), p=0.91 -stage II 79% vs. 89% -stage III 47% vs. 57%	CI=0.82 to 1.68), P=0.81 -stage II 64% vs. 66% -stage III 31% vs. 41		
EORTC 18871 plus DKG 80-1 Kleeberg, 2004 [179]	v3, M1, M2	1988-96 N=830 (423 EORTC; 407 DKG)	Stage IIA-B (>3 mm) or stage III	Melanoma (subtype not specified) Regional lymph node dissection not mandatory in Stage II pts	LD-rIFN-α2b (1 y) vs. rIFN-γ versus Iscador M (DKG 80-1 only) versus observation	rIFN-α2b (1 MU sc every other day) vs. rIFN-γ (0.2 mg sc every other day) vs. Iscador M (escalated dose from 0.01 to 1.0 mg/mL qod over 2 wk, 3 d without treatment then resumed for 14 doses of 20 mg/mL then 7 d no treatment) vs. none All treatments for 1 y or until progression	8.2 y	OS (vs. control): HR=0.96 (95% CI=0.76 to 1.21, p=0.72; HR=0.87 (95% CI=0.87 to 1.10), p=0.25; HR=1.21 (95% CI=0.84 to 1.75), p=0.31 OS: 42.9% IFNα vs. 46.7% IFNγ vs. 39.3% control OS: 41.2% Iscador M vs. 47.2% control	Disease-free interval (vs. control): HR=1.04 (95% CI=0.84 to 1.30), p=0.71; HR=0.96 (95% CI=0.77 to 1.20), p=0.73; HR=1.32 (95% CI=0.93 to 1.87), p=0.12	Also in LD- IFN section Data from the two trials was combined for comparisons of IFN rIFN-α2b vs. control and rIFN-γ vs. control; for ICADOR M vs. control, data was not combined	No clinical benefit (DFI or OS) of any treatments

Other Reviews:

- v3, in 8-1 version 3 (2009) and subsequent versions; v3* complete publication, although longer term results are available in publication of pooled data [132]; (v3), older publication, abstract, or less complete data was included in 8-1 version 3
- v4, in 8-1 version 4 (2012) data assessment and review table appendix but not incorporated into main document; v4* complete publication, although longer term results are available in publication of pooled data [132]; (v4), older publication, abstract, or less complete data was included in 8-1 version 4
- M1, included in individual patient data (IPD) meta-analysis of adjuvant IFN-α for high-risk melanoma by Ives et al. [14]; M1* summary data for the trials was used as IPD not available; (M1)
- M2, included in Cochrane meta-analysis by Mocellin et al. [33]; (M2) older publication, abstract, or less complete data was included in meta-analysis

Abbreviations: AEs, adverse events; CI, confidence interval; CLND, completion lymph node dissection; DFS, disease-free survival; DMFS, distant metastasis-free survival; DTIC, (dimethyltriazeno)imidazolecarboxamide, drug name dacarbazine; HD-IFN, high-dose interferon; HR, hazard ratio; HRQoL, health-related quality of life; HuIFN, human interferon; IFN, interferon; im, intramuscular; iv, intravenous; LD-IFN, low-dose interferon; LN, lymph node; OR, odds ratio; OS, overall survival; PEG-IFN, pegylated interferon; pN+, pathologically node positive; pt, patient; pts, patients; QoL, quality of life; RFS, recurrence-free survival; rIFN, recombinant interferon; RT, radiation therapy; RT-PCR, reverse transcriptase polymerase chain reaction; sc, subcutaneous; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy

Back to Results

Table 4-6. Adjuvant chemotherapy trials

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
ECOG E1673 Agarwala, 2004 [189]		1974-1978 N=734 randomized, 708 ITT analysis, 618 eligible analysis	Clark level ≥3, stage I-III; From text: Cohort 1 is Stage I/II (Clark level 3-5) or Stage III (26%; head, neck, extremities). Cohort 2: Stage III (trunk location) with synchronous or recurrent regional lymph node involvement	Cutaneous melanoma Table and text inconsistent regarding stage breakdown.	Cohort 1: BCG vs. observation; Cohort 2: BCG plus DTIC vs. BCG	Cohort I: BCG vs. observation Cohort II: BCG + DTIC vs. BCG DTIC 200 mg/m^2 iv daily ×5; 10 day delay; BCG q1w×4. Cycles repeated q8w for 18 mo (total of 10 cycles) [later modified to give DTIC 100 mg/m^2 iv daily for 5 d q4w for 18 mo with BCG staring the first week and continuing for 18 mo] BCG by multiple puncture technique weekly for first 4 wk in regional lymph node drainage area; then expanded to include other areas of lymphatic drainage by rotation, q2w×4, q4wx6, q8wx5	Median follow-up projected at 30 y	Cohort I: OS 67% vs. 62%, p=0.40 Cohort II: OS no difference, p=0.81	Cohort I: DFS, no difference, p=0.84 Cohort II: DFS, no difference, p=0.74	Punctuate abscesses in >66% of pts treated with BCG Confirms negative results for BCG found in previous smaller studies Also in immunotherapy table	No benefit in DFS or OS for BCG DTIC did not improve DFS or OS
COG 7040 (Central Oncology Group)	v3	1972-1976 N=174, 165 evaluable	Stage I (localized primary; solitary	Melanoma; anus, genitalia and mucous membrane melanoma	DTIC vs. control	DTIC: 4.5 mg/kg/d for 10 d iv for 4 courses (months 1 or 2, 5, 8, 11)	2.5 y (min 1 y)	Median OS 103 weeks vs. 133 weeks	Median DFS 40 weeks vs. 73 weeks; 28% vs. 44%, p=0.05	Nausea and vomiting in 89%, diarrhea in 14%, leukopenia 35%,	Worse outcomes with DTIC than placebo: DFI (p=0.04), DFS

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
Hill, 1981 [190]			recurrence within 5 cm) Stage II (metastatic to primary regional LN) Stage III (metastatic to distant site, extensive local recurrence)	also eligible but not reported separately Could receive other treatment upon recurrence or distant metastasis 24% stage I, 58% stage II, 18% stage III				43% vs. 55%, p=0.16		thrombocytopenia 25%;	(p=0.05), OS (p=0.16), Median disease-free interval was 73 wk control vs. 40 wk DTIC
EORTC 18761 Lejeune, 1988 [191]	v3	1976-1985 N=325, 274 eligible	Clark grade III and ≥1.5 mm; Clark grade IV or V. No evidence of LN metastasis	Cutaneous melanoma Lymph node dissection for limb melanomas, with exclusion if LN+ 33% ulceration; 4% satellitosis; thickness measured in some pts, 37% >3 mm	DTIC vs. levamisole vs. placebo	DTIC 250 mg/m^2, for 5d q28d for 6 cycles Levamisole 150-250 mg 2×/wk for 2 y Placebo	Median 241 week Mean 3 y	5-y OS 55% vs. 62% vs. 64%, p=0.412	DFI: no difference, p=0.915	Indicated that study ongoing but no follow-up publications found Also in immunotherapy table	Neither DTIC nor levamisole had effect on DFI or survival
World Health Organization International Melanoma Group Veronesi, 1982 [192]	v3	1974-1980 N=931, 761 evaluable	High-risk: stage II anywhere (lymph node metastases) or Stage I (Clark level 3-5) on trunk	Cutaneous melanoma Excisional regional lymphadenectomy. Separately randomized stage I (n=98 evaluable) and stage II pts (n=663 evaluable)	DTIC vs. BCG vs. DTIC + BCG vs. none	DTIC (200 mg/m^2 for 5d, q4w for 24 cycles) vs. BCG (75 mg in 0.5 mL saline by Heaf gun needles weekly until skin reaction then monthly) vs. DTIC + BCG (as above with BCG on day 5 of first cycle) vs. observation	41 mo (mean)	3-y OS 46.5% (p=0.64) vs. 48.7% (p=0.14) vs. 50.0% (p=0.35) vs. 41.6% [p values are compared with control]	3-y DFI 37.2% (p=0.16) vs. 34.8% (p=0.17) vs. 33.6% (=0.20) vs. 30.4% [p values are compared with control]	Also in immunotherapy table	No significant differences in DFS or OS. Study had power to detect 14% difference; either difference did not exist or was of limited clinical importance

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
[Canada] Quirt, 1983 [193]	v3	1974-1978 N=94 (37 stage III)	Stage I (Clark's level 3-5), stage III (in transit or lymph node metastases)	Cutaneous melanoma 57 pts stage I (16 level 3, 31 level 4, 10 level 5) 37 pts stage III	DTIC + BCG vs. observation	DTIC (850 mg/m^2 iv, wk 1 and 4) plus BCG (120 mg po or 0.1 mg injection q2w for 1 y and q4w for 1 y) Observation	6.4 y	Stage III group (from text): 3y-OS 61% vs. 47% (p=0.136); 5-y OS 55% vs. 36% (p=0.246)	Stage III group (from graph): 3-y RFS 44% vs. 32%; 5-y RFS 40% vs. 25%, not significant	Stage I and III reported separately Also in immunotherapy table	Stage I: no difference in relapse or OS Stage III: non-significant improvement in survival and recurrence; cannot recommend outside a clinical trial
DeCOG (Dermatologic Cooperative Oncology Group) Garbe, 2008 [177]	v3, M1, M2	1997-2001 N= 444 (148 in each of 3 arms); 441 eligible	pN+ (microscopic or macroscopic)	Cutaneous melanoma Complete lymphadenectomy, no satellite, in – transit, or distant metastases	LD-IFN-α2a (2 y) vs. IFN + DTIC vs. observation	IFN (3 MU sc 3×/wk for 2 y) vs IFN (2 y) + DTIC (850 mg/m^2 iv d1 q28d for 6 mo then q42 d months 7-12 then q56d months 13-24)	47 mo	IFN vs. none: 4-y OS 59.0% vs. 42.4%, HR=0.62 (97.5% CI=0.42 to 0.89), p=0.0045 DTIC + IFN vs. none: 4-y OS 45.2% vs. 42.4%, HR=0.96 (97.5% CI=0.67 to 1.33), p=0.76	IFN vs. none: 4-y DFS 39.0% vs. 27.3%, HR=0.69 (97.5% CI=0.49 to 0.96), p=0.018 DTIC + IFN vs. none: 4-y DFS 29.4% vs. 27.3%, HR=1.01 (97.5% CI=0.72 to 1.36), p=0.97	Grade 3 to 4 AEs: 13 pts IFN, 25 IFN + DTIC Also in IFN table	IFN improved OS and DFS; DTIC reversed (eliminated) IFN benefit
[Germany] Stadler, 2006 [180]	v3	1993-1997 N=252; n=236 per protocol	Stage II-III	Cutaneous melanoma (3 pts had location of mucous membrane or genito-anal region) Radical lymphadenectomy and excision of all	DTIC + low-dose natural human IFN-α (HuIFN-aLe) vs. none HuIFN-aLe comprises several IFN-a subtypes	DTIC 850 mg/m^2 d2 of wk 1 and 5. 4 wk after 2nd DTIC injection, HuIFN-αLe 3 MU 3×/wk for 6 mo	5.5 y (2001) 8.5 y long-term (2003/2004)	OS (2003/04): 58.6% vs. 41.9%, HR=0.71 (95% CI 0.49 to 1.00), p=0.052;	Median RFS 1002 d vs. 461 d, p=0.068; stage IIB-III subset RFS p=0.002 Melanoma-related deaths:	46 serious AEs in treatment arm (11 during DTIC, 22 during IFN, and 13 post-treatment) and 11 in control arm Also in IFN table	Results strongly suggest that DTIC + IFN is beneficial

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
				satellite metastases and/or in-transit metastases				Per protocol analysis: OS 59.6% vs. 41.8%, HR=0.66 (95% CI=0.46 to 0.96), p=0.029; High-risk subgroup (stage IIb-III): OS 52.4% vs. 25%, HR=0.58 (95% CI=0.38 to 0.86), p=0.008 Lower risk (stage IIa): p=0.93	analysis in 2001, p=0.97; analysis in 2003-2004, 35.2% vs. 54.0%, HR=0.65 (95% CI=0.46 to 0.97), p=0.022, p=0.002 after adjustment		
[New York] Karakousis, 1993 [194]	v3	1981-1990 N=173	Regional lymphatic metastases (clinically palpable) or distant disease (stage IIIA-IV)	Melanoma, subtype not specified	Chemotherapy (BCNU + actinomycin-D + vincristine) vs. observation	BCNU (80 mg/m^2 iv q4w) + actinomycin-D (10 µg/kg) + vincristine (1.0 mg/m^2 iv q2w) for 6 cycles Observation	57 mo	5-y OS 30% vs. 25%, p=0.59	5-y DFS 29% vs. 9%, p=0.03 Median DFS 10 mo vs. 8 mo		Improved DFS, non-significant improvement in OS
[National Cancer Institute, Bethesda, Maryland] Fisher, 1981 [195]	v3	1975- ≈1979 N=181, 166 evaluable	Poor prognosis Stage I (Clark level 4, >2.25 mm; Clark level 5; or local recurrence within 5 cm of	Cutaneous melanoma; excluded melanoma of eyes or mucous membranes Dissection of regional draining lymph nodes	BCG + neuraminidase-treated allogenic tissue cultured melanoma cells vs. BCG vs. methyl-CCNU vs. none	(BCG + mitomycin C-treated neuraminidase-treated cells; q1w×11 then every q2w for 2 yr total) vs. BCG (q1w×11 then q2w for ≈ 2 y total) vs. methyl-CCNU (200 mg/m^2	>29 mo	OS p=0.64 for overall comparison 4-y OS: 52% vs. 28% vs. 45% vs. 54%	DFS: methyl-CCNU vs. control p=0.064; Time to recurrence p=0.25 overall; vs. control: p=0.28 BCG +	Preliminary report; no full report located Also in vaccines table, immunotherapy table	No significant difference in time to recurrence or OS. No indication to recommend routine us of BCG, BCG + allogenic cell vaccine, or

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
			primary tumour) or or Stage II (histologically node positive)			po q6w for 18 mo) vs. none		3-y OS: 58% vs. 42% vs. 50% vs. 54% 2-y OS 65% vs. 61% vs. 65% vs. 70%	vaccine, p=0.66 BCG, p=0.068 methyl-CCNU No significant difference in disease-free interval (p=0.22; pairwise all p>0.33)		methyl-CCNU; further follow-up necessary
SWOG S0008, NCT00006237 Flaherty, 2014 [149]	(v4)	2000-2007 N=432	Stage IIIA-N2a to Stage IIIC-N3 (ulcerated plus SLN+; non-ulcerated plus 2+ positive SLN; regional LN macrometastasis; satellite or in-transit metastasis; regional nodal recurrence)	Excluded mucosal and uveal primaries 53% stage III, 9% stage IIb, 34% stage IIa Complete regional lymphadenectomy required	Biochemotherapy (cisplatin, vinblastine, DTIC, interleukin-2, IFN) vs. HD-IFN-α2b	Biochemotherapy q21d for 3 cycles (cisplatin 20 mg/m^2 iv d 1-4, vinblastine 1.2 mg/m^2 iv d1-4, DTIC 800 mg/m^2 iv d1, IL-2 9 MU/m^2 iv over 96 h, IFN 5 MU/m^2 d1-5) vs. HD-IFN (20 MU/m^2 iv 5d/wk for 4 wk then 10 MU/m^2 sc 3×/wk for 48 wk)	7.2 y	Median OS 9.9 y vs. 6.7 y, HR=0.98 (95% CI=0.74 to 1.31), p=0.55 5-y OS 56% vs. 56%	Median RFS 4.0 y vs. 1.9 , HR=0.75 (95% CI=0.58 to 0.97), p=0.029 5-y RFS 48% vs. 39%	Grade 3+ AEs 76% biochemotherapy vs. 64% IFN; profile varied by arm Also in IFN table Publications on minimal residual disease [150], unknown primary melanoma [151], brain metastases [152]	Conclude: biochemotherapy shorter alternative to HD-IFN, with improved RFS but no difference in OS and more toxicity than IFN alone
NCT00002882 USA, MD Anderson Kim, 2009 [153]	v4	1995-2003 N=138 (200 planned); stopped for futility	Regional lymph node metastasis with complete lymphadenectomy	Melanoma, subtype not specified in criteria; no pts had mucosal melanoma Stratified by prognosis: favorable (1 involved LN), intermediate (2-4 involved lymph nodes); unfavourable (>4 involved LN, extranodal tumour	Biochemotherapy (cisplatin, vinblastine, DTIC, IFN-α2b, interleukin-2) vs. IFN-α2b; IFN patients randomized again to high-does vs. intermediate-dose IFN	Biochemotherapy q3w for 4 cycles (cisplatin 20 mg/m^2 iv d1-4; vinblastine 1.5 mg/m^2 iv d1-4; DTIC 800 mg/m^2 iv d1; IFN 5MU/m^2 sc d1-5; IL-2 9 MU/m^2 iv over 96 h) vs. HD-IFN (20 MU/m^2 iv 5d/wk for	49.3 mo	Median OS 72 mo vs. 66 mo vs. >108 mo HD-IFN vs. ID-IFN, p=0.67 Biochemotherapy vs. IFN (groups combined): 5-y OS 61% vs. 65%, p=0.45	Median RFS >108 mo vs. 58 mo vs. >108 mo HD-IFN vs. ID-IFN, p=0.54 Biochemotherapy vs. IFN (groups combined): 5-y RFS 59% vs. 57%; 2-y RFS	Also in IFN table Majority of biochemotherapy group had grade 4 hematologic AEs vs. none in IFN group; gastrointestinal and dermatologic AEs more severe in biochemotherapy group; depression	Median RFS and OS not reached. No significant differences in median RFS or OS between HDI and IDI and therefore groups combined (although numbers too small to reveal a

