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Systemic Therapy for Cutaneous Melanoma

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Cancer Care Alberta

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Background

Cutaneous melanoma is an aggressive skin cancer originating from melanocytes. In Alberta, incidence rates increased from 2001 to 2019 by 2.4% annually in males and 2.3% in females.[1] In 2021, there were 1,115 new cases and 96 deaths in Alberta.[1] If trends continue, approximately 1,360 new cases are expected to be diagnosed in 2026.[1] Although mortality has remained stable between 2001 and 2021, five-year relative survival had increased from ~84% for cases diagnosed between 2001-2003 to ~91% for cases diagnosed between 2019 and 2021.[1] Ultraviolet (UV) radiation from sun or artificial sources (e.g., tanning beds) is the leading cause. Most cutaneous melanomas develop on the head, neck and trunk in males, and on upper and lower extremities in females.[2]

Surgery with curative intent is the standard of care for stage I-II melanoma. For most patients with stage III melanoma (i.e., those with nodal disease and rarely for in-transit metastasis), complete lymph node dissection (CLND) is no longer the standard after a positive sentinel lymph node biopsy (SLNB). Patients with regional lymph node involvement, particularly those with high-risk features in the primary tumour (i.e., increasing tumour thickness, presence of ulceration, microsatellosis), are at increased risk for recurrent disease and should be considered for adjuvant and/or neoadjuvant therapy.

Adjuvant therapy aims to improve recurrence-free survival (RFS) and overall survival (OS) in high-risk patients. Immunotherapies (e.g., checkpoint inhibitors) and targeted therapies are now standard of care.[3] More recently, neoadjuvant approaches have become available, demonstrating event-free survival (EFS) benefit through their capacity to take advantage of the intact tumour's antigenic environment, which potentially enhances immune activation and reduces tumor burden prior to resection.[3-5] Neoadjuvant therapy might also reduce the need for extensive adjuvant treatment and associated treatment toxicities.[3]

Metastatic melanoma accounts for less than 5% of all cases of melanoma and is associated with a lower rate of survival at 5 years (37%).[6] Common sites of metastases include regional (i.e., in-transit metastasis) and distant skin, lymph nodes, liver, lungs, brain, bone and GI tract. While surgery is still a reasonable treatment option for patients with a solitary resectable metastatic deposit, systemic therapy is used to manage virtually all patients with metastatic disease, regardless of resectability. Optimal selection of systemic agents depends on the mutation status of the tumour, tumour volume and rate of progression, symptoms and patient performance status. Certain agents may be better suited for selected subgroups of patients.

Guideline Questions

In patients with high-risk cutaneous melanoma who have undergone or are eligible for resection:

1. When and for whom is neoadjuvant therapy indicated?
2. When and for whom is adjuvant immunotherapy indicated?
3. When and for whom is adjuvant targeted therapy indicated?

In patients with metastatic cutaneous melanoma:

4. Which agents should be used as first-line therapy?
5. Which agents should be used as second- or third-line therapy?

Search Strategy

The Medline/EBSCO database was searched for relevant studies focusing on neoadjuvant and adjuvant systemic therapies for high-risk disease. Results were limited to clinical trials and randomized controlled trials, in English language, published between January 1, 2015, and May 22, 2025. Specific search strategy and search results are presented in the Evidence Table, and available upon request. Of the 291 studies identified, 58 were included after screening (15 neoadjuvant, 43 adjuvant). Online resources from oncology-based health organizations and guideline developers were also systematically searched. Specifically, guidelines from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and Scottish Intercollegiate Guidelines Network (SITC) were consulted to identify landmark studies on systemic treatment for metastatic disease.[7-9] The Canada's Drug Agency's (CDA) report on the melanoma provisional funding algorithm was also considered in developing our recommendations.[10]

Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with high-risk cutaneous melanoma who have undergone or are eligible for complete resection, and adults over the age of 18 years with unresectable metastatic melanoma without involvement of the central nervous system (CNS). Different principles may apply to pediatric patients. This guideline does not include recommendations for the management of in-transit and uveal melanomas. Given the limited evidence specifically guiding the treatment of cutaneous mucosal, and acral melanomas, these recommendations may be applied to these subtypes.

