JAMA | Review

Cutaneous Melanoma
A Review

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IMPORTANCE Melanoma, the fifth most common cancer in the US, has increased from 8.8 per 100 000 in 1975 to 28.42 per 100 000 in 2022. Cutaneous melanoma comprises 94% of cases, with 104 960 US cases projected for 2025.

OBSERVATIONS Cutaneous melanoma presents as a new, changing, or irregularly pigmented skin lesion. Cutaneous melanoma subtypes include superficial spreading (≈70%), lentigo maligna (≈15%), nodular (≈5%), desmoplastic (≈4%), amelanotic (2%-8%), spitzoid (<2%), and acral (≈1%). Risk factors for cutaneous melanoma include UV radiation exposure, skin type (eg, skin that always burns, never tans), presence of benign and atypical nevi, and personal or family history of melanoma. Primary prevention consists of avoiding direct sunlight and indoor tanning, and photoprotection (sunscreen and sun-protective clothing). Based on United States Cancer Statistics data from 1999 to 2021, 77% of patients with cutaneous melanoma had localized disease (involving only the primary site), 9.5% had regional (nodal) disease, 4.7% had distant metastasis, and 8.8% were unstaged. Melanoma staging, which includes tumor thickness and ulceration and presence of lymph node or distant metastasis, ranges from stage 0 (melanoma in situ) to stage IV (distant metastasis). Localized melanoma (stage IA-IIA) is surgically excised, with margins of 0.5 cm to 2 cm based on depth of invasion. Sentinel lymph node biopsy is recommended for cutaneous melanoma that is ulcerated or 0.8 mm or more thick. Following surgery, patients with stage IIB-C melanoma have improved recurrence-free survival with adjuvant anti–PD-1 immunotherapy compared with placebo (hazard ratio [HR] for recurrence or death, 0.62 [95% CI, 0.49-0.79] for pembrolizumab and 0.42 [95% CI, 0.30-0.59] for nivolumab). For stage III disease, recurrence risk is decreased with nivolumab (HR, 0.72 [95% CI, 0.60-0.86]), pembrolizumab (HR, 0.61 [95% CI, 0.51-0.72]), or BRAF + MEK inhibitor therapy (dabrafenib + trametinib) (HR, 0.52 [95% CI, 0.43-0.63]). First-line treatment for distant metastatic or unresectable melanoma is dual checkpoint blockade with ipilimumab (anti–CTLA-4) and nivolumab. In 2017, 10-year melanoma-specific survival rates were 98% to 94% for stage IA-B, 88% to 75% for stage IIA-C, 88% for stage IIIA, 77% to 60% for stage IIIB-C, and 24% for stage IIID. In 2024, patients with distant metastatic or unresectable melanoma treated with ipilimumab and nivolumab had a 10-year overall survival rate of 43%.

CONCLUSIONS AND RELEVANCE Melanoma is a common cancer in the US. Treatment for stage IA-IIA melanoma is surgical resection. Anti–PD-1 immunotherapy after surgical excision improves recurrence-free survival in stages IIB-C melanoma. For stage III melanoma, anti–PD-1 immunotherapy or BRAF + MEK inhibitor therapy decreases risk of melanoma recurrence. First-line therapy for metastatic melanoma is dual checkpoint blockade with ipilimumab and nivolumab.

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Multimedia

Supplemental content

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The incidence and prevalence of cutaneous melanoma in the US and worldwide have increased over the last 5 decades. In the US, invasive cutaneous melanoma (defined as invading the dermis) has increased from 8.8 per 100 000 persons in 1975 to 27.7 per 100 000 persons in 2021.[1,2] However, mortality in the US among patients with melanoma decreased 6.1% annually from 2013-2017 and 1.4% annually from 2017-2022.[3] Melanoma can progress from a noninvasive (in situ) stage to invasive disease with dermal involvement (**Figure 1**), although most in situ lesions do not progress to invasive melanoma (5%-15% lifetime risk of progression for melanoma in situ of lentigo maligna type).[4,5] Melanoma staging is outlined in eTable 1 in the Supplement.

Improvements in melanoma mortality over the last decade are attributed to the advent of multiple effective therapies,[6] including immune checkpoint blockade with anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) antibodies (ipilimumab), anti–programmed cell death protein 1 (PD-1) antibodies (nivolumab, pembrolizumab), and anti–lymphocyte activation gene 3 protein (LAG-3) antibodies (relatlimab), as well as oral combination targeted therapy with B-Raf protein (BRAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors (eg, encorafenib + binimetinib, vemurafenib + cobimetinib, dabrafenib + trametinib).

This review summarizes current evidence regarding epidemiology and risk factors, clinical presentation, diagnosis, and management of cutaneous melanoma (**Box**).

Methods

A PubMed search was performed for *melanoma*, including randomized clinical trials, meta-analyses, and systematic reviews about melanoma in adults, written in English, between January 1, 2014, and July 1, 2025. A total of 748 articles were retrieved. Articles were screened for study quality and relevance. Reference lists of systematic reviews were searched and additional relevant articles were added. A total of 93 articles were included, composed of 23 randomized clinical trials, 15 population-based registry studies, 16 cohort studies, 13 narrative reviews, 11 meta-analyses and systematic reviews, 8 clinical practice guidelines or society recommendations, 2 nonrandomized