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
				extension, or tumour recurrence in regional lymph node basin despite prior lymph node dissection)		4 wk then 10 MU/m^2 sc 3×/wk for 48 wk) vs. ID-IFN (10 MU/m^2 sc 3×/wk for 52 wk)			68% vs. 65%, p=0.86	and liver enzyme elevation common with IFN	modest survival benefit) Concluded biochemotherapy more toxic and not more effective than IFN; trial terminated early based on futility analysis. Trial not designed to prove equivalency. See larger SWOG S0008 trial
NCT03435302, BCHMMAT00 (Phase 3) Lian, 2018 [17] [abstract]		2014-2016 N=204	Mucosal Stage I-III	Mucosal melanoma Lymphadenectomy if involved regional lymph nodes	Temozolamide + cisplatin vs. HD-IFN-α2b	Chemotherapy: 200 mg/m^2/d temozolomide po days 1-5 plus 75 mg/m^2 cisplatin iv divided into 3 d and repeated q3w for 6 cycles HDI: 15 MU/m^2/d IFN-a2b iv days 1 to 5 each wk for 4 wk, then 9 MU sc 3×/wk for 48 wk	23.7 mo	Median OS 41.20 vs. 35.73 mo, p=0.083	Median RFS 15.53 mo vs. 9.47 mo, HR=0.56 (95% CI=0.40 to 0.77, p<0.001) Median DMFS 16.80 mo vs. 9.57 mo, HR=0.53 (95% CI=0.38 to 0.74, p<0.001)	Also in IFN table	RFS and distant-metastasis-free survival better in chemotherapy group
ChiCTR-TRC-11001798 (Phase 2) Lian, 2013 [16]	v4	2007-2009 N=189	Mucosal Stage II/III	Mucosal melanoma	Temozolamide + cisplatin vs. HD-IFN-α2b vs. observation	Chemotherapy q3w for 6 cycles: temozolomide (200 mg/m^2/d po d1-5) + cisplatin (75 mg/m^2 divided into 3 d)	26.8 mo	Median OS 48.7 mo vs. 40.4 mo vs. 21.2 mo, p<0.001 for chemo vs. observation;	Median RFS 20.8 mo vs. 9.4 mo vs. 5.4 mo; p<0.001 for chemo vs. observation; p<0.001 for IFN	Also in IFN table Fever, fatigue, hepatotoxicity higher with IFN then chemo (p<0.001);	RFS better with chemotherapy; chemotherapy and IFN both better than observation for OS

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
						vs. HD-IFN (15MU/m^2 d1-5 for 4 wk then 9 MU 3×/wk for 48 wk) vs. observation		p<0.001 for IFN vs. observation; p=0.009 chemo vs. IFN ≈3-y OS: 66.7% vs. 52.4% vs. 25.4%	vs. observation; p<0.001 chemo vs. IFN ≈3-y RFS 27% vs. 8% vs. 0%	anorexia, nausea/vomiting higher with chemo then IFN (p<0.001). All adverse effects were mild-moderate and managed by dose reduction or interruption, or supportive care	Chemotherapy may be better for mucosal melanoma
[North Central Cancer Treatment Group and Mayo Clinic] Markovic, 2002 [196]		1990-1995 N=271 accrued, 265 eligible	>1.7 mm and no regional lymph node involvement (high-risk stage I); or regional lymph node involvement (stage II)	Melanoma, subtype not specified in inclusion criteria; 3 pts had melanoma of vulva or vagina 29% >3.5 mm; 47% had nodal involvement	Megestrol acetate (Megace) vs. placebo	160 mg megestrol acetate po twice per day for maximum of 2 y or disease progression vs. placebo	until death or minimum of 4.5 y	Median OS 5.3 y vs. 3.9 y, HR=1.05 (95% CI=0.76 to 1.45), p=0.7797, adjusted p=0.3647	Median PFS 2.4 y vs. 2.3 y, HR=0.91 (95% CI=0.66 to 1.26), p=0.5624, adjusted p=0.6651	Accrual terminated (87% of planned) when ECOG trial reported survival benefit of HD-IFN-α	Conclude: not effective for PFS or OS
[European Cooperative Adjuvant Treatment Study Group] Richtig, 2005 [197]		1996-2002 N=407	Localized melanoma, stage IIA (1.5 to 4.0 mm or Clark level IV) or IIB (>4.0 mm or Clark level V) (AJCC 1988): 1	Melanoma, subtype not specified SLN biopsy in some patients, protocol modified May 1999 to allow in trial if SLN-, or SLN+ with micrometastasis only and negative nodes by radical lymphadenectomy 10% SLN+; 20% >4.0 mm, 14% 3-4 mm, 24% 2-3 mm	IFN-α + isotretinoin vs. IFN-α + placebo [Sponsored by Roche so may be IFN-α2a but not specified]	Isotretinoin (20 mg if pt ≤73 kg, 30 mg if >73 kg) + IFNα vs. IFNα + placebo IFN 3 MU sc 3×/wk for 24 mo		5-y OS 76% vs. 81%, p=0.8 Per-protocol analysis: 5-y OS 83% vs. 77%, p=0.25	5-y DFS 55% vs. 67%, p=0.25 Per-protocol analysis: 65% vs. 71%, p=0.61	Estimate about 50% meet our definition of high risk. Trial stopped for futility at interim analysis 9 mo after end of recruitment period	Stopped early for futility; no difference in DFS (p=0.25); 5-y DFS 55% vs. 67%. Conclude no significant effect on DFS or OS and isotretinoin is not recommended

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
[DeCOG] Eigentler, 2008 [198]		1997-2001 N=142, 139 eligible for analysis	Stage III or IV. Metastatic spread to regional sites, lymph nodes, distant sites; complete metastasectomy	Cutaneous melanoma	Vindesine vs. observation	Vindesine (3 mg/m^2 iv biweekly for first 26 wk then every 3 wk for additional 26 wk then every 4 wk for 52 wk) vs. observation	Median 46 mo follow-up	3-y OS 54.9% vs. 43.6%, p=0.07 Stage III pts: 55.3% vs. 35.4%	Median RFS 7.9 mo vs. 7.6 mo, p=0.40	No grade IV toxicity, but 10 pts discontinued due to grade III toxicity Vindesine group had better prognostic factors (tumour thickness) Trial underpowered	Conclude vindesine did not significantly prolong DFS or OS and use cannot be recommended
Hyperthermic perfusion, isolated limb perfusion											
[Sweden] Olofsson Bagge, 2014 [199] Hafstrom, 1991 [200]		1981-1989 N=80, 69 randomized	Recurrent malignant melanoma of extremities (satellite or in-transit) after wide resection	Melanoma of the extremities All had ilio-inguinal or axillary lymphadenectomy if not done previously <2 mm (n=20), 2 to 3.99 mm (n=28), >4 mm (n=13), not measured (n=8) 35 local recurrence, 34 in transit recurrence; 29 positive regional lymph nodes, 31 negative LN, 9 LN status not established	Wide re-excision ± adjuvant hyperthermic ILP with melphalan	Wide excision + melphalan ILP (40^{o}C, 0.45 mg/kg body weight for upper extremity and 0.9 mg/kg for lower extremity) vs. wide excision	25 y	Median OS 56 mo vs. 38 mo, p=0.52 OS 18% vs. 19%	Melanoma-specific survival: median 95 mo vs. 38 mo, p=0.24 Deaths due to melanoma: 61% vs. 72%, p=0.31	Low statistical power to detect survival benefit, need larger trial	Melanoma-specific survival: median 95 vs. 38 mo (p=0.24), 39% vs. 28% (p=0.31) Conclude no evidence ILP prolongs survival but trials are largely underpowered
EORTC 18832, World Health Organization Melanoma Program trial		1984-1994 N=852 randomized,	Limb melanoma >1.5 mm; no evidence of satellitosis,	Cutaneous melanoma of the limb Elective lymph node dissection of groin or axilla optional but	Wide excision ± ILP with melphalan and mild hyperthermia	Excision biopsy with 2-5 mm margin; then randomized to melphalan ILP (39^{o}C to 40^{o}C for 1 hr, 10			DFI: early difference (first 2-3 y) was significant (p=0.018;		Trend for benefit in disease free interval; significant for pts without lymph

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
15, North American Perfusion Group Southwest Oncology Group 8593 Schraffordt Koops, 1998 [201]		832 assessable	ITM, regional lymph node metastases or systemic metastases: AJCC stage II pT3N0M0 or stage III pT4N0M0 Stratified 1.5 to 2.99 mm vs. 3.0 to 3.99 mm vs. ≥4.0 mm; ulceration)	had to be applied consistently within each centre		mg/L for lower limb or 13 mg/L for upper limb) followed by wide excision in same operation vs. wide excision			p=0.027 stratified)		node dissection. No difference in distant metastasis or survival; cannot be recommended
EORTC 18832 (subgroup from Netherlands Cancer Institute) Vrouenraets, 1999 [202]		1986-1993 N=109; 65 pts in functional morbidity study	High-risk: Stage I >1.5 mm	Axillary lymph-node dissection if melanoma in upper limb	Wide local excision ± adjuvant isolated limb perfusion with melphalan	See main EORTC 18832 study				Subjective complaints only in ILP group: muscle cramps, diminished muscle strength, increases sensitivity, tired/heavy feeling in limb Atrophy in 20% of lower limb ILP patients; function of ankle significantly worse	Need to weigh risk of functional morbidity against possible advantages of ILP
[UK] Fenn, 1997 [203]		1987-1992 N=33 recruited, 30 randomized	AJCC stage I melanoma of the lower limb, ≥1.7 mm, no satellite nodules	Melanoma of lower limb	Standard excision ± prophylactic isolated hyperthermic limb perfusion with melphalan	Excision + melphalan (40°C, 2 mg/kg body weight for 1 hr) vs. excision	80 mo ILP and 63 mo control	Death 2/16 vs. 7/14, p<0.03	Recurrent disease 2/16 vs. 9/14, p<0.004	Planned as multicentre trial but conducted at one site due to poor recruitment	Recurrence: 2 vs. 9 pts (p<0.004); death 7 vs. 2 pts (p<0.03). Conclude that data support IHLP use

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcomes Other comments	Conclusions of trial authors
[Cologne, West Germany] Ghussen, 1989 [204] Ghussen, 1988 [205]		1980-1983 N=107	>1.5 mm/Clark's level >III; primary tumour in distal 2/3 of extremity, no prior lymphadenectomy	Melanoma of the extremities MD Anderson staging system stages I (localized primary, n=37), II (local recurrence and/or satellite lesion within 3 cm, n=37), III (in transit or regional lymph nodes, n=33) 1.5-3 mm (n=50) or >3 mm (n=57)	Wide excision of tumour and regional lymph node dissection ± hyperthermic perfusion with melphalan	Wide excision + regional lymph node dissection + ILP (melphalan, 42°C, 1 mg/kg upper extremity or 1.5 mg/kg lower extremity, 4 doses over 1 hour), vs. wide excision + regional lymph node dissection	Analysis (Sept 1988): 5 y 11 mo	OS 94% vs. 80%, p<0.01	RFS 89% vs. 52%, p<0.001 Subgroup 1.5 to 3.0 mm: 43% vs. 28% Subgroup >3.0 mm: 45% vs. 24%	Discontinued at intermediate analysis (July 1983) due to highly-significant difference	Perfusion was beneficial: 6 vs. 26 recurrences (p<0.001); 3 vs. 11 deaths (p<0.01)

Other Reviews:

- v3, in 8-1 version 3 (2009) and subsequent versions; v3* complete publication, although longer term results are available in publication of pooled data [132]; (v3), older publication, abstract, or less complete data was included in 8-1 version 3
- v4, in 8-1 version 4 (2012) data assessment and review table appendix but not incorporated into main document; v4* complete publication, although longer term results are available in publication of pooled data [132]; (v4), older publication, abstract, or less complete data was included in 8-1 version 4

Abbreviations: AEs, adverse events; BCG, Bacillus Calmette-Guerin; BCNU, bis-chloroethylnitrosourea, generic drug name carmustine; CI, confidence interval; DFI, disease-free interval; DFS, disease-free survival; DMFS, distant metastasis-free survival; DTIC, (dimethyltriazeno)imidazolecarboxamide, drug name dacarbazine; HD-IFN, high-dose interferon; HR, hazard ratio; HRQoL, health-related quality of life; HuIFN, human interferon; ID-IFN, intermediate-dose interferon; ILP, isolated limb perfusion; IFN, interferon; im, intramuscular; ITT, intention to treat; iv, intravenous; LD-IFN, low-dose interferon; LN, lymph node; methyl-CCNU, methyl-lomustine, semustine, 1-(2-Choroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; OS, overall survival; PEG-IFN, pegylated interferon; pN+, pathologically node positive; po, per os (by mouth); pt, patient; pts, patients; QoL, quality of life; RFS, recurrence-free survival; rIFN, recombinant interferon; sc, subcutaneous; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy

Back to Results

Table 4-7. Adjuvant vaccine trials

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
[California] Morton, 1982, 1978 [206,207]	v3	1974-1978 N=149, 140 evaluable	Stage II, histologically proven metastases to regional nodes	Melanoma, subtype not specified Regional lymphadenectomy	BCG + melanoma cell vaccine vs. BCG vs. none	BCG ($1\text{-}3\times10^8$ to axilla, groin, and around primary site q1w for 12 wk then q2w) + allogenic melanoma cell vaccine (10^8 cells intradermally) vs. BCG vs. none For pts receiving BCG + vaccine, 10^7 organisms BCG was admixed with vaccine for the first 2 inoculations only	50 mo (mean)	OS: 55% vs. 56% vs. 48% From graph: 4-y OS 51% vs. 53% vs. 46%, p>0.05 2-y OS 59% vs. 75% vs. 49%	Recurrence: 53% vs. 43% vs. 41%	Chemotherapy (plus continuation of randomized treatment) at relapse Also in Immunotherapy table	Differences not statistically significant. BCG + vaccine improved RFS and OS compared with none; BCG improved OS but not RFS
[National Cancer Institute, Bethesda, Maryland] Fisher, 1981 [195]	v3	1975-≈1979 N=181, 166 evaluable	Poor prognosis Stage I (Clark level 4, >2.25 mm; Clark level 5; or local recurrence within 5 cm of primary tumour) or or Stage II (histologically node positive)	Cutaneous melanoma; excluded melanoma of eyes or mucous membranes Dissection of regional draining lymph nodes	BCG + neuraminidase-treated allogenic tissue cultured melanoma cells vs. BCG vs. methyl-CCNU vs. none	(BCG + mitomycin C-treated neuraminidase-treated cells; q1w×11 then every q2w for 2 y total) vs. BCG (q1w×11 then q2w for ≈ 2 y total) vs. methyl-CCNU (200 mg/m^2 po q6w for 18 mo) vs. none	>29 mo	OS p=0.64 for overall comparison 4-y OS: 52% vs. 28% vs. 45% vs. 54% 3-y OS: 58% vs. 42% vs. 50% vs. 54% 2-y OS 65% vs. 61% vs. 65% vs. 70%	DFS: methyl-CCNU vs. control p=0.064; Time to recurrence p=0.25 overall; vs. control: p=0.28 BCG + vaccine, p=0.66 BCG, p=0.068 methyl-CCNU	Preliminary report; no full report located Also in chemotherapy table, immunotherapy table	No significant difference in time to recurrence or OS. No indication to recommend routine us of BCG, BCG + allogenic cell vaccine, or methyl-CCNU; further follow-up necessary

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
									No significant difference in disease-free interval (p=0.22; pairwise all p>0.33)		
[Australia] Hersey, 2002 [208]	v3	1988-1998 N=700, 675 eligible	AJCC (1988) stage IIB and III	Cutaneous melanoma 77% LN+, 66% cN+	Vaccine prepared from vaccinia melanoma cell lysates (VMCL) vs. control (surgery only)	VMCL vs. control (surgery only)	8 y	Median OS 151 mo vs. 88 mo, HR=0.81 (95% CI =0.64 to 1.02), p=0.068 5-y OS 60.6% vs. 54.8% 10-y OS 53.4% vs. 41%	Median RFS 83 mo vs. 43 mo, HR=0.86 (95% CI=0.7 to 1.07), p=0.17 5-y RFS 50.9% vs. 46.8%		Improved OS (p=0.068), RFS (p=0.17) although not statistically significant
[vaccinia melanoma oncolysate (VMO) vaccine] Suriano, 2013 [209]; Wallack, 1998 [210] Interim analysis: Wallack, 1997, 1996 [211,212]	(v3)	1988-1991 N=250	Histologically positive nodes, (any number until June 1989; 1-5 thereafter)	Melanoma, subtype not specified	Vaccinia melanoma oncolysate (VMO) vaccine vs. vaccinia vaccine virus (V); both arms had smallpox vaccine as immune booster	VMO or V q1w for 13 w then q2w for 1 y or recurrence All pts received smallpox vaccine 1 week before initiation of VMO or V therapy.	10 y	Median OS 7.71 y vs. 7.95 y, p=0.70 At earlier analysis ([210] median 46.3 mo follow-up), no difference in OS (p=0.79); 5-y OS 48.6% vs. 48.2%, 3-y OS 60.0% vs. 55.6%	Median DFI 6 y vs. not reached (≈5 y), p=0.76 At earlier analysis ([210] median 46.3 mo follow-up), no difference in DFI (p=0.61); 5-y DFI 41.7% vs. 40.4%, 3-y DFI 43.8% vs. 44.8%	Control arm (V) may be active as well	VMO did not improve OS or DFI compared with the other arm; however, the control arm may have been active as well
Ad Hoc Melanoma Working Group (Melacine)	(v3)	1997-2003 N=604	LN+, AJCC 1988 Stage III	Excluded ocular or mucosal melanoma	Allogeneic melanoma lysates (Melacine) +	IFN (5 MU/m^2 sc 3×/wk for 104 weeks) + allogeneic	32 mo overall; 42 mo for	Vaccine + LD-IFN vs. HD-IFN: median >84 mo vs. 83 mo,	Median RFS 58 mo vs. 50 mo, p=0.61; 5-y	More neuropsychiatric toxicity in HD-IFN arm, other serious	OS and DFS indistinguishable; more neuropsychiatric