Recommendations

Neoadjuvant Therapy

1. For patients with clinically detected (physical examination or imaging) nodal disease planned for surgical resection (including stage III disease with nodal involvement and limited satellite or in-transit metastases, as well as selected patients with resectable stage IV disease), who have not previously received immunotherapy, pembrolizumab or ipilimumab-nivolumab[*], surgery is generally recommended *(Level of Evidence: II[11, 12]; Strength of Recommendation: A)*.

[*] Ipilimumab-nivolumab is not provincially funded in the neoadjuvant setting (AHS OCDBP, as of August 27, 2025).

1.1. Following neoadjuvant pembrolizumab, adjuvant pembrolizumab after resection to complete 1 year of pembrolizumab treatment in total is recommended, as per the SWOG S1801 protocol, even for patients who achieve a major pathological response (≤10% residual viable tumor), a subgroup which has improved RFS[13] *(Level of Evidence: II[12]; Strength of Recommendation: B).* For patients with *BRAF* mutated disease, switching to adjuvant BRAF/MEK targeted therapy may be considered, particularly if patients progress during neoadjuvant immunotherapy, experience immunotherapy-related toxicity and/or lack of pathological response *(Level of Evidence: V; Strength of Recommendation: B)*.

1.2. Following neoadjuvant ipilimumab-nivolumab, no further adjuvant treatment is indicated if a major pathological response (≤10% residual viable tumor) is achieved, as per the NADINA protocol. If no major pathological response is achieved, adjuvant nivolumab (*BRAF* wild type) or dabrafenib-trametinib (*BRAF* mutation) is indicated as per NADINA protocol *(Level of Evidence: III[11]; Strength of Recommendation: B)*. Switching to adjuvant BRAF/MEK targeted therapy may also be considered in the instances described above *(Level of Evidence: V; Strength of Recommendation: B)*.

Adjuvant Therapy

2. For patients with completely resected stage IIB or IIC who have not previously received systemic treatment, nivolumab or pembrolizumab are recommended *(Level of Evidence: I[14-20]; Strength of Recommendation: B).*

3. For patients with completely resected stage III who have not previously received systemic treatment, or who progressed ≥6mo after treatment with a PD-1 inhibitor, pembrolizumab or nivolumab are recommended *(Level of Evidence: I[21-26]; Strength of Recommendation: A)*. Targeted therapy should be considered for patients with contraindications to immunotherapy or those with very high-risk disease.

4. For patients with completely resected stage III with *BRAF*-mutations who have not previously received systemic treatment, or who progressed ≥6mo after treatment with a PD-1 inhibitor, dabrafenib-trametinib *(Level of Evidence: I[27-30] II[31]; Strength of Recommendation: A)* can be recommended as an alternative to pembrolizumab or nivolumab, with no clear evidence of superiority of one approach over the other. Encorafenib-binimetinib† may be considered as well *(Level of Evidence: V; Strength of Recommendation: C)*.

† Encorafenib-binimetinib is not provincially funded in the adjuvant setting (AHS OCDBP, as of August 27, 2025).

5. For patients with completely resected stage IV, nivolumab monotherapy or ipilimumab-nivolumab for four cycles followed by nivolumab maintenance‡ can be considered as adjuvant therapy *(Level of Evidence: II[32, 33]; Strength of Recommendation: C)*.

Metastatic Disease

6. Systemic therapy is not recommended for patients with metastatic or advanced disease who have progressed after ≥2 prior lines of therapy and have a life expectancy of less than 3 months, despite available treatment options. Indicators of this poor prognosis are tumour site-specific but usually include ECOG 3-4, jaundice, leptomeningeal disease, hypercalcemia, rising LDH > 5xULN, severe pancytopenia.

7. For patients with *BRAF* mutant metastatic melanoma who either have never received adjuvant PD-1 therapy or relapsed with distant metastatic disease ≥6 months after completion of adjuvant PD-1 therapy, first-line treatment options are: nivolumab-relatlimab, pembrolizumab, nivolumab, ipilimumab-nivolumab followed by nivolumab maintenance, and *BRAF*-targeted therapy§ *(Level of Evidence: I[34-41] II[31, 42, 43]; Strength of Recommendation: A)*.

