Guideline 8-12

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

T. Petrella, S. Kellett, T. Baetz, G. Knight, E. McWhirter, A. Sun, X. Song, F. Wright and the Melanoma Disease Site Group

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For information about this document, please contact Teresa Petrella, the lead author, through the PEBC at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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PUBLICATIONS RELATED TO THIS REPORT

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

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

Systemic Treatments for Unresectable and Metastatic Cutaneous Melanoma

Section 1: Recommendations

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

GUIDELINE OBJECTIVES

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

PREAMBLE

Immunotherapy

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

Targeted Therapy

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

TARGET POPULATION

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

INTENDED USERS

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

RECOMMENDATIONS

RECOMMENDATION 1

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

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

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

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

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

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

QUALIFYING STATEMENTS FOR RECOMMENDATION 1

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

RECOMMENDATION 2

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

- Ipilimumab plus nivolumab
- Nivolumab

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

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

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

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

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

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

QUALIFYING STATEMENTS FOR RECOMMENDATION 2

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

RECOMMENDATION 3

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

- Ipilimumab plus nivolumab
- Pembrolizumab plus ipilimumab

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

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

QUALIFYING STATEMENTS FOR RECOMMENDATION 3

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

RECOMMENDATION 4

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

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

QUALIFYING STATEMENTS FOR RECOMMENDATION 4

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