Figure 1. Staging and Pattern of Spread of Cutaneous Melanoma

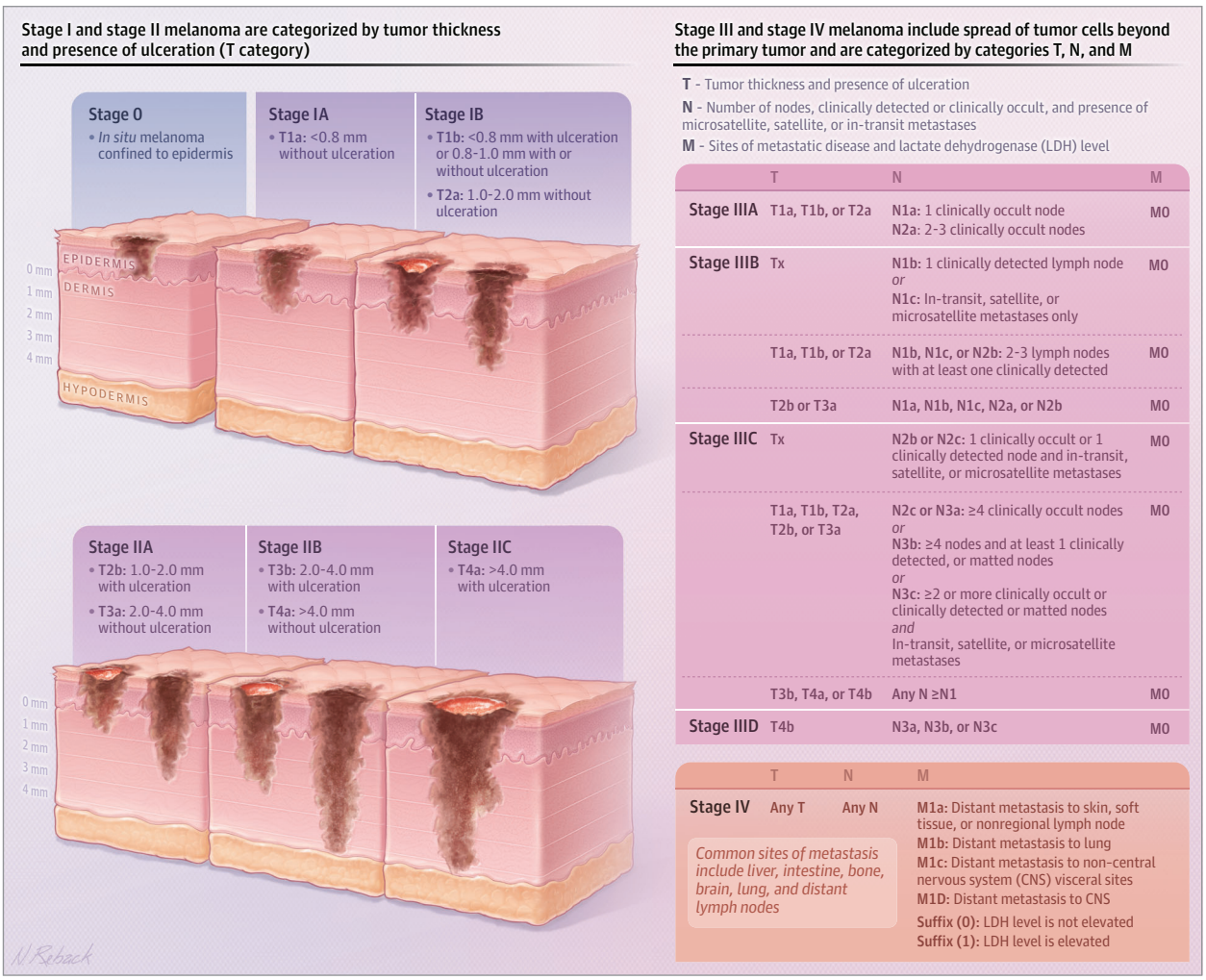


Figure illustrates primary tumor staging. Peripheral blood assays may be used to assess circulating tumor DNA.

Box. Frequently Asked Questions About Melanoma

What Are Risk Factors for Cutaneous Melanoma and How Can the Risk Be Reduced?
Risk factors for cutaneous melanoma include a personal history or family history of melanoma in a first-degree relative, lighter skin pigmentation, increased number of moles and atypical moles, immunosuppression (eg, transplant recipient), sunburn history, lighter eye color, UV exposure, and use of tanning beds. The risk of melanoma can be reduced by avoiding solar UV light during peak hours (typically 10 AM to 2 PM), using broad-spectrum sunscreens (mineral or chemical formulations with UVA and UVB protection, SPF ≥30), wearing hats and sun-protective clothing, and avoiding tanning beds.

What Are Recommended Treatments for Melanoma by Stage?
Recommended treatment for stage IA-IIA melanoma is surgical excision. For stage IIB-C melanoma, anti–PD-1 immunotherapy (pembrolizumab or nivolumab) after surgical excision significantly reduces recurrence risk. For stage III melanoma, anti–PD-1 immunotherapy or BRAF + MEK inhibitor therapy significantly decreases risk of melanoma recurrence. For patients with metastatic melanoma, first-line therapy is ipilimumab and nivolumab.

Which Patients With Melanoma Should Undergo Testing for *BRAF* V600E or V600K Genetic Variants?
Patients with stage III or IV cutaneous melanoma should be tested for the genetic variants *BRAF* V600E and V600K. Stage III melanoma with an activating genetic variant may be treated with adjuvant BRAF and MEK inhibitor therapy (dabrafenib and trametinib) to improve recurrence-free survival. Second-line therapy for patients with *BRAF*-variant metastatic melanoma who have progressed with dual checkpoint blockade immunotherapy is combined BRAF and MEK inhibition.

Abbreviations: *BRAF*, proto-oncogene B-Raf; BRAF, B-RAF protein; *MEK*, proto-oncogene MEK; MEK, mitogen-activated extracellular signal-regulated kinase; PD-1, programmed cell death protein 1; SPF, sun protection factor.

clinical trials, 3 consensus and policy statements, 1 laboratory study, and 1 cancer staging manual.

Epidemiology

Cutaneous melanoma is the fifth most common cancer in the US in 2025,[3] and is projected to be second most common cancer by 2040.[1] In 2024, the estimated incidence of cutaneous melanoma in the US was 100 640 cases with approximately 8290 deaths, and the estimated incidence of melanoma in situ was 99 700 cases. In 2025, approximately 104 960 new cases of cutaneous melanoma are anticipated to be diagnosed in the US, associated with 8430 deaths.[3] The estimated number of new cases of melanoma in situ (noninvasive or stage 0, involving epidermis only) in the US in 2025 is 107 240.[3] Melanoma incidence is also projected to increase globally from 331 722 cases in 2022[7] to approximately 510 000 cases per year worldwide by 2040.[1]

Melanoma incidence is elevated in high-income countries that have large populations with lighter skin pigmentation, including Australia, Europe, and North America.[1] Annual age-adjusted melanoma incidence in the US in 2024 was 1.3 per 100 000 persons for Asian, 1.0 per 100 000 for Black, 4.8 per 100 000 for Hispanic, 10.3 per 100 000 for Native American, and 30.6 per 100 000 for White individuals.[8] Data from 2006 to 2015 indicate a decrease among adolescents and young adults (−3.6% to −5.4% annually in US males and females aged 10-29 years).[9] However, melanoma incidence has been increasing in older adults globally, with 259 000 (79.7%) of all new global cases in 2020 occurring in persons older than 50 years.[1]

The US Cancer Statistics database (1999-2021) reported that among new cases of invasive melanoma, 77% were localized (involving only the primary site), 9.5% were regional (ie, nodal), 4.7% were metastatic to distant sites, and 8.8% were unstaged.[10] Melanoma among non-White individuals in the US is diagnosed at more advanced stages, which may be attributed to decreased skin cancer education, higher proportions of more aggressive subtypes, and/or socioeconomic barriers to medical care.[11]

Melanoma Subtypes

Cutaneous melanoma is the most common type of melanoma (94%). Other less common melanoma subtypes are uveal[12-14] (4%-5%) and mucosal (oral, nasal, conjunctival, or anogenital [1%-2%])[13,15,16] (**Figure 2**; eTable 2 in the Supplement). The most prevalent cutaneous melanoma subtypes are superficial spreading (associated with low cumulative sun damage [≈70%]), lentigo maligna (associated with high cumulative solar damage [≈15%]), and nodular (≈5%).[2,13] Less common melanoma subtypes are amelanotic (2%-8%), desmoplastic (4%), spitzoid (<2%), and acral (plantar/palmar and subungual [≈1%])[17] (Figure 2C-E). Unlike typical cutaneous melanoma, amelanotic melanoma has no or minimal pigmentation, appearing pink, reddish, or skin-colored.