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
Mitchell, 2007 [170]			Excluded ocular and mucosal melanoma		LD-IFN-α2b (2 y) vs. HD-IFN-α2b (1 y)	melanoma vaccine (Melacine; weekly for 1 mo, at week 8, then every 2 mo for 104 wk total) HD-IFN (20 MU/m^2 iv for 5 d then 10 MU/m^2 sc 3×/wk for 52 weeks total)	survivin g pts	p=0.56; 5-y OS 61% vs. 57%	RFS 50% vs. 48%, p=0.80	AEs same in both arms Also in IFN table Data in Table 3 does not match data in text or figures; data from text has been extracted	toxicity with HD-IFN
[New York] Livingston, 1994 [213]	v3	1987-1989 N=123, 122 eligible	Stage III	Melanoma, subtype not specified	Ganglioside GM2 vaccine + BCG vs. BCG	GM2 (200 µg, twice at 2 week intervals plus booster 2 and 5 mo later) mixed with BCG (10^7 units or $3×10^6$ units in pts with positive skin test). Cyclophosphamide administered (200 mg/m^2) to all pts 5-7 d prior to 1st and 4th vaccination	5.25 y	4-y OS 48% vs. 29%, p=0.09 2-y OS 50% vs. 33%	4-y DFS 56% vs. 43%, p=0.22 2-y DFS 67% vs. 65%		Improved DFS and OS with BM2/BCG, significant in subset with GM2 antibody detected or subset excluding pts with GM2 antibody before treatment
ECOG 1694 Kirkwood, 2001 [69] Update in pooled analysis, Kirkwood, 2004	(v3)	1996-99 N=880; 774 eligible for efficacy analysis	Stage IIB/III; or clinically node positive from unknown primary; or nodal recurrence	Cutaneous melanoma Allowed deep lesions (>4 mm) with microscopic satellite lesions within	GM2-KLH/QS-21 vaccine vs. IFN-α2b	vaccine (1mL sc on days 1, 8, 15, 22; then q12w for weeks 12-96) vs. IFN (20 MU/m^2 iv 5 d/wk for 4 wk then 10	2.1 y (16 mo at un-blinding)	71.1% GMK vs. 76.7% IFN, Calculated at median 16 mo: 2-y OS 73% vs. 78%, HR=1.52, p=0.009	54.0% GMK vs. 64.2% IFN, Calculated at median 16 mo: 2-y RFS 49% vs. 62%, HR=1.47, p=0.0015	Trial closed after interim analysis due to GMK inferiority Also in IFN table	IFN group had better RFS and OS

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
[132] and Najjar, 2019 [133]				2 cm; excluded T4 with gross SC invasion or grossly apparent satellite lesions		MU/m^2 sc 3×/wk for 48 wk)	16.0 y	IFN vs. vaccine HR=0.85 (95% CI=0.71 to 1.01), p=0.068	IFN vs. vaccine HR=0.82 (95% CI=0.68 to 0.98), p=0.34		
EORTC 18961, BCT000050NCT00 NCT00505252 Eggermont, 2013 [214] Michels, 2018 [215]	(v3), (v4)	2002-2005 N=1314	>1.5 mm, T3-4N0M0 (stage II), LN-	Excluded ocular or mucous membrane melanoma 23% >4 mm; 42% ulceration Excluded ocular or mucosal melanoma	Ganglioside GM2-KLH/QS-21 vaccination versus observation	GM2-KLH/QS-21: sc q1w for w1-4, then q3m starting week 12 until wk 96, then q6m up to week 144, for a total of 14 vaccinations in 3 y	4.2 y	4-y OS 81.5% vs. 83.6%, HR=1.16 (95% CI=0.90 to 1.51), p=0.25	4-y RFS 68.2% vs. 69.4%, HR=1.03 (95% CI=0.84 to 1.25), p=0.81 4-y DMFS 76.1% vs. 78.8%, HR=1.11 (95% CI=0.88 to 1.40), p=0.36	Trial had been stopped at 2nd interim analysis for futility (median 1.8 y follow-up)	Stopped after 2nd interim analysis as concluded vaccination ineffective in prolonging RFS
MMAIT-III (Malignant Melanoma Active Immunotherapy); CV-MMAIT-3-001; NCT00052130 Morton, 2007 [216] [abstract] CancerVax, 2006 [217] [press release]		1998-2005 N=1160 pts	Stage III	Cutaneous melanoma	BCG + melanoma vaccine (Canvaxin) vs. BCG + placebo	CanVaxin + BCG vs. placebo +BCG by intradermal injection; BCG included only in first two doses on days 0 and 14; CanVaxin or placebo treatment continued days 28, 42, 56 then monthly for year 1, every 2 mo year 2, every 3 mo years 3-5	≈15 mo based on MMAIT-IV [219]	5-y OS 59.1% vs. 67.7%, p=0.04 (not significant as boundary for interim analysis set at p=0.013)	Median DFS 42.6 mo vs. >47 mo; 5-y DFS 47.2% vs. 52.1%, p=0.047	Hoshimoto, 2012 [218] [CTC for prognosis] No full publication Terminated at interim analysis based on low probability of improvement in survival	Trial closed at interim analysis due to low probability of significant improvement in BCG + melanoma vaccine arm. BCG may have benefit.

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
MMAIT-IV; NCT00052156 Faries, 2017 [219]		1998-2005 N=496	Stage IV (AJCC 5th ed, 1998), complete resection of≤5 metastasis	Melanoma, subtype not specified	BCG + melanoma vaccine (Canvaxin) vs. BCG + placebo	CanVaxin + BCG vs. placebo +BCG by intradermal injection; BCG included only in first two doses on days 0 and 14; CanVaxin or placebo treatment continued days 28, 42, 56 then monthly for year 1, every 2 mo year 2, every 3 mo years 3-5 BCG was 3×10^6 colony-forming units (cfu) on day 0 and 1.5×10^6 cfu on day 14	19.7 mo	Median OS 34.9 mo vs. 39.1 mo; 5-y OS 42.5% vs. 43.3%; 10-y OS 36.4% vs. 33.3; HR=1.053, p=0.696	Median DFS 8.5 mo vs. 7.6 mo; 5-y DFS 30.0% vs. 23.8%; 10-y DFS 30.0% vs. 21.7%; HR=0.882, p=0.260	Hoshimoto, 2012 [220] [CTC for prognosis] Terminated at interim analysis based on low probability of improvement in survival	Enrolment closed at interim analysis due to low probability of significant survival benefit for the BCG + melanoma vaccine arm. BCG may have benefit.
[New York University] Bystryn, 2001 [221]	v3	(not stated, ≈1996) N=38 (210 planned)	Stage III, resected, with particularly high risk of recurrence	Melanoma, subtype not specified High risk due to nodes clinically palpable at presentation or ≥2 histologically positive nodes	Melanoma vaccine (polyvalent shed antigen vaccine from 4 cultured melanoma cell lines) vs. placebo (human albumin); both bound to alum as adjuvant	Vaccine (40 µg q3w×4 then monthly ×3 then every 3 mo ×2 then every 6 mo for total of 5 y or disease progression	2.5 y	Median 3.8 y vs. 2.7 y, ns 3-y OS 53% vs. 33% 2-y OS 67% vs. 61% 1-y OS 83% vs. 77%	RFS median 1.6 y vs. 0.6 y, p=0.03 2-y RFS 42% vs. 23% 1-y RFS 67% vs. 31%	Closed early after publication of ECOG 1684 trial showing IFN-α2b improved survival Randomized 2:1 (vaccine : placebo)	Longer time to disease progression (p=0.03), OS (ns); suggests melanoma vaccine my slow progression. Interpret with caution due to low number of pts

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
E4697. NCT01989572 Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group Lawson, 2015 [222] Butterfield, 2017 [223]		1999-2006 N=815	Resected stage IV or high-risk stage III	Patients with cutaneous, uveal, or mucosal primaries eligible. 30 pts with mucosal melanoma, results not reported separately	Grouped by human leukocyte antigen (HLA)-A2 status. HLA-A2 positive: GM-CSF + peptide vaccination (PV) vs. GM-CSF vs. PV vs. placebo HLA-A2-negative: GM-CSF vs. placebo	HLA-A2 positive: GM-CSF + PV vs. GM-CSF vs. PV vs. placebo HLA-A2-negative: GM-CSF vs. placebo Treatment for 1 y (13 cycles) or recurrence; pts encouraged to resume if recurrence resectable GM-CSF: 250 µg/d, days 1-14 of each 28-d cycle PV (tyrosinase, pg00 209-217, and MART-1 peptides in Montanide ISA-51), 2 sc injections into 3 different sites on days 1 and 15 of cycle 1 and day 1 of subsequent cycles	82.1 mo for surviving pts	GM-CSF vs. placebo: median OS 69.6 mo vs. 59.3 mo; 5-y OS 52.3% vs. 49.4%, HR=0.94 (95% CI=0.77 to 1.15), p=0.528 PV vs. no PV: p=0.60 For HLA-AS positive: No significant difference in OS between GM-CSF + PV and other 3 groups (p=0.44 compared with PV; p=0.43 compared with GM-CSF; p=0.77 compared with placebo)	GM-CSF vs. placebo: median RFS 11.4 mo vs. 8.8 mo; 5-y RFS 31.2% vs. 27.0%, HR=0.88 (95% CI=0.74 to 1.04), p=0.131 PV vs. no PV: p=0.71 For HLA-AS positive: No significant difference in DFS between GM-CSF + PV and other 3 groups (p=0.59 compared with PV; p=0.78 compared with GM-CSF; p=0.43 compared with placebo)	Neither GM-CSF nor PV significantly improved RFS or OS	Possible small improvement, but not significant as powered to detect 33% change
DERMA, NCT00796445 Dreno, 2018 [224]		2008-2011 N=3914 screened, 1391 randomize	Stage IIIb, IIIc, macroscopic lymph node involvement	Cutaneous melanoma; excluded mucosal or	Recombinant MAGE-A3 + AS15 immuno-stimulant	Up to 13 im injections of recombinant MAGE-A3 (300 µg MAGE-A3 + 420	Final analysis: 28 mo Follow-up	Final analysis: OS 65% vs. 66%; median OS not reached vs. 46.6 mo,	Final analysis: median DFS 11.0 mo vs. 11.2 mo, HR=1.01 (95%	Not effective, MAGE-A3 development stopped	Immunotherapy not effective and MAGE-3 immunotherapy

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
		d, 1345 started treatment		ocular melanoma MAGE-A3-positive melanoma	immunotherapy vs. placebo	µg CpG 7909 in AS01B) vs. placebo; 5 doses at 3-weekly intervals then 8 doses at 12-weekly intervals, 27 mo total	analysis: 54.3 mo	HR=1.07 (0.88 to 1.29), p=0.52 Follow-up analysis: Median OS not reached, HR=1.06 (95% CI 0.89 to 1.26), p=0.52	0.88 to 1.17), p=0.86; DFS 64% vs. 63% Follow-up analysis: median DFS 11.0 mo vs. 11.2 mo, HR=1.02 (95% CI 0.89 to 1.18), p=0.75 4-y DFS 31% vs. 33%		development stopped

Other reviews

- v3, in 8-1 version 3 (2009) and subsequent versions; v3* complete publication, although longer term results are available in publication of pooled data [132]; (v3), older publication, abstract, or less complete data was included in 8-1 version 3
- v4, in 8-1 version 4 (2012) data assessment and review table appendix but not incorporated into main document; v4* complete publication, although longer term results are available in publication of pooled data [132]; (v4), older publication, abstract, or less complete data was included in 8-1 version 4

Abbreviations: BCG, Bacillus Calmette-Guerin; CI, confidence interval; DFI, disease-free interval; DFS, disease-free survival; DMFS, distant metastasis-free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor; HD-IFN, high-dose interferon; HLA, human leukocyte antigen; HR, hazard ratio; IFN, interferon; im, intramuscular; iv, intravenous; LD-IFN, low-dose interferon; LN, lymph node; methyl-CCNU, methyl-lomustine, semustine, 1-(2-Choroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; ns, not significant; OS, overall survival; po, per os (by mouth); pts, patients; PV, peptide vaccination; RFS, recurrence-free survival; sc, subcutaneous; VMCL, vaccinia melanoma cell lysates; VMO, vaccinia melanoma oncolysate vaccine

Back to Results

Table 4-8. Immunotherapy (other than interferon) or gene therapy

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
[University of California] Spitler, 1991, 1980 [225,226]	v3	(Not reported to ≈1978) N=216 randomized; 203 eligible and analyzed	High risk of recurrence: Clark's level III, IV, V; mucosal; acral-lentiginous primary; recurrence (cutaneous, subcutaneous, LN)	Mucosal specifically included as part of high-risk melanoma 109 stage I (primary melanoma, local recurrence, or in transit metastasis; 82 were <4 mm), 100 stage II (regional lymph-node metastasis), 4 stage III (metastasis beyond regional lymphatic drainage)	Levamisole vs. placebo	Levamisole 150 mg for 3 d q2w for 2 y Placebo	10.5 y	5-y OS 60% vs. 62%, p=0.48 2-y OS 80% vs. 78% p=0.07 for stage I and p=0.78 for stage II subgroups No difference at long-term follow-up	RFS p=0.78 for stage II subgroup No difference at long-term follow-up	Time to visceral recurrence: p=0.27 for stage I and p=0.67 for stage II; no difference between groups at long-term follow-up	No difference in DFI, time to visceral metastasis, or survival
EORTC 18761 Lejeune, 1988 [191]	v3	1976-1985 N=325, 274 eligible	Clark grade III and ≥1.5 mm; Clark grade IV or V. No evidence of LN metastasis	Cutaneous melanoma Lymph node dissection for limb melanomas, with exclusion if LN+ 33% ulceration; 4% satellitosis; thickness measured in some pts, 37% >3 mm	DTIC vs. levamisole vs. placebo	DTIC 250 mg/m^2, for 5d q28d for 6 cycles Levamisole 150-250 mg 2×/wk for 2 y Placebo	Median 241 week Mean 3 y	5-y OS 55% vs. 62% vs. 64%, p=0.412	DFI: no difference, p=0.915	Indicated that study ongoing but no follow-up publications found Also in chemotherapy table	Neither DTIC nor levamisole had effect on DFI or survival
[National Cancer Institute of Canada, NCIC] Quirt, 1991 [227]	v3	1978-1982 N=577 randomized, 543 eligible	Level 3 and >0.75 mm; level 4, level 5; satellite lesions within 3 cm of primary; in-transit metastases;	Melanoma, subtype not specified (but excluded a case of conjunctival melanoma because it was not cutaneous)	Levamisole vs. BCG + levamisole vs. BCG vs. clinical assessment	Levamisole (2.5 mg/kg po 2 consecutive nights weekly for 3 y BCG (40 mg for 4 wk then every 4 wk for 3 y) Combined treatment for 3 y: BCG as above for 8 wk, then levamisole for 8 wk,	8.5 y	5-y OS: 74% vs. 65% vs. 59% vs. 62% Levamisole vs. control p=0.0268; p=0.0964 adjusted	5-y RFS: 66% vs. 58% vs. 50% vs. 55% Levamisole vs. control p=0.0672; p=0.0800 adjusted		Levamisole vs. no treatment had 29% reduction in death rate (p=0.08) and recurrence (p=0.09); BCG alone not effective, BCG +