   In treatment-naïve patients with BRAF-mutant disease, first-line immunotherapy is preferred over targeted therapy *(Level of Evidence: II[44-46]; Strength of Recommendation: B)*. There are no randomized comparative data demonstrating superiority of ipilimumab–nivolumab over nivolumab–relatlimab; but longer follow-up is available for ipilimumab–nivolumab.[36, 40]

   7.1. Following first line nivolumab-relatlimab, second line options can be ipilimumab** or *BRAF*-targeted therapy§.

   7.2. Following first-line ipilimumab-nivolumab then nivolumab maintenance, second line option is *BRAF*-targeted therapy§.

   7.3. Following first line pembrolizumab or nivolumab, the second line options can be ipilimumab-nivolumab with nivolumab maintenance**, *BRAF*-targeted therapy§, or ipilimumab monotherapy**.

   7.4. Following first line *BRAF*-targeted therapy, second-line options include pembrolizumab, nivolumab, nivolumab-relatlimab, ipilimumab-nivolumab then nivolumab maintenance**, or ipilimumab monotherapy**.

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‡ Ipilimumab-nivolumab is not provincially funded in the adjuvant setting (AHS OCDBP, as of August 27, 2025).
§ *BRAF*-therapy options (V600E and/or V600K mutations) include dabrafenib-trametinib and encorafenib-binimetinib
** Ipilimumab and ipilimumab-nivolumab are not provincially funded for second-line treatment in the metastatic setting (AHS OCDBP, as of August 27, 2025).

7.5. Third-line treatment rechallenge with the drug class not used in the immediate previous line can be considered.

8. For patients with *BRAF* mutant metastatic melanoma who relapsed with distant metastatic disease during adjuvant PD-1 therapy or <6 months after completion, first-line treatment options are ipilimumab-nivolumab then nivolumab maintenance and *BRAF* targeted therapy[§] *(Level of Evidence: II[44, 45, 47]; Strength of Recommendation: B)*. Nivolumab-relatlimab[††] may be considered *(Level of Evidence: V[48]; Strength of Recommendation: C).*

   8.1. Following first-line ipilimumab-nivolumab then nivolumab maintenance, second line option is *BRAF*-targeted therapy[§].

   8.2. Following first-line *BRAF*-targeted therapy, second-line options are ipilimumab-nivolumab then nivolumab maintenance[‡‡] or ipilimumab monotherapy[‡‡].

9. For patients with *BRAF* mutant metastatic melanoma who relapsed with distant metastatic disease during adjuvant targeted therapy or <6 months after completion, first-line treatment options are in no preferred order: ipilimumab-nivolumab then nivolumab maintenance, pembrolizumab[§§], nivolumab[§§], and nivolumab-relatlimab[§§] *(Level of Evidence: II[46, 49], III[50], V[48]; Strength of Recommendation: B).*

   9.1. Following first line pembrolizumab or nivolumab, the second line options are ipilimumab-nivolumab with nivolumab maintenance[‡‡], or ipilimumab monotherapy[‡‡].

   9.2. Following first line nivolumab-relatlimab, the second line option is ipilimumab monotherapy[‡‡].

10. For patients with *BRAF* wild-type metastatic melanoma who either never received adjuvant PD-1 therapy or relapsed with distant metastatic disease ≥6 months after completion, first-line treatment options are: nivolumab-relatlimab, ipilimumab-nivolumab then nivolumab maintenance, pembrolizumab or nivolumab *(Level of Evidence: I, II[42, 43, 51]; Strength of Recommendation: A)*.

    10.1. Following first-line nivolumab-relatlimab, second-line option can be ipilimumab[‡‡].

    10.2. Following first-line pembrolizumab or nivolumab, second-line option is ipilimumab-nivolumab with nivolumab maintenance therapy[‡‡].