Risk Factors

Modifiable or acquired risk factors for cutaneous melanoma include history of sunburn, tanning bed use, and immunosuppression. Heritable risk factors include lighter skin pigmentation that burns easily, hair color (red or blonde), eye pigmentation (blue, green, hazel, gray), and family history of melanoma in a first-degree relative (**Table 1**).[18-24]

Categorization of Skin Pigmentation

Skin phototyping classifies skin based on response to sun exposure. The Fitzpatrick classification is the most widely used and ranges from skin type I (lighter pigmentation that always burns, does not tan) to skin type IV (darker pigmentation that rarely burns, tans more than average) (Table 1).[25] The relative risk of developing melanoma for Fitzpatrick type I vs Fitzpatrick type IV is 2.09 (95% CI, 1.67-2.58).[19]

UV Radiation Exposure

The primary modifiable risk factor for cutaneous melanoma is UV radiation exposure. A meta-analysis with 57 case-control and cohort studies with 38 671 cases reported intermittent UV exposure as a risk factor for melanoma, with a relative risk of 1.61 (95% CI, 1.31-1.99).[21] An additional risk factor is a positive sunburn history,

Figure 2. Clinical Images of Dysplastic Nevi and Melanoma Subtypes

A, Atypical/dysplastic nevi display features of asymmetry, irregular borders, varied colors, and larger size (>5 mm). B, Superficial spreading (or low-cumulative solar damage) melanoma accounts for 70% of cutaneous melanoma cases. C, Amelanotic melanoma accounts for 2% to 8% of cutaneous melanoma cases. D, Desmoplastic melanoma accounts for 4% of cutaneous melanoma cases. E, Acral melanoma occurs on the palmar, plantar, and subungual surfaces and accounts for 1% to 2% of cutaneous melanoma cases and can occur in non-White individuals, as featured in this image. F, Lentigo maligna (or high-cumulative solar damage) melanoma accounts for approximately 15% of cutaneous melanoma cases. G, Mucosal melanoma is a noncutaneous subtype, comprising 1% of melanoma cases, and can occur in non-White individuals, as featured in this image.

with a relative risk of 2.03 (95% CI, 1.73-2.37).[21] However, UV exposure may be a less important risk factor for cutaneous melanoma among individuals with darker pigmentation. In a systematic review including 7727 melanomas, 11 of 13 studies reported no association between UV exposure and melanoma in patients with darker pigmented skin.[26] UV exposure from tanning bed use also increases melanoma risk. A meta-analysis with 27 observational studies and 11 428 cases reported a relative risk of 1.20 (95% CI, 1.08-1.34) for history of tanning bed use.[22]

Dysplastic Nevi

Dysplastic nevi (also called atypical moles) are skin lesions that may have asymmetry, irregular borders, and varied colors (Figure 2A); are characterized histopathologically by atypical architecture and cytology (eg, enlargement of nuclei); and frequently display molecular signatures including proto-oncogene B-Raf (*BRAF*) variants and signal transducer and activator of transcription 3 (STAT3) activation that are intermediate between a benign nevus and melanoma.[27] Approximately 30% of melanomas arise from preexisting melanocytic nevi.[28] However, the risk of an individual nevus progressing to melanoma is low (1 in 33 000 or less per year), and most dysplastic nevi remain stable or regress over time.[29] A meta-analysis including 47 datasets and 10 499 cases reported total body nevi and atypical nevi as a risk factor for melanoma, with a relative risk of up to 6.89 (95% CI, 4.63-10.25) for 101 to 120 total nevi and a relative risk of 10.49 (95% CI, 5.05-21.76) for 5 atypical nevi.[20]

Hereditary Melanoma

Approximately 5% to 12% of melanoma is hereditary.[30] A meta-analysis including 60 studies with 28 157 cases reported patients with a family history of melanoma in a first-degree relative had a relative risk of 1.74 (95% CI, 1.44-1.81) of developing melanoma.[19] Familial Atypical Multiple Mole and Melanoma (FAMMM) syndrome is a rare autosomal dominant condition that affects 1% to 2% of patients with a family history of melanoma and is characterized by multiple common and atypical nevi (typically >50-100). FAMMM syndrome is associated with an approximately 30% lifetime risk of melanoma,[31] and 20% to 40% of patients have germline *CDKN2A* variants.[32]

Immunosuppression

Immunosuppression is associated with an increased risk of melanoma. In a systematic review of 17 studies reporting incidence of melanoma in solid organ transplant recipients, transplant recipients were reported to have a pooled estimate of 2.4-fold (95% CI, 2.0-2.9) greater risk compared with the general population.[24]

Pathophysiology

Cutaneous melanoma develops through malignant transformation of melanocytes in the skin at the junction of the epidermis and dermis, which may be promoted by UV exposure. The primary genetic drivers of cutaneous melanoma include variants in the *BRAF*, *NF1*, and *NRAS* genes, which activate the mitogen-activated protein kinase (MAPK) pathway and promote uncontrolled cell growth. Approximately 50% of melanomas have *BRAF* gene variants.[33] Other somatic variants include *PTEN*, *KIT*, *TP53*, *CDKN2A*, and *TERT*, leading to aberrant activation of MAPK and PI3K/AKT pathways promoting cancer progression through dysregulated cell growth and division.[34] Metastasis may be promoted by somatic variants in genes that control cell proliferation (*BRAF*, *NRAS*, *NF1*), metabolism (*PTEN*, *KIT*), and resistance to apoptosis (*TP53*).[34]

Screening

In 2023 the US Preventive Services Task Force concluded that there was insufficient evidence to assess the utility of visual skin examination to screen asymptomatic individuals for skin cancer in the primary care setting.[35,36] Screening for melanoma should focus on dermatologic examination of individuals with multiple risk factors for melanoma, including history of substantial UV exposure (not quantified in the medical literature) or blistering sunburns; skin that burns easily (Fitzpatrick I-II); personal or family history of melanoma or other skin cancers, such as squamous cell carcinoma and basal cell carcinoma; many moles or atypical moles; and immunosuppression.