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
			regional lymph node involvement; recurrence to regional lymph node area	24% LN+, 2% satellitosis, 1% in-transit; Other (primary) melanomas: 28% ≤1.5 mm, 21% 1.51 to 2.5 mm, 13% 2.51 to 4.0 mm, 10% >4 mm		then alternated 8 wk courses with levamisole weekly or BCG twice per 8 wk period		Levamisole + BCG vs. control p=0.6329, p=0.5926 adjusted BCG vs. control p=0.6226, p=0.8053 adjusted	Levamisole + BCG vs. control p=0.7493, p=7280 adjusted BCG vs. control p=0.3987, p=0.8707 adjusted		levamisole results were intermediate between those of either agent alone. Results warrant further investigation of levamisole
[National Cancer Institute, Bethesda, Maryland] Fisher, 1981 [195]	v3	1975- ≈1979 N=181, 166 evaluable	Poor prognosis Stage I (Clark level 4, >2.25 mm; Clark level 5; or local recurrence within 5 cm of primary tumour) or or Stage II (histologically node positive)	Cutaneous melanoma; excluded melanoma of eyes or mucous membranes Dissection of regional draining lymph nodes	BCG + neuraminidase-treated allogenic tissue cultured melanoma cells vs. BCG vs. methyl-CCNU vs. none	(BCG + mitomycin C-treated neuraminidase-treated cells; q1w×11 then every q2w for 2 y total) vs. BCG (q1w×11 then q2w for ≈ 2 y total) vs. methyl-CCNU (200 mg/m^2 po q6w for 18 mo) vs. none	>29 mo	OS p=0.64 for overall comparison 4-y OS: 52% vs. 28% vs. 45% vs. 54% 3-y OS: 58% vs. 42% vs. 50% vs. 54% 2-y OS 65% vs. 61% vs. 65% vs. 70%	DFS: methyl-CCNU vs. control p=0.064; Time to recurrence p=0.25 overall; vs. control: p=0.28 BCG + vaccine, p=0.66 BCG, p=0.068 methyl-CCNU No significant difference in disease-free interval (p=0.22; pairwise all p>0.33)	Preliminary report; no full report located Also in vaccines table, immunotherapy table	No significant difference in time to recurrence or OS. No indication to recommend routine us of BCG, BCG + allogenic cell vaccine, or methyl-CCNU; further follow-up necessary

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
ECOG E1673 Agarwala, 2004 [189]		1974-1978 N=734 randomized, 708 ITT analysis, 618 eligible analysis	Clark level ≥3, stage I-III; From text: Cohort 1 is Stage I/II (Clark level 3-5) or Stage III (26%; head, neck, extremities). Cohort 2: Stage III (trunk location) with synchronous or recurrent regional lymph node involvement	Cutaneous melanoma Table and text inconsistent regarding stage breakdown.	Cohort 1: BCG vs. observation; Cohort 2: BCG plus DTIC vs. BCG	Cohort I: BCG vs. observation Cohort II: BCG + DTIC vs. BCG DTIC 200 mg/m^2 iv daily ×5; 10 d delay; BCG q1w×4. Cycles repeated q8w for 18 mo (total of 10 cycles) [later modified to give DTIC 100 mg/m^2 iv daily for 5 d q4w for 18 mo with BCG staring the first week and continuing for 18 mo] BCG by multiple puncture technique weekly for first 4 wk in regional lymph node drainage area; then expanded to include other areas of lymphatic drainage by rotation, q2w×4, q4wx6, q8wx5	Median follow-up projected at 30 y	Cohort I: OS 67% vs. 62%, p=0.40 Cohort II: OS no difference, p=0.81	Cohort I: DFS, no difference, p=0.84 Cohort II: DFS, no difference, p=0.74	Punctuate abscesses in >66% of pts treated with BCG Confirms negative results for BCG found in previous smaller studies Also in chemotherapy table	No benefit in DFS or OS for BCG DTIC did not improve DFS or OS
[California] Morton, 1982, 1978 [206,207]	v3	1974-1978 N=149, 140 evaluable	Stage II, histologically proven metastases to regional nodes	Melanoma, subtype not specified Regional lymphadenectomy	BCG + melanoma cell vaccine vs. BCG vs. none	BCG (1-3×10^8 to axilla, groin, and around primary site q1w for 12 wk then q2w) + allogenic melanoma cell vaccine (10^8 cells intradermally) vs. BCG vs. none For pts receiving BCG + vaccine, 10^7 organisms BCG was admixed with vaccine for the first 2 inoculations only	50 mo (mean)	OS: 55% vs. 56% vs. 48% From graph: 4-y OS 51% vs. 53% vs. 46%, p>0.05 2-y OS 59% vs. 75% vs. 49%	Recurrence: 53% vs. 43% vs. 41%	Chemotherapy (plus continuation of randomized treatment) at relapse Also in vaccine table	Differences not statistically significant. BCG + vaccine improved RFS and OS compared with none; BCG improved OS but not RFS.

Trial Name [country or trial group]	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	DFS or RFS	Other outcomes Other comments	Conclusions of trial authors
World Health Organization International Melanoma Group Veronesi, 1982 [192]	v3	1974-1980 N=931, 761 evaluable	High-risk: stage II anywhere (lymph node metastases) or Stage I (Clark level 3-5) on trunk	Cutaneous melanoma Excisional regional lymphadenectomy. Separately randomized stage I (n=98 evaluable) and stage II pts (n=663 evaluable)	DTIC vs. BCG vs. DTIC + BCG vs. none	DTIC (200 mg/m^2 for 5d, q4w for 24 cycles) vs. BCG (75 mg in 0.5 mL saline by Heaf gun needles weekly until skin reaction then monthly) vs. DTIC + BCG (as above with BCG on day 5 of first cycle) vs. observation	41 mo (mean)	3-y OS 46.5% (p=0.64) vs. 48.7% (p=0.14) vs. 50.0% (p=0.35) vs. 41.6% [p values are compared with control]	3-y DFI 37.2% (p=0.16) vs. 34.8% (p=0.17) vs. 33.6% (=0.20) vs. 30.4% [p values are compared with control]	Also in chemotherapy table	No significant differences in DFS or OS
[Canada] Quirt, 1983 [193]	v3	1974-1978 N=94 (37 stage III)	Stage I (Clark's level 3-5), stage III (in transit or lymph node metastases)	Cutaneous melanoma 57 pts stage I (16 level 3, 31 level 4, 10 level 5) 37 pts stage III	DTIC + BCG vs. observation	DTIC (850 mg/m^2 iv, wk 1 and 4) plus BCG (120 mg po or 0.1 mg injection q2w for 1 y and q4w for 1 y) Observation	6.4 y	Stage III group (from text): 3y-OS 61% vs. 47% (p=0.136); 5-y OS 55% vs. 36% (p=0.246)	Stage III group (from graph): 3-y RFS 44% vs. 32%; 5-y RFS 40% vs. 25%, not significant	Stage I and III reported separately Also in chemotherapy table	Stage I: No difference in relapse or OS Stage III: non-significant improvement in survival and recurrence
[China] Li, 2011 [228] [abstract] Phase II		Not stated (≈2008-2010) N=57	Melanoma of oral mucosa		rAd-p5 intratumoral injection + surgery + adjuvant rAD-p53 vs. surgery	Intratumoral injection of rAD-p53 at 2×10^9 virus particles/cm^2 for 5 times at interval of 3 d, radical surgery 24-48 h after last injection, 7 d after surgery was 15-d cycle of rAD-p53 at 2×10^{12} virus particles/infusion for 5 infusions vs. control (radical surgery)	24 mo	2-y OS 39.6% vs. 16.7% (significant)		Phase II study in oral mucosa melanoma	2-y OS significantly higher in experimental group compared with surgery alone

Abbreviations: BCG, Bacillus Calmette-Guerin; DFI, disease-free interval; DFS, disease-free survival; DTIC, (dimethyltriazeno)imidazolecarboxamide, drug name dacarbazine; ITT, intention to treat; iv, intravenous; LN, lymph node; methyl-CCNU, methyl-lomustine, semustine, 1-(2-Choroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; OS, overall survival; po, per os (by mouth); pts, patients; RFS, recurrence-free survival Back to Results

Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent Melanoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel (see members in Appendix 1), the PEBC Report Approval Panel (RAP), and the Patient and Caregiver-Specific Consultation Group. The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the nine members of the GDG Expert Panel, seven members cast votes, for a total of 78% response in April-May 2019. Of those that cast votes, all 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. Comments from the Expert Panel and the Working Group's responses

Comments	Responses
1. Add that a patient with resectable palpable nodal disease should have a dissection of that area (axillary, groin, head and neck) prior to adjuvant therapy. If they have unresectable disease, they should be considered for up-front systemic therapy. There seems to be confusion from the community about sentinel node positive versus palpable nodal disease (i.e., some suggestions that people not wanting to do dissections for palpable disease).	This has been added to the Qualifying Statements for Recommendation 1.
2. Consider clarifying why there is inclusion of patients with distant metastasis or recurrence in adjuvant treatment	A sentence has been added to the Target Population and Research Questions to make this clearer.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in May to June 2019. The RAP approved the document. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Comments from RAP and the Working Group's responses

Comments	Responses
1. Well done and easy to read. Suggest expanding the objectives (question 1 and 2) to better reflect the recommendations	The wording of the objective has been revised.
2. In the systematic review it is unclear the relative role of the Cochrane review and other individual trials, how they fit together, and if they are double counted. Indicate meta-analyses before individual trials	The Interferon subsection of Results has been revised to stress that both the Cochrane review and the individual patient meta-analysis of interferon versus placebo/none are the foundation. Results

	stated in the preamble of this section have been removed and historical material on interferon dosing moved to the introduction.
3. Consider reordering clauses in Recommendation 1 for clarity	The authors prefer the recommendation as written
4. For Recommendation 1, harms were not calculated. Indicate this so that it does not look like one can use the harm argument to advocate for one for the other.	This was dealt with in the first qualifying statement; however, we have added additional details to Table 4-4 and the Qualifying Statements for Recommendation 1.
5. For Recommendation 3, add AEs to key evidence, as they play a key role in the recommendation, or expand rationale/interpretation	This has been added to Key Evidence and repetition removed from the Interpretation section.
6. Recommendation 5 seems understated; consider making it more like Recommendation 1. Expand on interpretation of evidence if studies are ongoing.	The authors prefer the recommendation as written.
7. Further qualifying statements: be more explicit in describing the AEs. It currently focuses on benefits without the balance. Management of AEs does not have to be discussed.	Additional information about adverse events has been added to the Qualifying Statements for Recommendation 1 and Key Evidence for Recommendation 3.
8. Consider revising Table 4-3 headings to make it easier to follow and interpret.	Table 4-3 has been revised for clarity.
9. Isolated limb perfusion is included in review but not recommendations.	This was inadvertently omitted from Recommendation 4 and has been added there.

Patient and Caregiver-Specific Consultation Group

Four members of the Patient and Caregiver-Specific Consultation Group reviewed the document and provided feedback in June 2019. All agreed the recommendations were clear, reflect the evidence, consider issues and outcomes that are important to patients, and do not recommend treatment/care that would be considered unacceptable to patients. As funding and approval decisions in Ontario are ongoing, issues such as cost and availability could not be addressed, and this is noted in Section 2 under implementation considerations.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

One targeted peer reviewer from Ontario and five from other provinces in Canada who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two agreed to be the reviewers and two responses were received. Results of the feedback survey are summarized in Table 5-3. The 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

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	1
2. Rate the guideline presentation.					2
3. Rate the guideline recommendations.					2
4. Rate the completeness of reporting.					2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?					2
6. Rate the overall quality of the guideline report.					2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					2
8. I would recommend this guideline for use in practice.					2
9. What are the barriers or enablers to the implementation of this guideline report?	Dissemination of information. No identifiable barriers. There is clear level I evidence for the use of PD1 inhibitors and targeted therapy (dabrafenib and trametinib for *BRAF* mutations). There should be a link in these recommendations to the separate recommendations regarding radiotherapy.				

Table 5-4. Targeted peer reviewer comments and the Working Group's responses

Comments	Responses
1. Guideline is comprehensive, with clear recommendations and appropriate supporting evidence. The systematic review portion is a bit overly complete.	
2. The authors acknowledge the different trial populations and have recommended that more broad inclusion into guidelines should be undertaken. This reviewer agrees with the proposal to include any stage 3 patient with *BRAF* mutations for either nivolumab or pembrolizumab or dabrafenib/trametinib. The only evidence for resected stage 4 is from the CheckMate 238 trial with nivolumab; however, as the authors point out, data from metastatic setting supports that this agents are equivalent. Of note, the authors rightly point out there are very little data in the adjuvant setting for mucosal melanoma; however, they were included in CheckMate 238 and extrapolation from the metastatic setting would support efficacy in this population. Given the disease rarity an adjuvant trial specifically in mucosal melanoma will never be conducted.	

3. There is sufficient information for decisions except there should be clarification that high-risk stage 2 patients are not included in these guidelines. The authors recommend that IFN not be used in any setting which is appropriate. High-risk stage 2 patients are a challenge to include in these guidelines. On page 2, stage 2 patients are included in the high-risk definition and on page 4 (3rd bullet), there is a notation that the risks and benefits in stage 2 should be discussed with the patient (and unclear if this is only in the context of a clinical trial). It is this reviewer's assumption that stage 2 (and stage 3A <1mm) will not be included in the treatment recommendation guidelines. Although there is a strong rationale, the data are not yet available and there would be significant cost implications.	For Recommendation 1, the reviewer is correct in that no recommendation for use of adjuvant therapy (either for or against) is being made for high risk stage II and stage 3A <1mm disease. This is discussed in the qualifying statement, where both individual discussion between the physician and patient and inclusion in clinical trials is encouraged. The relevant sentence has been rearranged to clarify this.
4. There also should be a statement regarding uveal melanoma highlighting exclusion from all trials and adjuvant therapy cannot be supported from the available evidence.	Uveal melanoma was specifically outside the scope of this document, and evidence was not looked for. Only cutaneous and mucosal melanomas are included in the research questions and target population.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals in Ontario that are included in the PEBC database. Professionals with melanoma or skin as an area of interest, all dermatologists, and all medical oncologists without a stated specialty were contacted by email to inform them of the survey. Of 96 people contacted, 14 responses were received (14.6%). Of these, five 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 nine 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. Professional consultation questionnaire results

	Number of Responses				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1	2	6
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				1	8
3. I would recommend this guideline for use in practice.				1	8
4. What are the barriers or enablers to the implementation of this guideline report?	<u>Enablers</u> I really like the fact that each of the Recommendations has Qualifying Statements and Key Evidence to support it.				

	I appreciated the fact that the trials that did not report OS, DFS, RFS or DMFS were not included in the guideline. Huge volume of evidence summarized in clear, readily accessible format for ready reference. <u>Barriers</u> Access to the therapies - these indications are currently not funded in Ontario. The draft guidelines and recommendations are very important in aiding patient care but some are not clearly worded. Operating room time for melanoma surgery and sentinel node surgery in general. Nuclear medicine access for CT/PET and CT/SPECT imaging. Resources at treatment facilities.

Table 5-6. Professional consultation comments and Working Group responses

Comments	Responses
1. The guidelines are lengthy; however, contain all of the relevant and critical information to make an informed decision on the targeted populations. This is an excellent resource for clinicians.	
2. Very important topic to address so glad it's here!	
3. This is one of the clearest, most comprehensive summary and guideline I have read.	
4. It is recognized that mucosal melanoma has a different origin and biology but the recommendation is based on extrapolation of evidence from cutaneous melanoma.	It is stated in the qualifying statements and key evidence that data for adjuvant treatment of mucosal melanoma are limited. However, effectiveness of an agent in both cutaneous melanoma and non-resectable mucosal melanoma suggests adjuvant use in mucosal melanoma is reasonable. For targeted agents, it is also considered reasonable that cases with the same mutation (whether cutaneous or mucosal) may benefit from the same therapy.

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

Member and Role	Affiliation	COI Declaration(s)*
Teresa M. Petrella Co-Chair of Working Group	Medical Oncologist Associate Professor, University of Toronto Chair, CCTG Melanoma Clinical Trials Group Chair, Melanoma Site Group Odette Cancer Centre	Research grants from Roche, Novartis, BMS, Merck. Principle investigator of trials sponsored by Roche, Merck, Novartis. Received funds from Merck for funding a clinical fellow in melanoma.
Tara D. Baetz Co-Chair of Working Group	Medical Oncologist Cancer Centre of Southeastern Ontario, Kingston and Queen's University, Kingston	Principle investigator for COMBI I (Novartis), MasterKey-265, and CCTG ME.13 Stop Gap trials
Glenn G. Fletcher Working Group	Health Research Methodologist Program in Evidence Based Care, McMaster University/Cancer Care Ontario, Hamilton	None declared
Gregory Knight Working Group	Medical Oncologist Grand River Regional Cancer Center, Kitchener and Department of Oncology, McMaster University, Hamilton	Participated in advisory boards and received travel support from BMS, Merck, Roche, Sanofi
Elaine McWhirter Working Group	Medical Oncologist Juravinski Cancer Center, Hamilton Department of Oncology, McMaster University, Hamilton	Local principle investigator on the BRF115532 adjuvant study COMBI-AD (dabrafenib + trametinib vs. placebo); MEC.5 (physician/patient choice of either high dose interferon or ipilimumab to pembrolizumab); and COMBI-APlus (dabrafenib in COMBInation with trametinib). Published editorial, commentary, or opinion on topic: Melanoma Network of Canada "Patient Connection" newsletter, spring 2018 - describes promising new treatments in adjuvant and metastatic melanoma
Sudha Rajagopal Working Group	Medical Oncologist Credit Valley Hospital, Mississauga	None declared
Xinni Song Working Group	Medical Oncologist The Ottawa Hospital Cancer Centre and Department of Medicine, University of Ottawa	Consulting as a member of BMS advisory board. Principal investigator for BMS Checkmate 067/047/915, Merck Echo, Keynote 054, BRIM8, COMBI-D/V, and COMB-AD trials
Frances C. Wright	Surgical Oncologist	Research grants from Roche for a PI Investigator led study

Working Group (June-Dec 2018); Expert Panel	Sunnybrook Health Sciences Centre/Odette Regional Cancer Center, Toronto and Department of Surgery, University of Toronto	
Annette Cyr Expert Panel	Patient Representative Melanoma Network of Canada Toronto	Chair of board of Melanoma Network and along with other board members has fiduciary responsibility for >$5000 in grants from pharmaceutical companies in support of patient programs
Caroline Hamm Expert Panel	Medical Oncologist Windsor Regional Cancer Centre (WRH)	Principle investigator of NCIC sponsored clinical trial using pembrolizumab in adjuvant melanoma, stage III
Danny Ghazarian Expert Panel	Pathologist Toronto General Hospital	None
Alexandra M. Easson Expert Panel	Surgical Oncologist Princess Margaret Hospital, Toronto	None
Christian A. Murray Expert Panel	Dermatologist Skin Surgery Centre, University of Toronto	None
David R. McCready Expert Panel	Surgical Oncologist Princess Margaret Hospital, Toronto	Financial interest >$1000 over all categories combined (salary, consulting, grants, investments, other). Published opinion or commentaries on melanoma, but not specific drugs.