11. For patients with *BRAF* wild-type metastatic melanoma who relapsed with distant metastatic disease during adjuvant PD-1 therapy or <6 months after completion, first-line treatment option is

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[††] Nivolumab-relatlimab is not provincially funded within 6 months of PD-1 therapy (AHS OCDBP, as of August 27, 2025).
[‡‡] Ipilimumab and ipilimumab-nivolumab are not provincially funded for second-line treatment in the metastatic setting (AHS OCDBP, as of August 27, 2025).
[§§] Pembrolizumab, nivolumab, and nivolumab-relatlimab are not provincially funded for first-line treatment in the metastatic setting within 6 months of targeted therapy (AHS OCDBP, as of August 27, 2025).

ipilimumab-nivolumab then nivolumab maintenance‡‡ *(Level of Evidence: II[47]; Strength of Recommendation: B)*.

12. Chemotherapy may be considered beyond immunotherapy and/or targeted therapy for patients with metastatic melanoma when no further options exist *(Level of Evidence: V; Strength of Recommendation: C).*

Discussion

Neoadjuvant and Adjuvant Therapy

To reduce the risk of recurrence of melanoma and to improve oncological outcomes, patients with locally advanced, invasive melanomas (generally stage III with lymph node involvement) should be considered for neoadjuvant immunotherapy followed by adjuvant therapy as indicated. Patients with stage IIB, IIC, and stage III melanomas that are managed with surgical resection up-front may be considered for adjuvant therapy following a balanced discussion of the risk/benefit profile specific to their stage of disease and eligibility for treatment. Note that these stages are determined by classification risk categories which are based on the characteristics of the primary tumour as well as regional lymph node involvement. The American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition, see Appendix A) is the basis for specific recommendations about adjuvant therapy.[52] Within the primary tumour, increasing tumour thickness, a high mitotic rate, the presence of ulceration and microsatellitosis are associated with an increased risk of recurrence and correspond to higher stage disease accordingly.[53]

Clinical trials which assess immunotherapy in the neoadjuvant and adjuvant settings for melanoma have focused on treating patients at a high risk for recurrence (based on AJCC stage) with checkpoint inhibitors targeting PD-1 (nivolumab and pembrolizumab) and CTLA-4 (ipilimumab) to improve RFS, distant metastasis-free survival (DMFS) and OS. Targeted therapies investigated in clinical trials in the neoadjuvant and adjuvant settings utilize BRAF/MEK inhibitors in patients with melanomas found to have BRAF V600 mutations (50% of those with metastatic disease)[54].These inhibitors block the mitogen-activated protein kinase (MAPK) signaling pathway and microphthalmia-associated transcription factor (MITF), a transcriptional regulator of the pigment pathway in melanocytes; both key factors in the development of melanoma.[55] Note that the efficacy of BRAF/MEK inhibitors in the adjuvant setting has only been demonstrated in patients with stage III disease and therefore it is not approved for those with stage II disease. While neoadjuvant therapy may also be considered for patients who experience relapse, these individuals have generally not been included in neoadjuvant clinical trials; thus, no evidence-based recommendations can be made for this population. Discussion at multidisciplinary rounds is recommended to determine management for these patients whenever possible.

Immunotherapy in the Neoadjuvant Setting

Pembrolizumab is currently standard of care treatment choice for neoadjuvant therapy, based on results from the phase II SWOG S1801 trial.[12] Compared to the adjuvant treatment only arm, the

S1801 trial reported that 2-yr EFS was 23% higher in the neoadjuvant arm, with comparable toxicity profile.[12] Currently awaiting funding approval, neoadjuvant treatment with ipilimumab-nivolumab combination has also demonstrated the ability to induce major pathological responses (MPR) in 59% of patients in practice-changing phase III NADINA trial, confirming results from prior phase II and phase Ib clinical trials.[14-16, 56] In the NADINA trial, 1-yr EFS rate was 84%,[15] in the phase II OpACIN-neo trial 3-yr RFS and OS rates were 79% and 93%,[57] in the phase II single-arm PRADO trial 2-yr RFS and OS rates were 93% and 95%,[56] and in the phase Ib OpACIN trial 5-yr RFS and OS rates were 70% and 90%.[57]