Melanoma Overdiagnosis

Several studies raise concerns about overdiagnosis of melanoma, which involves diagnosis of a melanoma that would not have caused harm if left untreated.[5,37] A cohort study using Surveillance, Epidemiology, and End Results registry data (1975-2014) estimated melanoma overdiagnosis at 59% (95% CI, 45%-70%) among White women and 60% (95% CI, 32%-75%) among White men in the US.[38] In an observational study, routine annual screening (conducted by primary care clinicians trained in melanoma identification) of 595 799 US individuals was associated with increased diagnoses of melanoma in situ (0.1% screened vs 0.05% unscreened, $P < .001$).[39] Increased surveillance of the general population with annual clinician screening for melanoma was associated with increased subsequent biopsy rates (hazard ratio [HR], 1.85 [95% CI, 1.69-2.04]) and diagnoses of in situ melanoma (HR, 1.45 [95% CI, 1.09-1.92]).[40]

Clinical Presentation

Patients with melanoma commonly report a changing skin lesion (54%). Symptoms of bleeding or ulceration (6%) or pruritus (3%) are less common.[41] In a prospective, population-based cohort study of 2452 patients with 291 in situ and 2161 invasive cutaneous melanoma diagnosed from 2006-2007, melanoma was self-detected (47%) or identified during routine skin check (35%) or during evaluation of another skin lesion (12%).[41]

Table 1. Risk Factors for Cutaneous Melanoma

Risk factor	Relative risk (95% CI)[a]
Personal history of melanoma[18]	8.40 (8.04-8.78)
Inherited	
Skin pigmentation[19] by Fitzpatrick phototype[b]	
I vs IV	2.09 (1.67-2.58)
II vs IV	1.84 (1.43-2.36)
III vs IV	1.77 (1.23-2.56)
Eye color (light vs dark)[c,19]	1.62 (1.44-1.81)
Family history of melanoma in a first-degree relative[19]	1.74 (1.41-2.14)
Modifiable	
Total body nevi[20]	
0-15	1.00 (1.36-1.59)
16-40	1.47 (1.90-2.64)
41-60	2.24 (2.55-4.15)
61-80	3.26 (4.63-10)
81-100	4.74 (3.44-6.53)
101-120	6.89 (4.63-10.25)
Atypical nevi[20]	
0	1.00
1	1.60 (1.38-1.85)
2	2.56 (1.91-3.43)
3	4.10 (2.64-6.35)
4	6.55 (3.65-11.75)
5	10.49 (5.05-21.76)
Intermittent UV exposure[21]	1.61 (1.31-1.99)
Sunburn history[21]	2.03 (1.73-2.37)
Tanning bed use[22]	1.20 (1.08-1.34)
Immunosuppression	
Kidney transplant recipient[23]	3.60 (3.10-4.10)
Solid organ transplant recipient[24]	2.40 (2.0-2.9)

[a] Absolute rates not available.

[b] Fitzpatrick phototypes defined as I (always burns, never tans), II (usually burns, tans less than average), III (sometimes mild burns, tans about average), and IV (rarely burns, tans more than average).

[c] Light defined as blue, green, hazel, or gray. Dark defined as brown or black.

Melanoma secondary to chronic sun exposure (such as lentigo maligna melanoma, with histopathologic features of solar elastosis, characterized by abnormal changes in elastic tissue) typically arises in the head, neck, and extremities in older patients (eg, ≥55 years). In contrast, melanoma that develops with intermittent sun exposure (with histopathologic features of low cumulative solar damage, also known as superficial spreading melanoma) tends to arise in the trunk and extremities in younger patients.[13]

Characteristic findings of melanoma include asymmetry, border irregularity, color variegation, diameter greater than 6 mm, and/or evolving appearance (change in size, shape, or color).[13] New or changing pigmented lesions, and those that differ from other nevi ("ugly duckling sign"), should be closely examined.[42] A prospective study including 135 dermatologists and 4036 cases of resected nevi and melanoma identified the most important factors for discriminating melanoma as overall irregularity (odds ratio, 10.42 [95% CI, 4.18-25.60]) and the ugly duckling sign (odds ratio, 3.30 [95% CI, 1.74-6.26]).[42]

Approximately 10% to 20% of melanomas are amelanotic or hypomelanotic, presenting as an elevated, changing lesion with a shiny surface and partial or absent pigmentation.[43] Nodular, desmoplastic, and acral subtypes are more commonly hypomelanotic (30%-40% of cases) than superficial spreading melanoma (10%-25%).[43]

Approximately 4.7% of patients with melanoma present with symptoms of distant metastatic disease, such as new neurologic deficits with brain or spinal involvement.[10] Up to 3% of melanomas present with metastatic disease of unknown primary, typically involving a lymph node.[44]

Diagnosis

Melanoma is diagnosed based on histologic examination of a skin lesion biopsy. A useful adjunct to skin inspection is dermoscopy, a procedure performed by trained dermatology practitioners that involves use of a handheld device to magnify and illuminate a skin lesion.[45] Biopsy techniques include excisional, shave, or punch biopsy to remove the entire lesion for pathologic assessment. These biopsies are typically performed by dermatologists, surgeons, or dermatology-trained family practitioners, and standardized pathologic assessments are used for dermatopathologic classification of melanoma.[46,47]

Referral

Any skin lesion considered suspicious for melanoma should be referred to dermatology for further evaluation and possible biopsy. Patients at high risk for melanoma, such as those with prior melanoma or multiple atypical moles, may be referred for evaluation and surveillance to a pigmented lesion clinic, which is typically available at regional tertiary referral centers. Biopsy-confirmed melanoma should be referred to surgery for wide local excision and possible sentinel lymph node biopsy. Melanoma of stage IIB and higher should be referred to medical oncology for consideration of adjuvant therapy.

Staging

Current staging of melanoma is based on the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*, 8th edition. Melanoma in situ is confined to the epidermis and is noninvasive (stage 0), whereas invasive melanoma involves the dermis. Primary tumor staging is determined by melanoma thickness and ulceration (eTable 1 in the Supplement). Histological criteria such as mitotic rate,[48] presence of lymphovascular/perineural invasion, and tumor-infiltrating lymphocytes provide additional prognostic information (Figure 1).[49] Additional staging criteria include presence of regional metastases (lymph node involvement) or distant metastases. Radiographic imaging with computed tomography (CT) or positron emission tomography is generally reserved for stage IIB and above (eTable 3 in the Supplement).[50]

For patients with melanoma and no palpable regional lymphadenopathy, sentinel lymph node biopsy is recommended if the melanoma is ulcerated or 0.8 mm or more thick.[51] Sentinel lymph node biopsy, an outpatient surgical procedure, identifies the first draining lymph node and is performed by injecting radioactive tracer around the tumor, followed by scintigraphic identification of draining nodes for subsequent surgical removal and histopathologic examination. If the sentinel lymph node is positive for melanoma, patients should undergo serial ultrasound or CT imaging every 3 months per National Comprehensive Cancer Network (NCCN) guidelines. Completion lymph node dissection (surgical removal of all lymph nodes in a lymphatic basin) is no longer recommended per NCCN guidelines.[50] In the per-protocol analysis of a randomized phase 3 trial that included 1934 patients with sentinel node metastases, 3-year melanoma-specific survival was 86% (SD, 1.3%) with completion lymph node dissection vs 86% (SD, 1.2%) with observation (P = .42) at a median follow up of 43 months.[52] Consensus statements and NCCN guidelines do not currently support the routine use of commercial gene expression profiling for selection of patients to undergo sentinel lymph node biopsy[53] because gene expression profiles have demonstrated substantial variation in performance across disease stages.[54] However, molecular testing for *BRAF* V600E or V600K variants in patients with stage IIIA or higher guides consideration of BRAF-targeted therapy.