* Working Group members completed the Conflict of Interest Declaration Form in accordance with the policy in effect at the start of the project. It contained a requirement for reporting financial interests (employment, consulting, or investments) of ≥$5000 a year in the past five years. Subsequently, the reporting limit was changed to $500, and other participants made declarations according to this limit. The policies were otherwise identical.

In accordance with the PEBC Conflict of Interest (COI) Policy, authors and reviewers were asked to disclose potential COIs. Potential COIs declared by the authors are included in the table above. Participants in the Report Approval Panel and the Patient and Caregiver-Specific Consultation Group declared they had no conflicts of interest. For the targeted peer reviewers, WM declared consulting with Merck, BMS, Sanofi, Novartis, EMD Serono, and Amgen (WM); being principal investigator on relevant clinical trials funded by Merck and BMS; and grants in support of several other clinical trials. KS declared consulting on advisory boards for BMS and Merck; travel support from Seattle Genetics (Health Canada expert role); and was principle investigator for BMS 066, 067, 238, 915, 205(HL) and Merck (HL) trials.

As indicated in Section 3, The Director of the PEBC waived the requirement that the lead author and 50% of members of the Working Group have no declared interests, with the provision that co-chairs be appointed. With this proviso, the COI declared above did not disqualify any individuals from performing their designated role in the development of this

guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

Back to Section 3

Appendix 2: Literature Search Strategy*

Database(s): Embase 1996 to 2018 June 11, EBM Reviews - Cochrane Central Register of Controlled Trials May 2018, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 7, 2018, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to June 06, 2018 Search Strategy:

#	Searches	Results
1	exp Melanoma/ or melanoma.ti,kw.	218712
2	exp chemotherapy/ or exp immunotherapy/ or exp systemic therapy/ or exp Antineoplastic Agents/ or exp interferon/ or exp interleukin 2/ or exp levamisole/ or exp lomustine/ or exp carmustine/ or exp vincristine/ or exp ipilimumab/ or exp nivolumab/ or exp vemurafenib/ or exp dabrafenib/ or exp trametinib/ or exp pembrolizumab/ or exp cobimetinib/ or exp imatinib/ or exp binimetinib/ or exp pimasertib/ or exp talimogene laherparepvec/ or exp melacine/ or exp onamelatucel L/ or exp dendritic cell vaccine/ or exp BCG vaccine/ or exp dacarbazine/ or exp temozolomide/ or exp encorafenib/ or exp B Raf kinase inhibitor/ or exp monoclonal antibody/ or exp carboplatin/ or exp paclitaxel/ or exp pyrimidine derivative/ or exp protein kinase inhibitor/ or exp indole derivative/ or exp imidazole derivative/ or exp mitogen activated protein kinase kinase inhibitor/ or exp piperazine derivative/ or exp benzamide derivative/ or exp sulfonamide/	5,820,830
3	(Interferon or IFN-alpha or Interleukin-2 or IL-2 or lomustine or levamisole or CCNU or carmustine or BCNU or vincristine or Ipilimumab or Nivolumab or Encorafenib or Opdivo or Vemurafenib or Zelboraf or Dabrafenib or Tafinlar or Trametinib or Mekinist or Pembrolizumab or Cobimetinib or Imatinib or Imatinib-mesylate or Binimetinib or Pimasertib or T-VEC or talimogene laherparepvec or Melacine or onamelatucel L or Canvaxin or Dendritic cell therapy or CSF-470 or dacarbazine or DTIC or temozolamide or MTIC or monoclonal antibod: or MEK inhibitor: or CKIT inhibitor: or carboplatin or paclitaxel).mp.	1,303,959
4	(chemotherap: or chemoradio: or radiochemo: or immuno: or vaccin: or adjuvant).mp.	7,130,634
5	1 and (2 or 3 or 4)	115,043
6	5 not ((comment or letter or note or editorial or case reports or historical article).pt. or exp case report/ or exp case study/)	99,061
7	exp practice guideline/ or guideline.pt. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti,kw.	783,321
8	6 and 7	1,276
9	limit 8 to yr=2013-current	602
10	remove duplicates from 9	525
11	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp	631,550

	"review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.	
12	6 and 11	1,551
13	limit 12 to yr=2013-current	954
14	13 not 9	886
15	remove duplicates from 14	730
16	exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp randomized controlled trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treple$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.	2,901,549
17	6 and 16	10,559
18	17 not (9 or 14)	9,951
19	limit 18 to yr=2011-current	5,877
20	remove duplicates from 19	4,770
21	limit 18 to yr=1996-2010	3,548
22	remove duplicates from 21	2,720

*The same literature search was rerun May 28, 2019 to obtain any publications indexed since the original search.

Back to Section 3

Back to Section 4

Appendix 3: Guidelines

Search for Guidelines. 2013-2018 from developer websites, MEDLINE, and Embase

Organization	Citation	Topic	Search details	Comments and recommendations
Cancer Council Australia	Cancer Council Australia Melanoma Guidelines Working Party, 2018 [41]	Diagnosis and management of melanoma. Chapter on adjuvant systemic therapy in resected stage II and III melanoma	Embase until Feb 27, 2017; PubMed until Feb 2, 2017 plus monthly until Mar 5, 2018; non-systematic search thereafter	Wiki format with continuous minor revisions , staged updates cycling through topics Stage II: adjuvant systemic therapy not recommended outside a clinical trial Stage III: • Discuss with medical oncologist and MDT • Dabrafenib/trametinib for *BRAF* V600E/K • Consider nivolumab, pembrolizumab • Routine follow-up if above not appropriate; patients may consider IFN-α after discussing toxicity and potential benefit • Ipilimumab not recommended
Society for Immunotherapy of Cancer [international but based in USA; all 27 authors from USA]	Sullivan, 2018 [42]	Immunotherapy, for cutaneous melanoma, stages II-IV	MEDLINE until Nov 6, 2017; started 1992 or 2011 depending on topic. Up to May 2012 covered in previous version	Focused on drugs approved by the U.S. Food and Drug Administration (FDA). -IFN-α2b, pegylated IFN-α2b, ipilimumab, nivolumab, pembrolizumab, *BRAF*-targeted therapy (dabrafenib, trametinib, vemurafenib), T-VEC Recommendations for immunotherapy • Lower-risk stage I and IIA: observation • Higher-risk stage IIB-C: panel divided, 55% enrolment in clinical

Organization	Citation	Topic	Search details	Comments and recommendations
				trial, 20% observation, 10% IFN-α2b (high dose), 0% pegylated IFN-α2b • Currently no evidence for use of ipilimumab, nivolumab, pembrolizumab, *BRAF*-targeted therapy in stage II melanoma • Stage III with microscopic metastasis to one node (N1a) may need to be considered separately: 58% clinical trial, 10% observation, 5% ipilimumab (10 mg/kg), 10% IFN-α2b • Stage III with *BRAF* V600E/K mutation: consider dabrafenib plus trametinib • Stage III (N1b, N2-N3): clinical trial if available (56%); or nivolumab or pembrolizumab (46% of panel); ipilimumab (8%); IFN-α2b not recommended • Resected Stage IIIB-IV: nivolumab or pembrolizumab (46%), ipilimumab (8%), dabrafenib + trametinib if *BRAF* mutation (13%)
Ano-Uro-Genital Mucosal Melanoma Guideline Development Group, Melanoma Focus (UK)	Gore, 2018 [248]	Ano-uro-genital mucosal melanoma	Medline, Embase, Cochrane to 1990-March 2017	Based on metastatic cutaneous and mucosal melanoma and on adjuvant use in cutaneous melanoma, consider immune checkpoint inhibitors and *BRAF*-targeted agents; extrapolation of high-dose ipilimumab data not recommended
National Comprehensive	Coit, 2019 [46]	Cutaneous melanoma	Not stated, although documents throughout 2018 are cited, and this	Includes key trials for Is a major revision to incorporate immune-checkpoint inhibitors and

Organization	Citation	Topic	Search details	Comments and recommendations
Cancer Network (NCCN)			is the second version for 2019	targeted therapy, includes the key adjuvant trials for these agents. No longer recommends IFN-α or biochemotherapy Includes related topics such as biopsy and pathology, molecular testing, SLNB, CLND, radiation therapy
German Guideline Program in Oncology	Leitlinienprogramm Onkologie, 2018 [249]	Diagnosis, therapy, follow-up of melanoma	Adjuvant questions (Section 6) Medline and Cochrane. 2013 version: Jan 2012; 2018 version: until Sept-Nov 2016	Current version: text in German, search and evidence tables in English. 2013 version also in English [250] Vaccination, extremity perfusion, immune stimulation: adapted from other guidelines Bevacizumab, Ipilimumab, interferon: from original data Do NOT recommend DTIC; DTIC + cisplatin + vinblastine + interleukin-2 + IFN-α2b + GCSF; vaccination therapy; limb perfusion with melphalan; the immune stimulants levamisole or BCG; mistletoe; bevacizumab May offer ipilimumab; serious side effects should be included in decision Should offer IFN for stage IIB/C and IIIA-C May offer low-dose IFN for stage IIA, with consideration of benefits, side effects, and QoL
Healthcare Improvement Scotland / SIGN [SIGN 146]	Healthcare Improvement Scotland, 2017 [251]	Cutaneous melanoma	MEDLINE, Embase, CINAHL, PsycIFNO, and the Cochrane Library, 2004-2016; also various websites. Month of search not reported, but likely	Recommendations • Consider adjuvant RT for completely resected stage IIIB or IIIC • Do not use adjuvant IFN Immunotherapy trials are ongoing

Organization	Citation	Topic	Search details	Comments and recommendations
			early 2016 as the guideline was published Jan 2017	
la Société Française de Dermatologie	Guillot, 2017 [252] ; Guillot, 2016 [253] [254]	Melanoma treatment and management, Stages I-III	MEDLINE and Cochrane 2005-May 30 2015	Adjuvant medical treatments are LD-IFN (non-pegylated), observation, or clinical trials. Recommends against HD-IFN, isolated limb perfusion Adjuvant RT an option if node positive
la Société Française de Dermatologie	Guillot, 2018, 2019 [43-45]	Stage III melanoma		Includes Stage III-IV resected melanoma. Stage IV (resected): recommends nivolumab, regardless of *BRAF* status Stage IIIA-D: recommends nivolumab or pembrolizumab regardless of *BRAF* status; dabrafenib plus trametinib is also recommended if *BRAF* mutated Does not recommend interferon, ipilimumab, or vemurafenib
PEBC/CCO	Sun, 2016 [12]	Adjuvant radiotherapy for resected cutaneous melanoma	MEDLINE and Embase, 2000-Jul 2015	Adjuvant RT if inadequate clear margins or if positive lymph nodes or nodal recurrence
Cancer Care Ontario	Petrella, 2013 [100]	Adjuvant systemic therapy in high-risk melanoma	MEDLINE, Embase, and Cochrane until Sept 2013	Assessed 2017 as requiring updating Recommendations, not changed from 2009 version 3 (search until Jul 2008) • Encourage participation in clinical trials • HD-IFN-α2b should be discussed and offered; patients should be made aware of risks and benefits

Organization	Citation	Topic	Search details	Comments and recommendations
				• PEG-IFN can be considered as a reasonable alternative
Alberta Health Services	Weis, 2016 [62]; Alberta Health Services, 2014 [63]	Uveal melanoma	PubMed 2000-Dec 2014 PubMed 2000-Jul 2013	Recommendation: There is no evidence to support the use of adjuvant systemic therapy in high-risk patients. Consider enrolment in clinical trials -Guideline was to have formal review in 2016
Alberta Health Services	Alberta Health Services, 2014 [255]	Adjuvant IFN in cutaneous melanoma; disease-free after resection and at high-risk of recurrence	MEDLINE 1966-Dec 2010, CINAHL, Cochrane, ASCO abstracts, CANCERLIT; update using PubMed Jan 2012-Jan 2013 and Jan 2013-Jan 2014	No changes to recommendations in 2013 and 2014 updates Recommendations adapted from 2006 guideline by Canadian Expert Panel on Malignant Melanoma Recommendation: enrol in clinical trial, consider for adjuvant therapy, eligible for IFN-α (HD-IFN) -Guideline was to have formal review in 2016
Alberta Health Services	Alberta Health Services, 2013 [256]	Resectable stage IV without nodal disease	Medline, Cochrane, ASCO abstracts, CANCERLIT 1985-Nov 2009; update using PubMed Dec 2009-Jan 2013	No major changes in recommendations in the 2013 update -Recommendation for systemic therapy: enrolment in clinical trial or observation - Guideline was to have formal review in 2015
Alberta Health Services	Alberta Health Services, 2013 [257]	Stage III melanoma with in-transit disease of the limbs	Medline, Cochrane, ASCO abstracts, CANCERLIT 1985-Nov 2009; update using PubMed Dec 2009-Jan 2013	No major changes in recommendations in the 2013 update -Recommendations adapted from NCCN (2009) and modified based on ESMO (2009), Australia (1999), German (2008) guidelines -Adjuvant treatment if disease free: clinical trial, IFN-alpha, or observation -Guideline was to have formal review in 2015

Organization	Citation	Topic	Search details	Comments and recommendations
Japan Society of Gynecologic Oncology	Saito, 2018 [258]	Vulvar and vaginal cancer, including melanoma	Evidence up to Dec 2013	English publication of 2015 guideline These melanomas are mucosal and distinct from cutaneous melanomas DTIC-based chemotherapy may be considered DAV-Feron, consisting of DTIC, nimustine, and vincristine combined with local injection of IFN-beta has been used for cutaneous melanoma

Abbreviations: BCG, Bacillus Calmette-Guerin; DTIC, (dimethyltriazeno)imidazolecarboxamide, drug name dacarbazine; HD-IFN, high-dose interferon; IFN, interferon; LD-IFN, low-dose interferon; MDT, multidisciplinary team; PEG-IFN, pegylated interferon; QoL, quality of life; RT, radiation therapy

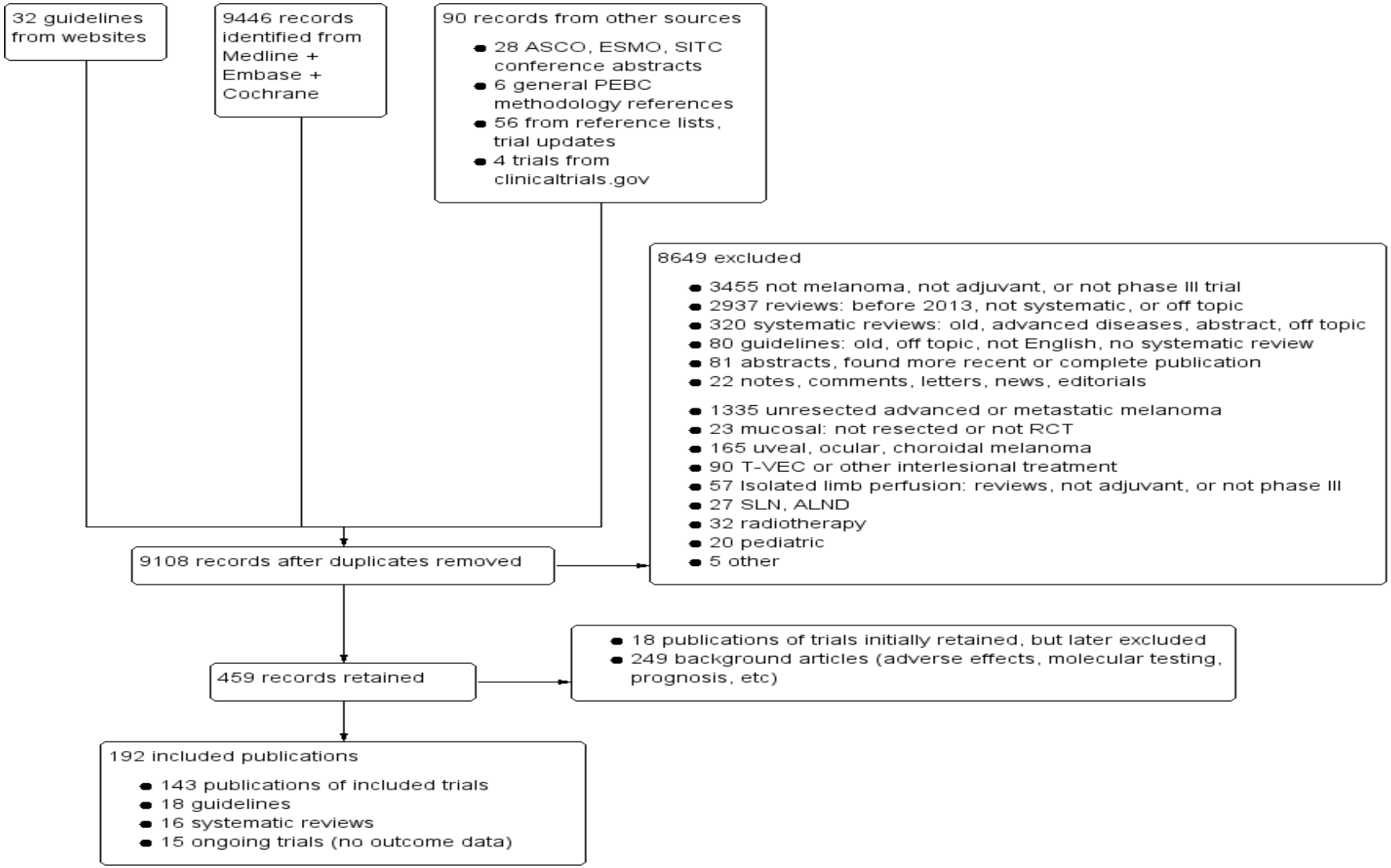
Agree II Evaluation of Guidelines Considered for Possible Endorsement