Specifically, patients with a pathological response demonstrated consistently higher survival outcomes after lymph node dissection. Partial pathological response (pPR) is generally defined as <50% viable tumour cells in the treated tumour bed, and major pathological response (MPR) or near pathologic complete response (pCR) as <10% viable tumour in the treated tumour bed.[58] In the phase II OpACIN-neo trial 2-yr RFS rate was 97% for patients with pPR vs 36% for those with no pathological response,[57] and in the phase II single-arm PRADO trial 2-yr RFS rate was of 93% for patients with MPR vs 71% for those with no MPR.[56] In another phase II trial with 30 patients, higher 4-yr RFS rates were noted for patients with MPR after neoadjuvant nivolumab-relatlimab (95% vs 60%).[59]

High toxicity was reported for the neoadjuvant ipilimumab-nivolumab treatments, especially among patients receiving 3mg/kg ipilimumab,[57] compared to less severe adverse events with neoadjuvant nivolumab monotherapy at the cost of reduced pathological response.[60] Conversely, neoadjuvant nivolumab-relatlimab resulted in higher response rates that nivolumab-ipilimumab therapy but with more adverse events.[61]

Targeted Therapy in the Neoadjuvant Setting

Neoadjuvant treatment with BRAF/MEK inhibitors for patients with melanomas harbouring BRAF-V600 mutations is not currently recommended due to a lack of durable responses.[62] MPR was achieved in 69% of patients in the single-arm phase II NeoCombi trial,[63, 64] but in the COMBI-AD trial (adjuvant dabrafenib and trametinib vs placebo), 2-yr RFS rate (43%) was similar to the placebo arm (44%).[27] In contrast, the phase II Combi-Neo trial was terminated early due to the complete response of 7/21 patients in the dabrafenib and trametinib treatment arm.[65] Combining dabrafenib-trametinib with pembrolizumab, the phase II NeoTrio trial did achieve higher survival outcomes; among patients in the sequential treatment arm, 2-y RFS and OS were 80% and 89% respectively.[66]

Immunotherapy in the Adjuvant Setting

Adjuvant nivolumab for patients with stage III cutaneous melanoma improved RFS (HR 0.46) compared to placebo, in a meta-analysis of phase III CheckMate 238[67, 68] (nivolumab vs ipilumab) and phase III EORTC 18071[69, 70] (ipilimumab vs placebo) trials.[26] Ipilimumab-nivolumab combination therapy did not improve survival outcomes in the phase III CheckMate 915 trial compared to nivolumab monotherapy.[52]

Adjuvant pembrolizumab improved long-term survival outcomes in phase III trials for patients with resected stage IIB/C (KEYNOTE-716 trial)[16] and stage III cutaneous melanoma (KEYNOTE-054 trial).[21] In stage IIB/C patients, 2-yr RFS and DMFS rates were 81% (vs 73% placebo) and 88% (vs 82%) respectively; 4-yr RFS and DMFS rates were 71% (vs 58%) and 81% (vs 70%) respectively.[15, 16] For patients with stage III, 3.5-yr RFS and DMFS rates were 64% (vs 44% placebo) and 65% (vs 49%) respectively; and 5-yr RFS and DMFS rates were 55% (vs 38%) and 67% (vs 45%) respectively.[23, 24] A multivariable analysis for stage IIB/C patients found that tumour thickness >4 mm and mitotic rate ≥5/mm² were associated with improved RFS, while tumour location was not associated.[19, 20] In contrast, the phase III SWOG S1404 trial, which included stage III and IV patients, found no RFS or OS benefit for pembrolizumab compared to standard-of-care high-dose IFN-α or ipilimumab.[71]

For patients with stage IV melanoma, nivolumab monotherapy did not improve survival outcomes in the phase II IMMUNED trial.[54] Adding ipilimumab to the first 4 cycles of nivolumab however, did result in improved RFS compared to placebo (HR 0.23) and nivolumab only (HR 0.41), and improved OS compared to placebo (HR 0.41), but no OS benefit compared to nivolumab (95% CI 0.22-1.38). Higher toxicity rates were noted with ipilimumab/nivolumab, as anticipated.[32] For patients with stage IIB-C melanoma, adjuvant nivolumab therapy can improve RFS and DMFS outcomes. In the phase III CheckMate 76K trial, 1-yr RFS and DMFS rates were 89% and 92% compared to placebo (79% and 85%, respectively), with only 10% severe toxicities reported.[14]