Treatment

The systemic treatment of melanoma has been transformed over the past 15 years with the development and regulatory approval of multiple immunotherapies and targeted therapies (eFigure in the Supplement).

Melanoma In Situ (Stage 0) and Stage IA-IIA Melanoma

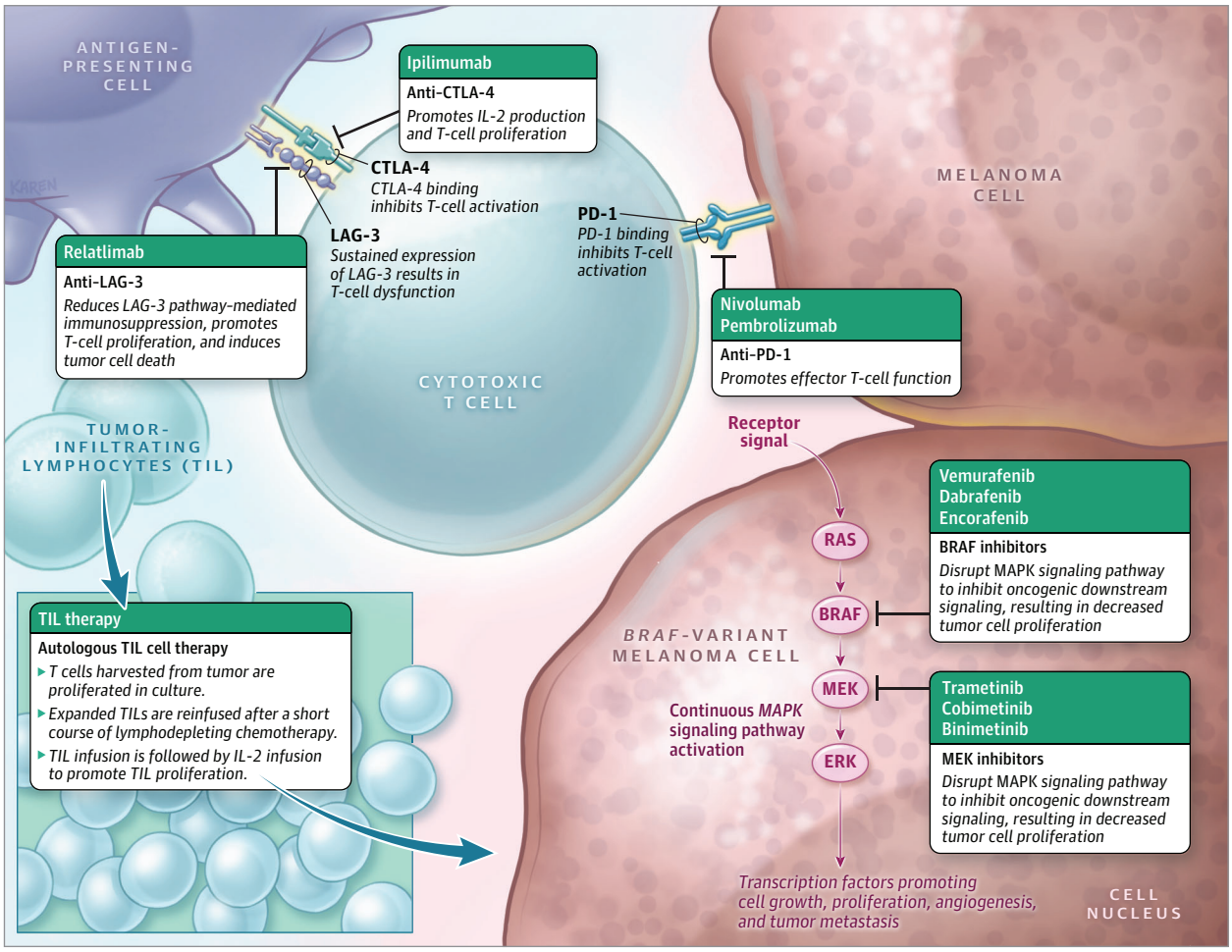
Definitive treatment for in situ melanoma (stage 0) and early stage cutaneous melanoma (stage IA-IIA) is wide excision of the primary lesion.[55] The recommended width of excision in current international guidelines is gauged by Breslow thickness of the primary tumor, ranging from 5-mm margins for melanoma in situ up to 2-cm margins for melanoma 2 mm or more thick.[56]

Stage IIB-C Melanoma

Anti–PD-1, anti–CTLA-4, and anti–LAG-3 antibodies are immune checkpoint inhibitor therapies that block inhibitory receptors on effector T cells (**Figure 3**).[57,58] For patients with resected stage IIB-C melanoma, 12 months of immunotherapy with nivolumab or pembrolizumab is approved by the US Food and Drug Administration (FDA) and recommended by NCCN and European Society for Medical Oncology guidelines, based on prolonged recurrence-free survival.[50,59] Following discussion of the risks and benefits (**Table 2**), observation is also an option, because currently there is no overall survival benefit with adjuvant therapy in stage II disease.

The 5-year recurrence risk of stage IIB and IIC is approximately 35% and 50%, respectively.[49] A randomized clinical trial (RCT) of 976 patients with resected stage IIB-C melanoma reported a significant increase in 36-month recurrence-free survival with adjuvant pembrolizumab compared with placebo (76.2% vs 63.4%; hazard ratio [HR], 0.62 [95% CI, 0.49-0.79]).[63] Another RCT including 790 patients with resected stage IIB-C melanoma reported 12-month recurrence-free survival of 89.0% in the

Figure 3. Mechanism of Action of Current Immunotherapies and Targeted Therapies in Melanoma



Programmed cell death protein 1 (PD-1) receptors on the surface of effector T cells, regulatory T cells, B cells, and natural killer cells block interactions with PD-L1 and PD-L2.[57] PD-1 receptor signaling inhibits effector T-cell function. Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) is present on CD4 and CD8 lymphocytes, and its binding reduces interleukin 2 production and T-cell proliferation.[57] Lymphocyte activation gene 3 protein (LAG-3) interacts with several ligands to modulate T-cell activation and cytokine secretion and function.[58] Treatment with checkpoint inhibitors disrupts these inhibitory pathways, leading to antitumor response via increased T-cell proliferation and effector function. *BRAF* indicates proto-oncogene B-Raf; BRAF, B-Raf protein; ERK, extracellular signal–regulated kinase; IL, interleukin; LAG-3, lymphocyte activation gene 3 protein; MEK, mitogen-activated extracellular signal-regulated kinase; RAS, rat sarcoma virus protein family.

adjuvant nivolumab group vs 79.4% in the placebo group (HR, 0.42 [95% CI, 0.30-0.59]).[64]

Stage IIIA-D Melanoma

Adjuvant Therapy (Stage IIIA-D)

For patients with resected stage IIIA-D melanoma, NCCN and European Society for Medical Oncology guidelines recommend 12 months of adjuvant therapy with either nivolumab or pembrolizumab or with dabrafenib + trametinib in *BRAF*-variant melanoma (Table 2).[50,59] Observation is also an option, particularly for patients with stage IIIA disease, given their higher melanoma-specific survival (88% 10-year survival per *AJCC Cancer Staging Manual*, 8th edition) and lack of data regarding overall survival benefit.