Domain	Domain Score	
	Australia [41]*	Society for Immunotherapy [42]
Scope and purpose	78	78
Stakeholder involvement	50	56
Rigor of development	73	40
Clarity of presentation	67	33
Applicability	29	4
Editorial independence	42	67

* evaluated the section on adjuvant therapy, not the full guideline

Back to Section 3

Appendix 4: PRISMA Flow Diagram



Back to Results (Section 4)

Appendix 5: Other Published Systematic Reviews on Adjuvant Therapy for Melanoma

Citation	Topic	Other details	Literature Search	Comments	Conclusion of Authors
Ives, 2017 [14]	Adjuvant IFN-α in high-risk melanoma	Individual patient data (IPD) meta-analysis of IFN-α vs. no IFN-α. Did not include trials of IFN-α vs. other agents or vaccines for primary analysis	Identified trials from Cochrane, MEDLINE, Embase, PubMed, Web of Science, abstracts of conferences (ASCO, World Melanoma Congress, ESMO), contact with trialists; requested IPD from investigators	15 IFN trials (14 trials of IFN and 1 of PEG-IFN) with 7744 pts (7699 analysed); IPD from 11 of these trials with IPD for 5861 pts Also 2 trials of IFN vs. vaccine	EFS and OS significantly improved by IFN; no evidence that benefit difference depending on does or duration
Mocellin, 2013 [33] (a Cochrane review)	Adjuvant IFN-α for cutaneous melanoma	Meta-analysis. IFN-α vs. observation or other regimen	Search until Aug 2012: Cochrane; Medline 2005-, Embase 2010-, AMED 1985-, LILACS 1982-; ASCO meetings 2000-2011. A search in September 2015 found no relevant new results and therefore it was not updated.	DFS and OS effects; 18 RCTs with 10,499 pts; included 17 trials in meta-analysis for DFS and 15 for OS	IFN associated with significantly improved DFS and OS
Ascierto, 2013 [105]	Adjuvant IFN-α in melanoma	Recent trials (mostly abstracts) that were not included in other meta-analyses [33]	PubMed plus ASCO 2011 abstracts. No details provided on search or results.	Contains a few trials that Cochrane review excluded but did not redo meta-analysis	Studies support clear DFS and modest OS benefits; do not clarify optimal dose or duration
Di Trolio, 2015 [106]	IFN in melanoma	Phase II-IV trials; both adjuvant and metastatic settings	PubMed 1990-Oct 2014; ASCO and ESMO abstracts 2005-2014 also considered	Includes 19 trials on adjuvant IFN (including EADO and EORTC 18991 on PEG-IFN)	IFN effective adjuvant treatment in selected pts; need to better determine selection factors. Ulceration is promising predictive factor

Citation	Topic	Other details	Literature Search	Comments	Conclusion of Authors
D'Aniello, 2018 [107]	Adjuvant; cutaneous melanoma		PubMed 2000-June 2015; recent abstracts from ASCO and ESMO	No statement on literature search results or data tables 17 trials IFN 2 trials PEG-IFN Trials on biochemotherapy, vaccines, other treatment	IFN. Ipilimumab possible breakthrough based on DFS in EORTC 18701 (OS data pending). BRAF inhibitors could be upcoming therapy
Van Zeijl, 2017 [108]	Adjuvant or neoadjuvant systemic therapy for melanoma	RCTs, Phase II/III trials, stage I-III resected melanoma	PubMed Jan 2000-March 2016, Clinicaltrials.gov, clinicaltrialsregister.eu	9 IFN; 2 PEG-IFN; 1 IFN vs. PEG-IFN; 4 vaccine; 1 ipilimumab; 1 chemotherapy	IFN approved but high risk-benefit ratio; ongoing trials on new agents
Trinh, 2017 [35]	Adjuvant IFN-α in high-risk melanoma		PubMed; no details on search reported	Includes 9 trials on IFN-α and 3 on PEG-IFN-α. EORTC 18071 on ipilimumab (plus listed 7 ongoing studies on new therapies) Not as comprehensive as other reviews	
Patel, 2012 [109]	Pegylated IFN-α2b (Sylatron) in melanoma	Pharmacology, pharmacokinetics, clinical activity, safety	PubMed 1976-Feb 2012; ASCO abstracts	EORTC 18991 is main trial	Improved RFS and marginal impact on OS compared with observation; PEG-IFN has pharmacokinetic and cost advantage over IFN
Barbee, 2015 [110]	Immune checkpoint inhibitors Ipilimumab, nivolumab, and pembrolizumab in oncology	Various cancers	PubMed 1966-2015; prospective interventional trials	Recommendations on adverse effects, response criteria, efficacy	Nivolumab and pembrolizumab have better safety profiles than ipilimumab;

Citation	Topic	Other details	Literature Search	Comments	Conclusion of Authors
					more trials for ipilimumab
Davar, 2013 [111]	Adjuvant immunotherapy of melanoma		MEDLINE, Embase, CANCERLIT, Cochrane, ISI, Web of Science 2002-May 2012	17 studies on IFN	
Zenga, 2017 [112]	Management of head and neck melanoma		MEDLINE, Embase, CINAHL, Cochrane until Oct 2015	Covers IFN (Cochrane review), ipilimumab (EORTC 18071). Trials and results of adjuvant therapy not specific to head and neck melanoma	
Nguyen, 2017 [113]	Stereotactic radiosurgery ± ipilimumab in melanoma brain metastases	Systematic review plus meta-analysis	MEDLINE and Cochrane Central (≈ April 2017)	4 cohort studies found	Low-quality evidence exists for superiority of ipilimumab + SRS compared with SRS alone (OS HR=0.38, 95% CI=0.28 to 0.52, p<0.01)
Goyal, 2015 [114]	Multiple brain metastases from melanoma		PubMed 1995-Jan 2015	3 retrospective cohort studies of SRS ± ipilimumab suggest benefit of ipilimumab; chemotherapy not effective	Targeted therapies and immunotherapies have been reported to have high response rates and need further study
Garant, 2017 [115]	Corticosteroids + immune checkpoint inhibitors in hematologic or solid neoplasms		Search until Nov 2016: MEDLINE, Embase, BIOSIS Previews, Cochrane, Web of Science, Scopus, abstracts from ESMO, ASCO, ASH, ASTRO, ESTRO, ESRO,		Concomitant administration of corticosteroids and immune checkpoint inhibitors may not necessarily lead to poorer clinical outcomes
Jarrom, 2017 [116]	Mucosal melanoma of the upper airways tract		MEDLINE, PreMEDLINE, Embase, Cochrane	All studies involved surgery and radiotherapy; none	

Citation	Topic	Other details	Literature Search	Comments	Conclusion of Authors
			Library, Web of Science until June 2015	used chemotherapy or biological treatments; no randomized trials	
Gorry, 2018 [117]	Neoadjuvant therapy for cutaneous melanoma,	Protocol only Stage III-IV with planned surgical procedure, RCTs only	Cochrane, Medline, Embase, LILACS		

Abbreviations: DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; IFN, interferon; IPD, individual patient data; OS, overall survival; PEG-IFN, pegylated interferon; RCTs, randomized controlled trials; SRS, stereotactic radiosurgery

Back to Results (Section 4)

Appendix 6: Excluded Trials

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
Intermediate-dose IFN											
DeCOG Hauschild, 2009 [259]		Oct 1997-Nov 2001 N=674; 650 assessable	≥1.5 mm; node-negative (clinical, SLNB, or LN dissection)	Mucosal and ocular melanoma excluded	Intermediate-dose IFN-α2b for 4 weeks then LD-IFN vs. LD-IFN	10 MU/m^2 IFN-α2b iv 5×/wk for 2 wk then 10 MU/m^2 IFN-α2b sc 5×/wk for 2 wk then 3 MU IFN-α2b sc 3×/wk for 23 mo vs. 3 MU IFN-α2b 3×/wk for 24 mo		5-y OS 80.2% vs. 82.9%	5-y RFS 68.0% vs. 67.1%	Exclude: <50% high-risk	Addition of 4 weeks intermediate dose IFN did not improve outcome
LD-IFN											
[Germany + Switzerland] Hauschild, 2003 [260]	v3	1990-1995 N=225, 223 eligible	>1.5 mm (pT3-4) and cN0	Melanoma (subtype not mentioned in inclusion criteria; mucosal not listed in pt characteristics table)	IFN-α2b + interleukin-2 vs. observation	IFN 3 (MU/m^2 sc daily for 1 wk, then 3×/wk for 4 wk) + IL-2 (9 MU/m^2 sc d8-11). Repeat 8 times (total of 48 wk)	79.4 mo	OS 77% vs. 74.5%, p=0.93 5-y OS 78% vs. 79% 2-y OS 95% vs. 92%	DFS 68.1% vs. 69.1%, p=0.93	Exclude: <50% high risk	Adjuvant treatment did not improve DFS or OS
[Italy] Rusciani, 1997 [233]	M2	Not stated (≈1993) N=154	Stage I (<1.5 mm) or II (1.5-4 mm) (AJCC 1992), no regional lymph node metastasis	Controls matched for age and gender. Disease characteristics other than stage not reported	IFN-α2b vs. control	IFN (3 MU im, 3×/wk for cycles of 6 mo with 1 mo between cycles for 3 y)	Median not stated; 3 y for all pts, 5 y for 75 pts		3-y recurrence: 13.1% vs. 28.6% (stage I 3% vs. 7%, ns; stage II 20% vs. 60%, p<0.0001)	Exclude: not high risk, randomization suspect, likely not phase III trial. Groups unequal in number of pts (84 vs. 70) and	Survival time could not be studied due to small number of cases

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
										stage distribution (33 vs. 40 stage I; 51 vs. 30 stage II)	
Pegylated IFN											
European Association for Dermato-Oncology (EADO), NCT00228448 Grob, 2013 [261]	v4	2003-2005 N=898, 896 evaluable	≥1.5 mm; clinically node negative; microscopic disease by SLNB allowed	Cutaneous melanoma 30% ulceration, 22% SLN+ (micrometastasis), 22% >4 mm Pts with SLNB: 41.5% stage IIB-IIIB Pts without SLNB: 42% stage IIB-IIC	Pegylated IFN vs. LD-IFN-α2b	PEG-IFN (100 µg sc q1w for 36 mo) vs. IFN (3 MU sc 3×/wk for 18 mo)	56.9 mo	5-y OS: 77.0% vs. 78.4%, p=0.55; HR=1.09 (95% CI: 0.82–1.45)	DFS: 65.9% vs. 64.8%, p=0.47; HR= 0.91 (95% CI: 0.73–1.15) DMFS: 71.1% vs. 72.6%, p=0.80; HR=1.02 (95% CI:0.80–1.32)	Exclude: <50% high risk Grade 3 to 4 AEs: 47.3% vs. 25.2%, p<0.0001 Discontinuation 54.3% vs. 30.4%	Trial did not show superiority of PEG-IFN over IFN; no difference in DFS, DMFS, OS PEG-IFN had higher rates of adverse effects and discontinuation
Vaccines											
[University of Nottingham] McIllmurray, 1977 [262]	v3	Not stated (≈1975) N=15	Stage IIB, LN+	Melanoma, subtype not specified Primary tumour treated by wide excision, regional lymph nodes excised	BCG + autologous irradiated tumour cells vs. no further treatment	Vaccine (3×10^7 live BCG and 5×10^7 irradiated cells intradermally on day 14) Observation	At least 2 y	At 3 mo: OS 75% vs. 100% At 12 mo: OS: 43% vs. 100	3-m RFS 67% 12-m RFS: 43% vs. 40%	Exclude; not phase III trial Terminated due to poor outcome in BCG group	
[University of Minnesota, Minneapolis, sponsored by National Cancer Institute (NCI)] Aranha, 1979 [263]	v3	Not stated (≈1970-1976) 31 randomized with stage II disease	Stage I-III (McNeed and Das Gupta classification) Exclude stage (not high risk) and stage III (non-resectable)	Melanoma, subtype not specified Stage II (clinically positive regional nodes): resection + LN dissection then randomized to Immunotherapy (BCG +VCN) or none	Irradiated Vibrio chokrae neuraminidase (VCN) treated autochthonous tumor cells plus BCG vs. observation	VCN treated cells (number of applications not stated) plus BCG (5×10^8 cfu q1w×6 then q2w×12 then monthly for life)	16 mo stage II	3-y OS 25% vs. 43% 2-y OS 33% vs. 53% 1-y OS 83% vs. 75%	3-y DFS 12% vs. 34% 2-y DFS 12% vs. 42% 1-y DFS 72% vs. 57%	Exclude: not phase III trial The chance of detecting a significant therapeutic difference in the various treatment arms	VCN + BCG has no substantial benefit

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
										for Stage II patients with the available number of patients was only 17%	
SWOG S9035 Carson, 2014 [264] Sondak, 2002 [265]; Sosman, 2002 [266]	(v3)	1992-1996 N=689; 600 eligible; 553 for HLA class I serotyping portion	1-5 to 4.0 mm (or Clark level IV if thickness unavailable); T3N0M0 in AJCC staging system in use in 2002, Clinically negative nodes and pathologically negative if surgical staging performed	Cutaneous melanoma 26% ulceration; 79% 1.5 to 3.0 mm, 18% 3.1 to 4.0 mm	Melacine vaccine vs. observation		12.1 y	10-y OS 67% vs. 67%, HR=0.93 (95% CI=0.72 to 1.21), p=0.61 Subgroup HLA-A2 and/or HLA-Cw3 serotype: 10-y OS 75% vs. 63%, HR=0.62 (99% CI=0.37 to 1.02), p=0.01	10-y RFS 56% vs. 54%, HR=0.94 (95% CI=0.74 to 1.18), p=0.58 Subgroup HLA-A2 and/or HLA-Cw3 serotype: marginally improved 10-y RFS, 66% vs. 54%, HR=0.67 (99% CI 0.43 to 1.04), p=0.02	Exclude: not high risk	Overall no differences in RFS or OS Improved OS and RFS in subgroup with HLA-A2 or HLA-C23 serotype
Other											
[Montreal?] Loutfi, 1987 [267]	v3	1976-1982 N=156 randomized, 137 evaluable	Stage I node-negative (Clark's level III-V)	Cutaneous melanoma 55% Clark level III; 7 of 82 pts assessed ≥4 mm	Levamisole vs. placebo	Levamisole 150 mg po 2×/wk for 3 y (or until progression or severe toxicity)	5 y	5-y OS 74% vs. 80%, p=0.7 2-y OS 92% vs. 93%	Recurrence 30% vs. 26% 5-y DFS 62% vs. 73%, p=0.7	Exclude: not high-risk Discontinuation due to adverse effects in 39% vs. 14%	Trend to improvement in time until distant metastasis (30 vs. 9 mo), but no difference in recurrence or DFS at median 5-y follow-up

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
EORTC 18781 Czarnetzki, 1993 [268] Henz, 1996 [269]		1979-1987 N=353, 327 evaluable	≥1.5 mm, Clark level ≥III, Stage I	Melanoma, subtype not specified 16.5% ulceration, 10% ≥5 mm, 20% between 3 and 5 mm	BCG RIV vs. BCG Pasteur vs. none	BCG RIV (3 y) vs. BCG Pasteur (3 y) vs. follow-up. First 4 vaccinations at extremity closest to lymph nodes draining the primary tumour; subsequent vaccinations given in clockwise sequence on all 4 extremities, weekly for 10 weeks then monthly thereafter	6 y	No difference in 3 arms for duration of survival, p=0.82	No difference in 3 arms for time to progression, p=0.55	Exclude: not high-risk	No difference in time to progression or duration of survival
Groupe de Recherches sur les Melanomes malins (Paris, France) 2-NK-73 Jacquillat, 1982 [270]	v3	1973-1976 N=117	Clark level III, IV, V [no other pt details reported]	Cutaneous melanoma Some patients with limb melanoma had second randomization to intra-arterial chemotherapy (neoadjuvant vincristine + DTIC); this was not reported separately Prophylactic LND was not performed	Systemic chemotherapy (vinblastine + thiotepa + rufocromycine + methotrexate + procarbazine) vs. control (surgery alone)	Intraarterial (2 cycles prior to surgery): vincristine (1 mg/m^2 on day 1) then DTIC (starting day 3; 80 mg/m^2×5d) Chemotherapy started 1 mo after surgery: Vinblastine (60 mg/ m^2) + thiotepa (60 mg/m^2) +	Not stated; DFS curve to 6 y		DFS 65% vs. 60%, ns 2-y DFS: men 90% vs. 60%, ns; women 84% vs. 70%, ns	Exclude: not phase III trial. Exclude: not high risk. Drug doses in text and abstract do not match Neoadjuvant intra-arterial treatment made no difference in DFS so authors	DFS difference not significant overall, suggestion that effect is larger in men. After stratification for prognostic factors, chemotherapy had significant DFS benefit