Targeted Therapy in the Adjuvant Setting

Adjuvant dabrafenib-trametinib combination treatment improved long-term outcomes (RFS and DMFS) in patients with resected stage III BRAF V600-mutant cutaneous melanoma in the phase III COMBI-AD trial.[30] Compared to placebo, reported 5-yr RFS and DMFS rates were 52% (vs 36%) and 65% (vs 54%).[72] Reported 10-yr RFS and DMFS rates were 48% (vs 32%) and 63% (vs 48%). No difference in OS was reported, except for patients with BRAF V600E–positive melanoma (8-yr OS HR 0.75).[28] Adjuvant vemurafenib*** improved disease-free survival but not overall survival among patients with stage IIC-IIIB melanoma included in the phase III BRIM8 trial, with 1-yr and 2-yr DFS rates of 84% (vs 66%) and 71% (vs 57%).[73] No benefits were observed among patients with stage IIIC melanoma. These findings from these trials led to the approval of BRAF/MEK inhibitors in the setting of resected stage III disease, but not in those with stage II.

Experimental Approaches

In the adjuvant setting, different agents have been investigated in clinical trials, but none have demonstrated meaningful clinical benefit. The phase IIb KEYNOTE-942 trial reported an improved

*** Currently only approved in Alberta for treatment of unresectable or metastatic melanoma that did not progress under dabrafenib plus trametinib. See https://www.cda-amc.ca/sites/default/files/pcodr/pcodr_provfund_vemurafenib_zelboraf-advmel.pdf

distant metastasis-free survival (HR 0.35), despite no RFS benefit with mRNA-4157 in addition to pembrolizumab.[74] The phase III AVAST-M trial did not find an impact of bevacizumab, an anti angiogenesis treatment that inhibits vascular endothelial growth factor.[75] The phase III trial by Khammari *et al.* was unable to validate the efficacy of adoptive tumour-infiltrating therapy combined with interleuking-2 from previous trials.[76] The phase III MIND-DC trial did not find an impact of natural dendritic cells.[77] The phase IIb trial by Vreeland *et al.* did not see a benefit from adjuvant dendritic cell vaccine in the intention-to-treat population.[78] Lastly, vaccine therapy including with MAGE-A3, allogenic whole-cell vaccine plus bacillus Calmette-Guerin, granulocyte-macrophage colony-stimulating factor, and peptide vaccination have been investigated in several trials in patients with stage III melanoma in the adjuvant setting; however, none have been shown to be effective.[79-83]

In the neoadjuvant setting, promising results were reported for talimogene laherparepvec in the phase II trial by Dummer *et al.*[84, 85] Reported 2-yr RFS and OS rates were 30% (vs 7% placebo) and 89% (vs 77%); 5-yr RFS and OS rates were 22% (vs 15%) and 77% (vs 63%); adverse effects were minimal.[84, 85]

Adjuvant Therapies of Historical Significance

Prior to the development of immunotherapy and targeted therapy, interferon-α (IFN-α) was the only effective adjuvant therapy for high-risk melanoma. High-dose IFN-α (20 megaunits [MU]/m^2/d × 5 days a week for 4 weeks and 10 MU/m2 three times per week for 48 weeks) was considered the gold standard based on results from the ECOG 1684and Intergroup E1694 trials that showed improved RFS and OS.[86, 87] A range of IFN-α doses, forms and comparisons to observation or other treatments have since been studied.[88-100] However, IFN-α is associated with significant toxicities that affect numerous organ systems and is no longer routinely used.