Nivolumab and pembrolizumab are approved by the FDA as adjuvant therapy for resected stage III melanoma regardless of *BRAF* variant status. A randomized clinical trial including 906 patients with resected stage IIIB-IV melanoma demonstrated improved 5-year recurrence-free survival rates with 1 year of adjuvant treatment with nivolumab (50%) vs ipilimumab (39%) (HR, 0.72 [95% CI, 0.60-0.86]).[67] A phase 3 randomized trial included 1019 patients and demonstrated 5-year recurrence-free survival of 55.4% for adjuvant pembrolizumab vs 38.3% for placebo (HR, 0.61 [95% CI, 0.51-0.72]).[66]

For patients with stage III melanoma who have the activating *BRAF* V600E or V600K variant, oral therapy with 1 year of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) is an alternative, similarly effective option to anti–PD-1 immunotherapy. A randomized clinical trial including 870 patients with resected stage III melanoma and *BRAF* V600 gene variants reported 10-year relapse-free survival of 48% (95% CI, 43%-54%) with adjuvant dabrafenib + trametinib vs 32% (95% CI, 26%-40%) with placebo (HR for relapse or death, 0.52 [95% CI, 0.43-0.63]), although 8-year overall survival was not significantly different (71% with dabrafenib + trametinib vs 65% with placebo, $P = .06$).[65]

Table 2. Systemic Therapy, Targets, Indications, Efficacy, and Common Adverse Events From Clinical Trials

Drug	Target	No. of patients	Efficacy (primary end point)	Common treatment-related adverse events (% of patients)
Neoadjuvant (resectable stage IIIB-IVC)[a]				
Pembrolizumab	Anti-PD-1	313	Two-year event-free survival[b]: 72% (95% CI, 64%-80%) for neoadjuvant/adjuvant pembrolizumab vs 49% (95% CI, 41%-59%) for adjuvant pembrolizumab (P = .004)	Grade 3 or 4, neoadjuvant: ALT or AST increased (3.3), hyperglycemia (1.3), WBC count decreased (1.3)
Ipilimumab + nivolumab	Anti-CTLA-4 + anti-PD-1	423[60]	One-year event-free survival[c]: 83.7% (99.9% CI, 73.8%-94.8%) for neoadjuvant ipilimumab plus nivolumab vs 57.2% (99.9% CI, 45.1%-72.7%) for adjuvant nivolumab (HR, 0.32 [99.9% CI, 0.15-0.66])	Any grade, neoadjuvant: rash (37.3), fatigue (29.7), pruritus (19.8), hyperthyroidism (19.8), diarrhea (16.0)
Dabrafenib + trametinib	BRAF inhibitor + MEK inhibitor	35[61]	Complete pathological response, 49% (95% CI, 31%-66%)	Any grade: pyrexia (80), fatigue (77), chills (69), nausea (60), vomiting (40), diarrhea (34)
Relatlimab + nivolumab	Anti-LAG-3 + anti-PD-1	30[62]	Complete pathological response, 57% (95% CI, 37%-75%)	Any grade, neoadjuvant: rash (17), fatigue (17), increased ALT/AST (10), anemia (10), troponin increase (10), hyponatremia (10)
Adjuvant (resectable stage IIB-C)[d]				
Pembrolizumab	Anti-PD-1	976[63]	Three-year recurrence-free survival: 76.2% for adjuvant pembrolizumab vs 63.4% for placebo (HR, 0.62 [95% CI, 0.49-0.79])	Any grade: pruritus (23), fatigue (20), diarrhea (18), rash (16), arthralgia (14), hypothyroidism (14)
Nivolumab	Anti-PD-1	790[64]	One-year recurrence-free survival: 89.0% for adjuvant nivolumab (95% CI, 85.6%-91.6%) vs 79.4% (95% CI, 73.5%-84.1%) for placebo (HR, 0.42 [95% CI, 0.30-0.59])	Any grade: fatigue (20.2), pruritus (18.5), diarrhea (15.3), rash (10.9)
Adjuvant (resectable stage III/IV)[d]				
Dabrafenib/trametinib	BRAF inhibitor + MEK inhibitor	870[65]	Ten-year recurrence-free survival: 48% (95% CI, 43%-54%) for adjuvant dabrafenib + trametinib vs 32% (95% CI, 26%-40%) for placebo (HR, 0.52 [95% CI, 0.43-0.63])	Any grade: pyrexia (63), fatigue (63), nausea (40), headache (39), chills (37), diarrhea (33)
Pembrolizumab	Anti-PD-1	1019[66]	Ten-year recurrence-free survival: 55.4% (95% CI, 50.8%-59.8%) for adjuvant pembrolizumab vs 38.3% (95% CI, 33.9%-42.7%) for placebo (HR, 0.61 [95% CI, 0.51-0.72])	Any grade: fatigue (37.1), rash (16.1), pruritus (17.7), diarrhea (19.1), arthralgia (12.0)
Nivolumab	Anti-PD-1	906[67]	Five-year recurrence-free survival: 50% for nivolumab vs 39% for placebo (HR, 0.72 [95% CI 0.60-0.86])	Any grade: fatigue (34.5), diarrhea (24.3), pruritus (23.2), rash (19.9), nausea (15.0)
Metastatic/advanced unresectable (stage IIID-IV)[e]				
Encorafenib + binimetinib	BRAF inhibitor + MEK inhibitor	577[68]	Seven-year progression-free survival: 21.2% (95% CI, 14.7%-28.4%) with encorafenib + binimetinib vs 15.8% (95% CI, 9.3%-23.8%) with encorafenib vs 6.4% (95% CI, 2.1%-14.0%) with vemurafenib	Any grade: nausea (40), diarrhea (34), vomiting (28), fatigue (27), arthralgia (25)
Dabrafenib + trametinib	BRAF inhibitor + MEK inhibitor	563[69]	Five-year progression-free survival: 19% (95% CI, 15%-22%) with dabrafenib + trametinib Five-year overall survival: 34% (95% CI, 30%-38%) with dabrafenib + trametinib	Any grade: pyrexia (58), nausea (37), diarrhea (36), fatigue (35), headache (35), chills (34)
Vemurafenib + cobimetinib	BRAF inhibitor + MEK inhibitor	495[70]	Five-year progression-free survival: 14% (95% CI, 9%-19%) for vemurafenib + cobimetinib vs 10% (95% CI, 12%-22%) for vemurafenib + placebo	Any grade: diarrhea (56), nausea (40), rash (39), arthralgia (32), fatigue (32), pyrexia (26), vomiting (21)
Ipilimumab + nivolumab	Anti-CTLA-4 + anti-PD-1	1296[71]	Ten-year overall survival: 43% for ipilimumab + nivolumab, 37% for nivolumab, 19% for ipilimumab	Any grade: diarrhea (45), fatigue (38), pruritus (35), rash (30), nausea (28), hypothyroidism (17), arthralgia (14), colitis (13), pneumonitis (7)
Relatlimab + nivolumab	Anti-LAG-3 + anti-PD-1	714[72]	Three-year progression-free survival: 31.8% (95% CI, 26.6%-37.1%) for relatlimab + nivolumab vs 26.9% (95% CI, 22.1%-31.9%) for nivolumab	Any grade: pruritus (23.4), fatigue (23.1), rash (15.5), arthralgia (14.4), hypothyroidism (14.4)
Pembrolizumab	Anti-PD-1	834[73]	Ten-year progression-free survival: 22.0% for pembrolizumab vs 12.8% for ipilimumab Ten-year overall survival: 34.0% for pembrolizumab vs 23.6% for ipilimumab	Any grade: fatigue (19.1), diarrhea (14.4), pruritus (14.1), rash (13.4)
Talimogene laherparepvec	Viral oncolytic immunotherapy	436[74]	Durable response rate[f]: 19.3% with talimogene laherparepvec vs 1.4% with granulocyte-macrophage colony-stimulating factor (OR, 16.6 [95% CI, 4.0-69.2]; P < .001)	Any grade: fatigue (50.7), chills (49.3), pyrexia (43.2), nausea (36.3), flu-like illness (30.8), injection site pain (28.4)