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
						rufocromycin (60 µg/m^2) + methotrexate (15 mg/m^2) on day 1 plus procarbazine (30 mg/m^2×7d) Courses repeated every q2w×6 then q4w×15 Observation				combined these arms	
Groupe de Recherches sur les Melanomes malins (Paris, France) 4-NK-76 Jacquillat, 1982 [270]	v3	1976 -1979 N=195 women N=157 men	Clark level III, IV, V [no other pt details reported]	Cutaneous melanoma	Women: chemoimmuno-therapy vs. surgery Men: chemo-immunotherapy vs. chemotherapy Chemotherapy: DTIC + vinblastine + thiotepa + rufocromycine + methotrexate + procarbazine Immunotherapy : BCG + *C. parvum*	Chemotherapy was as for 2-NK-73 except added DTIC (300 mg/m^2) for each course of chemotherapy Immunotherapy : 0.1 mL BCG intradermally q4 wk + 2 mL *C. parvum* sc	Not stated; DFS curve to 3 y		Men: 2-y DFS 68% vs. 60%, ns Women: 2-y DFS 75% vs. 70%, ns	Exclude: not phase III trial. Exclude: not high risk.	In men, no difference in DFS between chemo-immunotherapy and chemotherapy In women, no difference in DFS between chemoimmuno-therapy and surgery alone
SWOG 7521 Tranum, 1982, 1987 [245,271]		1975-1981 N=123, 121 eligible	Localized melanoma, stage I, Clark	Melanoma, subtype not part of method; patient characteristics	Carmustine (BCNU) +	Carmustine (150 mg/m^2 iv q8w) + hydroxyurea (1500 mg/m^2 po	(not stated)	6-y OS 65% vs. 65%	Median DFS 6 y vs. 7.1 y	Exclude: not high risk	Concluded tested chemotherapy of no value as

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
			level III or deeper	indicates 10 pts with melanoma at other site (includes eye and mucous cavities) Lymph node dissection not routinely carried out	hydroxyurea + DTIC vs. control	d1-5, q4w) + DTIC (150 mg/m^2 iv d1-5 q4w) for 12 courses					adjuvant treatment
[Sweden] Hansson, 1985 [272]	v3	1977-1978 N=26	Stage I (>2.25mm and/or Clark level IV) or Stage II (regional lymph node metastases)	Melanoma, subtype not specified 18 stage I, 8 stage II (text); 22 stage I and 4 stage II (table) 4 pts cLN+ and 5 cLN- had lymph node dissection	DTIC vs. DTIC + CCNU + vincristine vs. control (no treatment) Two non-control groups were combined for analysis	DTIC (250 mg/m^2 iv for 5d q4w for 1 y) vs. DTIC (200 mg/m^2 iv for 3d weeks 1 and 6) + CCNU (130 mg/m^2 po day 1, week 1 and 6) + vincristine (1 mg q2w) (after 12 weeks changed dosage [DTIC 200 mg/m^2 for 3 d q2w + vincristine 1 mg q2w + CCNU 80 mg/m^2 q4w]) vs. Observation	36 mo	4-y OS 94% vs. 52%, p<0.025 3-y OS 95% vs. 79%	RFS p<0.025	Exclude: Pilot study	Improved RFS and OS with chemotherapy compared with control
[New York] Karakousis, 1987 [273]	v3	(not stated, median 73 mo follow-up as of 1986) N=82	Clinical stage I or regional lymphatic recurrence	Melanoma, subtype not specified 57 stage I (72 had LN dissection, and 7 found to have	TICE BCG vs. DTIC + Estracyt vs. observation	TICE BCG (1 mL q4w for 1 y) vs DTIC 200 mg/m^2 iv for 5d q4w for 1 y plus	73.4 mo	OS: No difference, p=0.48 6-y 68% vs. 55% vs. 57%	DFS: No difference, p=0.81 6-y: 62% vs. 58% vs. 60%	Exclude : not high risk Exclude: not phase III trial	No significant difference, but small sample size so weak effect cannot be ruled out

Trial Name Citation	Other reviews	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Median follow-up	OS	RFS or DFS	Other outcome Other comments	Conclusion of trial authors
				histologic involvement) 25 recurrence (5 local within 3 cm of primary site, 1 in-transit, 17 regional lymph nodes, 2 in-transit + nodes)		Estracyt 15 mg/kg po daily for 1 y Observation		5-y 71% vs. 55% vs. 63% 3=y 77% vs. 59% vs. 68%	5-y: 62% vs. 58% vs. 65% 3-y: 68% vs. 58% vs. 65%		
[Ireland] Kerin, 1995 [274]	v3	N=26	High risk stage I (Clark's grade III-IV or >1.5 mm)	No ulcerating lesions Control group: mean 2.6 mm (range 1.5 to 4.8 mm); treatment group: mean 2.8 mm (range 1.5 to 5.0 mm)	DTIC + IFN-α2a (Roferon-A) vs. none	DTIC (single dose 800 mg iv) + IFN (9 MU im q1d for 3 wk); regimen repeated q3w for 3 cycles	57 mo (mean)	OS 57% vs. 83%, p<0.5 (0.6 to 10.4) at interim analysis, mortality RR=2.6		Exclude: not high risk	study terminated

Other **reviews**

- v3, in 8-1 version 3 (2009) and subsequent versions; (v3), older publication, abstract, or less complete data was included in 8-1 version 3
- v4, in 8-1 version 4 (2012) data assessment and review table appendix but not incorporated into main document
- M2, included in Cochrane meta-analysis by Mocellin et al. [33] but data not used

Abbreviations: AJCC, American Joint Committee on Cancer; BCG, Bacillus Calmette-Guerin; BCNU, bis-chloroethylnitrosourea, generic drug name carmustine; CCNU, lomustine, 1-(2-Choroethyl)-3-(cyclohexyl)-1-nitrosourea; CI, confidence interval; DFS, disease-free survival; DMFS, distant metastasis-free survival; DTIC, (dimethyltriazeno)imidazolecarboxamide, drug name dacarbazine; HD-IFN, high-dose interferon; HLA, human leukocyte antigen; HR, hazard ratio; IL-2, interleukin-2; IFN, interferon; ITT, intention to treat; iv, intravenous; LD-IFN, low-dose interferon; LN, lymph node; LND, lymph node dissection; OS, overall survival; PEG-IFN, pegylated interferon; pt, patient; pts, patients; RFS, recurrence-free survival; sc, subcutaneous; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; VCN, vibrio chokrae neuraminidase

Back to Methods (Section 3)

Back to Results (Section 4)

Appendix 7: Ongoing Trials

Trial Name Citation	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Status, other comments
EORTC 18081, NCT01502696 In NCT, no publication	2012-2017 N=1200 (estimated)	Ulcerated melanoma >1 mm; T(2-4)bN0	Ulcerated cutaneous melanoma	PEG-IFN-α2b vs. observation	3 µg/kg weekly injections for 2 y	Follow-up ongoing, estimated completion April 2019
JCOG1309, J-FERON. Dermatologic Oncology Group of Japan Clinical Oncology Group. UMIN000017494 Namikawa, 2017 [275]	≈2015-2021 (planned) N=240 (planned)	Stage II-III	Cutaneous melanoma	IFN-beta vs. surgery alone		Ongoing, still enrolling
MAVIS NCT01546571	2012-2016 1059	Stage IIb, IIc, III	Excluded non-cutaneous; complete lymphadenectomy if SLN+	POL-103A + API vs. POL-103A	4 injections (0.2 mL each injection) of POL-103A vaccine; number of cycles not stated	Estimated primary completion Jan 2019; final completion June 2019
CASVAC-0401, NCT01729663 Mordoh, 2017 [276] Pampena, 2018 [277]	2009-2014 for phase II; 31 pts Phase III ongoing, total of 108 pts planned	Stage IIB, IIC, or III	Cutaneous melanoma	Vaccination with CSF-470 (Vaccimel) plus BCG plus GM-CSF versus IFN-α2b	CSF-470 vaccine + BCG + rhGM-CSF vs. IFN-α2b CSF-470: on day 1 of each visit 1.6×10^7 irradiated CSF-470 cells plus 10^6 cfu BCG + 100 µg rhGM-CSF intradermally, then 100 µg rhGM-CSF on days 2-4; total of 13 vaccinations over 2 y (4 doses 3 weeks apart, then every 2 mo in	Phase II portion reported, phase III portion ongoing Dose and schedule from Phase II study

Trial Name Citation	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Status, other comments
					first year and every 3 mo in second year IFN: 10 MU/day, 5 d a week for 4 weeks, then 5 MU 3 times a week for 23 mo	
NCT02993315 (The Netherlands)	2016-2021 (estimated) N=210 (estimated)	Stage IIIB or IIIC (AJCC 2009). Completely resected in-transit or satellite metastases or unknown primary are allowed	Cutaneous melanoma	Immunization with natural dendritic cells pulsed with synthetic peptides vs. placebo	Natural dendritic cells (nDC) + synthetic peptide vaccination (3 cycles of 3 injections intranodally, 3-8×10^6 nDC) vs. placebo	Ongoing, still recruiting
MELABLOCK NCT02962947	2017-2019 (planned); N=546 (planned)	Stage 1b-IIIA	Cutaneous melanoma	Propanolol vs. placebo	80 mg retard (R) once daily for at least 1 y	Start 2017, no updates available since 2016; estimated primary completion 2019, overall completion 2022
Neo-DREAM NCT03567889	2018-2020 (planned); N=248 (planned)	IIIB/C resectable	Post-surgery: high-dose interferon-α2b, Ipilimumab, anti-PD-1and other adjuvant therapies	Neoadjuvant intratumoral Daromun + surgery vs. surgery	Weekly for up to 4 weeks then surgery vs. surgery alone; dose not stated	Recruiting; estimated primary completion 2020, final completion 2022
Pivotal NCT02938299	2016-2018 (planned); N=214 (planned)	IIIB/C resectable	Malignant melanoma of skin, exclude uveal or mucosal	Neoadjuvant intratumoral L19IL2 + L19TFN + surgery vs. surgery	Weekly for up to 4 weeks	Recruiting; estimated primary completion 2018

Trial Name Citation	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Status, other comments
ViDMe NCT01748448 EudraCT No: 2012-002125-30 DeSmedt, 2017 [278]	2012-2019 (estimated) N=500 (planned)	High risk of recurrence: Stage IB-III	Cutaneous melanoma	Vitamin D supplementation: 100,000 International units cholecalciferol vs. arachidis oleum raffinatum used as a placebo	100,000 IU cholecalciferol or arachidis oleum raffinatum (placebo) po monthly for a maximum of 3.5 y	Ongoing, still enrolling
NCT00200577, BRD/04/01-D [Nantes University Hospital]	≈2005-2013 N=70	Stage III with one invaded lymph node	Melanoma, subtype not specified	Tumor-infiltrating lymphocytes (TIL) plus interleukin-2 vs. none	2 injections of tumour infiltrating lymphocytes (TIL; about 6 and 10 wk post-surgery) + interleukin 2 (IL2; 6 million UI/d from J1-J5 and J8-J12 following the day of TIL infusion) vs. none	Ongoing
CheckMate 915 NCT03068455 EudraCT 2016-003729-41	2017 – 2020 (planned) N=2000 (estimated)	Stage IIIb/c/d or Stage IV	Melanoma, subtype not specified (except to exclude uveal melanoma) Complete sentinel lymph node dissection required if SLN+	Low-dose ipilimumab + nivolumab vs. nivolumab Separate ipilimumab arm in European trial registry but not NCT registry		Ongoing (still enrolling)
SWOG 1404, SWOG S1404 NCT02506153 Grossman, 2016 [279,280] [abstracts]	2015-2017 N=1378 (planned)	Stage IIIA (n2), IIIB, IIIC, IV (M1a, b,c); exclude brain metastases or ocular melanoma	Cutaneous, as well as mucosal or other non-cutaneous, are eligible. Patients with non-ulcerated T1b N1a were not eligible	Pembrolizumab vs. physician/patient choice of FDA-approved therapy (either HD-IFN-α2b or ipilimumab)	Pembrolizumab (200 mg day 1, q3w for 52 wk) vs. IFN-α2b (20 MU/m^2 days 1-5, weeks 1-4, then 10 MU/m^2/d sc days 1,3,5, weeks 5-52) Amendment (≈May 2016) to include patient/physician choice	https://www.swog.org/media/4201 indicates completed accrual, hope for interim analysis Summer 2018 and final analysis end of 2018.

Trial Name Citation	Enrolment period and # pts	Stage or disease extent	Other characteristics or treatment	Comparison	Dose and Schedule	Status, other comments
					between IFN and ipilimumab (10 mg/kg ipilimumab iv over 90 min day 1, repeated q3w for 4 courses total; then ipilimumab iv over 90 min day 1 repeated q12 w for 3 y)	NCT website indicates expected primary completion Sep 2023
Keynote 716 NCT03553836 Luke, 2018, 2019 [281,282]; Carlino, 2019 [283] [Abstracts]	2018-2022 (planned) N=954 (estimated)	Stage IIb or IIc (AJCC 8th ed); mucosal or uveal excluded	Pts without recurrence after end of Part 1 (17 cycles pembrolizumab or placebo) may receive pembrolizumab in Part 2	Pembrolizumab vs. placebo	Pembrolizumab (200 mg iv if age ≥18 y [2 mg/kg but max 200 mg if age 12-17 y] q3w, up to 17 cycles) vs. placebo Pts in either group with disease recurrence after the 17 wk may receive pembrolizumab for 17 cycles (resected) or 35 cycles (unresectable)	Ongoing (enrolling)

Abbreviations: AJCC, American Joint Committee on Cancer; BCG, Bacillus Calmette-Guerin; IFN, interferon; ITT, intention to treat; iv, intravenous; LD-IFN, low-dose interferon; LN, lymph node; PEG-IFN, pegylated interferon; SLN, sentinel lymph node; rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor

Back to Methods (Section 3)

Back to Results (Section 4)

Appendix 8: Quality Assessment of Trials of Adjuvant Targeted Therapy or Immune Checkpoint Inhibitors

Trial Name Citation	Randomization details	Blinding details	Intention to treat analysis	Study withdrawals	Loss to follow-up	Funding	Expected effect size and power calculations	Length of follow-up	Balanced baseline characteristics
AVAST-M ISRCTN 81261306 Corrie, 2014, 2018 [79,95]	Randomly assigned 1:1 by computer minimisation algorithm, within 12 weeks of resection.	Open label	Analyses on intention-to-treat basis	Censored at time of withdrawal if withdrew consent. Discontinuation reasons reported	3% lost to follow-up or withdrew consent	Bevacizumab provided by Roche; supported by Cancer Research UK and NHS Foundation Trust; funder had no role in study design, analysis, interpretation	660 pts/arm to detect 8% increase in 5-y OS from 40% to 48% with 85% power and 5% significance level, equal to HR=0.80 Results: 1343 enrolled; OS 64% vs. 64%, HR=0.98, p=0.78	Median 6.4 y	Stratified by Breslow thickness, N stage, ulceration status, patient sex Characteristics similar
EORTC 18071, NCT00636168 Eggermont, 2016, 2015, 2019 [29,30] [31]	1:1 centrally by interactive voice response system, using minimization technique. Resection within 12 weeks of randomization	Double blind. Clinical investigators, those collection or analyzing data masked	Intention-to-treat analysis. Sensitivity analyses based on per-protocol treatment or using RFS reported by investigators	Discontinuation reasons reported. If still disease-free at last assessment, censored RFS at that time. Adverse effects analysis censored at last know alive date if non-resolved grade 3 to 4 immune-related AEs	Not reported	Bristol-Myers Squibb; jointly designed by writing committee (coordinator, EORTC team, funder representative). Data analyzed independently at EORTC and by Bristol-Myers Squibb	Required 512 RFS events to provide 90% power to detect HR=0.75 (2-sided α of 0.05), corresponding to an increase from 58·3% to 66·% in 1-y RFS and from 35·4% to 45·9% in 3-y RFS. Planned 950 pts 491 deaths to give 85% power to detect difference in 4.5 –y OS of 42.3% placebo and 52.0% ipilimumab, HR=0.76; revised at 376 events to use α=0.049 and CI of 95.1% with power of 75.8% Results: Enrolled 951 pts. 528 RFS events reported at median 2.7 y follow-up, RFS longer with ipilimumab HR=0.75, p=0.0013. 587 RFS events and 376 deaths at final analysis	Median 5.3 y RFS, OS, DMFS significantly better with ipilimumab Abstract reported to median 6.9 y	Stratified by disease stage and geographical region
US Intergroup E1609, ECOG E1609; NCT01274338 Tarhini, 2017, 2019 [10] [32] [abstracts]	Randomized (no details reported)	None (open label)	Intention-to-treat analysis	Not reported	Not reported	National Cancer Institute (NCI)	Not reported 3-y RFS 54% vs. 56; more adverse effects with higher dose (ipi10)	Unplanned RFS analysis of ipi3 and ipi10 arms at median 3.1 y Planned up to 20 y (ongoing)	Not reported