Adjuvant ipilimumab used to be standard of care, demonstrating efficacy in improved long-term survival (RFS, DMFS, OS) in patients with stage III cutaneous melanoma in the large phase III EORTC 18071 clinical trial, with 3-yr RFS and OS rates of 46.5% and 65.4% compared to 34.8% and 54.4% in placebo.[69, 70] However, due to high treatment-related adverse events (38-57%, depending on dosage),[101, 102] its clinical use has declined in favor of other available adjuvant therapy options such as adjuvant nivolumab. This was further supported by the phase III CheckMate 238 trial which reported higher 4-yr RFS for the nivolumab arm (52%) compared to the ipilimumab arm (41%), even though OS was similar.[67, 68]

Systemic Therapy for Metastatic Melanoma

Systemic therapy for metastatic melanoma is given with the intent to control the disease and delay progression while prolonging overall survival and maintaining quality of life. As systemic therapy options include many of the regimens offered in the neoadjuvant/adjuvant setting, treatment decisions must take prior therapies into account, as well as BRAF mutational status, disease burden, and patient performance status to optimize outcomes while mitigating toxicity.

Immunotherapy and Targeted Therapy

First-line treatments for advanced melanoma include single agent PD-1 inhibitors (nivolumab or pembrolizumab), PD-1 combined with CTLA-4 blockade (nivolumab plus ipilimumab), PD-1 combined with LAG-3 blockade (nivolumab plus relatlimab), and for BRAF V600-mutated melanoma, BRAF inhibitors (vemurafenib, dabrafenib, or encorafenib) paired with MEK inhibitors (cobimetinib, trametinib, or binimetinib).

Treatment with nivolumab and pembrolizumab monotherapy have demonstrated improved survival and progression free survival in phase III clinical trials. The phase III CheckMate 067 trial showed improved PFS and OS with nivolumab compared to ipilimumab monotherapy (HR 0.55 & HR 0.63).[38-40] The KEYNOTE-006 trial demonstrated efficacy of pembrolizumab compared to ipilimumab, with better OS (HR 0.73) and PFS (HR 0.57).[42, 43] These trials also demonstrated a median PFS of 5–8 months, a median OS of 24–32 months, and a favorable safety profile with grade 3–4 adverse events in only 10–15% of patients, a marked improvement over ipilimumab's toxicity. The combination of nivolumab and ipilimumab, also demonstrated in phase III CheckMate 067 trial, shows improved PFS and OS compared to ipilimumab (HR 0.55 & HR 0.55) and nivolumab monotherapy (HR 0.78 & HR 0.63).[38-40] However, its high toxicity (grade 3–4 in up to 59%) requires careful patient selection to balance efficacy and safety.

The combination of nivolumab-relatlimab offers another first-line option which was recently approved by Health Canada. In treatment-naïve patients, the phase II/III RELATIVITY-047 trial demonstrated a median PFS of 10.1 months (vs 4.6 months with nivolumab alone; HR 0.75) and a 12-month PFS rate of 47.7% versus 36%.[34-36] With grade 3–4 occurring in 22% of patients, this regimen provides a more tolerable alternative to nivolumab-ipilimumab, making it suitable for a broad patient population, including those with a history of autoimmune disease who are at a higher risk of developed immune related adverse events (IrAEs) than the general population.

For BRAF V600-mutated melanoma, combined BRAF and MEK inhibitors offer additional first-line options, demonstrating superior response rates, PFS, and OS compared to single-agent BRAF inhibitors in the COMBI-d, COMBI-v and COLUMBUS trials.[31, 41] These targeted therapies provide a critical alternative for patients with actionable mutations, further personalizing treatment strategies.

Therapies After Disease Progression

For BRAF wild-type melanoma, approved second-line treatment options are limited, often necessitating enrollment in clinical trials or personalized treatment strategies. In patients who progressed on first-line anti-PD-1 monotherapy or exhibited primary refractory disease following anti-PD-1 therapy, ipilimumab monotherapy or the combination of nivolumab plus ipilimumab are viable options. The SWOG S1616 trial demonstrated efficacy of the combination in this setting, with improved response rates and PFS compared to ipilimumab alone.[47] Additionally, RELATIVITY-020 trial demonstrated that nivolumab plus relatlimab may serve as an alternative for patients with melanoma that progressed after single-agent anti-PD-1 therapy.[48]

For BRAF V600-mutated melanoma, all second-line options available for BRAF-WT melanoma remain applicable. Additionally, combined BRAF and MEK inhibitor therapy (e.g., dabrafenib plus trametinib, encorafenib plus binimetinib, or vemurafenib plus cobimetinib) is recommended if not used as the immediate prior treatment.