(continued)

Table 2. Systemic Therapy, Targets, Indications, Efficacy, and Common Adverse Events From Clinical Trials (continued)

Drug	Target	No. of patients	Efficacy (primary end point)	Common treatment-related adverse events (% of patients)
Tumor-infiltrating lymphocyte (TIL) therapy	Autologous TIL cell therapy	168[75]	Six-month progression-free survival: 52.7% (95% CI, 42.9%-64.7%) for TIL vs 21.4% (95% CI, 14.2%-32.2%) for ipilimumab	Any grade, TIL + IL-2: fever (92), chills (84), dyspnea (79), febrile neutropenia (74), hypophosphatemia (71), fatigue (68), nausea (51), sinus tachycardia (50)
Lifileucel	Autologous TIL cell therapy	153[76]	Objective response rate: 31.4% (95% CI, 24.1%-39.4%) for lifileucel	Any grade: thrombocytopenia (82.7), chills (75.0), anemia (62.2), fever (51.9), neutropenia (42.3), febrile neutropenia (41.7), hypophosphatemia (37.2)

Abbreviations: ALT, alanine aminotransferase; AST aspartate aminotransferase; BRAF, proto-oncogene B-Raf protein; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; HR, hazard ratio; IL, interleukin; LAG-3, lymphocyte activation gene 3 protein; MEK, mitogen-activated extracellular signal-regulated kinase; OR, odds ratio; PD-1, programmed cell death protein 1; WBC, white blood cell.

[a] Duration of neoadjuvant therapy: 6 to 12 weeks in preoperative setting.

[b] Event-free survival defined as disease progression or toxicity precluding surgery or initiation of adjuvant therapy, inability to resect all gross disease, postsurgical recurrence, or death.

[c] Event-free survival defined as disease progression, recurrence, or death.

[d] Duration of adjuvant therapy: 1 year in postoperative setting.

[e] Duration of systemic therapy in metastatic disease: up to 2 years or until disease progression or dose-limiting toxicity. For talimogene laherparepvec: until disease progression or dose limiting toxicity. For TIL therapies: administered as 1-time dose.

[f] Durable response rate defined as partial or complete response continuously for 6 or more months starting within 12 months.

Neoadjuvant Therapy (Stage IIIB or Higher)

According to NCCN and American Society of Clinical Oncology (ASCO) guidelines,[77] neoadjuvant therapy may be considered prior to surgical excision for patients with clinically node-positive melanoma (ie, palpable or radiographic, pathologically confirmed) without evidence of distant metastases on CT or positron emission tomography scan (any T, N1b-N3c), particularly with bulky tumors that may be difficult to resect. Neoadjuvant regimens include pembrolizumab,[78] relatlimab + nivolumab,[62] ipilimumab + nivolumab,[60] or dabrafenib + trametinib in *BRAF*-variant melanoma[61] (Table 2).

First-Line Therapy for Unresectable Stage III or Stage IV Melanoma

First-line therapy per ASCO guidelines for unresectable stage III and stage IV metastatic melanoma is combination immunotherapy with nivolumab (anti–PD-1) and ipilimumab (anti-CTLA4) for 4 cycles given every 3 weeks, followed by maintenance nivolumab every 4 weeks for up to 2 years, or until disease progression or dose-limiting toxicity.[77]

A randomized clinical trial including 1296 patients with previously untreated unresectable stage III or stage IV melanoma reported higher median overall survival with combination nivolumab + ipilimumab (71.9 months [95% CI, 38.2-114.4]) compared with either agent alone (nivolumab, 36.9 months [95% CI, 28.2-58.7]; ipilimumab, 19.9 months [95% CI, 16.8-24.6]). The HR for death with nivolumab + ipilimumab compared with ipilimumab monotherapy was 0.53 (95% CI, 0.44-0.65) and the HR for death for nivolumab vs ipilimumab was 0.63 (95% CI, 0.52-0.76).[71]

Another FDA-approved immune checkpoint combination therapy for unresectable stage III or stage IV melanoma is nivolumab and relatlimab (anti–LAG-3). A randomized trial including 714 patients with untreated metastatic or unresectable melanoma demonstrated median overall survival of 51.0 months (95% CI, 34.0-not reached) with relatlimab + nivolumab vs 34.1 months (95% CI, 25.2-44.7) with nivolumab alone (HR, 0.80 [95% CI, 0.66-0.99]).[72]