Trial Name Citation	Randomization details	Blinding details	Intention to treat analysis	Study withdrawals	Loss to follow-up	Funding	Expected effect size and power calculations	Length of follow-up	Balanced baseline characteristics
CheckMate 238, NCT02388906 Weber, 2017 [1] Weber, 2018 [11] [abstract]	Registration by the sponsor Randomization stratified according to stage, and PD-L1 status	Double-blinded; clinical investigators and those collecting or analyzing data blinded	Intention-to treat analysis	Table with reasons for discontinuation	5 pts	Bristol-Myers Squibb (collected data, involved along with academic authors in trial design, collaborated in analysis) and Ono Pharmaceutical (funding only)	800 pts planned for RFS analysis at minimum of 36 mo follow-up, 507 events anticipated with 90% power to detect HR=0.75 (type I error 0.05); revised to 450 events to provide power of 85% to detect HR=0.75 (under the 0.83 cut-off for significance) with two-sided type I error rate of 0.05. Amendment mandated interim analysis at 18 mo follow-up for all pts, with stopping boundary based on 360 events and HR=0.78, adjusted alpha=0.0244 Results: 906 pts randomized; 360 events at interim analysis; statistically longer RFS with nivolumab at 24-mo analysis	Minimum 18 mo at interim analysis (median 19.5 mo). Abstract at minimum 24 mo. Ongoing (4 y planned)	Groups were similar
Keynote 054, EORTC 1325-MG, NCT023649, EudraCT 2014-004944-37 Eggermont, 2018 [2]	Registration centrally at EORTC headquarters; central interactive voice-response system for randomization Stratified by stage and geographic region	Blinding of clinical investigators, patients, those collecting or analyzing data	Intention-to-treat and subgroup analysis; also per protocol	Table with reasons for discontinuation of treatment	Not reported	Merck (also involved in trial oversight, design, and protocol conception)	900 pts with 409 events (recurrence or death) to provide 92% power to detect HR=0.70, corresponding to 1-y RFS of 58.3% placebo vs. 68.5% pembrolizumab; 3-y RFS of 35.3% vs. 48.3%, one-sided alpha=1.4% If RFS significant, then compare in subgroup PD-L1 positive with one-sided alpha of 2.5% Amended based on CheckMate 238 trial to include interim analysis of RFS on 1019 pts (351 events) with one-sided alpha of 0.8% and this became final RFS analysis Results: significantly longer RFS with pembrolizumab (HR=0.54, p<0.001	Median 15.1 mo. Ongoing for OS and DMFS	Similar
BRIM8, NCT01667419 Maio, 2018 [28]	Randomized by permuted blocks (size 6) stratified by stage and region (Cohort 1) or region (Cohort 2) using	Double-blind. Investigators, patients, and sponsor masked	Intention-to-treat analysis for efficacy	Table with reasons for discontinuation of treatment	Not reported	F Hoffman-La Roche Ltd (design and funding, collected and analyzed the data)	Cohort 1 sample size of 300 pts for 80% power to detect HR=0.60 with two-sided log-rank test at 0.05 level, assuming median DFS of 24 mo placebo vs. 40 mo vemurafenib and 5% annual loss to follow-up. Primary analysis at 120 DFS events in both cohorts Cohort 2 sample size of 175 pts for 80% power to detect HR=0.58 at 0.05 level, assuming	Median 33.5 mo Cohort 2 and 30.8 mo Cohort 1	Well balanced (except ulceration less in placebo group of Cohort 1)

Trial Name Citation	Randomization details	Blinding details	Intention to treat analysis	Study withdrawals	Loss to follow-up	Funding	Expected effect size and power calculations	Length of follow-up	Balanced baseline characteristics
	interactive voice or web response system						median DFS of 7.7 mo placebo vs. 13.3 mo vemurafenib Amended due to slower DFS event rate: reduced DFS events to 105 in Cohort 2 Hierarchical analysis of Cohort 2 before Cohort 1 was prespecified to maintain overall type I error rate of 0.05; specified that only a p value for Cohort 2 of 0.05 or less would allow for analysis of cohort 1 to be considered significant		
COMBI-AD; NCT01682083 Hauschild, 2018 [9]; Long, 2017 [3]	Randomized (no details), stratified by *BRAF* status (V600E or V600K) and stage	Double-blind	Intention-to-treat for efficacy	Recorded in Consort diagram, still included in analysis	30 pts	GlaxoSmithKline and Novartis (took over March 2, 2015); design by GlaxoSmithKline and academic authors; data analyzed by funders	870 pts to give RFS in 410 pts with two=-sided type I error of 5% and power of >90% to detect HR=0.71, corresponding to median RFS of 21 mo therapy vs. 15 mo placebo OS tested in hierarchical manner if RFS significant, threshold at OS interim analysis of p=0.000019 Results: Dabrafenib + trametinib significantly better RFS. Interim OS better but not significant due to interim threshold set	Median 2.8 y for RFS and interim OS; update at median 43 mo for RFS OS follow-up ongoing	Similar

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; pts, patients; RFS, recurrence-free survival

Back to Results (Section 4)

Appendix 9: Guideline Document History

GUIDELINE VERSION	Systematic Review Search Dates	Systematic Review Data	PUBLICATIONS	NOTES and KEY CHANGES
Original May 27 1998		Full Report	PEBC website	Not applicable
Revised Jan 1999, Sept 2000	To Sept 2000			New data on ECOG 1690 trial which was inconsistent with previous report
Revised Nov 2002	To Sept 2002			New references added; recommendations need revision in future version
Version 2.2004. March 24, 2004; June 30, 2004	1980-Feb 2004	Full report	CCO website. Cancer 2006; 106(7):1431-42 [231]	Complete rewrite, replaces 1998 report
Version 2.2004 August 30, 2005	1980-July 2005	Added results from missing trials	CCO website. Curr Oncol 2005;12(2):31-6 [284]	A minor update due to comments from submission for journal publication
Version 3.2009 June 22, 2009	July 2005-July 2008	New systematic review section and updated recommendations	CCO website	New review in Section 2A; previous review moved to Section 2B. New recommendations
	July 2005-June 2010		Clin Oncol 2012 24(6): 413-23 [229]	
Version 4 November 7, 2013	July 2008-September 2013	New data appended in Section 4	CCO website	New data appended in Section 4; 2009 recommendations endorsed
Version 4 December 8, 2017	2013 to October 2017	New data replace previous Section 4	CCO website	Section 4 of 2013 version has been relabelled Appendix 1. Recommendations require updating in a new version
Version 5 August 14, 2019	1996- June 2018 trials; 2013-2018 reviews or guidelines	Guideline rewritten	CCO website	Systematic reviews merged, recommendations rewritten
Update of version 5 June 2023	NA	2 Trials added to Section 1 and 2 Only	Updated web publication on CCO/OH website	Recommendation 1 was updated with evidence from 2 RCTs. For details see **Appendix 10**

Back to Section 2

Back to Methods (Section 3)

Appendix 10: 2023 Update of Recommendation 1

In January 2023 the Melanoma disease site group was made aware of two new trials which evaluated pembrolizumab (KEYNOTE-716/NCT03553836)) [1] and nivolumab (CheckMate 76K/NCT04099251) [2] in stage IIB and IIC melanoma patients. These were practice changing trials, and as a result the members of the Melanoma DSG (TP, FW) determined that recommendation 1 would require updating based on the study conclusions. The original recommendation did not include stage II patients; however, it was identified in the qualifying statements that trials including high-risk stage II patients were ongoing. The qualifying statement read as follows: *"High-risk stage II patients were not included in the key trials, and some trials excluded all (Checkmate 238) or a portion of stage IIIA patients (Keynote 054, COMBI-AD). For stage IIIA diseases, Keynote 054 excluded N1a melanomas with nodal metastasis <1mm, and the COMBI-AD trial excluded any nodal metastases <1 mm. The absolute benefit in patients with stage II or IIIA with <1 mm of nodal disease is unknown. The patient and physician should discuss benefits and risks (adverse effects) and these patients should be enrolled in a clinical trial when possible. Such clinical trials are currently ongoing"*. To facilitate this update, the DSG chair evaluated the current recommendation and made edits in concert with the original working group members and DSG members.

New Evidence added in 2023

KeyNote-716 was a multicenter randomized, double blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma [1]. Patients were randomized to pembrolizumab 200 mg or 2 mg/kg intravenously (maximum of 200 mg in pediatric participants) every three weeks for 17 cycles or placebo for up to one year. Treatment continued until disease recurrence or unacceptable toxicity. The critical outcome was recurrence-free survival and adverse events were also analyzed. 976 patients were randomly assigned to receive pembrolizumab (n=487) or placebo (n=489). Baseline characteristics were well balanced between the treatment groups. At first interim analysis median follow-up time was 14.4 months in the pembrolizumab group and 14.3 months in the placebo group. A statistically significant improvement in RFS was shown at the time of the initial interim analysis for patients in the pembrolizumab arm compared with placebo, with a hazard ratio of 0.65 (95% CI: 0.46, 0.92; p=0.0066). At second interim analysis follow-up for both treatment groups was 20.9 months. RFS had an HR of 0.61 (95%CI 0.45-0.82) favouring pembrolizumab.

Investigators for the randomized, double-blind CheckMate76K study enrolled patients with previously untreated, histologically confirmed resected stage IIB and IIC cutaneous melanoma [2]. Patients received either nivolumab 480 mg or placebo every 4 weeks for 12 months. The critical endpoint of the trial was recurrence-free survival and secondary endpoints included distant-metastasis-free survival and adverse events. Post-randomization, the baseline characteristics of the intervention and control groups were well balanced. Patients received a median of 12 doses of nivolumab for a median duration of 11.0 months and a median of 13 doses of placebo for a median duration of 11.1 months. At the time of interim analysis, there was a HR for RFS of 0.42 (95%CI: 0.30-0.59 p<0.0001) favouring nivolumab. In a subgroup analysis stratified by stage, the RFS benefit of nivolumab was consistent across disease stages with an HR of 0.34 (95% CI: 0.20–0.56) for patients with stage IIB disease and 0.51 (95% CI: 0.32–0.81) for patients with stage IIC disease. DMFS had an HR of 0.47 (95% CI: 0.30–0.72), favouring nivolumab. 10% of patients in the nivolumab arm experienced grade 3 or 4 treatment-related adverse effects compared with 2% for those in the placebo arm. Adverse events led to treatment discontinuation in 15% of patients in the nivolumab arm and 3% in the placebo arm.

Table A10-1. Summary of the New Evidence in 2023

Trial Name Citation	Enrolment period and # pts	Stage or extent of disease	Dose and Schedule	Median follow-up	DFS or RFS, DMFS	Other outcomes Other comments	Conclusion of trial authors
Luke et al, 2022 KeyNote 716 [1]	Pembro n=483 Placebo n=486 Enrolment period: ni	Completely resected, ≥ 12 years of age, histologically confirmed stage IIB/C cutaneous melanoma	Arm A: 200 mg of pembro IV (2 mg/kg up to a maximum of 200 mg in paediatric patients) every 3 week for 17 cycles Arm B: placebo IV every 3 weeks for 17 cycles	20.9 mo	RFS: HR: 0.64 (95% CI 0.50-0.84) *favours pembro*	SAE Pembro: n=49 (10%) Placebo: n=11 (2%)	Overall benefit of pembro is positive in the adjuvant setting for Stage IIB/C patients
Kirkwood et al, 2023 CheckMate 76K [2]	Nivo n=526 Placebo n=264 Enrolment period: 28/10/2019-3/11/2021	treatment-naive patients ≥ 12 years of age, with completely resected stage IIB or IIC melanoma	Arm A: Nivo 480 mg every 4 weeks for 12 months Arm B: placebo every 4 weeks for 12 months	15.8 mo	RFS: 0.42 (95% CI: 0.30–0.59; P < 0.0001) *favours nivo* DMFS: (HR = 0.47; 95% CI: 0.30–0.72)	SAE: Nivo: n=54 (10.3%) Placebo: n=6 (2.3%)	Nivo is an effective and generally well-tolerated adjuvant treatment in patients with resected stage IIB/C melanoma

Abbreviations: CI: confidence interval; DMFS: distant metastasis-free survival; HR: hazard ratio; IV: intravenously; ni: no information; NR: not reached; Mo: months; Nivo: Nivolumab; Pembro: pembrolizumab; RFS: relapse-free survival; SAE: serious adverse events

Table A10-2. Quality Assessment of New Trials Identified in 2023

Study	Risk of bias arising from the randomization process	Bias due to deviations from the intended interventions	Bias in measurement of interventions	Bias due to missing outcome data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Luke et al, 2022 [1]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk of Bias for OS and RFS
Kirkwood et al, 2023 [2]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low risk for RFS, DMFS and OS

Draft Recommendation based on new evidence.
Based on the clinical trials above a preliminary recommendation was drafted by TP and FW. *"Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected, node-negative cutaneous melanoma with and without BRAF V600E or V600K mutations with high risk of recurrence (Stage IIB and IIC)."*

Expert Panel Review of New Recommendation
The new recommendation was distributed to the Melanoma DSG which consists of 14 members as well as the Scientific Director of the PEBC (JS). 12 members completed COI declarations and were eligible to review the targeted update of the guideline and 0 abstained in November of 2023. Of the 12 members who voted all approved the document (100%). All reviewers approved the guideline with no further comments or conditions.

Final Recommendation after Review
After final review by the Melanoma DSG and the PEBC Scientific Director the final recommendation is as follows:
"Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected, node-negative cutaneous melanoma with and without BRAF V600E or V600K mutations with high risk of recurrence (Stage IIB and IIC)."

References
1. Luke JJ, Rutkowski P, Queirolo P, Del Vecchio M, Mackiewicz J, Chiarion-Sileni V, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. The Lancet. 2022;399(10336):1718-29.

2. Kirkwood J, Del Vecchio M, Weber J, Hoeller C, Grob JJ, Mohr P, et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. Nature Medicine. 2023.

Affiliation and Conflict of Interest Declarations for Targeted Update

Member and Role	Affiliation	COI Declaration(s)*
Teresa M. Petrella Co-Chair of Working Group; co-lead on Targeted Update	Medical Oncologist Associate Professor, University of Toronto Chair, CCTG Melanoma Clinical Trials Group	Research grants from Roche, Novartis, BMS, Merck. Principle investigator of trials sponsored by Roche, Merck, Novartis.

Member and Role	Affiliation	COI Declaration(s)*
	Chair, Melanoma Site Group Odette Cancer Centre	Received funds from Merck for funding a clinical fellow in melanoma.
Frances C. Wright Working Group Member; co-lead on Targeted Update	Surgical Oncologist Sunnybrook Health Sciences Centre/Odette Regional Cancer Center, Toronto and Department of Surgery, University of Toronto	None declared
Sarah Kellett Working Group; Health Research Methodologist responsible for targeted update	Health Research Methodologist Program in Evidence Based Care, McMaster University/Cancer Care Ontario, Hamilton	None declared
Tara D. Baetz Expert Panel	Medical Oncologist Cancer Centre of Southeastern Ontario, Kingston and Queen's University, Kingston	Principle investigator for COMBI I (Novartis), MasterKey-265, and CCTG ME.13 Stop Gap trials
Alexander Sun Expert Panel	Radiation Oncologist Princess Margaret Hospital Toronto	None declared
Gregory Knight Expert Panel	Medical Oncologist Grand River Regional Cancer Center, Kitchener and Department of Oncology, McMaster University, Hamilton	Participated in advisory boards and received travel support from BMS, Merck, Roche, Sanofi
Sudha Rajagopal Expert Panel	Medical Oncologist Credit Valley Hospital, Mississauga	None declared
Xinni Song Expert Panel	Medical Oncologist The Ottawa Hospital Cancer Centre and Department of Medicine, University of Ottawa	Consulting as a member of BMS, Novartis, MERCK and Pfizer advisory boards. Principal investigator for BMS Checkmate 067/047/915, Merck Echo, Keynote 054, KeyNote 716, BRIM8, COMBI-D/V, and COMB-AD trials
Annette Cyr Expert Panel	Patient Representative Melanoma Network of Canada Toronto	Chair of board of Melanoma Network and along with other board members has fiduciary responsibility for >$5000 in grants from pharmaceutical companies in support of patient programs
Caroline Hamm Expert Panel	Medical Oncologist Windsor Regional Cancer Centre (WRH)	Participated in advisory boards for Astra Zeneca, Gilead and Novartis Principle investigator of NCIC sponsored clinical trial using pembrolizumab in adjuvant melanoma, stage III
Alexandra M. Easson Expert Panel	Surgical Oncologist	None declared

Member and Role	Affiliation	COI Declaration(s)*
	Princess Margaret Hospital, Toronto	
Christian A. Murray Expert Panel	Dermatologist Skin Surgery Centre, University of Toronto	None declared
David R. McCready Expert Panel	Surgical Oncologist Princess Margaret Hospital, Toronto	Financial interest >$1000 over all categories combined (salary, consulting, grants, investments, other). Published opinion or commentaries on melanoma, but not specific drugs.
Jonathan Sussman	Scientific Director Program in Evidence Based Care McMaster University Hamilton ON	None declared