Other Options

Lastly, therapeutic options for advanced melanoma after PD-1 failure are expanding, with TIL therapy, anti-LAG-3 inhibitors, TVEC, and targeted agents under active investigation; with lifileucel TIL therapy recently approved by the FDA for patients with unresectable or metastatic melanoma previously treated with anti-PD-1 immunotherapy.[103-105]

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Appendix A: Melanoma TNM Definitions and Prognostic Stage Groups, AJCC 8th Edition

Table 1. TNM Definitions - Primary Tumour (T)

T Category	Thickness	Ulceration Status
TX: Primary tumour thickness cannot be assessed (e.g., diagnosis by curettage)	N/A	N/A
T0: No evidence of primary tumour (e.g., unknown primary of completely regressed melanoma)	N/A	N/A
Tis (melanoma *in situ*)	N/A	N/A
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8mm	With ulceration
	0.8 to 1.0 mm	With or without ulceration
T2	>1 to 2 mm	Unknown or unspecified
T2a	>1 to 2 mm	Without ulceration
T2b	>1 to 2 mm	With ulceration
T3	>2 to 4 mm	Unknown or unspecified
T3a	>2 to 4 mm	Without ulceration
T3b	>2 to 4 mm	With ulceration
T4	>4 mm	Unknown or unspecified
T4a	>4 mm	Without ulceration
T4b	>4 mm	With ulceration

Table 2. TNM Definitions - Regional Lymph Nodes (N)

N Category	Extent of Regional Lymph Node and/or Lymphatic Metastasis	
	Number of Tumour-Involved Regional Lymph Nodes	Presence of In-Transit, Satellite, and/or Microsatellite Metastases
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: Pathological N category is not required for T1 melanomas, use cN	No
N0	No regional metastases detected	No
N1	One tumour-involved node or in-transit, satellite, and/or microsatellite metastases with no tumour-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumour-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumour-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumour-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumour-	

	involved nodes, or any number of mattes nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

SLN, sentinel lymph node

Table 3. TNM Definitions - Distant Metastasis (M)

M Category*	M Criteria	
	Anatomic Site	**LDH Level**
M0	No evidence of distant metastasis	N/A
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

*Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or unspecified.
CNS, central nervous system; LDH, lactate dehydrogenase

Table 4. TNM Prognostic Stage Groups

Clinical (cTNM)*			
When T is…	**And N is…**	**And M is…**	**Then the clinical stage group is…**
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV
*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.			
Pathological (pTNM)†			
When T is…	**And N is…**	**And M is…**	**Then the clinical stage group is…§**
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b, or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥ N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV
†Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumour surgical treatment and pathological information about the regional lymph nodes after SLN biopsy of therapeutic lymph node dissection for clinically evident regional lymph node disease. §Pathological Stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Cutaneous Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Cutaneous Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, and dermatologists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was developed in 2026.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2028. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; AJCC, American Joint Committee on Cancer; ASCO, American Society of Clinical Oncology; BRAF, B-Raf proto-oncogene; CCA, Cancer Care Alberta; CDA, Canada's Drug Agency; ChT, chemotherapy; CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DFS, disease-free survival; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; ESMO, European Society for Medical Oncology; HR, hazard ratio; IFN-α, interferon alpha; MAPK, mitogen-activated protein kinase; MITF, microphthalmia-associated transcription factor; MPR, major pathologic response; MU, megaunits; OCDBP, outpatient cancer pharmacy and drug benefit program; OS, overall survival; PD-1, programmed cell death protein 1; pNR, pathological non-response; pPR, pathological partial response; RFS, relapse-free survival; SITC, Society for Immunotherapy of Cancer; TLND, therapeutic lymph node dissection; UV, ultraviolet.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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Dr. Claire Temple-Oberle, plastic & reconstructive surgeon, has nothing to disclose**.**
Dr. Eva Thiboutot, surgical oncologist, has nothing to disclose.
Ellen de Jong, PhD, methodologist, has nothing to disclose.

*Working group lead

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