Immune-Related Adverse Events

Compared with immune checkpoint monotherapy, combination therapy is associated with increased risks of immune-related adverse events, including dermatitis, hypothyroidism, colitis, arthritis, and pneumonitis (Table 2). Grade 3-4 (moderate to severe) immune-related adverse events (defined by Common Terminology Criteria for Adverse Events) occurred in 59% of patients receiving nivolumab + ipilimumab vs 21% with nivolumab alone[71] and in 22% with relatlimab + nivolumab vs 9.7% with nivolumab alone.[72]

However, immune-related adverse events are associated with improved tumor response[79] and increased survival in patients with melanoma. In a cohort study of 492 patients receiving immune checkpoint blockade for metastatic melanoma, patients experiencing any grade 2 or greater vs no immune-related adverse event had improved overall survival (56.3 vs 18.5 months, $P < .001$).[80]

Nivolumab or pembrolizumab monotherapy[71,73] may be considered for patients with autoimmune conditions (eg, rheumatoid arthritis, lupus) that may worsen with immunotherapy[81] and/or those who prefer to avoid increase in treatment-related adverse effects associated with dual immune checkpoint inhibitor therapy.[50]

Second-Line Therapy for Unresectable Stage III or Stage IV Melanoma

For patients with melanoma and an activating *BRAF* V600E or V600K genetic variant, combination therapy with dabrafenib + trametinib,[69] encorafenib + binimetinib,[68] or vemurafenib + cobimetinib[70] may be used as second-line therapy (Table 2). BRAF + MEK inhibitors should be used sequentially after immunotherapy at disease progression.[82,83]

Tumor-infiltrating lymphocyte therapy is a second-line therapy for patients with previously treated unresectable or metastatic melanoma.[59] Lifileucel is an FDA-approved adoptive T-cell transfer in which T cells are harvested from a patient's tumor, expanded in the laboratory, and administered to the patient after lymphodepleting chemotherapy. Lifileucel is followed by interleukin 2 to promote

lymphocyte growth and activity.[76] A multicenter randomized trial of 168 patients with anti–PD-1 refractory, unresectable/metastatic melanoma reported median progression-free survival of 7.2 months (95% CI, 4.2-13.1) with tumor-infiltrating lymphocytes vs 3.1 months (95% CI, 3.0-4.3) with ipilimumab ($P < .001$).[75] The most common adverse events associated with tumor-infiltrating lymphocyte therapy included thrombocytopenia (91%), anemia (91%), and febrile neutropenia (86%).

Intralesional/intratumoral oncolytic virus talimogene laherparepvec, an injectable modified oncolytic herpes virus designed to stimulate local and systemic antitumor response via production of granulocyte-macrophage colony-stimulating factor (GM-CSF)[74] is a FDA-approved second-line therapy that may be used for locoregional disease control. A phase 3 RCT including 436 patients with unresectable stage IIIB-IVM1c melanoma reported durable responses (defined as objective antitumor response lasting ≥6 months) in 19.0% with talimogene laherparepvec vs 1.4% with GM-CSF ($P < .001$) and a median overall survival of 23.3 vs 18.9 months (unstratified HR, 0.79 [95% CI, 0.62-1.00]; $P = .049$).[74]

Prevention

Primary Prevention

To decrease the risk of melanoma, ASCO recommends reducing UV exposure (seeking shade during peak hours of sunlight), avoiding indoor tanning, and using UV protection with sunprotective clothing and/or UVA/UVB sunscreens.[84] The US Preventive Services Task Force recommends minimizing UV exposure in individuals younger than 24 years with lighter pigmented skin.[35] The American Academy of Dermatology recommends routine photoprotection, including daily sunscreen use on uncovered skin (sun protection factor ≥30 with broad spectrum UVA and UVB protection) for individuals of all skin pigmentations.[85] Other photoprotection strategies include use of wide-brimmed hats, clothing, UV protective sunglasses, and seeking shade during peak hours of sunlight (generally 10 AM-2 PM).[86] An RCT in Australia assigned 1621 patients to discretionary or daily sunscreen application in combination with beta carotene or placebo for 4 years. At 10-year follow-up, there was no significant difference in the rate of melanoma in situ and invasive melanoma between groups; however, there were significantly fewer invasive melanomas in the daily sunscreen group compared with the discretionary sunscreen group (0.37% vs 1.36%; HR, 0.27 [95% CI, 0.08-0.97]).[87]

Secondary Prevention

Secondary prevention in patients with melanoma includes regular skin self-examination and examination by a dermatology clinician for early detection of additional melanomas.[88] Patients with localized melanoma should undergo routine 3- to 12-month follow-up (based on disease stage and recurrence risk) primary care, dermatology or oncology visits including history and physical for at least 5 years after diagnosis (eTable 3 in the Supplement).[50]

Prognosis

The 15-year melanoma-specific survival for melanoma in situ is 98.4% (95% CI, 98.3%-98.5%).[89] For invasive melanoma, in 2017, 10-year survival rates per the *AJCC Cancer Staging Manual*, 8th edition[49] (prior to the widespread availability of effective systemic therapies) were reported as 98% to 94% for stage IA-B, 88% to 75% for stage IIA-C, 88% for stage IIIA, 77% to 60% for stage IIIB-C, and 24% for stage IIID.[49] In 2024, a trial that included 1296 patients with unresectable stage III or stage IV melanoma, reported a 10-year overall survival rate of 43% for those treated with nivolumab + ipilimumab vs 37% with nivolumab and 19% with ipilimumab.[71]

Non-White individuals in the US have lower melanoma-specific survival than White individuals, attributed to lead-time, length-time, and overdiagnosis biases, with 5-year overall survival rates of 72.2% to 81.1% for minorities (American Indian, Asian/Pacific islander, Black/African American, Hispanic individuals) vs 89.6% for White individuals ($P < .001$).[90]

Emerging Diagnostics

Tumor-informed circulating tumor DNA (ctDNA) assayed in peripheral blood with probes developed from the tumor is an emerging assay for stage II-IV melanoma. Small cohort studies demonstrate that molecular signs of residual disease (ctDNA positivity) may be prognostic of radiographic and clinical relapse.[91,92] An ongoing phase 2/3 multicenter study in patients with resected stage IIB-C melanoma is investigating whether early relapse can be identified by ctDNA, and if outcomes can be improved with treatment after detection of molecular recurrence.[93]

Limitations

This review has several limitations. First, the quality of the included literature was not formally evaluated. Second, some relevant articles may have been missed. Third, this review focused on cutaneous melanoma and did not discuss less common forms of melanoma (eg, uveal and mucosal).

Conclusions

Melanoma is the fifth most common cancer in the US. Definitive treatment for stage IA-IIA melanoma is surgical resection. Anti–PD-1 immunotherapy after surgical excision improves recurrence-free survival in stage IIB-C melanoma. For stage III melanoma, anti–PD-1 immunotherapy or BRAF + MEK inhibitor therapy decreases risk of melanoma recurrence. First-line therapy for patients with metastatic melanoma is dual checkpoint blockade with ipilimumab and nivolumab.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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